

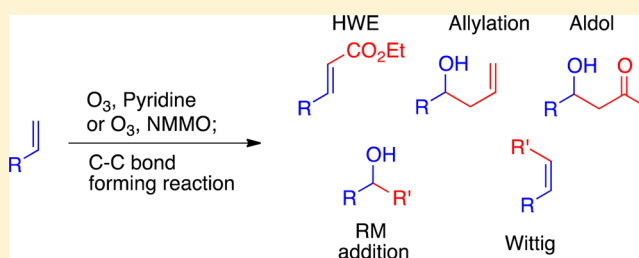
Tandem Application of C–C Bond-Forming Reactions with Reductive Ozonolysis

Rachel Willand-Charnley and Patrick H. Dussault*

Department of Chemistry, University of Nebraska–Lincoln, Lincoln, Nebraska 68588-0304, United States

Supporting Information

ABSTRACT: Several variants of reductive ozonolysis, defined here as the in situ generation of aldehydes or ketones during ozonolytic cleavage of alkenes, are demonstrated to work effectively in tandem with a number of C–C bond-forming reactions. For reactions involving basic nucleophiles (1,2-addition of Grignard reagents, Wittig or Horner–Emmons olefinations), and directed aldol reactions of lithium enolates), the one-pot process offers a rapid and high-yielding alternative to traditional two-step protocols.



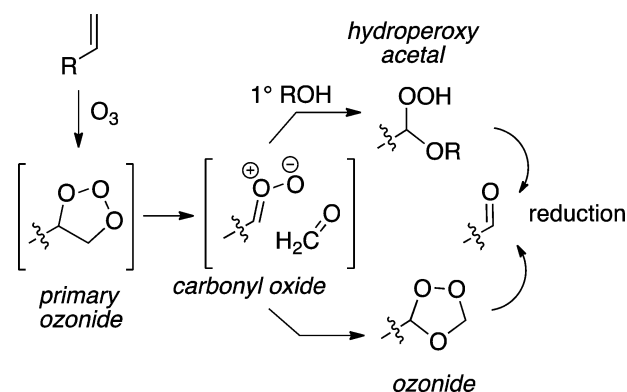
INTRODUCTION

Methods for generation of new carbon–carbon bonds from carbonyl electrophiles are among the most fundamental of synthetic transformations. The aldehyde and ketone starting materials are frequently generated via cleavage of alkenes with ozone. As a method for oxidative carbonyl generation, ozonolysis has many attractive features: compatibility with either protic or aprotic media, useful selectivity for cleavage of alkenes in the presence of other functional groups, the need for only oxygen and electricity as inputs, and the absence of metal-containing byproducts.¹ However, on the negative side, the intermediate ozonides or hydroperoxyacetals are often capable of dangerously exothermic self-accelerating decomposition reactions.² The potential hazards related to accumulation of energetic intermediates have limited large-scale application of ozonolysis³ and motivated the development of flow-based or modular reactor systems.⁴ We have recently reported several methods for “reductive” ozonolysis that directly generate carbonyl products, avoiding formation of isolable peroxides.^{5a–c}

We now report the successful application of reductive ozonolyses in tandem with a number of the most common methods for carbon–carbon bond-forming reactions.

To understand the potential value of one-pot application of reductive ozonolysis and C–C bond-forming reactions, it is useful to look at a traditional ozonolysis pathway (Scheme 1).^{1a,6} Cycloaddition of an alkene with ozone generates a 1,2,3-trioxolane, or “primary ozonide”,⁷ which undergoes cycloreversion even at low temperatures to generate a carbonyl and a short-lived carbonyl O-oxide.^{6,8} Reaction in aprotic media favors cycloaddition with a dipolarophile, frequently the cogenerated aldehyde, to furnish 1,2,4-trioxolanes (ozonides).⁹ Alternatively, nucleophilic trapping by unhindered alcohols generates hydroperoxyacetals.^{10,11} Ozonides and hydroperoxyacetals are most often decomposed to aldehydes or ketones by reduction,¹² although alternative workups are known on the basis of base-promoted fragmentations.¹³ Reduction can be

Scheme 1. Overview of Alkene Ozonolysis (Traditional)



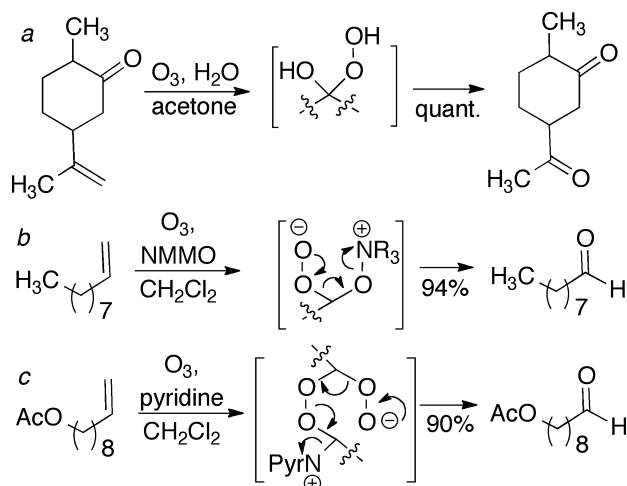
accomplished with many reagents, but three are used most frequently.^{1a,12} Me₂S is a mild and chemoselective reagent which can be used in excess and generates DMSO as a byproduct. However, as became obvious in the course of this work, the reaction of Me₂S with ozonides is often slow, so slow in the case of hindered ozonides as to result in potentially hazardous situations.¹⁴ Zn/HOAc rapidly reduces most peroxides, but the acidic conditions are incompatible with many substrates. Ph₃P reduces all hydroperoxyacetals and most ozonides, but the formation of stoichiometric phosphine oxide can complicate product isolation.¹⁵

Reductive Ozonolysis. We have recently described three protocols for reductive ozonolysis. The first (Scheme 2, path a) involves an operationally simple protocol, ozonolysis in wet acetonitrile or wet acetone.^{5b} In this case, attack of solubilized water on the carbonyl oxide generates a tetrahedral

Special Issue: Robert Ireland Memorial Issue

Received: July 24, 2012

Scheme 2. Overview of Reductive Ozonolyses



intermediate that decomposes to furnish the carbonyl product(s) and hydrogen peroxide. The second (Scheme 2, path b) involves ozonolysis in the presence of *N*-methylmorpholine *N*-oxide (NMMO) or related *N*-oxides.^{5a} Nucleophilic trapping of the carbonyl oxide generates unstable zwitterionic acetals, which fragment to generate the target carbonyl, O₂, and a molecule of amine.¹⁶ Finally, we recently described a general and high-yielding protocol for direct conversion of alkenes to aldehydes and ketones based upon ozonolysis in the presence of added pyridine.^{5c} This transformation (Scheme 2, path c) appears to involve an unprecedented pyridine-promoted dimerization and fragmentation of carbonyl oxides. Of particular relevance to the current studies, the *N*-oxide and pyridine-promoted protocols are conducted under anhydrous conditions and generate by-products (amines, *N*-oxides, or pyridine) not expected to interfere with transformations based upon carbon nucleophiles.

RESULTS

We investigated *in situ* ozonolytic generation of aldehydes and ketones in conjunction with several widely used methods for carbon–carbon bond formation: 1,2-organometallic additions, Wittig and Horner–Emmons olefinations, aldol reactions, and allylations. Because the majority of these transformations involve the use of water-sensitive reagents, we focused our efforts on the reductive protocols based upon *N*-oxides (Scheme 2b) and pyridine (Scheme 2c).

Horner–Emmons Olefinations. As illustrated in Table 1, addition of lithiated triethyl phosphonoacetate to the crude reaction mixtures resulting from reductive ozonolysis provided very good yields of α,β -unsaturated esters. Similar yields were available through a traditional multistep route involving Me₂S (3–5 equiv) reduction of the intermediate ozonide (*vide infra*); however, the reduction step required up to 24 h for removal of ozonide.

Wittig Olefination. Wittig olefination with nonstabilized ylides also paired effectively with reductive ozonolysis (Table 2). In the case of the *N*-oxide protocol, we found it most effective to conduct the subsequent Wittig reaction at 0 °C or above to avoid precipitation of reagents.

Organometallic Addition. Direct addition of organometallics to solutions of ozonolysis-derived aldehydes was investigated with Grignard reagents (Table 3). Good yields of

Table 1. One-Pot Reductive Ozonolysis and Horner–Emmons Reaction

alkene	method ^a	enoate	yield
	A		94%
	B		82%
	A		83%
	B		73%
	A		89%
	B		88%

^aKey: (A) O₃, NMMO (3 equiv), CH₂Cl₂, 0 °C; then Wittig ylide (1.1 equiv) in THF. B) O₃, pyridine (3 equiv), CH₂Cl₂, –78 °C; then Wittig ylide.

Table 2. One-Pot Ozonolysis and Wittig Olefination

alkene	method ^a	product	yield
	A		86%
	B		84%
	A		80%
	B		79%
	A		86%
	B		77%

^aKey: (A) O₃, NMMO (3 equiv), CH₂Cl₂, 0 °C; then Wittig ylide (1.1 equiv) in THF; (B) O₃, pyridine (3 equiv), CH₂Cl₂, –78 °C; then Wittig ylide.

secondary or tertiary alcohols were obtained using only a slight excess (1.1 equiv) of the alkyl- or arylmagnesium reagent.

Aldol Reactions. Addition of the lithium enolate of cyclohexanone to the crude reaction mixtures resulting from the pyridine- or NMMO-promoted reductive ozonolyses furnished good yields of 3-hydroxy ketones as ~3:1 mixtures of *anti/syn* diastereomers (Table 4). The yields and sense of

Table 3. One-Pot Ozonolysis and Organometallic Addition

alkene	method ^a	R	product	yield
	A	Ph		88%
	B	Me		76%
	B	Ph		60%
	B	Ph		45%
	A	Me		78%
	B	Me		68%
	A	Ph		92%
	B	Ph		88%
	A	Ph		79%
	B	Ph		88%

^aKey: (A) O₃, NMMO, CH₂Cl₂, 0 °C; add RMgX in ether; (B) O₃, pyridine, CH₂Cl₂, 0 °C; then RMgX.

Table 4. One-Pot Ozonolysis and Aldol Reaction

alkene	method ^a	product	yield
	A B		84% 80%
	A B		81% 76%
	A B		76% 78%

^aKey: (A) O₃, NMMO, CH₂Cl₂, 0 °C; lithium enolate of cyclohexanone; (B) same except O₃, pyridine, CH₂Cl₂, 0 °C.

stereoselection were very similar to results previously reported for analogous reactions of isolated aldehydes (see the Experimental Section). In contrast, attempts to perform the corresponding Lewis acid catalyzed Mukaiyama aldol reactions with a trimethylsilyl enol ether were unsuccessful (not shown); in fact, addition of enol ethers and TiCl₄ to pyridine-containing solutions resulted in the formation of a viscous, dark material.

Allylations. Lewis acid catalyzed allylations were investigated in tandem with both the *N*-oxide and the pyridine protocols (Table 5).¹⁷ Treatment of the products of either

Table 5. One-Pot Ozonolysis and Lewis Acid-Mediated Allylation

alkene	method ^a	product	yield
	A B C D		88% - 70% 85%
	A B		85% -
	A B		78% -

^aKey: (A) O₃, NMMO, CH₂Cl₂, 0 °C; then TiCl₄, allylSiMe₃; (B) same, but O₃, pyridine, CH₂Cl₂, -78 °C; (C) O₃, pyridine, CH₂Cl₂, -78 °C; then BF₃·OEt₂, allylSiMe₃; (D) Same except O₃, NMMO, CH₂Cl₂, 0 °C.

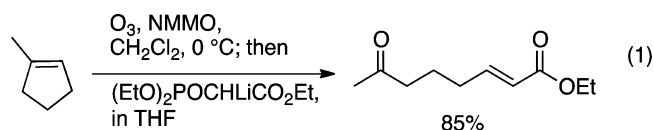
protocol with allylsilane and BF₃·OEt₂ (excess) furnished homoallyl alcohols in good yield. In contrast, TiCl₄-promoted allylation was unsuccessful when applied in tandem with pyridine-promoted reductive ozonolysis and could be applied in tandem with the NMMO protocol only if the Lewis acid was used in excess relative to the *N*-oxide. Attempted allylations in the presence of more oxophilic Lewis acids such as Yb(OTf)₃ and TMSOTf were unsuccessful.

DISCUSSION

Ozonolysis has been previously investigated as a one-pot reaction in tandem with a number of reductive transformations, including borohydride reduction,¹⁸ reductive amination,¹⁹ hydrogenation,²⁰ and Clemmensen reduction.²¹ Oxidation of ozonolysis products with H₂O₂ has been employed for the synthesis of carboxylic acids,^{22,23} and chromic acid oxidation has been used to digest ozonides.²⁴

However, the record related to C–C bond formation is much thinner. Building upon an efficient synthesis of aldehydes via base-promoted fragmentation of terminal ozonides,¹³ Hon's laboratory demonstrated the ability to convert the same ozonides directly to unsaturated esters upon reaction with stabilized Wittig ylides.²⁵ The combination of SnCl₂ and ethyl diazoacetate has been shown to achieve the direct conversion of ozonolysis-derived peroxides to 3-ketoesters.²⁶ Cyclic oxonitriles have been prepared by pairing the ozonolysis of unsaturated nitriles with a subsequent intramolecular aldol reaction.²⁷ Ozonides are also known to react directly with organometallic reagents.²⁸ However, this methodology requires handling of a peroxide intermediate and the use of excess organometallic (to cleave the O–O bond and then react with the liberated carbonyl).²⁹

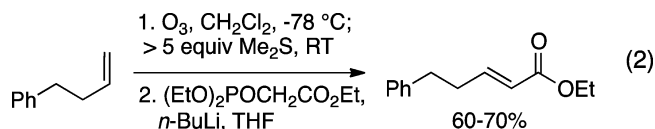
Reductive ozonolyses, which achieve the direct conversion of alkenes to ketones or aldehydes, were anticipated to partner well with methods for carbon–carbon bond formation. In particular, the pyridine or amine *N*-oxide promoters were not expected to interfere with reactions involving basic nucleophiles. This assumption was supported by our results, which found no significant change in stoichiometry or yield relative to a traditional two-step procedure for reactions with phosphonate anions, Wittig ylides, Grignard reagents, or lithium enolates. Curiously, although the ozonolysis of terminal alkenes generates formaldehyde as a byproduct,^{1a,6,8} we did not observe products of one-carbon homologation, even in the presence of PhMgBr, a reagent for which the derived alcohol would have been easily observed and isolated. The failure to trap formaldehyde, which is a definite plus in terms of avoiding unnecessary consumption of reagent, presumably reflects loss of this highly volatile byproduct under reaction conditions. In contrast, application of a one-pot ozonolysis/Horner–Emmons protocol to a cyclic alkene furnished a good yield of the product derived from a ketoaldehyde (eq 1).



In contrast, Mukaiyama aldol reactions failed completely under the tandem conditions, while Hosomi–Sakurai allylations were successful only in the presence of a significant excess of Lewis acid. These results are not completely surprising; pyridine and NMMO are strong Lewis bases, and we found no examples of previous pairings of ozonolysis with Lewis-acid promoted allylation chemistry.³⁰ Based upon our results, we cannot recommend the tandem application of reductive ozonolysis in sequences employing strong Lewis acids.

Although we did not explore enamine-based aldol or Michael chemistry, the conditions of the pyridine-mediated reductive ozonolyses are likely to pair well with these increasingly popular approaches for carbon–carbon bond formation.

A comparison with traditional methodology reveals practical advantages of the new approach. Application of a traditional ozonolysis/Horner–Emmons reaction sequence (ozonolysis; Me₂S reduction; Horner–Emmons olefination) to 3-butenylbenzene (eq 2) furnishes ethyl 5-phenyl-2-pentenoate in a yield



only slightly lower than for the one-pot approach (see Table 1) but requires 24 h or more for complete consumption of the ozonide by Me₂S (6–8 equiv) compared with minutes in the one-pot procedures.

In conclusion, the application of convenient and high-yielding approaches for reductive ozonolysis in tandem with a number of widely used methods for C–C bond-forming reactions is shown to result in streamlined synthetic sequences. It is hoped that the methodology will be as widely applied as an analogous strategy partnering C–C bond-forming reactions with Swern oxidations.³¹

Notes on Safety. Although the procedures described above typically preclude formation of significant amounts of ozonides and other peroxides, experimenters are urged to verify the absence of significant amounts of peroxides before concentrating crude reaction mixtures.³² Ozonolyses should always be conducted with an awareness of the potential for spontaneous and exothermic decompositions.²

EXPERIMENTAL SECTION

All reagents and solvents were used as supplied commercially, except CH₂Cl₂ (distilled from CaH₂), THF (distilled from Na/benzophenone) and pyridine (stored over activated 4 Å sieves). All reactions were conducted under an atmosphere of N₂ except where noted. NMR spectra were acquired in CDCl₃; chemical shifts are reported in ppm referenced to the solvent peaks of CDCl₃ (7.26 ppm for ¹H and 77.1 (±0.1) ppm for ¹³C). The sample was analyzed by GC/MS (30 m DB-5MS column with a 1:200 injector split and 1 mL/min flow of He gas, analysis on an ion trap scanning in EI mode over 50–650 *m/z* range, with the ion source set at 200 °C). IR was acquired via ATR as neat films on a ZrSe crystal with selected absorbances reported in cm^{−1}. Silica gel was used for flash column chromatography. Thin-layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates containing a fluorescent indicator. Developed TLC plates were visualized with a hand-held UV lamp or by charring after staining with 1% ceric sulfate/10% ammonium molybdate in 10% H₂SO₄.

Reductive Ozonolysis in the Presence of Pyridine. The alkene (internal or terminal) substrate (1–3 mmol) and dry pyridine (3–9 mmol) were dissolved in dry CH₂Cl₂ (15–20 mL) in a flame-dried flask under N₂. The solution was cooled to −78 °C, at which point a stream of O₃/O₂ (delivering ~1 mmol/min of O₃) was introduced through a disposable pipet for a period proportional to the amount of alkene. Once consumption of alkene was complete, the reaction was sparged with O₂ and then N₂. The resulting solution was added dropwise (syringe or cannula) to the next reaction mixture.

Reductive Ozonolysis in the Presence of *N*-Methylmorpholine *N*-Oxide (NMMO). The alkene (internal or terminal) substrate (1–3 mmol) and NMMO (3–5 equiv relative to alkene) were dissolved in dry CH₂Cl₂ (15–20 mL) in a flame-dried flask under N₂. The solution was cooled to 0 °C, after which ozonolysis carried out as described in the previous procedure, as was application of the reaction mixture to the following reaction.

Tandem Application of Reductive Ozonolysis and Horner–Emmons Olefination. To a −78 °C solution of triethyl phosphonoacetate (4 mmol) in THF (20 mL) was dropwise added *n*-butyllithium (5 mmol, as a nominally 2.3 M solution in hexane). The

reaction was allowed to stir for 1 h, whereupon the CH₂Cl₂ solution of the carbonyl product of ozonolysis (nominally 3 mmol based upon alkene starting material) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 2.5 h. The reaction was quenched with saturated NH₄Cl (4 mL) and the mixture extracted with 30 mL of ether (3×). The combined organic layers were washed with brine and extracted. The aqueous washes were back extracted with a small amount of ether (3×), the combined organic layers were dried with sodium sulfate, and the residue obtained upon concentration was purified via flash chromatography with EA/Hex to furnish the desired product.

Tandem Application of Reductive Ozonolysis and Grignard Reactions. A solution of CH₂Cl₂ and carbonyl product (nominally 3 mmol), prepared from an alkene via ozonolysis as already discussed,^{5a,c} was recooled to 0 °C, whereupon a stoichiometric amount of phenyl- or methylmagnesium bromide (3 mmol, 1 equiv, nominally 1 M in THF) was added. The reaction was monitored by TLC and, when complete, was quenched by dropwise addition of water followed by a few drops of 6 M aq HCl. The mixture was diluted with a volume of saturated aq NH₄Cl, and the separated aqueous layer was extracted three times with CH₂Cl₂. The remainder of the workup was performed as for the Horner–Emmons sequence described above.

Tandem Application of Reductive Ozonolysis and Allylation Reactions. To a room temperature CH₂Cl₂ solution of the carbonyl product (nominally 3 mmol), prepared from an alkene via ozonolysis as already discussed,^{5a,c} was dropwise added TiCl₄ (6 mmol, neat). After approximately 10 min, allyltrimethylsilane (2 mmol) was added dropwise and the reaction mixture was allowed to stir for 45 min. The reaction was quenched with deionized water. The organic layer was extracted with 30 mL of ether (3×). The combined organic layers were dried and concentrated as described previously followed by drying, concentration, and purification by procedures similar to those described above.

Tandem Application of Reductive Ozonolysis and Wittig Olefination. A CH₂Cl₂ solution of carbonyl product (nominally 3 mmol) was prepared from an alkene via ozonolysis as discussed above.^{5a,c} A stoichiometric (3 mmol; 1 equiv relative to nominal amount of carbonyl) amount of pentyltriphenylphosphonium bromide was placed in a flame-dried 50 mL RBF capped with a septa. The atmosphere was removed under vacuum and backfilled with N₂. The salt was dissolved in THF (10–15 mL) and the solution cooled to 0 °C. The mixture was allowed to stir for 10 min, whereupon a solution of *n*-BuLi (3 mmol, nominally 2.3 M in Hex) was added dropwise. The reaction was allowed to stir for 0.5 h, after which the solution of aldehyde was added dropwise. The reaction, when complete (~0.5–1 h, TLC) was quenched by dropwise addition of water and the resulting mixture extracted with 30 mL of ether. The organic layer was washed successively with aqueous sodium bicarbonate, water, and bleach. The aqueous washes were back-extracted three times with a small amount of ether. The combined organic layers were dried and concentrated as described previously followed by drying, concentration, and purification by procedures similar to those described above.

Tandem Application of Reductive Ozonolysis with Aldol Reactions. The aldehyde (nominally 3 mmol) was prepared from an alkene via ozonolysis as already discussed.^{5a,c} To a stirring 0 °C solution of diisopropylamine (3 mmol) in 7 mL of THF in a flame-dried RBF was added *n*-butyllithium (3 mmol, as a nominally 2.3 M solution in hexane). After 15 min, a solution of cyclohexanone (3 mmol) in THF (2 mL) was added. The reaction was cooled to −78 °C, and the CH₂Cl₂ solution of the aldehyde product was added. After 15 min, the aldehyde was completely consumed (TLC), and the reaction was quenched with 1 M HCl (1–2 equiv). The solution (emulsion) was extracted with 30 mL of ether, and the organic layer was washed successively with aqueous sodium bicarbonate, water, and aqueous sodium chloride. The aqueous washes were back-extracted with a small amount of ether (3×). The combined organic layers were dried and concentrated as described previously followed by drying, concentration, and purification by procedures similar to those described above. The *syn/anti* ratios (~1:3 in all cases) were assigned by comparison of the ¹H NMR spectra with literature reports.^{33–37}

Products Prepared via Tandem Ozonolysis. The following were prepared according to the experimental procedures described. All compounds afforded spectral data identical to values described in the literature.

(E)-Ethyl 11-acetoxyundec-2-enoate (via Horner–Emmons reaction): colorless oil; $R_f = 0.5$ (10% EA/hex); ^1H (400 MHz, CDCl_3) δ 6.98 (1H, dt, 7.0, 15.7), 5.82 (1H, dt, 1.5, 15.6), 4.21 (2H, q, 7.1), 4.07 (2H, t, 6.7), 2.19 (2H, dq, ~1, 6.7), 2.06 (3H, s), 1.63 (2H, p, 6.7), 1.47 (2H, p, 6.9), 1.30 (11H, t, 7.1); ^{13}C (100.6 MHz, CDCl_3) δ 171.4, 166.8, 149.4, 121.3, 64.6, 60.1, 32.2, 29.2, 29.1, 29.0, 28.6, 28.0, 25.9, 21.0, 14.3; IR 2929, 2856, 1717 cm^{-1} ; HRMS (ESI, $\text{MeOH}/\text{H}_2\text{O}$, NaOAc), calcd for $\text{C}_{15}\text{H}_{26}\text{NaO}_4$ ($\text{M} + \text{Na}$) $^+$ 293.1729, found 293.1722 (–2.0 ppm).

(E)-Ethyl 5-phenylpent-2-enoate (via Horner–Emmons reaction): $R_f = 0.7$ in (10% EA/hex).³⁸

(E)-Ethyl 4-acetoxybut-2-enoate (via Horner–Emmons reaction): $R_f = 0.4$ in (10% EA/hex).³⁹

(E)-Ethyl 7-oxooct-2-enoate (via Horner–Emmons reaction): $R_f = 0.7$ in (10% EA/hex).⁴⁰

(Z)-Tridec-5-ene (via Wittig reaction): $R_f = 0.92$ (10% EA/hex).⁴¹

(Z)-Tetradec-5-ene (via Wittig reaction): $R_f = 0.70$ (10% EA/hex).⁴¹

(Z)-Oct-3-en-1-ylbenzene (via Wittig reaction): $R_f = 0.75$ (10% EA/hex).⁴²

2-(1-Hydroxy-3-phenylpropyl)cyclohexanone (via aldol reaction): $R_f = 0.22$ (10% EA/hex), isolated as an approximately 3:1 mixture of *anti* and *syn* isomers, determined by comparison on NMR spectra with literature reports. The stereochemical outcome is very similar to that reported for corresponding reactions of 3-phenylpropanal.³³

2-(1-Hydroxynonyl)cyclohexanone (via aldol reaction): $R_f = 0.38$ (10% EA/hex), isolated as an approximately 3:1 mixture of *anti* and *syn* isomers, determined by comparison on NMR spectra against literature reports. The stereochemical outcome is very similar to that reported for corresponding reactions of analogous aldehydes.³⁴

2-(1-Hydroxyoctyl)cyclohexanone (via aldol reaction): $R_f = 0.40$ (10% EA/hex).³⁵

Decan-2-ol (via Grignard reaction): $R_f = 0.20$ (10% EA/hex).⁴³

1-Phenyldecan-1-ol (via Grignard reaction): $R_f = 0.26$ in (10% EA/hex).⁴⁴

2-Phenylnopinol (via Grignard reaction): $R_f = 0.20$ (10% EA/hex).⁴⁵

4-tert-Butyl-1-methylcyclohexanol (via Grignard reaction): $R_f = 0.20$ (10% EA/hex).⁴⁶

1,3-Diphenylpropan-1-ol (via Grignard reaction): $R_f = 0.22$ (10% EA/hex).⁴⁷

1-Phenylloctan-1-ol (via Grignard reaction): $R_f = 0.33$ (10% EA/hex).⁴⁶

1-Phenylhex-5-en-3-ol (via allylation reaction): $R_f = 0.8$ (10% EA/hex).⁴⁸

Dodec-1-en-4-ol (via allylation reaction): $R_f = 0.36$ (10% EA/hex).⁴⁹

Undec-1-en-4-ol (via allylation reaction): $R_f = 0.34$ (10% EA/hex).⁵⁰

■ ASSOCIATED CONTENT

● Supporting Information

^1H NMR of known molecules prepared as described above and characterization (^1H , ^{13}C , IR and HRMS) for ethyl 11-acetoxy-2-undecenoate. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pdussault1@unl.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research was conducted with funding from the NSF (CHE-1057982) in facilities remodeled with support from the NIH (RR016544).

■ DEDICATION

Dedicated to the memory of Robert E. Ireland.

■ REFERENCES

- (1) (a) Bailey, P. S. *Ozonation in Organic Chemistry: Vol 1 (Olefinic Compounds)*; Academic Press: New York, 1982. For more recent overviews of ozonolysis, see: (b) McGuire, J.; Bond, G.; Haslam, P. J. In *Handbook of Chiral Chemicals*, 2nd ed.; Taylor & Francis: Boca Raton, 2006; 165; (c) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990. (d) East, M. *Chem. Today (Chim. Oggi)* **2006**, *24*, 46.
- (2) See, for example: Kula, J. *Chem. Health Saf.* **1999**, *6*, 21. Zabicky, J. In *The Chemistry of the Peroxide Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 2006; Vol. 2, Part 2, p 597. Ragan, J. A.; am Ende, D. J.; Brenek, S. J.; Eisenbeis, S. A.; Singer, R. A.; Tickner, D. L.; Teixeira, J. J.; Vanderplas, B. C.; Weston, N. *Org. Process Res. Dev.* **2003**, *7*, 155. Hida, T.; Kikuchi, J.; Kakinuma, M.; Nogusa, H. *Org. Process Res. Dev.* **2010**, *14*, 1485.
- (3) For a description of an ozonolysis reactor designed to achieve formation and decomposition of ozonides, see: <http://www.thalesnano.com/products/o-cube>.
- (4) For an example of a flow-based process, see: O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596.
- (5) (a) Willand-Charnley, R.; Fisher, T.; Johnson, B.; Dussault, P. H. *Org. Lett.* **2012**, *14*, 2242. (b) Schiaffo, C. E.; Dussault, P. H. *J. Org. Chem.* **2008**, *73*, 4688. (c) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Tetrahedron* **2006**, *62*, 10747.
- (6) Criegee, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 745.
- (7) Although primary ozonide and molozonide are often used interchangeably in older literature, the latter term is now predominantly used to describe alternate structures.
- (8) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335.
- (9) Kuczkowski, R. L. *Chem. Soc. Rev.* **1992**, *21*, 79.
- (10) Yamamoto, Y.; Niki, E.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2677.
- (11) Steinfeldt, N.; Bentrup, U.; Jaehnisch, K. *Ind. Eng. Chem. Res.* **2010**, *49*, 72.
- (12) Kropf, H. In *Houben-Weyl Methoden Der Organische Chemie*; Kropf, H., Ed.; Georg Thieme: Stuttgart, 1988; Vol. E13/2, p 1111.
- (13) Hon, Y. S.; Lin, S. W.; Chen, Y. J. *Synth. Commun.* **1993**, *23*, 1543–53. Hon, Y. S.; Lin, S. W.; Ling, L.; Chen, Y. J. *Tetrahedron* **1995**, *51*, 5019. For the direct conversion of terminal alkenes to methyl esters in basic methanol, see: Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.
- (14) See, for example: Chen, L.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 7561.
- (15) See, for example: Årstad, E.; Barrett, A. G. M.; Hopkins, B. T.; Koebberling, J. *Org. Lett.* **2002**, *4*, 1975.
- (16) For a theoretical exploration of the N-oxide fragmentation, see: Hang, J.; Ghorai, P.; Finkenshaedt-Quinn, S. A.; Findik, I.; Sliz, E.; Kuwata, K. T.; Dussault, P. H. *J. Org. Chem.* **2012**, *77*, 1233.
- (17) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.
- (18) Chandrasekhar, S.; Shyamsunder, T.; Prakash, S. J.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 47.
- (19) Kyasa, S.-K.; Fisher, T. J.; Dussault, P. H. *Synthesis* **2011**, 3475.
- (20) (a) For leading references, see ref 1a and: Pryde, E. H.; Anders, D. E.; Teeter, H. M.; Cowan, J. C. *J. Org. Chem.* **1962**, *27*, 3055. For sequential application of ozonolysis and hydrogenation within modular units, see ref 3.
- (21) Xu, S.; Toyama, T.; Nakamura, J.; Arimoto, H. *Tetrahedron Lett.* **2010**, *51*, 4534.
- (22) Biellmann, J. F.; Rodriguez, G. H. *J. Org. Chem.* **1996**, *61*, 1822.
- (23) Bailey, P. S. *J. Org. Chem.* **1957**, *22*, 1548.

- (24) Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627–31.
- (25) Hon, Y. S.; Lu, L.; Chang, R. C.; Lin, S. W.; Sun, P. P.; Lee, C. L. *Tetrahedron* **2000**, *56*, 9269.
- (26) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1990**, *31*, 4991.
- (27) Fleming, F. F.; Huang, A.; Sharief, V. A.; Pu, Y. *J. Org. Chem.* **1997**, *62*, 3036.
- (28) Sparks J. W.; Knobloch, J. O. U.S. Patent No 2671812, 1954; *Chem. Abstr.* **1955**, 28287. Greenwood, F. L.; Haske, B. J. *J. Org. Chem.* **1965**, *30*, 1276.
- (29) Paquette has reported that reaction of ozonides with Zn in the presence of allyl bromides results in both reduction and allylation: Schloss, J. D.; Paquette, L. A. *Synth. Commun.* **1998**, *28*, 2887.
- (30) The Lewis acid promoted allylation of ozonides and related peroxides has been investigated: Dussault, P. H.; Lee, H.-J.; Liu, X. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3006.
- (31) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.
- (32) Smith, L. L.; Hill, F. L. *J. Chromatogr.* **1972**, *66*, 101.
- (33) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8331.
- (34) Spreitzer, H.; Anderwald, C.; Buchbauer, G. *Flavour Fragrance J.* **1995**, *10*, 287.
- (35) Findlay, J. A.; Desai, D. N.; Macaulay, J. B. *Can. J. Chem.* **1981**, *59*, 3303.
- (36) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.
- (37) Estevez, R. E.; Paradas, M.; Millan, A.; Jimenez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2009**, *73*, 1616.
- (38) Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.
- (39) Yamane, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Tetrahedron* **1973**, *29*, 955.
- (40) Lory, P. M. J.; Jones, R. C. F.; Iley, J. N.; Coles, S. J.; Hursthouse, M. B. *Org. Biomol. Chem.* **2006**, *4*, 3155.
- (41) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.
- (42) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897.
- (43) Nakamura, K.; Matsuda, T. *J. Org. Chem.* **1998**, *63*, 8957.
- (44) Kose, O.; Saito, S. *Org. Biomol. Chem.* **2010**, *8*, 896.
- (45) Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217.
- (46) Bouffard, J.; Itami, K. *Org. Lett.* **2009**, *11*, 4410.
- (47) Liao, S.; Yu, K.; Li, Q.; Tian, H.; Zhang, Z.; Yu, X.; Xu, Q. *Org. Biomol. Chem.* **2012**, *10*, 2973.
- (48) Wang, T.; Hao, X.-Q.; Zhang, X.-X.; Gong, J.-F.; Song, M.-P. *Dalton Trans.* **2011**, *40*, 8964.
- (49) Lin, M.-H.; Lun, L.-Z.; Chuang, T.-H.; Liu, H.-J. *Tetrahedron* **2012**, *68*, 2630.
- (50) Bhuyan, B. K.; Borah, A. J.; Senapati, K. K.; Phukan, P. *Tetrahedron Lett.* **2011**, *52*, 2649–2651.