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Rapid Epoxidation of α,β-Unsaturated Olefin in Microdroplets without Any Catalysts

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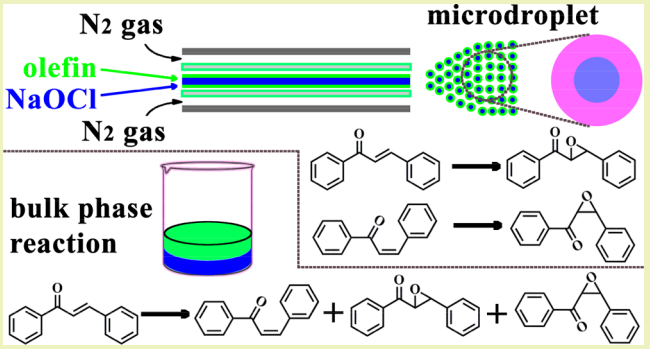
Supporting Information

ABSTRACT: Epoxy compounds are an important class of organic intermediates that are generally used to synthesize many important compounds and natural products. Herein, we carried out two-phase epoxidation of α,β-unsaturated olefins in microdroplets without any catalysts, where all the yield measurements were made upon microdroplet collection using high performance liquid chromatography. The epoxidation reaction can only take place under thermal irradiation both in microdroplets and in bulk phase, and an optimal yield was obtained in microdroplets at a reaction temperature of 35 °C. The epoxidation yield in microdroplets (85%) was superior over that in bulk phase (13%). In addition, the microdroplet epoxidation also produced configuration-selective epoxy compounds (only E-epoxides from the corresponding E-olefins and only Z-epoxides from the corresponding Z-olefins) compared to more byproducts (E-/Z-olefins and E-/Z-epoxides obtained from either E-olefins or Z-olefins) in bulk phase. It was attributed to E/Z configuration conversion under light irradiation in bulk phase, whereas such conversion was trivial in microdroplets. We also found that the epoxidation yields of *trans*-chalcones into their corresponding E-epoxides were apparently higher than *cis*-chalcones.



KEYWORDS: *Epoxidation, Microdroplet synthesis, Configuration transformation, Chalcones, Two-phase reaction, Reaction acceleration*

INTRODUCTION

Epoxy compounds are an important class of organic intermediates[1,2] that are generally used to synthesize structural materials and natural products.[3,4] A series of useful compounds (surfactants, polymers, glycols, glues, etc.) can be produced by means of ring opening and functional group conversion.[5] Chalcone epoxide (α,β-epoxyketone) can be used as a component in perfume formulation and also as an intermediate in the production of flavoring substances.[6,7] Chalcones have unique structural characteristics and high synthetic utility because they are not only capable of carrying out conventional reactions of epoxides but are also susceptible to other conversions due to the existence of carbonyl groups.[8,9] In the epoxidation of unsaturated chalcones, various catalysts including small organic molecules,[10] Schiff base complexes,[11] phase transfer catalysts (PTCs),[12] and phosphotungstic acid quaternary ammonium salts[13] have been reported, where hydrogen peroxide, hypochlorite, and organic peroxides were used as the oxidizing agents. Phase transfer catalysis is a special type of heterogeneous catalysis that facilitates the transfer of one reactant to a phase containing another reactant to initiate the reaction. PTC-induced reactions can take place in both organic and aqueous phases, and there are two types of liquid−liquid phase transfer catalysis methods. In the mid-1970s, the application of PTCs in asymmetric synthesis was explored,[14] among which PTCs have attracted wide interest to asymmetrically epoxidize electron-deficient olefins, particularly, α,β-ketones.[15] Although such a catalyst can give a high yield for α,β-unsaturated chalcone epoxide, there exist several disadvantages such as difficult isolation of the catalyst from a homogeneous system for product purification and the need for recycling the catalyst, etc.

It is well known that ultrasonication and microwaves have been used to accelerate the reaction.[16,17] In addition, microreactors such as microdroplets, microemulsions, and microfluidics have also been reported for reaction acceleration.

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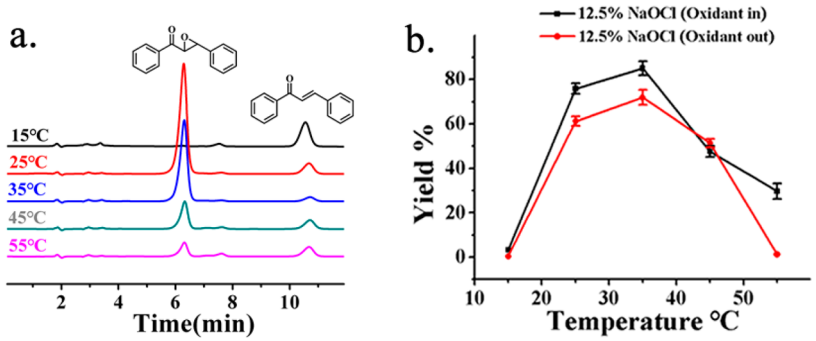
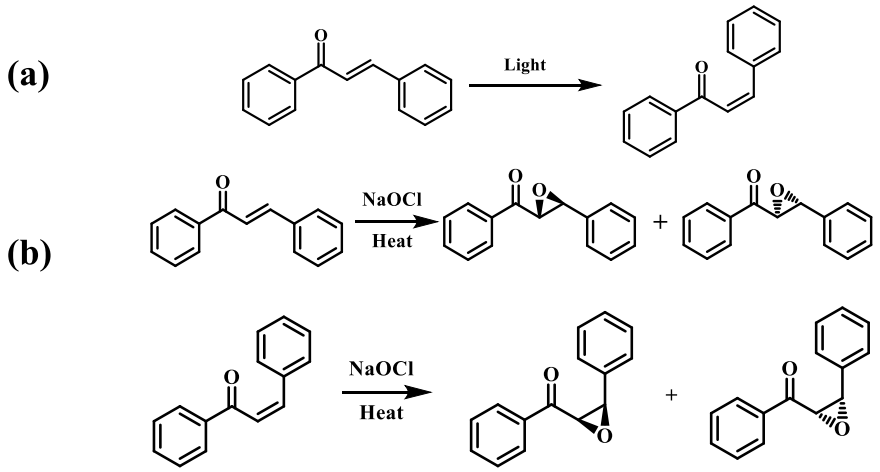


Figure 1. (a) HPLC chromatograms showing the conversion of E-chalcone to epoxide at different temperatures. (b.) Effect of different devices on the yields of epoxides at different temperatures.

Scheme 1. (a) Conversion of E-Chalcone to Z-Chalcone under Light (a); (b) Epoxidation of E-/Z-Chalcone by NaOCl under Thermal Conditions



Due to simple operation, mild experimental conditions, short reaction time, and high yield, microdroplet-based reactions have attracted much attention from the analytical and synthetic communities.[18] Several major factors including solvent evaporation, pH, and large specific surface area[19] were found to contribute to reaction acceleration in microdroplets. It has been reported that two-phase oxidation can be accelerated in microdroplets without a phase transfer catalyst,[20,21] where a coaxial spray arrangement has been used in the microdroplet synthesis of aldehydes and amides due to high reaction efficiency and easy operation.[20−22] Yan et al. found that various alcohols can be converted into their corresponding aldehydes and ketones without PTC.[20] To the best of our knowledge, however, there are no reports regarding the epoxidation of α,β-unsaturated olefins in microdroplets.

In this study, chalcone compounds bearing different substituents were epoxidized without a phase transfer catalyst in microdroplets. We explored various conditions for optimizing the synthesis of epoxides, such as reaction temperature and experimental device. Compared with traditional methods, the microdroplet method not only offers high yield and produces minimal byproducts but also greatly shortens the reaction time, saves the reaction solvent, avoids using PTC, and minimizes environmental pollution.

EXPERIMENTAL SECTION

General Methods. Sodium hypochlorite (12.5%) was obtained from Aladdin Chemical (Shanghai, China). 4-Methoxychalcone and 4′-methoxychalcone were obtained from Alfa Aesar (Shanghai, China). 4-Fluorochalcone, 4-nitrochalcone, 3-nitrochalcone, 4,4′-difluorochalcone, 4-fluoro-4′-methylchalcone, and 1,3-diphenyl-2,3-epoxy-1-propanone were purchased from TCI (Shanghai, China). All these obtained chalcones were in E-configuration. Ethyl acetate, hydrogen peroxide (30%), dichloromethane, petroleum ether, and *n*-hexane were supplied by Sinopharm Chemical Reagent (Shanghai, China). Methanol of chromatographic grade was provided by J&K (Shanghai, China). Fused-silica capillaries of 150 μm ID and 365 μm OD and 470 μm ID and 630 μm OD were purchased from Yongnian Optic Fiber Factory (Hebei, China). A dual-flow syringe pump from Harvard Apparatus (Model 35-2226, Harvard Apparatus, Inc., MA, USA) was used for solution feeding. All yields were measured by high-performance liquid chromatography (HPLC) on a LC-20AT system (Shimadzu (Suzhou) Co., Ltd., Suzhou, China). This HPLC system was composed of two high-pressure pumps, a microtee mixer, a manual six-port injector with a 20 μL loop, an Agilent Zorbax C_{18} column (5 μm × 4.6 mm ID × 25 cm long), and an ultraviolet−visible detector under the conditions in Table S1. ^{1}H NMR spectra were collected on a Bruker Avance spectroscopy (Bruker, Germany) at a 500 MHz frequency with tetramethylsilane as an internal standard while high-resolution mass spectra were recorded on a positive electrospray mass spectrometer (Hewlett-Packard 5989A, Agilent, CA, USA).

Synthesis of Epoxide in Microdroplets. For the synthesis of epoxide (Figure S1A), chalcone (E-/Z-configuration) in ethyl acetate (0.1 mol L^{-1}) and sodium hypochlorite solution (12.5%) were put in two airtight glass syringes, respectively. A 150 μm ID capillary was surrounded by a 470 μm ID capillary, and the tip of the inner capillary was fixed at 0.1 mm outside of the outer capillary tip. The outer capillary was placed in a nebulizer with dry nitrogen gas at 100 psi.

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Table 1. Oxidation of α,β-Unsaturated Olefins with Different Substituents To Form Epoxides in Microdroplets and in Bulk Phase

Entry	R_1	R_2	Yield[a] (%)	Yield[b] (%)	Yield[c] (%)	Yield[d] (%)
1	Ph	Ph	85.0	13.3	93.0	38.8
2	Ph	4-$OCH_3C_6H_4$	88.3	10.6	68.5	46.3
3	Ph	4-FC_6H_4	92.8	39.4	28.7	24.7
4	Ph	4-$NO_2C_6H_4$	89.2	35.2	80.8	19.5
5	Ph	3-$NO_2C_6H_4$	79.2	4.9	66.0	56.9
6	4-FC_6H_4	4-FC_6H_4	89.9	58.2	33.1	28.7
7	4-$OCH_3C_6H_4$	Ph	80.7	37.7	61.8	33.7
8	4-$CH_3C_6H_4$	4-FC_6H_4	78.6	20.3	32.4	3.2

[a]Syntheses of various epoxides in microdroplets from *trans*-α,β-unsaturated olefins. [b]Syntheses of various epoxides in bulk solution from *trans*-α,β-unsaturated olefins. [c]Syntheses of various epoxides in microdroplets from *cis*-α,β-unsaturated olefins. [d]Syntheses of various epoxides in bulk solution from *cis*-α,β-unsaturated olefins.

The microdroplets were sprayed into an electrically heated glass tube with temperature monitored by a thermocouple thermometer. The syringe pump introduced 0.1 mol L^{-1} chalcone into the outer capillary and sodium hypochlorite (12.5%) into the inner capillary at 15 μL min^{-1}. The microdroplets were collected in a 25 mL glass beaker with 10 mL of ethyl acetate for 10 min (collecting a volume of 300 μL). After being extracted with EtOAc and drying by Na_2SO_3, the product was analyzed by HPLC with an external standard calibration. Microdroplet synthesis of epoxides with other substituents was similar to the above methods.

Synthesis of Epoxides in Bulk Phase. Here, 100 μL of chalcone (E-/Z-configuration) in ethyl acetate (0.1 mol L^{-1}) and 100 μL of sodium hypochlorite solution (12.5%) were mixed and stirred vigorously to facilitate the reaction at 50 °C for 10 min. After the reaction was completed, the crude epoxide was diluted with EtOAc and dried by Na_2SO_3. The suspension was filtered through a 0.22 μm filter, diluted with methanol, and finally measured by HPLC for calculating the yield.

RESULTS AND DISCUSSION

In a previous work by Yan et al.,[20] two-phase transformation of aromatic alcohols to the corresponding aldehydes was accomplished in fused microdroplets under ambient conditions. Herein, we tried the epoxidation of chalcone in microdroplets by using a similar experimental design as in the preliminary experiment. However, no epoxide product is observed from the chromatogram (Figure 1a) even using intact NaOCl. Instead, a small amount of *cis*-chalcone (~1%) is produced in the presence of such a highly oxidative reactant (Scheme 1a). Considering reaction enhancement in microdroplet-based two-phase oxidation under light irradiation in our previous work,[21] we adopted various lights to initiate the microdroplet epoxidation of chalcone. To our surprise, we still found no presence of any epoxide product and instead found more *cis*-chalcone (increased to 2%−6% from Figure S2) in comparison with the ambient condition (natural light irradiation). From a comparison experiment performed in bulk phase (Figure S2), more chalcones are converted into their corresponding *cis*-chalcones, and the E/Z transformation yield is increased by using short-wavelength lights (Table S2). A further bulk-phase investigation (Figure S3) demonstrates that the E/Z transformation yield is gradually improved with the increased reaction time and reaches the maximum (~85%) after 15 min UV irradiation. Similar E/Z transformation results are also obtained for other chalcones with different substituents (Figure S2). High-energy light (short wavelengths) has been reported to facilitate olefin isomerization.[23−25] Direct energy transfer produces an excited state of the substrate that induces double bond cleavage to form a zwitterion, a double radical, or a free radical pair, leading to the isomerization. The presence of an additional conjugated π system can significantly reduce the energy gap between the ground state and the excited state, facilitating the E/Z isomerization using low energy light with/without the help of a photocatalyst.[23] As the reaction time in microdroplets is typically in the second scale compared to the minute scale in bulk phase, an apparent E/Z configuration flip was induced in the bulk phase versus a minimal transformation in microdroplets. These results may be beneficial for obtaining pure epoxide products with simple purification in microdroplets. By taking advantage of the photo-assisted E/Z transformation in bulk phase, *cis*-chalcones were synthesized from *trans*-chalcones and purified by column chromatography for the next epoxidation experiment (structural certification by NMR spectroscopy in Figures S13−S21).

Bulk-phase epoxidation of chalcone can be facilitated by high reaction temperature. Such a temperature enhancement effect was also observed in microdroplets in our previous work.[21] We then tried microdroplet epoxidation of chalcone at high reaction temperatures (Scheme 1b) by using a previous instrumental setup (Figure S1B). It can be seen from Figure 1a that the epoxide yield increases gradually as the temperature increases (15−35 °C), followed by a reversely decreased yield on further increasing the reaction temperature (45−55 °C). On one hand, high reaction temperature has a positive enhancement effect on the reaction rate. Hypochlorite decay into reactive oxygen species is also facilitated by high temperature, leading to epoxidation acceleration. On the other hand, rapid solvent evaporation in microdroplets at high temperatures leads to an increased concentration of the reagent to enhance the reaction rate. However, it should be noted that the NaOCl solution was apt to crystallize at high temperatures, inhibiting the two-phase reaction and eventually leading to decreased yields. An optimal reaction temperature of 35 °C was selected for the following experiment considering the best yield.

Apart from the reaction temperature, we find the microdroplet epoxidation is also moderately correlated with the mixing setups for chalcone and NaOCl (Figure 1b). In comparison with the off-sprayer mixing of two independent flows of chalcone and NaOCl using a microtee (an epoxide yield of about 28% from Figure S4), the in-sprayer concentric setup produces more epoxides. Furthermore, the flow configuration also affects the microdroplet conversion using the same concentric device (Figure S1B). The yield is slightly increased when the oxidant flows into the inner capillary

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(concentric setup "a") instead of the outer capillary (concentric setup "b"). A high-temperature nitrogen gas stream directly passes heat to the sodium hypochlorite solution in the outer capillary, leading to possible salt crystallization to decrease yields. Therefore, the concentric setup "a" was chosen for the epoxidation in microdroplets.

Under the above conditions, we explored the general applicability of the microdroplet epoxidation. 3-Nitrochalcone and 4-nitrochalcone were dissolved in dichloromethane, while the other chalcones were dissolved in ethyl acetate. Three conclusions can be drawn from the experimental results (Table 1 and Figures S6–S12 and S22–S37). First, the epoxidation yields in microdroplets are apparently higher than those in bulk solution even though the microdroplet reaction took several seconds compared to tens of minutes in bulk phase. Second, the microdroplet epoxidation produces configuration-selective epoxide products. However, E- and Z-chalcones, and their corresponding epoxides can be synthesized in bulk phase, and more of these products are generated using longer reaction time in bulk phase (Figure S5). It leads to tedious and difficult purification of desirable epoxides. Moreover, *trans*-chalcones can be more readily epoxidized into the corresponding epoxides than *cis*-chalcones (especially 4-fluorochalcone, 4-fluoro-4′-methylchalcone, and 4,4′-difluorochalcone) in microdroplets. In comparison, three *trans*-chalcones (chalcone, 4-methoxychalcone, and 3-nitrochalcone) but four *cis*-chalcones (4-fluorochalcone, 4-nitrochalcone, 4-fluoro-4′-methylchalcone and 4,4′-difluorochalcone) generate more epoxides in bulk phase. However, it should be noted that the epoxidation in both microdroplets and bulk phase in this study shows no stereospecificity without specific catalysts from the chiral HPLC chromatogram in Figure S38. Furthermore, the amounts of the synthesized products (0.32 mg min^{-1}) may be scaled up by multiplex and array sprayers[20,26,27] or high flux devices using the array internal-mix nozzles[18] for extending its application in large-scale synthesis comparable to bulk phase reactions. Overall, the microdroplet method not only offers high yield and minimal byproducts but also greatly shortens the reaction time, saves the reaction solvent, avoids using a phase transfer catalyst, and minimizes environmental pollution.

CONCLUSION

Reaction temperature and light irradiation were found to play completely different roles in the epoxidation and E/Z configuration flip of α,β-unsaturated carbonyl compounds both in microdroplets and in bulk phase. At high reaction temperatures, chalcone compounds were more efficiently oxidized by sodium hypochlorite to their corresponding epoxides in microdroplets without a phase transfer catalyst than in bulk phase. However, they underwent only E/Z configuration conversion in the presence of intact NaOCl solution at room temperature under illumination in bulk solution, and higher conversion ratios can be obtained with lights of shorter wavelengths. Accordingly, many side reactions can occur in bulk phase in comparison with minimal byproducts in microdroplets. Moreover, the epoxidation yield in microdroplets was remarkably improved with greatly shortened reaction time and reduced environmental pollution. These features prove it as a highly efficient, reliable, and green synthesis method.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.9b04059.

Instrumental setups, HPLC mobile phases, HPLC chromatograms of chalcone epoxides under different conditions, ^{1}H NMR spectra and high-resolution mass spectra, and chiral separation of chalcone epoxides. (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Lau, E. Y.; Newby, Z. E.; Bruice, T. C. A theoretical examination of the acid-catalyzed and noncatalyzed ring-opening reaction of an oxirane by nucleophilic addition of acetate. Implications to epoxide hydrolases. *J. Am. Chem. Soc.* **2001**, *123* (14), 3350–3357.

(2) Rink, R.; Lutje Spelberg, J. H.; Pieters, R. J.; Kingma, J.; Nardini, M.; Kellogg, R. M.; Dijkstra, B. W.; Janssen, D. B. Mutation of tyrosine residues involved in the alkylation half reaction of epoxide hydrolase from agrobacterium radiobacter AD1 results in improved enantioselectivity. *J. Am. Chem. Soc.* **1999**, *121* (32), 7417–7418.

(3) Wu, F.; Li, H.; Hong, R.; Deng, L. Construction of quaternary stereocenters by efficient and practical conjugate additions to α,β-unsaturated ketones with a chiral organic catalyst. *Angew. Chem.* **2006**, *118* (6), 961–964.

(4) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. Design of new chiral phase-transfer catalysts with dual functions for highly enantioselective epoxidation of α,β-unsaturated ketones. *J. Am. Chem. Soc.* **2004**, *126* (22), 6844–6845.

(5) Lattanzi, A. Enantioselective epoxidation of α,β-enones promoted by α, α-diphenyl-l-prolinol as bifunctional organocatalyst. *Org. Lett.* **2005**, *7* (13), 2579–2582.

(6) Huo, C.; Xu, X.; Jia, X.; Wang, X.; An, J.; Sun, C. Friedel-Crafts alkylation between chalcone epoxides and heteroarenes induced by triarylaminium salt. *Tetrahedron* **2012**, *68* (1), 190–196.

(7) Ho, T.-L.; Liu, S.-H. Synthesis of 2-hydroxy-3-methyl-2-cyclopentenone from isoprene. *Synth. Commun.* **1983**, *13* (8), 685–690.

(8) Joy, B.; Ghosh, S.; Padmaja, P.; Lalithambika, M. A facile 1,2 proton migration of chalcone epoxide using acid activated palygorskites. *Catal. Commun.* **2005**, *6* (9), 573–577.

(9) Chang, C.-L.; Kumar, M. P.; Liu, R.-S. A highly efficient ruthenium-catalyzed rearrangement of α,β-epoxyketones to 1,2-diketones. *J. Org. Chem.* **2004**, *69* (8), 2793–2796.

DOI: 10.1021/acssuschemeng.9b04059
ACS Sustainable Chem. Eng. 2019, 7, 14389–14393

(10) Wu, M.; Wang, B.; Wang, S.; Xia, C.; Sun, W. Asymmetric epoxidation of olefins with chiral bioinspired manganese complexes. *Org. Lett.* **2009**, *11* (16), 3622−3625.
(11) Okamoto, S.; Takano, K.; Ishikawa, T.; Ishigami, S.; Tsuhako, A. Activity and behavior of imidazolium salts as a phase transfer catalyst for a liquid−liquid phase system. *Tetrahedron Lett.* **2006**, *47* (46), 8055−8058.
(12) Yoo, M.-S.; Kim, D.-G.; Ha, M. W.; Jew, S.-s.; Park, H.-g.; Jeong, B.-S. Synthesis of (αR,βS)-epoxyketones by asymmetric epoxidation of chalcones with cinchona phase-transfer catalysts. *Tetrahedron Lett.* **2010**, *51* (42), 5601−5603.
(13) Geng, X.-L.; Wang, Z.; Li, X.-Q.; Zhang, C. A simple method for epoxidation of olefins using sodium chlorite as an oxidant without a catalyst. *J. Org. Chem.* **2005**, *70* (23), 9610−9613.
(14) Noe, E.; Raban, M. Additions and corrections - effect of crown ether on the conformational equilibrium of sodium acetylacetonate. *J. Am. Chem. Soc.* **1976**, *98* (2), 641−641.
(15) Diez, D.; Nunez, M.; Anton, A.; Garcia, P.; Moro, R.; Garrido, N.; Marcos, I.; Basabe, P.; Urones, J. Asymmetric epoxidation of electron-deficient olefins. *Curr. Org. Synth.* **2008**, *5* (3), 186−216.
(16) Koduri, N. D.; Hileman, B.; Cox, J. D.; Scott, H.; Hoang, P.; Robbins, A.; Bowers, K.; Tsebaot, L.; Miao, K.; Castaneda, M.; Coffin, M.; Wei, G.; Claridge, T. D. W.; Roberts, K. P.; Hussaini, S. R. Acceleration of the Eschenmoser coupling reaction by sonication: efficient synthesis of enaminones. *RSC Adv.* **2013**, *3* (1), 181−188.
(17) Gawande, M. B.; Shelke, S. N.; Zboril, R.; Varma, R. S. Microwave-assisted chemistry: Synthetic applications for rapid assembly of nanomaterials and organics. *Acc. Chem. Res.* **2014**, *47* (4), 1338−1348.
(18) Yan, X.; Lai, Y.-H.; Zare, R. N. Preparative microdroplet synthesis of carboxylic acids from aerobic oxidation of aldehydes. *Chem. Sci.* **2018**, *9* (23), 5207−5211.
(19) Yan, X.; Bain, R. M.; Cooks, R. G. Organic reactions in microdroplets: Reaction acceleration revealed by Mass Spectrometry. *Angew. Chem., Int. Ed.* **2016**, *55* (42), 12960−12972.
(20) Yan, X.; Cheng, H.; Zare, R. N. Two-phase reactions in microdroplets without the use of phase-transfer catalysts. *Angew. Chem., Int. Ed.* **2017**, *56* (13), 3562−3565.
(21) Zhang, W.; Cheng, H.; Liu, J. Accelerated two-phase oxidation in microdroplets assisted by light and heat without the use of phase-transfer catalysts. *ACS Sustainable Chem. Eng.* **2018**, *6* (7), 8125−8129.
(22) Zhang, W.; Yang, S.; Lin, Q.; Cheng, H.; Liu, J. Microdroplets as Microreactors for Fast Synthesis of Ketoximes and Amides. *J. Org. Chem.* **2019**, *84* (2), 851−859.
(23) Zhan, K.; Li, Y. Visible-Light photocatalytic E to Z isomerization of activated olefins and its application for the syntheses of coumarins. *Catalysts* **2017**, *7* (11), 337−345.
(24) Guignard, R. F.; Petit, L.; Zard, S. Z. A method for the net vontra-thermodynamic isomerization of cyclic trisubstituted alkenes. *Org. Lett.* **2013**, *15* (16), 4178−4181.
(25) Metternich, J. B.; Gilmour, R. A bio-inspired, catalytic E → Z isomerization of activated olefins. *J. Am. Chem. Soc.* **2015**, *137* (35), 11254−11257.
(26) Wleklinski, M.; Loren, B. P.; Ferreira, C. R.; Jaman, Z.; Avramova, L.; Sobreira, T. J. P.; Thompson, D. H.; Cooks, R. G. High throughput reaction screening using desorption electrospray ionization mass spectrometry. *Chem. Sci.* **2018**, *9* (6), 1647−1653.
(27) Müller, T.; Badu-Tawiah, A.; Cooks, R. G. Accelerated Carbon−Carbon Bond-Forming Reactions in Preparative Electrospray. *Angew. Chem., Int. Ed.* **2012**, *51* (47), 11832−11835.

DOI: 10.1021/acssuschemeng.9b04059
ACS Sustainable Chem. Eng. 2019, 7, 14389−14393