JACS Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/jacsau

Article

Bidirectional Iterative Approach to Sequence-Defined Unsaturated Oligoesters

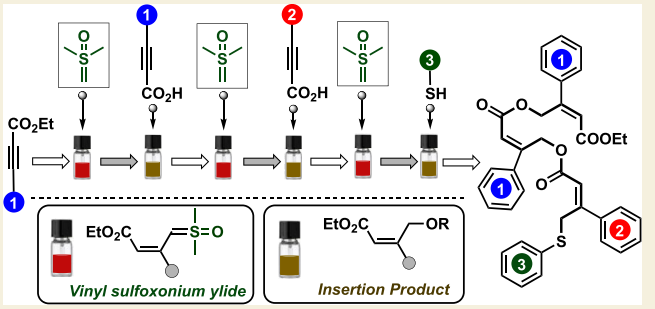
Srashti Bhardwaj, Dinesh Kumar Gopalakrishnan, Divya Garg, and Janakiram Vaitla*

Cite This: *JACS Au* 2023, 3, 252−260

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Herein, we describe the development of a new strategy for the synthesis of unsaturated oligoesters *via* sequential metal- and reagent-free insertion of vinyl sulfoxonium ylides into the O−H bond of carboxylic acid. Like two directional coupling of amino acids (N- to C-terminal and C- to N-terminal) in peptide synthesis, the present approach offers a strategy in both directions to synthesize oligoesters. The sequential addition of the vinyl sulfoxonium ylide to the carboxylic acids (acid iteration sequence) in one direction and the sequential addition of the carboxylic acids to the vinyl sulfoxonium ylide (ylide iteration sequence) in another direction yield (Z)-configured unsaturated oligoesters. To perform this iteration, we have developed a highly regioselective insertion of vinyl sulfoxonium ylide into the X−H (X = O, N, C, S, halogen) bond of acids, thiols, phenols, amines, indoles, and halogen acids under metal-free reaction conditions. The insertion reaction is applied to a broad range of substrates (>50 examples, up to 99% yield) and eight iterative sequences. Mechanistic studies suggest that the rate-limiting step depends on the type of X−H insertion.



KEYWORDS: *sequence-defined polymerization, metal-free insertion, sulfur ylide, oligoester, iterative synthesis*

INTRODUCTION

In nature, sequence-defined polymers, such as peptides, are produced in a highly defined manner. Their precise composition provides unique chemical and biological properties to the materials.[1] However, unlike peptides and nucleotides, synthetic methods for sequence-defined polymers are rare.[1,2] The discrete units of monomers in the sequence-specific synthetic polymer can produce more diversity than the biological polymer.[3,4] Therefore, it is of great utility to achieve precise control of monomer sequence.[5] The total number of combinations of sequence-controlled polymer depends on the number of monomeric units; as a result, each combination produces a distinct synthetic polymer and possesses unique properties (Figure 1a). This approach opens new opportunities for controlling the structural and macroscopic properties of the materials.[1,6−9] Appropriate monomeric templates and a strategy for successively assembling these units are essential components of sequence-controlled polymerization.

The ribosome machinery in a living organism produces sequence-defined polymers *via* the complex biological mechanism. By utilizing this technology, the Suga group developed the mRNA-directed synthesis of polyesters (up to 4 monomeric units), composed of different α-hydroxy acids, whose length and sequence are controlled through reprogramming of the genetic code using flexizyme,[10] and the wPURE (protein synthesis using recombinant elements) system (Scheme 1a).[11−13] In 2013, the Junkers group reported the

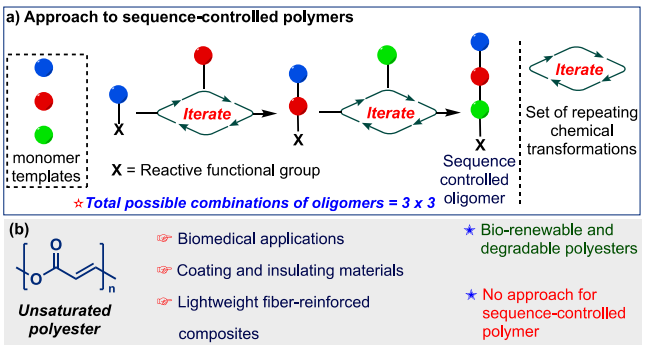
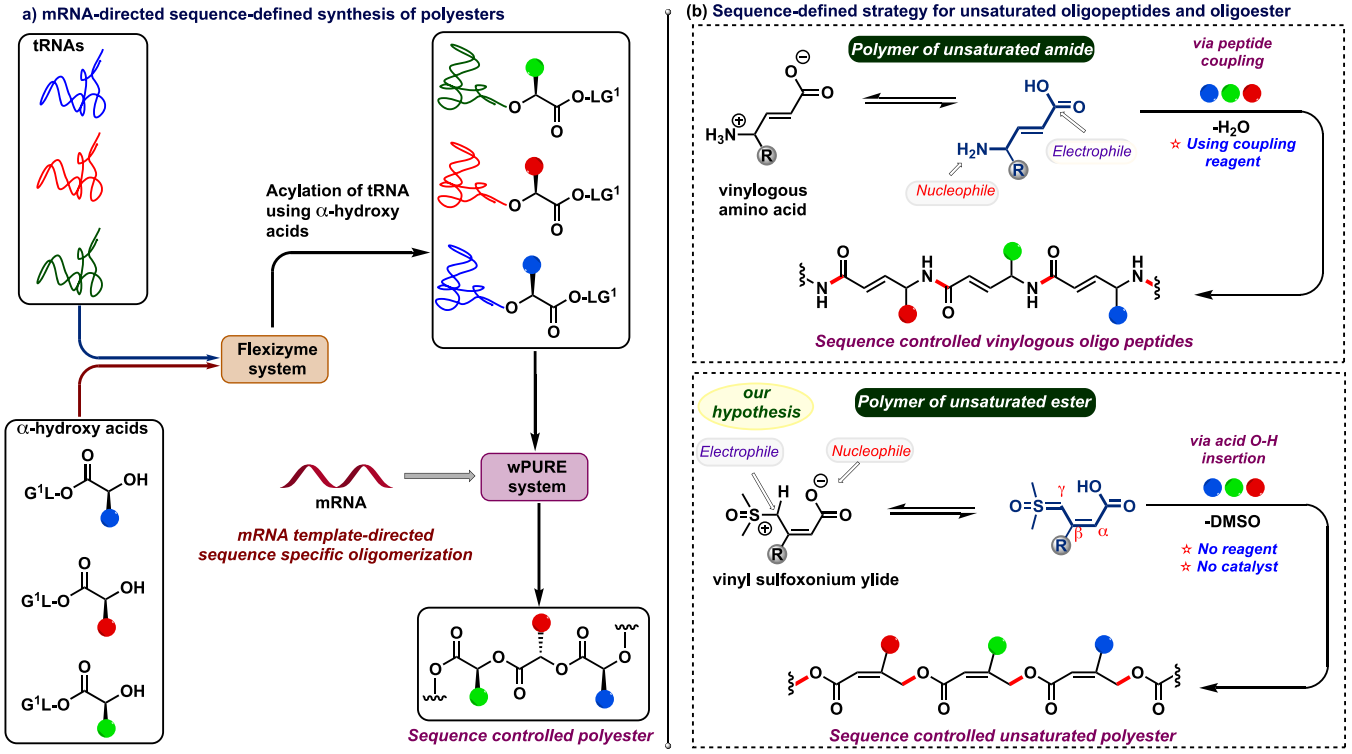


Figure 1. (a) Concept for the sequence-controlled oligomers and (b) importance and applications of unsaturated polyesters.

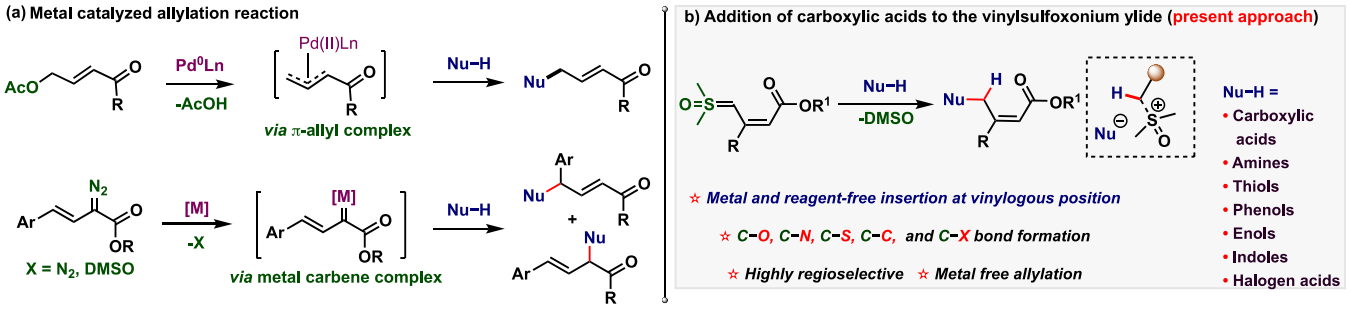
synthesis of sequence-controlled polyesters (up to 4 monomers) by sequential addition of monomers using the reversible addition−fragmentation radical transfer technique.[14] Despite the few reports on sequence-defined polyesters synthesis, to the best of our knowledge, there is no report for unsaturated

Received: November 23, 2022
Revised: December 22, 2022
Accepted: December 22, 2022
Published: January 3, 2023

Scheme 1. (a) Sequence-Defined Polyester Synthesis and (b) Design for the Sequence-Defined Unsaturated Polyesters from Vinyl Sulfoxonium Ylide



Scheme 2. (a) Vinylogous Addition of Nucleophiles and (b) Insertion of Diazo and Sulfoxonium Ylides into the Acids



polyesters which are the third-largest class of thermoset molding resins.[2] These polymers are well known for their biodegradability and biocompatibility[15−17] and represent an interesting category due to their remarkable mechanical properties, chemical resistance such as corrosion, and lightness.[18] Unsaturated polyesters are employed in many fields such as biomedical applications,[19,20] coating and insulating materials,[21] and lightweight fiber-reinforced composites for the automotive industry (Figure 1b).[22] Moreover, the olefin group in the template can be chemically modified *via* Michael addition of various nucleophiles to the *α,β*-unsaturated esters.[17,23,24] Therefore, developing efficient methods that can effectively generate sequence-defined unsaturated polymers is of great interest.[1,6−9,25] Thus, we would like to develop a novel strategy for the template-based sequence-defined unsaturated oligoesters by the C−O coupling of *α,β*-unsaturated acids under mild reaction conditions (Scheme 1b, right). The conceptual design of the monomer template is crucial for a sequence-defined oligomer approach.[26,27]

In the present approach, similar to a vinylogous amino acid which can be used to synthesize unsaturated oligopeptide (Scheme 1b, left),[28] we visualized a vinyl sulfoxonium ylide monomeric template that contains a carboxylic acid and ylide groups may exist in a zwitterionic form, as shown in Scheme 1b, right. These ylide monomers can be coupled by the addition of a nucleophilic carboxylate ion of one monomer to the *γ*-(vinylogous) position of the other monomer ylide.

The addition of electrophiles at the vinylogous position, such as vinylogous aldol//Michael/Mannich reactions, has been extensively explored using metal and metal-free catalysis.[29−32] However, introducing nucleophiles to the *γ*-position under catalytic conditions is challenging and it can be obtained *via* either electron-deficient *π*-allylmetal complexes[33−35] or *in situ*-generated diazo-derived metal vinyl carbenes (Scheme 2a).[36−38]

The addition reactions with carboxylic acids as a nucleophile are quite challenging because the oxygen atom of acid is less nucleophilic and also, these reactions are difficult using the Tsuji−Trost method due to the leaving ability of these groups during the formation of the *π*-allylpalladium complex. In fact, metal carbenes are highly reactive electrophilic intermediates. The Davies group developed an elegant method for silver-

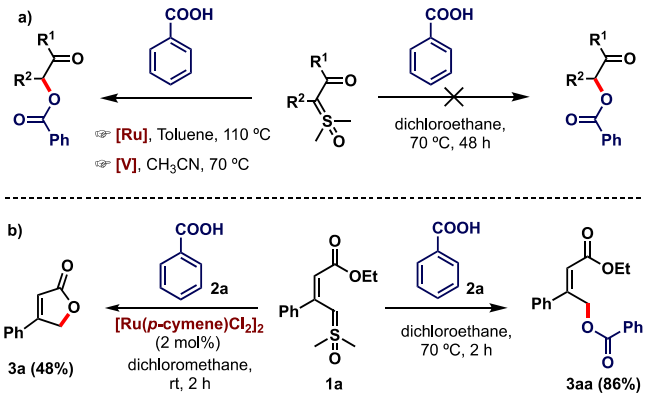
https://doi.org/10.1021/jacsau.2c00641
JACS Au 2023, 3, 252−260

catalyzed insertion of vinyl diazo compounds into the carboxylic acid.[36,39] However, the stability of diazo compounds and regioselectivity for the nucleophilic addition are major concerns in this approach (Scheme 2a). Sulfoxonium ylides have proven to be alternative surrogates to diazo compounds for the insertion and carbene-mediated reactions.[40−42] Recently, α-keto sulfoxonium ylides have been widely utilized for various X−H (X = N, O, S, C) insertion reactions under metal- and metal-free conditions.[42−51] Despite the progress on the insertion reactions of α-keto sulfoxonium ylides, the chemistry of vinyl sulfoxonium ylides has been underexplored. Remarkably, our previous studies have demonstrated that the reactivity and stability of α-keto sulfoxonium ylides differ from vinyl sulfoxonium ylides.[52] In this regard, our ongoing interest in the chemistry of sulfoxonium ylides,[52−55] and the importance of regioselective allylation reactions in various applications,[56−59] prompted us to develop a new allylation strategy using vinyl sulfoxonium ylides with variety of nucleophiles (Scheme 2b). Herein, we describe the insertion reactions of vinyl sulfoxonium ylides into the X−H (X = N, O, S, C, halogen) bond and apply this method to the synthesis of various sequence-defined unsaturated oligoesters.

RESULTS AND DISCUSSION

At the outset, we investigated vinyl sulfoxonium ylide insertion into the O−H bond of carboxylic acids. Recently, Mu and Sivasankar groups have reported the metal-carbene mediated insertion of α-keto sulfoxonium ylides into the carboxylic acids in good yields. No product formation was observed in the absence of the catalyst (Scheme 3a).[60,61] For the present study,

Scheme 3. Insertion of Sulfoxonium Ylide into the O−H Bond of Acid under Metal and Metal-Free Conditions



the reaction between 0.5 mmol of vinyl sulfoxonium ylide **1a** (easily prepared from phenyl propiolate and dimethylsulfoxonium methylide) and 0.6 mmol of benzoic acid in the presence of the Ru-catalyst at room temperature did not yield the desired O−H insertion product; instead, afforded furanone **3a** in 48% yield (Scheme 3b, left).[62] The optimization of the acid insertion was explored with various Brønsted and Lewis acid catalytic conditions and catalyst-free conditions (see the Supporting Information). Gratifyingly, in contrast to the reported literature,[60,61] the insertion of ylide at 70 °C without any catalyst afforded the corresponding acid insertion product **3aa** in 86% isolated yield (Scheme 3b, right).

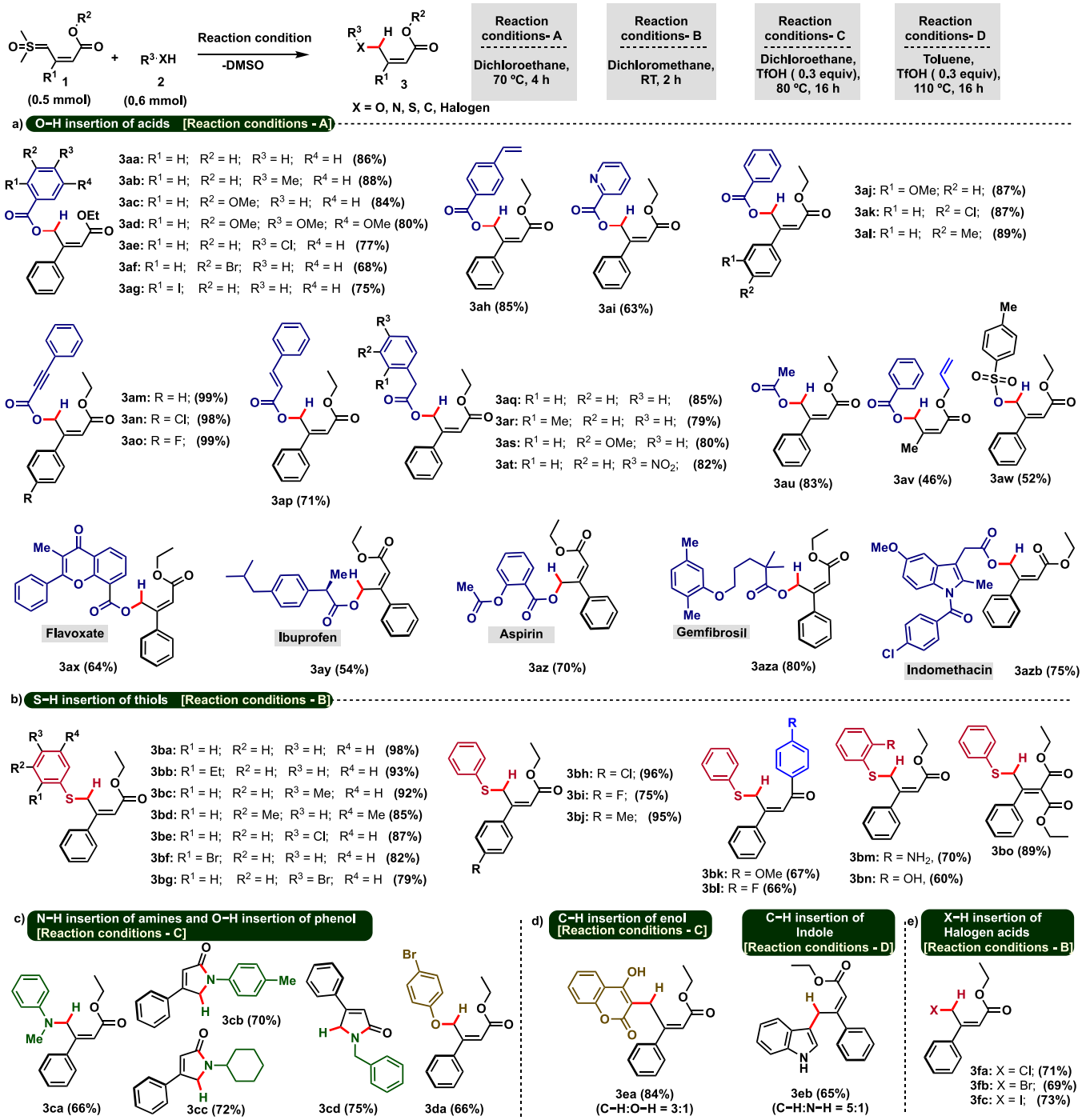
We then explored the effect of various substituents on the aryl groups of the acid and vinyl sulfoxonium ylide, as summarized in Scheme 4a. Benzoic acid with the *p*-methyl group gave insertion product **3ab** in 88% yield. The presence of electron-donating groups in benzoic acid did not improve the reaction yield, giving insertion products **3ac** and **3ad** in 84 and 80% yields, respectively. A slight decrease in the yields was observed with halogen substituents at para, meta, and ortho positions on the benzene ring, affording **3ae**, **3af**, and **3ag** in 77, 68, and 75% yields, respectively. When using 4-vinylbenzoic acid, the corresponding insertion product **3ah** was obtained in 85% yield. Lower yields were obtained when the heteroaromatic groups, such as pyridine, were incorporated (**3ai**, 63%), likely due to the reduced protonation of the ylide carbon. The substituents on the benzene ring of the vinyl sulfoxonium moiety did not affect the reaction yields and afforded the corresponding γ-insertion products **3aj**−**3al** in 87−89% yields. The insertion of vinyl sulfoxonium ylide into alkynoic and alkenoic acids was also investigated. The reaction with propargylic acids afforded insertion products **3am**−**3ao** in excellent yields (98−99%). Due to the presence of electron-deficient alkyne and alkene units in the template of **3am**−**3ao**, they can be useful in various metal- and radical-mediated reactions.[63−65] Cinnamic acid also gave its corresponding insertion product **3ap** but in a decreased yield (71%). Alkyl acids, such as various arene-substituted 2-arylacetic acids, gave their corresponding insertion products **3aq**−**3at** in good yields. The reaction is also compatible with acetic acid and afforded corresponding insertion product **3au** in 83% yield. An alkyl-substituted vinyl sulfoxonium ylide gave insertion product **3av** in low yield (46%), which was possibly due to the low stability of its corresponding ylide. Interestingly, strong acids, such as sulfonic acids, which produce weak conjugate tosylate nucleophile, also underwent insertion reactions and afforded corresponding sulfonates **3aw** in 52% yield. It is noteworthy that the reaction could be readily scaled up to a 5.0 mmol scale and obtained 1.25 g of the product **3aa**. Moreover, the robustness of the insertion reaction was illustrated by the efficient derivatization of several marketed drugs, such as flavoxate (**3ax, 64%**), ibuprofen (**3ay, 54%**), aspirin (**3az, 70%**), gemfibrozil (**3aza, 80%**), and indomethacin (**3azb, 75%**) indicating the potential of this protocol for the generation of lead compounds in drug discovery.

Next, we would like to explore the present method with various nucleophiles such as thiols, amines, phenols, enols, indoles, and halogen acids (Scheme 4b−e). The reaction of the ylide with the benzenethiol gave the insertion product **3ba** in 98% yield (Scheme 4b). Interestingly, the reaction did not require heating and proceeded smoothly at room temperature. Alkyl groups at the ortho, meta, and para positions and halogen groups at the ortho and para positions of the benzene ring of aryl thiol gave good yields of S−H inserted products **3bb**−**3bg**. The S−H insertion was also tolerated with keto-stabilized vinyl sulfoxonium ylides and obtained their corresponding γ-insertion products **3bk** and **3bl** in 67 and 66% yields, respectively. The reaction is highly chemoselective toward S−H insertion in the presence of other nucleophilic groups, such as $-NH_2$ or −OH, and afforded the insertion products **3bm** and **3bn** in 70 and 60% yields, respectively. Moreover, the reaction was also investigated using α,β-disubstituted vinyl sulfoxonium ylide with benzene thiol, affording a corresponding S−H insertion product **3bo** in 89% yield.

With the success of acid and thiol insertion, we endeavored to extend the method to the −NH and −OH insertion of amines and alcohols, respectively (Scheme 4c). The optimized reaction conditions utilized for acid and thiols did not afford

https://doi.org/10.1021/jacsau.2c00641
JACS Au 2023, 3, 252−260

Scheme 4. X−H Insertion of Vinyl Sulfoxonium Ylides into Acids, Thiols, Amines, Phenol, Enols, Indoles, and Halogen Acids



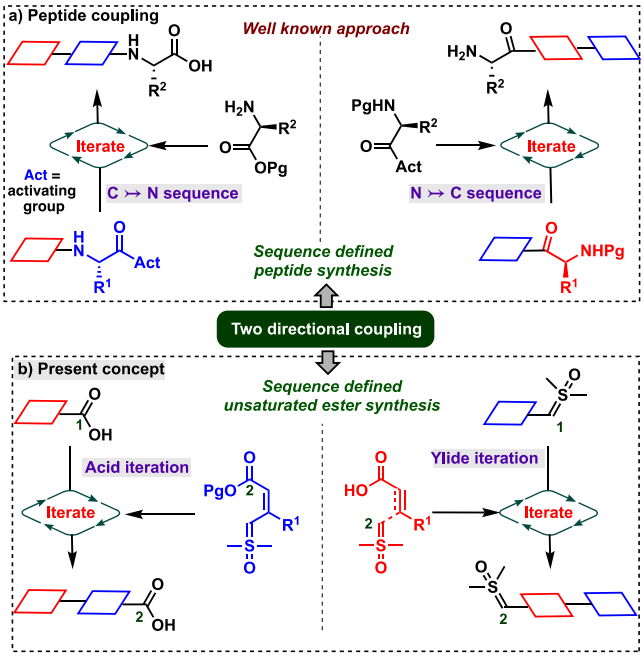
the N−H insertion of amines. The reaction requires an additional acid source to promote the salt formation with sulfoxonium ylide. In the presence of TfOH (30 mol %), the reaction of *N*-methyl aniline with vinyl sulfoxonium ylide afforded the N−H insertion product **3ca** in a 66% yield (Scheme 4c). Using primary amines, the reaction yielded lactams **3cb**−**3cd** in 70−75% yields. Similarly, the reaction of vinyl sulfoxonium ylide with 4-bromo phenol also afforded the corresponding O−H insertion product **3da** in 66% yield. We then investigated the reactivity of compounds containing an enol ether, such as 4-hydroxycoumarin, with the ylide that gave a mixture of regioisomers resulting from C−H and O−H insertion products **3ea** in 84% yield with 3:1 rr (C−H/O−H) (Scheme 4d). Moreover, we observed regioselective C−H insertion of unprotected indole with the ylide that gave **3eb** in 61% yield and 5:1 rr (C−H/N−H). We next explored the γ-insertion of the ylide into the halogen acids (Scheme 4e). The reaction of vinyl sulfoxonium ylides with HCl, HBr, and HI afforded corresponding X−H inserted products **3fa** (71%), **3fb** (69%), and **3fc** (73%), respectively (Scheme 4e).

With the success of these vinylogous insertion reactions, we would like to utilize this method for the iterative synthesis of sequence-defined unsaturated oligoesters in either direction. Generally, peptides are obtained by the coupling of protected

https://doi.org/10.1021/jacsau.2c00641
JACS Au 2023, 3, 252−260

amino acids in either N-to C-terminal direction (Scheme 5a, right) or C- to N-terminal direction (Scheme 5a, left) *via* solid-phase peptide synthesis or conventional solution-mediated synthesis.[66]

Scheme 5. Concept for the Bidirectional Iterative Process



Although peptide coupling has been well known over the past 13 decades, coupling of an amide bond without a coupling reagent is challenging in both the solution and solid phases.[67,68] Inspired by the coupling of amino acids in either direction (Scheme 5a), we conceptualized reagent-free synthesis of the sequence-defined unsaturated ester by C−O coupling in the solution phase (Scheme 5b). Based on our developed method, the addition of an acid to the vinyl sulfoxonium ylide can lead to the O−H insertion at the γ-position (Scheme 5b, left). Selective saponification of the terminal ester in the insertion product may lead to its corresponding acid, which can be further utilized in the acid iteration sequence. In the other direction, as shown in Scheme 5b (right), the addition of a propargylic acid to the vinyl sulfoxonium ylide gives the insertion products such as **3am**−**3ao**, as shown in Scheme 4a. To this ynoate, adding dimethylsulfoxonium methylide at the propargylic ester part may lead to new vinyl sulfoxonium ylide, which can be utilized for further iteration.[69] To the best of our knowledge, no studies have reported the use of a bidirectional iterative coupling process for the synthesis of organic molecules, with the exception of peptide synthesis.[1,2,70]

At the outset, the iteration was carried out by the sequential addition of an acid to the vinyl sulfoxonium ylide (Scheme 6). The basic strategy for all these sequences is shown in Scheme 6a. Initially, the addition of acid to the trimethyl silyl ethanol-protected vinyl sulfoxonium ylide **4** leads to O−H insertion to give **5**, which contains two ester linkages. Treating insertion product **5** with tetra-*n*-butylammonium fluoride in tetrahydrofuran afforded mono-iterated acid **6**. This acid can be further used in the iteration sequence. Using this strategy (Scheme 6a), seven different iterative sequences were designed to obtain various unsaturated oligoesters, as shown in Scheme 6b. These sequences were initiated using aryl, alkyl, and alkenyl carboxylic acids and aryl thiols. This oligomerization was propagated using trimethylsilyl ethanol-protected vinyl sulfoxonium ylides (**A**−**D**) as iterative building blocks. Finally, the sequence ends with ethyl or methyl ester-substituted vinyl sulfoxonium ylides (**E**−**H**) as the terminating building blocks and afforded unsaturated oligoesters **7a**−**7g**. After the first insertion, the reaction mixture was subjected to deprotection of trimethyl silyl ethanol part to obtain **6**, which does not require chromatographic purification for further insertion. However, our attempt to one-pot multi-iteration *via* sequential addition of reagents to obtain the unsaturated oligoesters was unsuccessful. Sequences I−IV and VI are two unit sequences containing three ester linkages. Remarkably, we applied this iteration approach to the four-unit oligomer (sequence-VII). The generated Z-configured unsaturated oligoesters are the basic scaffolds of biologically important compounds. In 2005, researchers from Merck patented that unsaturated oligoesters containing molecules show the ability of prodrugs that convert *in vivo* to diaryl-2-(5*H*)-furanones, useful in the treatment of cyclooxygenase-2 mediated diseases.[71]

With the success of the acid iteration, we next turned our attention to performing the ylide iteration (Scheme 7). Treating phenyl propiolate with dimethylsulfoxonium methylide (obtained from trimethyl sulfoxonium iodide with base) gave vinyl sulfoxonium ylide **1a** in 70% yield. The reaction of phenyl propiolic acid with the vinyl sulfoxonium ylide followed by the addition of dimethylsulfoxonium methylide gave iterated sulfoxonium ylide **8** in 45% yield, and its structure was unambiguously confirmed using X-ray crystallography. A similar sequence was applied using 4-chlorophenylpropiolic acid to obtain extended sulfoxonium ylide (**9**, 48%), which can be further utilized in either similar unsaturated oligoesters synthesis or can be used for the carbene-mediated transformation.[52] It is noteworthy that the iterative generation of carbene precursor was not reported to date. Finally, this sequence was terminated with thiophenol to obtain compound **10** in 72% yield.

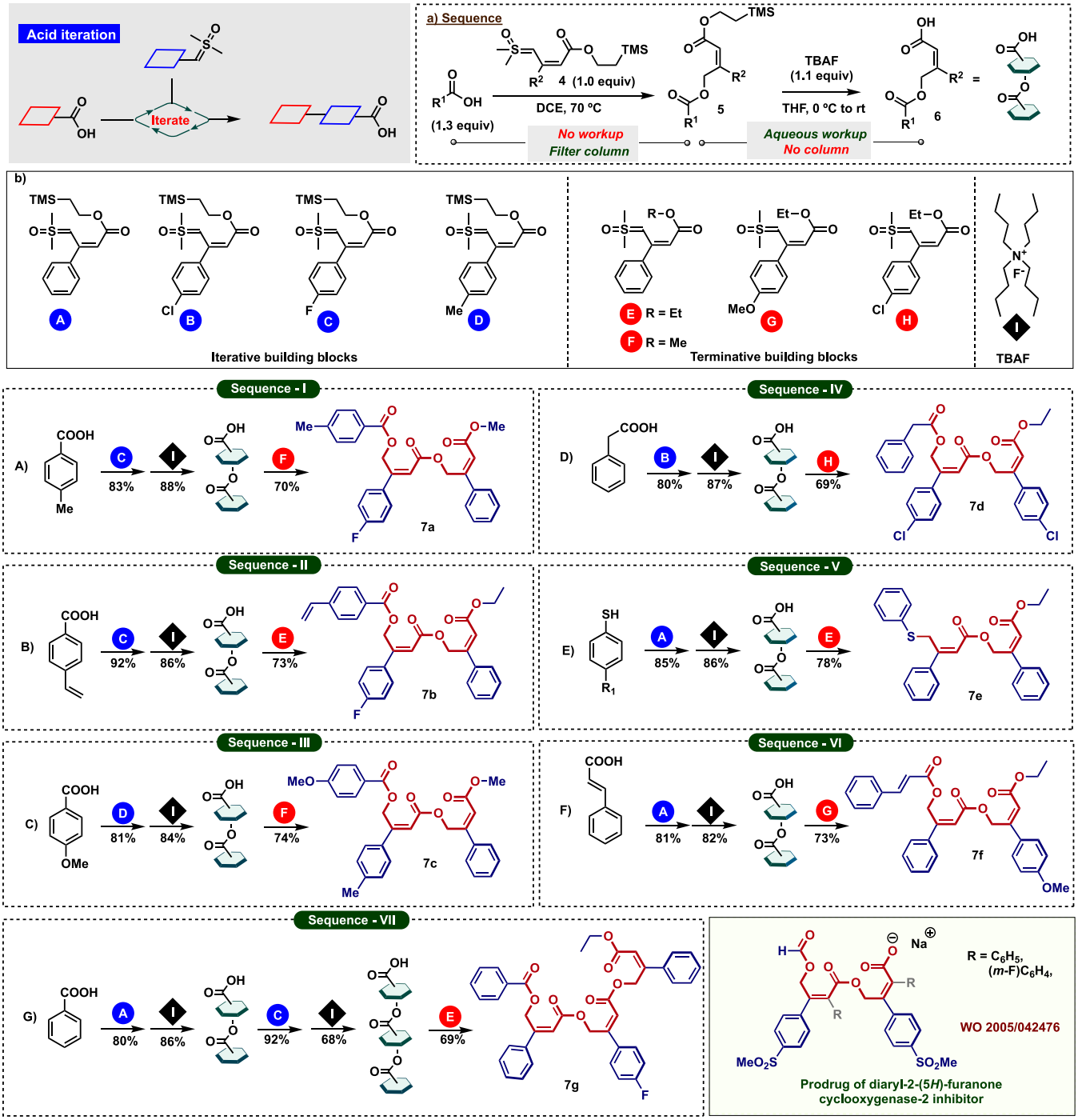
The insertion reaction of vinyl sulfoxonium ylide with benzoic acid was monitored using React IR (Scheme 8, left). The reaction of the benzoic acid with the sulfoxonium ylide gave a salt at room temperature, which was indicated by the continuous decay of the ylide concentration and a gradual increase in salt formation. Upon heating the reaction at 70 °C, the resulting salt was converted into the insertion product **3aa**, which indicates that step 2 is the rate-determining step. The similar experiment was performed using thiophenol (Scheme 8, right). We did not notice any salt formation during the reaction at room temperature. This indicates that the second step may be very fast after protonation in the case of thiol addition. This observation strongly suggests that protonation was the rate-limiting step for S−H insertion.

CONCLUSIONS

In conclusion, we have developed a novel bidirectional X−H insertion for the synthesis of unsaturated oligoesters from aryl-substituted vinyl sulfoxonium ylide under metal- and reagent-free conditions. Inspired by vinylogous oligopeptides, we envisioned that vinyl sulfoxonium ylide containing acid derivative could serve as a template to synthesize the Z-configured unsaturated oligoesters *via* sequential acid iteration or sequential ylide iteration. To perform this assembly line synthesis, we have developed a method for the insertion of

https://doi.org/10.1021/jacsau.2c00641
JACS Au 2023, 3, 252−260

Scheme 6. Unsaturated Oligoester Synthesis *via* Acid Iteration



vinyl sulfoxonium ylide into X−H (X = O, N, S, C, halogen) bonds of acids, thiols, amines, phenols, enols, indoles, and halogen acids under mild reaction conditions. Considering the importance and applications of allylation reactions and metal- and reagent-free coupling of monomers for oligomerization, we believe this simple and convenient strategy will be useful in the pharmaceutical and medicinal chemistry.

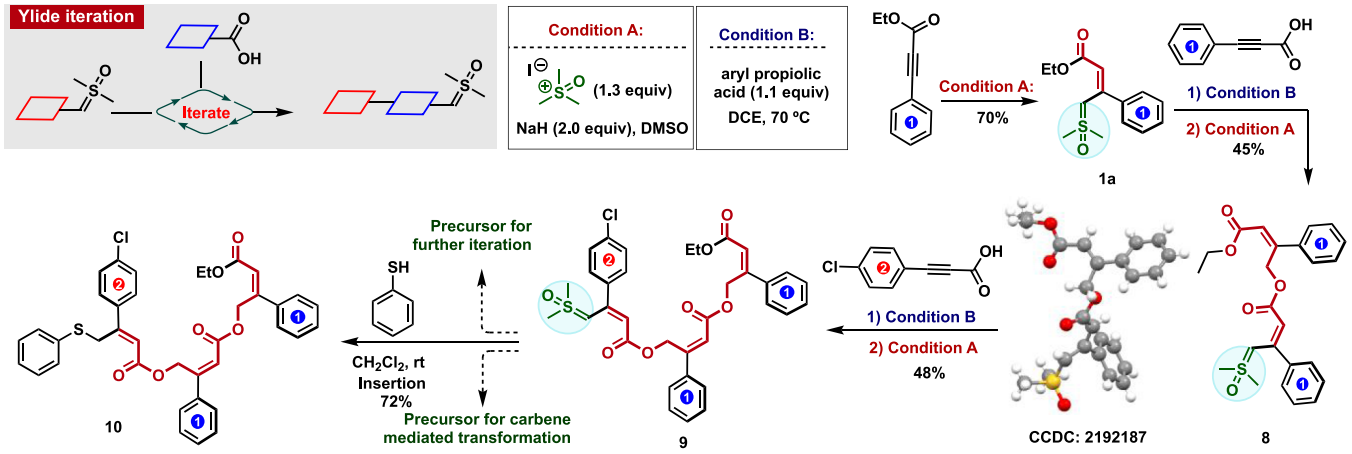
METHODS

General Procedure for Ylide Insertion into the O−H Bond of the Acids (Scheme 4a)

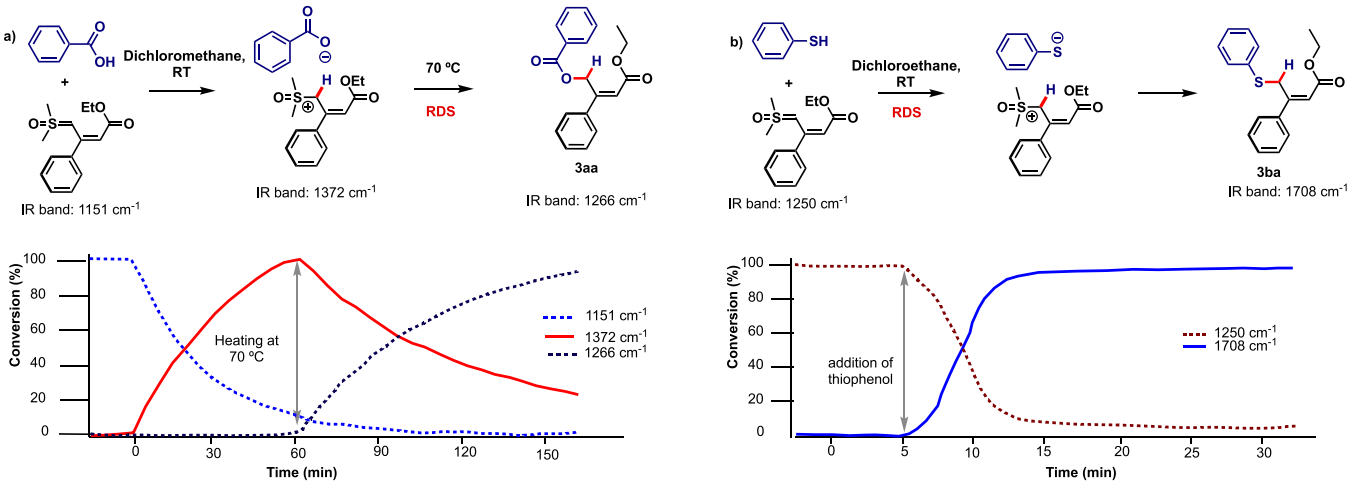
To a reaction tube, crushed 4 Å molecular sieves were added and then the sieves were flame-dried under an argon atmosphere. Vinyl sulfoxonium ylide (0.5 mmol) in dichloroethane (2 mL) was added to the cooled reaction tube. Then, to the stirring solution, aryl or alkyl acid (0.6 mmol) in dichloroethane (3 mL) was added at a time. Then, the reaction was kept on heating at 70 °C for 3−4 h. The reaction mixture was filtered through a pad of Celite (and eluting with dichloromethane) and the filtrate was concentrated *in vacuo*. The residue was purified using flash column chromatography.

https://doi.org/10.1021/jacsau.2c00641
JACS Au 2023, 3, 252−260

Scheme 7. Unsaturated Oligoester Synthesis *via* Ylide Iteration



Scheme 8. React-IR Studies for the Insertion of Vinyl Sulfoxonium Ylide into the X−H Bond of Benzoic Acid and Thiophenol



General Procedure for Thiol S−H and Halogen Acid Insertion Reactions (Scheme 4b,e)

To a reaction tube, crushed 4 Å molecular sieves were added and then the sieves were flame-dried under an argon atmosphere. Vinyl sulfoxonium ylide (0.5 mmol) in dichloromethane (2 mL) was added to the cooled reaction tube. Then, to the stirring solution, benzenethiols or halogen acids (0.6 mmol) in dichloromethane (3 mL) were added at a time. Then, the reaction was kept on stirring at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite by eluting with dichloromethane and the filtrate was concentrated *in vacuo*. The residue was purified using flash column chromatography.

General Procedure for the X−H Insertion of Amines and Phenols (Scheme 4c)

To a reaction tube, crushed 4 Å molecular sieves were added and then the sieves were flame-dried under an argon atmosphere. Vinyl sulfoxonium ylide (0.5 mmol) in dichloroethane (2 mL) was added to the cooled reaction tube. Then, to the stirring solution, primary and secondary amines and phenols (0.6 mmol) in dichloroethane (3 mL) and TfOH (0.3 equiv) were added at a time. Then, the reaction was kept on heating at 80 °C for 16 h. The reaction mixture was filtered through a pad of Celite by eluting with dichloromethane and the filtrate was concentrated *in vacuo*. The residue was purified using flash column chromatography.

General Procedure for Enol and Indole C−H Insertion Reactions (Scheme 4d)

To a reaction tube, crushed 4 Å molecular sieves were added and then the sieves were flame-dried under an argon atmosphere. Vinyl sulfoxonium ylide (0.5 mmol) in dichloroethane (2 mL) was added the cooled reaction tube. Then, to the stirring solution, indole (0.6 mmol) in toluene (3 mL) and TfOH (0.3 equiv) was added at a time. Then, the reaction was kept on heating at 110 °C for 8−10 h. The reaction mixture was filtered through a pad of Celite by eluting with dichloromethane and the filtrate was concentrated *in vacuo*. The residue was purified using flash column chromatography.

General Procedure for the Acid Iteration (Scheme 6a)

To a reaction tube, crushed 4 Å molecular sieves were added and then the sieves were flame-dried under an argon atmosphere. Vinyl sulfoxonium ylide (0.5 mmol) in dichloroethane (2 mL) was added to the cooled reaction tube. Then, to the stirring solution, carboxylic acid (0.6 mmol) in dichloroethane (3 mL) was added at a time. Then, the reaction was kept on heating at 70 °C for 3−4 h. Then, the concentrated reaction mixture was filtered through a pad of silica using dichloromethane (20 ml). The eluted sulfoxonium ylide was concentrated and dissolved in tetrahydrofuran (0.20 M). To this reaction mixture, tetrabutylammonium fluoride (1.1 equiv) was added dropwise at 0 °C and stirred at room temperature for 2−3 h. After the disappearance of the starting material, the reaction was quenched using water and extracted with diethyl ether and dried over anhydrous Na_2SO_4. The solvent was evaporated and concentrated under high *vacuo*.

https://doi.org/10.1021/jacsau.2c00641
JACS Au 2023, 3, 252−260

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00641.

Representative experimental procedures, characterization data, and spectra for all new compounds (PDF)

Crystal data and structure refinement for **8** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Janakiram Vaitla − *Department of Chemistry, Indian Institute of Technology Delhi, New Delhi 110016, India;* orcid.org/0000-0003-4068-5916; Email: vaitla@chemistry.iitd.ac.in

Authors

Srashti Bhardwaj − *Department of Chemistry, Indian Institute of Technology Delhi, New Delhi 110016, India*

Dinesh Kumar Gopalakrishnan − *Department of Chemistry, Indian Institute of Technology Delhi, New Delhi 110016, India*

Divya Garg − *Department of Chemistry, Indian Institute of Technology Delhi, New Delhi 110016, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.2c00641

Author Contributions

J.V. supervised this study. The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.V. acknowledges the financial support from SERB, New Delhi (grant no. SRG/2020/000275). S.B. thanks the University Grants Commission of India for the UGC fellowship. D.K.G. thanks MHRD (GoI) for the Prime Minister's Research Fellowship. We thank Central Research Facility (IIT Delhi) for providing instrumentation facility.

■ REFERENCES

(1) Lutz, J. F.; Ouchi, M.; Liu, D. R.; Sawamoto, M. Sequence-controlled polymers. *Science* **2013**, *341*, 1238149.

(2) Deng, Z.; Shi, Q.; Tan, J.; Hu, J.; Liu, S. Sequence-Defined Synthetic Polymers for New-Generation Functional Biomaterials. *ACS Mater. Lett.* **2021**, *3*, 1339−1356.

(3) Nanjan, P.; Porel, M. Sequence-defined non-natural polymers: synthesis and applications. *Polym. Chem.* **2019**, *10*, 5406−5424.

(4) Meier, M. A. R.; Barner-Kowollik, C. A New Class of Materials: Sequence-Defined Macromolecules and Their Emerging Applications. *Adv. Mater.* **2019**, *31*, No. e1806027.

(5) Liu, R.; Zhang, L.; Huang, Z.; Xu, J. Sequential and alternating RAFT single unit monomer insertion: model trimers as the guide for discrete oligomer synthesis. *Polym. Chem.* **2020**, *11*, 4557−4567.

(6) Lutz, J.-F. Sequence-controlled polymerizations: the next Holy Grail in polymer science? *Polym. Chem.* **2010**, *1*, 55−62.

(7) Zhang, J.; Matta, M. E.; Hillmyer, M. A. Synthesis of Sequence-Specific Vinyl Copolymers by Regioselective ROMP of Multiply Substituted Cyclooctenes. *ACS Macro Lett.* **2012**, *1*, 1383−1387.

(8) Norris, B. N.; Pan, T.; Meyer, T. Y. Iterative synthesis of heterotelechelic oligo(phenylene-vinylene)s by olefin cross-metathesis. *Org. Lett.* **2010**, *12*, 5514−5517.

(9) Hartmann, L. Polymers for Control Freaks: Sequence-Defined Poly(amidoamine)s and Their Biomedical Applications. *Macromol. Chem. Phys.* **2011**, *212*, 8−13.

(10) Ohuchi, M.; Murakami, H.; Suga, H. The flexizyme system: a highly flexible tRNA aminoacylation tool for the translation apparatus. *Curr. Opin. Chem. Biol.* **2007**, *11*, 537−542.

(11) Ohta, A.; Murakami, H.; Suga, H. Polymerization of alpha-hydroxy acids by ribosomes. *Chembiochem* **2008**, *9*, 2773−2778.

(12) Fahnestock, S.; Rich, A. Ribosome-catalyzed polyester formation. *Science* **1971**, *173*, 340−343.

(13) Ohta, A.; Murakami, H.; Higashimura, E.; Suga, H. Synthesis of polyester by means of genetic code reprogramming. *Chem. Biol.* **2007**, *14*, 1315−1322.

(14) Vandenbergh, J.; Reekmans, G.; Adriaensens, P.; Junkers, T. Synthesis of sequence controlled acrylate oligomers via consecutive RAFT monomer additions. *Chem. Commun.* **2013**, *49*, 10358−10360.

(15) Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. Controlled ring-opening polymerization of lactide and glycolide. *Chem. Rev.* **2004**, *104*, 6147−6176.

(16) Müller, H.-M.; Seebach, D. Poly(hydroxyalkanoates): A Fifth Class of Physiologically Important Organic Biopolymers? *Angew. Chem., Int. Ed.* **1993**, *32*, 477−502.

(17) Tang, X.; Hong, M.; Falivene, L.; Caporaso, L.; Cavallo, L.; Chen, E. Y. The Quest for Converting Biorenewable Bifunctional alpha-Methylene-gamma-butyrolactone into Degradable and Recyclable Polyester: Controlling Vinyl-Addition/Ring-Opening/Cross-Linking Pathways. *J. Am. Chem. Soc.* **2016**, *138*, 14326−14337.

(18) Penczek, P.; Czub, P.; Pielichowski, J. Unsaturated polyester resins: chemistry and technology. *Adv. Polym. Sci.* **2005**, *184*, 1−95.

(19) Guo, B.; Chen, Y.; Lei, Y.; Zhang, L.; Zhou, W. Y.; Rabie, A. B.; Zhao, J. Biobased poly(propylene sebacate) as shape memory polymer with tunable switching temperature for potential biomedical applications. *Biomacromolecules* **2011**, *12*, 1312−1321.

(20) Cai, L.; Wang, S. Parabolic dependence of material properties and cell behavior on the composition of polymer networks via simultaneously controlling crosslinking density and crystallinity. *Biomaterials* **2010**, *31*, 7423−7434.

(21) Malik, M.; Choudhary, V.; Varma, I. K. Current Status of Unsaturated Polyester Resins. *J. Macromol. Sci., Polym. Rev.* **2000**, *40*, 139−165.

(22) Margolis, J. M. *Advanced Thermoset Composites, Industrial and Commercial Application*; Van Nostrand Reinhold: New York, 1986.

(23) Binda, P.; Barnes, Z.; Guthrie, D.; Ford, R. Highly Branched Poly(α-Methylene-γ-Butyrolactone) from Ring-Opening Homopolymerization. *Open J. Polym. Chem.* **2017**, *07*, 76−91.

(24) Pignatello, R.; Impallomeni, G.; Cupri, S.; Puzzo, G.; Curcio, C.; Rizzo, M. G.; Guglielmino, S.; Ballistreri, A. Unsaturated Poly(Hydroxyalkanoates) for the Production of Nanoparticles and the Effect of Cross-Linking on Nanoparticle Features. *Materials* **2019**, *12*, 868.

(25) Tong, X.; Guo, B. H.; Huang, Y. Toward the synthesis of sequence-controlled vinyl copolymers. *Chem. Commun.* **2011**, *47*, 1455−1457.

(26) Brudno, Y.; Liu, D. R. Recent progress toward the templated synthesis and directed evolution of sequence-defined synthetic polymers. *Chem. Biol.* **2009**, *16*, 265−276.

(27) Hibi, Y.; Tokuoka, S.; Terashima, T.; Ouchi, M.; Sawamoto, M. Design of AB divinyl "template monomers" toward alternating sequence control in metal-catalyzed living radical polymerization. *Polym. Chem.* **2011**, *2*, 341−347.

(28) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. Vinylogous polypeptides: an alternative peptide backbone. *J. Am. Chem. Soc.* **2002**, *114*, 6568−6570.

(29) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. The vinylogous aldol reaction: a valuable, yet understated carbon-carbon bond-forming maneuver. *Chem. Rev.* **2000**, *100*, 1929−1972.

(30) Bur, S. K.; Martin, S. F. Vinylogous Mannich reactions: selectivity and synthetic utility. *Tetrahedron* **2001**, *57*, 3221−3242.
(31) Kalesse, M.; Cordes, M.; Symkenberg, G.; Lu, H. H. The vinylogous Mukaiyama aldol reaction (VMAR) in natural product synthesis. *Nat. Prod. Rep.* **2014**, *31*, 563−594.
(32) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. The vinylogous aldol and related addition reactions: ten years of progress. *Chem. Rev.* **2011**, *111*, 3076−3154.
(33) Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. Exploiting the modularity of ion-paired chiral ligands for palladium-catalyzed enantioselective allylation of benzofuran-2(3H)-ones. *J. Am. Chem. Soc.* **2013**, *135*, 590−593.
(34) Lee, J. H.; Lee, S.-g. Iridium-catalyzed regiospecific and stereospecific allylic amination for the syntheses of α,β-unsaturated γ-amino esters and the bifurcation of the reaction pathway leading to the formation of oxazolidin-2-ones. *Chem. Sci.* **2013**, *4*, 2922−2927.
(35) Hutchings-Goetz, L.; Yang, C.; Snaddon, T. N. Enantioselective alpha-Allylation of Aryl Acetic Acid Esters via C1-Ammonium Enolate Nucleophiles: Identification of a Broadly Effective Palladium Catalyst for Electron-Deficient Electrophiles. *ACS Catal.* **2018**, *8*, 10537−10544.
(36) Hansen, J. H.; Davies, H. M. L. Vinylogous reactivity of silver(i) vinylcarbenoids. *Chem. Sci.* **2011**, *2*, 457−461.
(37) Kalepu, J.; Katukojvala, S. Dienamine Activation of Diazoenals: Application to the Direct Synthesis of Functionalized 1,4-Oxazines. *Angew. Chem., Int. Ed.* **2016**, *55*, 7831−7835.
(38) Yang, W.; Pu, M.; Lin, X.; Chen, M.; Song, Y.; Liu, X.; Wu, Y. D.; Feng, X. Enantioselective Formal Vinylogous N-H Insertion of Secondary Aliphatic Amines Catalyzed by a High-Spin Cobalt(II) Complex. *J. Am. Chem. Soc.* **2021**, *143*, 9648−9656.
(39) Yue, Y.; Wang, Y.; Hu, W. Regioselectivity in Lewis acids catalyzed X−H (O, S, N) insertions of methyl styryldiazoacetate with benzyl alcohol, benzyl thiol, and aniline. *Tetrahedron Lett.* **2007**, *48*, 3975−3977.
(40) Mangion, I. K.; Nwamba, I. K.; Shevlin, M.; Huffman, M. A. Iridium-catalyzed X-H insertions of sulfoxonium ylides. *Org. Lett.* **2009**, *11*, 3566−3569.
(41) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Vaughan, J. G. A novel entry to carbenoid species via[small beta]-ketosulfoxonium ylides. *J. Chem. Soc., Chem. Commun.* **1993**, 1434−1435.
(42) Bisag, G. D.; Ruggieri, S.; Fochi, M.; Bernardi, L. Sulfoxonium ylides: simple compounds with chameleonic reactivity. *Org. Biomol. Chem.* **2020**, *18*, 8793−8809.
(43) Vaitla, J.; Bayer, A. Sulfoxonium Ylide Derived Metal Carbenoids in Organic Synthesis. *Synthesis* **2019**, *51*, 612−628.
(44) Caiuby, C. A. D.; Furniel, L. G.; Burtoloso, A. C. B. Asymmetric transformations from sulfoxonium ylides. *Chem. Sci.* **2022**, *13*, 1192−1209.
(45) Zhang, S. S.; Xie, H.; Shu, B.; Che, T.; Wang, X. T.; Peng, D.; Yang, F.; Zhang, L. Iridium-catalyzed B-H insertion of sulfoxonium ylides and borane adducts: a versatile platform to alpha-boryl carbonyls. *Chem. Commun.* **2020**, *56*, 423−426.
(46) Zhang, X.; Zhang, Y.; Liang, C.; Jiang, J. Copper-catalyzed P-H insertion reactions of sulfoxonium ylides. *Org. Biomol. Chem.* **2021**, *19*, 5767−5771.
(47) Dias, R. M.; Burtoloso, A. C. Catalyst-Free Insertion of Sulfoxonium Ylides into Aryl Thiols. A Direct Preparation of beta-Keto Thioethers. *Org. Lett.* **2016**, *18*, 3034−3037.
(48) Momo, P. B.; Leveille, A. N.; Farrar, E. H. E.; Grayson, M. N.; Mattson, A. E.; Burtoloso, A. C. B. Enantioselective S-H Insertion Reactions of alpha-Carbonyl Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2020**, *59*, 15554−15559.
(49) Furniel, L. G.; Echemendía, R.; Burtoloso, A. C. B. Cooperative copper-squaramide catalysis for the enantioselective N-H insertion reaction with sulfoxonium ylides. *Chem. Sci.* **2021**, *12*, 7453−7459.
(50) Leveille, A. N.; Echemendía, R.; Mattson, A. E.; Burtoloso, A. C. B. Enantioselective Indole Insertion Reactions of alpha-Carbonyl Sulfoxonium Ylides. *Org. Lett.* **2021**, *23*, 9446−9450.
(51) Guo, W.; Jiang, F.; Li, S.; Sun, J. Organocatalytic asymmetric azidation of sulfoxonium ylides: mild synthesis of enantioenriched alpha-azido ketones bearing a labile tertiary stereocenter. *Chem. Sci.* **2022**, *13*, 11648−11655.
(52) Vaitla, J.; Bayer, A.; Hopmann, K. H. Iron-Catalyzed Carbenoid-Transfer Reactions of Vinyl Sulfoxonium Ylides: An Experimental and Computational Study. *Angew. Chem., Int. Ed.* **2018**, *57*, 16180−16184.
(53) Vaitla, J.; Bayer, A.; Hopmann, K. H. Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4277−4281.
(54) Vaitla, J.; Hopmann, K. H.; Bayer, A. Rhodium-Catalyzed Synthesis of Sulfur Ylides via in Situ Generated Iodonium Ylides. *Org. Lett.* **2017**, *19*, 6688−6691.
(55) Vaitla, J.; Bayer, A.; Hopmann, K. H. Vinyl Sulfoxonium Ylide: A New Vinyl Carbenoid Transfer Reagent for the Synthesis of Heterocycles. *Synlett* **2019**, *30*, 1377−1383.
(56) Weaver, J. D.; Recio, A., 3rd; Grenning, A. J.; Tunge, J. A. Transition metal-catalyzed decarboxylative allylation and benzylation reactions. *Chem. Rev.* **2011**, *111*, 1846−1913.
(57) Boiarska, Z.; Braga, T.; Silvani, A.; Passarella, D. Brown Allylation: Application to the Synthesis of Natural Products. *Eur. J. Org. Chem.* **2021**, *2021*, 3214−3222.
(58) Abdul Fattah, T.; Saeed, A. Applications of Keck allylation in the synthesis of natural products. *New J. Chem.* **2017**, *41*, 14804−14821.
(59) Trost, B. M. Metal Catalyzed Allylic Alkylation: Its Development in the Trost Laboratories. *Tetrahedron* **2015**, *71*, 5708−5733.
(60) Mu, Y.; Chen, Y.; Gao, Y.; Sun, J.; Iqbal, Z.; Wan, Y.; Yang, M.; Yang, Z.; Tang, D. Ru-Catalyzed O-H Insertion of Sulfoxonium Ylide and Carboxylic Acid to Synthesize α-Acyloxy Ketones. *ChemistrySelect* **2020**, *5*, 1705−1708.
(61) Koothradan, F. F.; Suresh Babu, A.; Pushpakaran, K. P.; Jayarani, A.; Sivasankar, C. Carboxylic Acid Functionalization Using Sulfoxonium Ylides as a Carbene Source. *J. Org. Chem.* **2022**, *87*, 10564−10575.
(62) Davas, D. S.; Gopalakrishnan, D. K.; Kumar, D.; Vaitla, J. Ru-Catalyzed Benzannulation of Vinyl Sulfoxonium Ylide with Electron-Deficient Alkynes and Alkenes. *Org. Lett.* **2022**, *24*, 8359−8363.
(63) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. Synthesis of cyclopropanes via Pd(II/IV)-catalyzed reactions of enynes. *J. Am. Chem. Soc.* **2007**, *129*, 5836−5837.
(64) Jiang, Z.; Niu, S. L.; Zeng, Q.; Ouyang, Q.; Chen, Y. C.; Xiao, Q. Selective Alkynylallylation of the C-C sigma Bond of Cyclopropenes. *Angew. Chem., Int. Ed.* **2021**, *60*, 297−303.
(65) Lei, A.; He, M.; Zhang, X. Highly enantioselective syntheses of functionalized alpha-methylene-gamma-butyrolactones via Rh(I)-catalyzed intramolecular Alder ene reaction: application to formal synthesis of (+)-pilocarpine. *J. Am. Chem. Soc.* **2002**, *124*, 8198−8199.
(66) Suppo, J. S.; Subra, G.; Bergès, M.; Marcia de Figueiredo, R.; Campagne, J. M. Inverse peptide synthesis via activated alpha-aminoesters. *Angew. Chem., Int. Ed.* **2014**, *53*, 5389−5393.
(67) El-Faham, A.; Albericio, F. Peptide coupling reagents, more than a letter soup. *Chem. Rev.* **2011**, *111*, 6557−6602.
(68) Humphrey, J. M.; Chamberlin, A. R. Chemical Synthesis of Natural Product Peptides: Coupling Methods for the Incorporation of Noncoded Amino Acids into Peptides. *Chem. Rev.* **1997**, *97*, 2243−2266.
(69) Ide, J.; Kishida, Y. Studies on acetylenic compounds. XLIV. Sulfoxonium ylide chemistry. I. Formation of stable sulfoxonium ylides from acetylenic compounds. *Chem. Pharm. Bull.* **1968**, *16*, 784−792.
(70) Lehmann, J. W.; Blair, D. J.; Burke, M. D. Towards the generalized iterative synthesis of small molecules. *Nat. Rev. Chem.* **2018**, *2*, 115.
(71) Arruda, J. M.; Munoz, B.; Stearns, B. A. Prodrugs of diaryl-2-(5H)-furanone cyclooxygenase-2 inhibitors. WO 2005042476 A2, 2005.

https://doi.org/10.1021/jacsau.2c00641
JACS Au 2023, 3, 252−260