ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Rapid and Multi-gram Synthesis of Vinylogous Esters under Continuous-Flow: An Access to Transetherification and Reverse Reaction of Vinylogous Esters

Nirmala Mohanta, Moreshwar Bhagwan Chaudhari, Naveen Kumar Digrawal, and Boopathy Gnanaprakasam

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00067 • Publication Date (Web): 15 Mar 2019

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

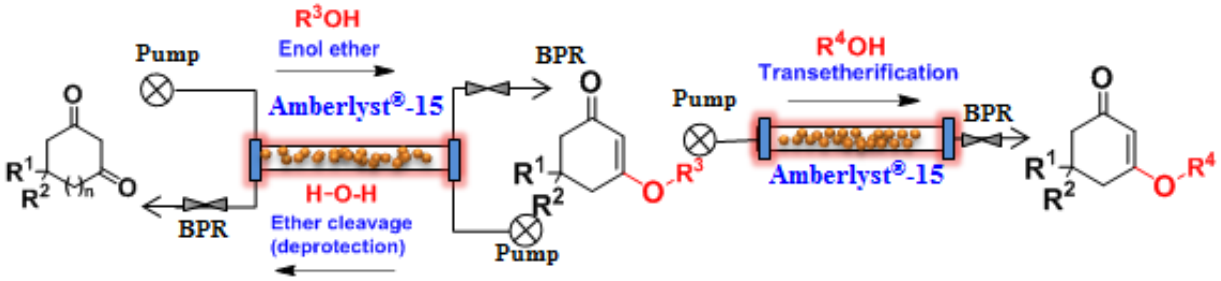
Rapid and Multi-gram Synthesis of Vinylogous Esters under Continuous-Flow: An Access to Transetherification and Reverse Reaction of Vinylogous Esters

*Nirmala Mohanta, Moreshwar B. Chaudhari, Naveen Kumar Digrawal and Boopathy Gnanaprakasam**

Department of Chemistry, Indian Institute of Science Education and Research, Pune-411008, India.

E-mail:gnanaprakasam@iiserpune.ac.in

Table of Contents:



- Sustainable approach and gram scale synthesis in continuous flow
- 22 examples and one example in continuous production for 40 hr
- Solvent and metal free condition
- Reversible transformation: ketone to vinylogous ester and vice versa
- Transetherification in continuous flow

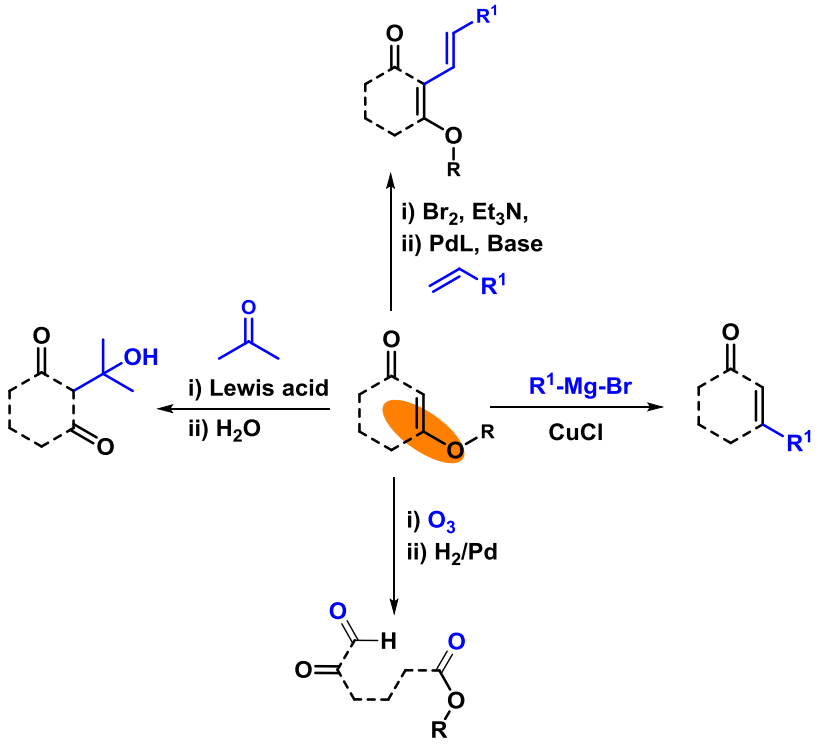
ABSTRACT: An environmentally benign approach for the synthesis of vinylogous esters from 1,3-diketone and its reverse reaction under continuous flow has been developed with alcohols in the presence of inexpensive Amberlyst®-15 as a catalyst. This methodology is highly selective and general for a range of cyclic 1,3-dicarbonyl compounds which gives a library of linear alkylated and arylated vinylogous esters in good to excellent yield under solvent and metal free condition. Furthermore, the long-time experiment in a continuous-flow up to 40 hrs afforded 8.0 g of the vinylogous ester with TON = 28.6 and TOF = 0.715 h^{-1} using Amberlyst-15 as a catalyst. Furthermore, a continuous flow sequential transetherification of vinylogous esters with various alcohols has been achieved in high yield. Reversibly, this vinylogous ester was deprotected or hydrolysed into ketone using environmentally benign water as a solvent and Amberlyst-15 as a catalyst under continuous flow process.

KEYWORDS: Vinylogous Esters, Transetherification, Vinylogous ethers Hydrolysis, Reverse Reaction, Continuous Flow Reaction, Amberlyst-15

INTRODUCTION:

Functional group interconversions (FGI) are the imperative reactions in organic synthesis and among the most common synthetic methods. The development of new strategy for the protection/deprotection of functional groups in chemical synthesis remains attractive research area and wide array of synthetic methodologies continuing to be reported.[1] The vinylogous esters are considered as a versatile and reactive key intermediates in many chemical transformations due to their ability to undergo FGI.[2] Numerous studies have been performed to convert β-keto-vinylogous esters into other functional groups, such as C-C bond formation[3] (coupling reactions), ene reaction,[4] cycloaddition,[5] oxidation,[6] homologation,[7] acid catalyzed reactions with acetals or

ketals to give aldol-type adducts, and other reactions[7] (Scheme 1). The widespread applications in the synthesis of natural products,[8] bioactive molecules,[9] and materials[10] make β-keto-vinylogous esters promising precursor in synthetic organic chemistry. A plethora of synthetic methods are available for the synthesis of β-keto-vinylogous esters starting from di-keto compounds and alcohols using stoichiometric or catalytic pathway.[11] The use of stoichiometric strong organic acids, higher temperature, and longer reaction time precludes their use with the substrate bearing sensitive functionalities.



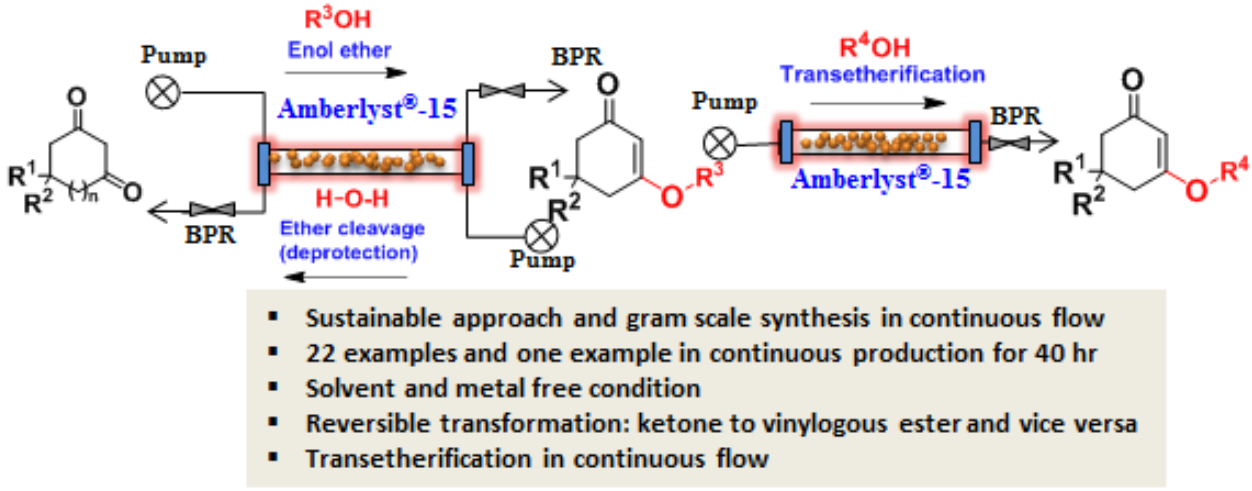
Scheme 1. The versatility of cyclic vinylogous ester

The vinylogous esters are reactive functional groups towards the acids (Brönsted and Lewis), which has been prepared in the presence of stoichiometric/catalytic acid with great care i.e. continuous removal of water being produced in this transformation is required. This is due to the equilibrium between ketone and vinylogous ester under prolonged acidic reaction condition in

the presence of water. Further, this reversible nature of the vinylogous esters renders direct impact on the yield and stability of the vinylogous esters in the course of the reaction.

Continuous-flow chemistry has emerged as a powerful process intensification technology for various synthetic transformations[12] which comprises several advantages includes precise control of reaction time, temperature, concentration and stoichiometry. As a result, it obeys the many of the green chemistry principles such as reduced energy requirements and time, minimized exposure to hazardous chemicals or reactive intermediates and avoids the generation of unwanted by-products and waste. Consequently, manufacturing of bulk chemicals, pharmaceuticals, and petrochemicals has been carried out in a continuous passion. This machine-assisted approach is very useful to avoid labor-intensive practices and gives access to work on 24/7 regime. Furthermore, it permits to access safer and greener route along with on-demand synthesis as a choice.

Thus, we envision in developing the reactive vinylogous ester synthesis under continuous flow in shorter duration; which can shift the equilibrium into vinylogous ester avoiding the prolonged exposure to hydrated acidic condition. To overcome the drawbacks mentioned above, catalysis integrated with continuous-flow often has the superior choice due to greater selectivity, increased safety, improved yield, and expeditious nature. In an extension of our efforts to develop greener and efficient process for the valuable chemical synthesis, we have anticipated the synthesis of chemically important intermediate vinylogous esters in a continuous flow.



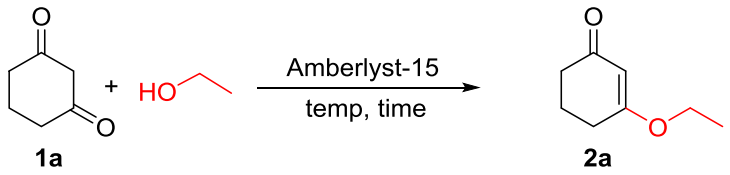
Scheme 2. Present studies on the synthesis of enol ether, reverse reaction and trans-etherification in continuous flow.

Herein, we report, Amberlyst®-15 as the H^+ source, catalyzed the synthesis of β-keto-vinylogous esters, transetherification and there reverse reaction in continuous flow using simple and ample precursors such as di-keto compounds, alcohols and water (Scheme 2). To the best of our knowledge, this is the first report on the selective synthesis of β-vinylogous esters in a continuous flow process using Amberlyst®-15 as a supported catalyst.

RESULTS AND DISCUSSION

In the course of our investigation, we have chosen cyclohexane-1,3-dione and ethanol as a model substrate. Initially, we do not observe any product in control experiments which were performed in the absence of any acidic source at room temperature and 80 ^{o}C (Table 1, entry 1-2). The addition of 25 mg of amberlyst-15 in 0.5 mmol ketone and 2 mL ethanol at room temperature afforded **2a**, in 72% isolated yield (Table 1, entry 3). Higher yield for the formation of **2a** was observed when increasing the catalyst concentration to 50 mg at room temperature and heating at 60 ^{o}C (Table 1, entries 4-5).

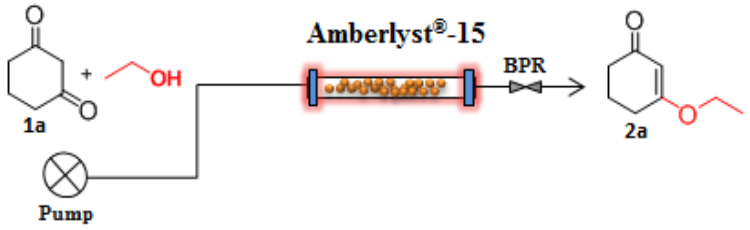
Table 1. Optimization of reaction conditions in batch



entry	catalyst in (mg)	temp (^{o}C)	time	yield (%)
1	-	rt	5 h	no reaction
2	-	80	5 h	no reaction
3	25	rt	5 h	72
4	50	rt	5 h	76
5	50	60	5 h	82
6	50	80	5 h	88

Reaction condition: 1,3-cyclohexanedione (0.5 mmol), amberlyst-15, and ethanol (2 mL) were stirred at specified temperature.

Tfable 2 Optimization of reaction conditions in continuous-flow[a]



Entry	flow rate in (mL)	temp (^{o}C)	substrate concentration (M)	t_R/number of runs	yield (%)
1	0.3	rt	0.2 M	4.6/1	48
2	0.3	Rt	0.2 M	4.6/2	93

3	0.3	60	0.1 M	4.6/1	95
4	0.3	80	0.2 M	4.6/1	73
5	0.3	100	0.2 M	4.6/1	86
5	0.2	80	0.2 M	6.8/1	93
6	0.2	100	0.2 M	6.8/1	88
7	0.3	80	0.15 M	4.6/1	83
8	0.3	80	0.1 M	4.6/1	99
9	0.5	80	0.1 M	2.7/1	78
10[b]	0.3	80	0.1 M	4.6/1	72

[a]**Reaction condition:** 0.1 molar solution of **1a** in ethanol were prepared and was flown through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height) (Vapourtec R-series) at a specified temperature, t_R= residence time in minute.[b] Reaction carried out using Amberlite-120. The mentioned yields are isolated yields.

However, a slight improvement in yield (88%) was observed when the reaction mixture heated at 80 ^{o}C (Table 1, entry 6). With these optimized conditions in the batch, we sought to transform them in a continuous flow.

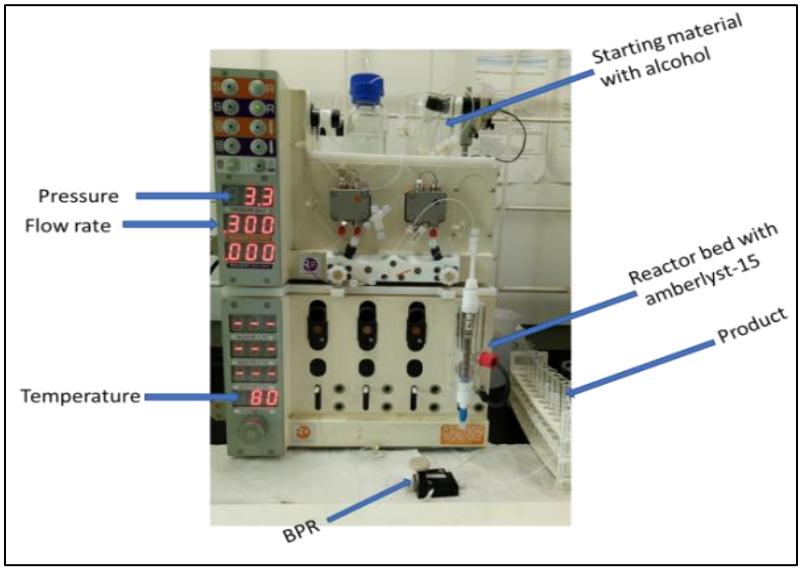
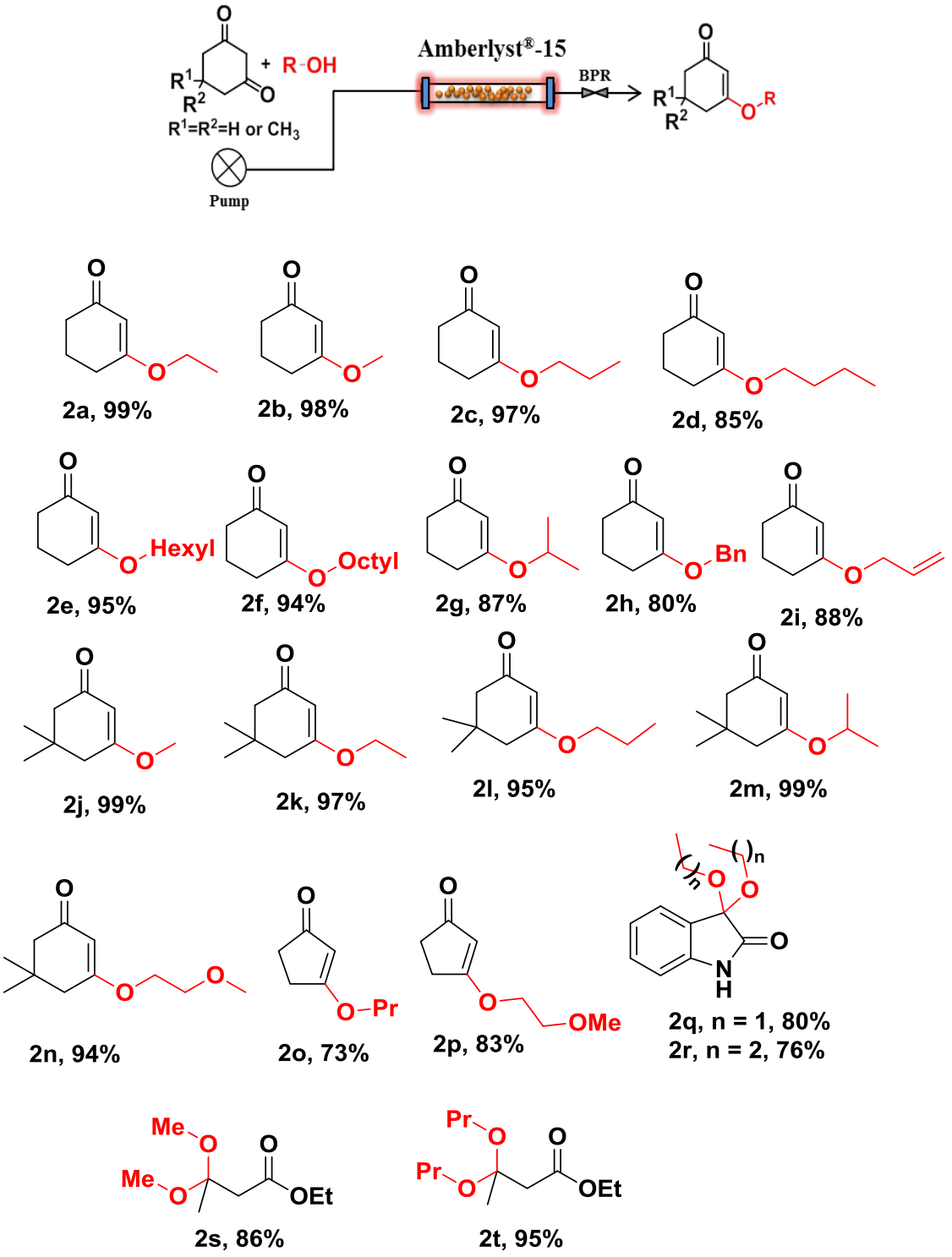


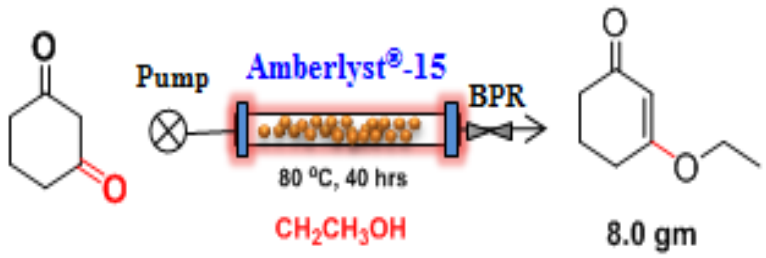
Figure 1. Full setup for continuous-flow reactor

Initial optimization was performed at room temperature with one and two runs with 0.3 mL flow rate and 0.2 M concentration, which provided 48 and 93% isolated yield of the product **2a** (Table 2, entries 1-2). To check the effect of temperature, flow rate, and concentration various experiments were performed, and results are summarized in Table 2 (entries 3-9). For instance, 0.1 M solution of **1a** in ethanol at 0.3 mL flow rate at 60 ^{o}C afforded 95% of product **2a** (Table 2, entry 3). Later, decrease in yield was observed when the concentration increased to 0.2 M at 80 ^{o}C and 100 ^{o}C (Table 2, entries 4, 5). Finally reaction with 0.3 mL flow rate and 0.1 M solution at 80 ^{o}C proven to be the best-optimized condition which afforded **2a** (99%) in 4.6 minutes of residence time (t_R) (Table 2, entry 8). The use of other resin *viz* Amberlite-120 afforded **2a** in 72% yield (Table 2, entry 10).



Scheme 3. Substrate scope for β-keto-enol ether in continuous-flow. **Reaction condition**: 0.1 molar solution of 1,3-diketone **1** in alcohol was prepared and 0.3 mL/min was flown through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height, residence time t_R = 4.6 min) (Vapourtec R-series) at 80 °C.

With these investigations, the generality of the reaction was explored with a variety of alcohols using different di-keto compounds. The reaction of cyclohexane-1,3-dione with linear alcohols such as ethanol, methanol, propanol, butanol, hexanol and octanol afforded an excellent yield of the products (Scheme 3, **2a-2f**). Furthermore, the reaction of secondary alcohol iso-propyl alcohol with the diketone afforded **2g** excellent yield (Scheme 3). To our delight, this reaction is not only restricted to aliphatic alcohols, the reaction of benzyl alcohol and allyl alcohol with cyclohexane-1,3-dione provided 3-(benzyloxy)cyclohex-2-en-1-one **2h** and 3-(allyloxy)cyclohex-2-en-1-one **2i** in very good yield. Additionally, we have extended the reaction scope with 5,5-dimethylcyclohexane-1,3-dione and cyclopentane-1,3-dione using linear or branched alcohols to yield **2j-2p** in excellent yield. However, the reaction of isatin with ethanol and propanol provided 3,3-dialkoxyindolin-2-one **2q** and **2r** in very good yield (Scheme 3). Interestingly, reaction of acyclic 1,3-dicarbonyl compounds with methanol and propanol under similar reaction condition afforded the respective ketal **2s** and **2t** in 86% and 96% yield respectively (Scheme 3).



Scheme 4. Gram-scale synthesis in continuous flow

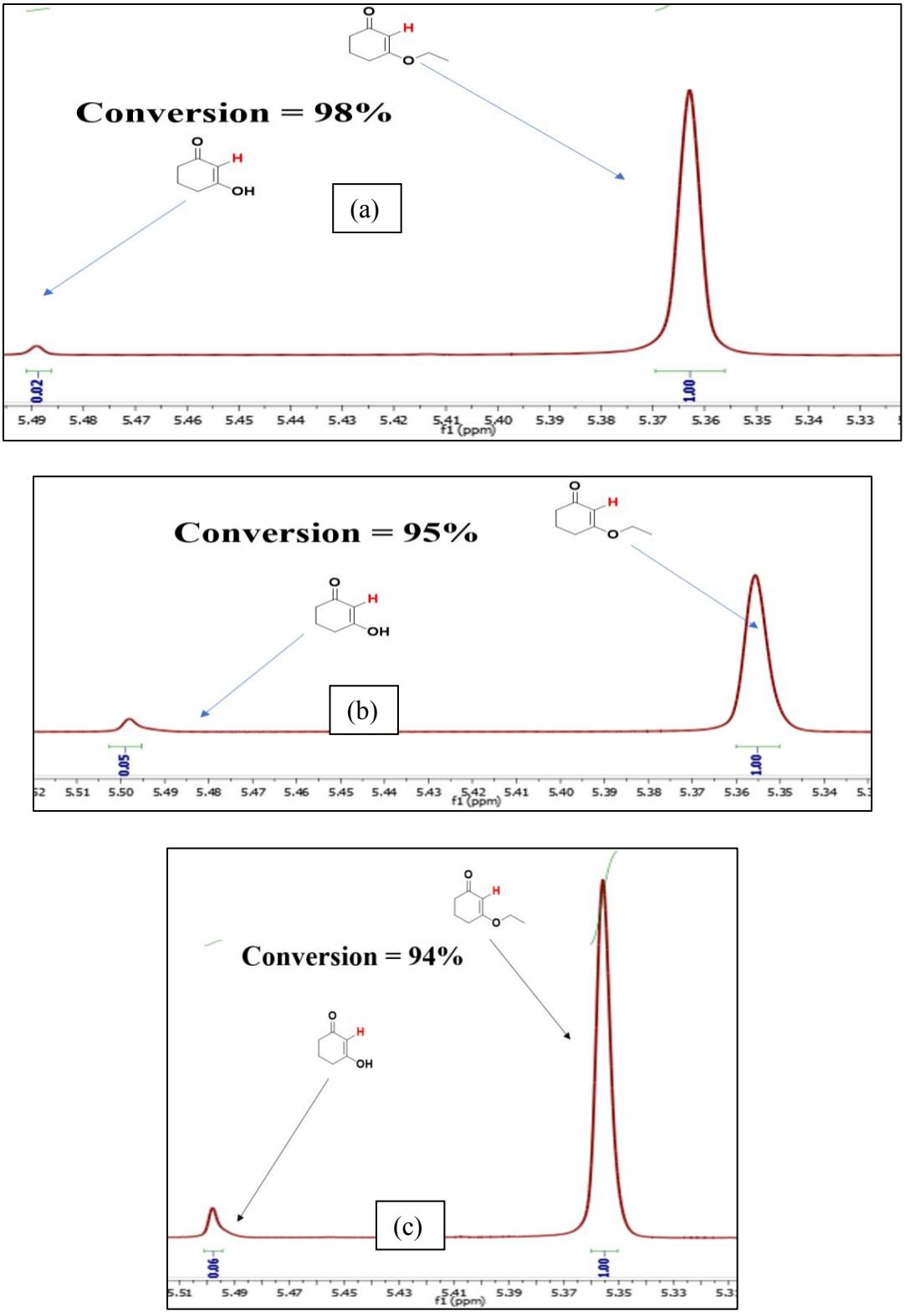


Figure 2. ^{1}H-NMR monitoring of the reaction in long run experiments; (a) after 2 h,(b) after 10 h, (c) after 20 h.

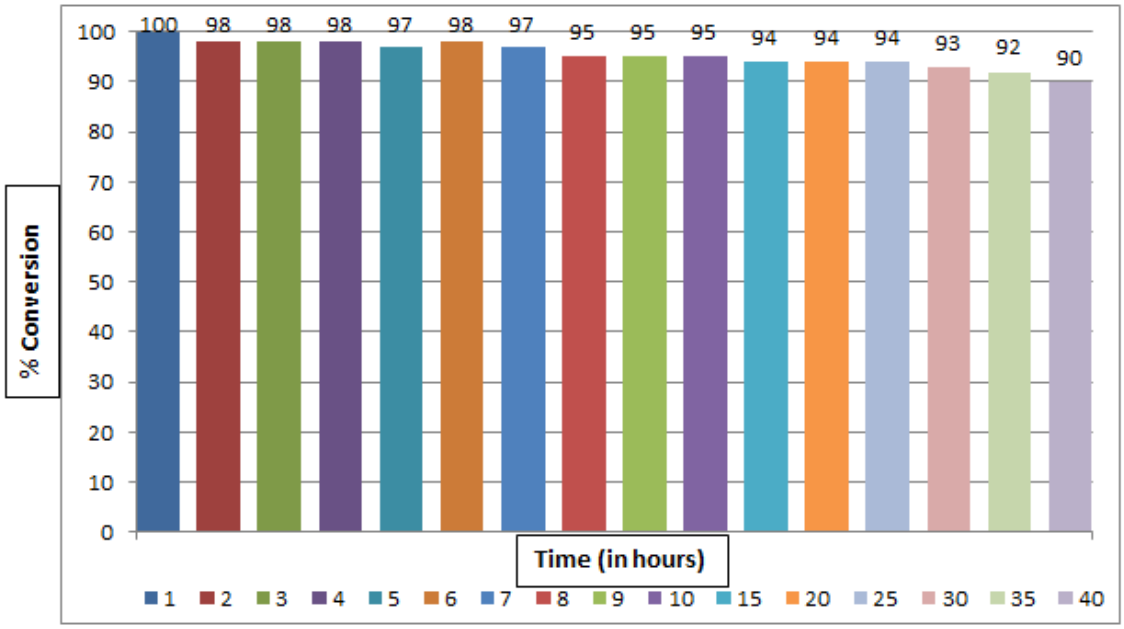
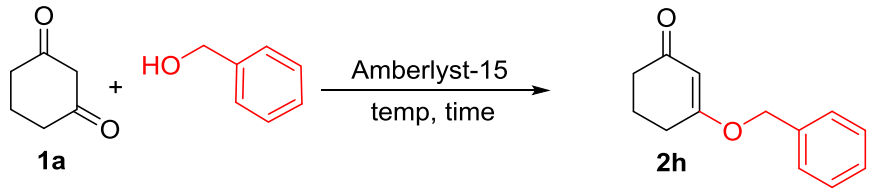


Figure 3. Continuous-flow synthesis of **2a** over 40 hrs.

To show the stability and efficiency of the Amberlyst-15, we have performed long time experiment in continuous flow. The substrate **1a** and ethanol was chosen as a model substrate for this purpose. For instance, 72.12 mmol of reactant was pumped continuously for 40 hrs with a flow rate of 0.3 mL/min to afford 57.22 mmol of product with TON (turnover number) = 28.61 and TOF (turnover frequency) = 0.715 h^{-1} (Scheme 4). The conversion of the product **2a** was determined by using ^{1}H-NMR, clearly indicates that up to 20 hrs of continuous flow synthesis led to compound **2a** in >94% yield (Figure 2). Continuing the synthesis after 20 hrs, the yield is slightly decreased to 90% after 40 hrs. Periodically, the yield of the continuous flow synthesis of **2a** was monitored by ^{1}H-NMR and accounted in Figure 3. Although we have stopped our reaction after 40 hrs, the catalyst is still affording 90% of the product **2a**. This clearly shows that the Amberlyst-15 is still active for this transformation. Although it is known that significant loss in activity of Amberlyst-15 for the other chemical transformation,[16] we found that very nominal loss in activity was observed over longer period of the reaction.

Table 3. Optimization of reaction conditions in continuous-flow

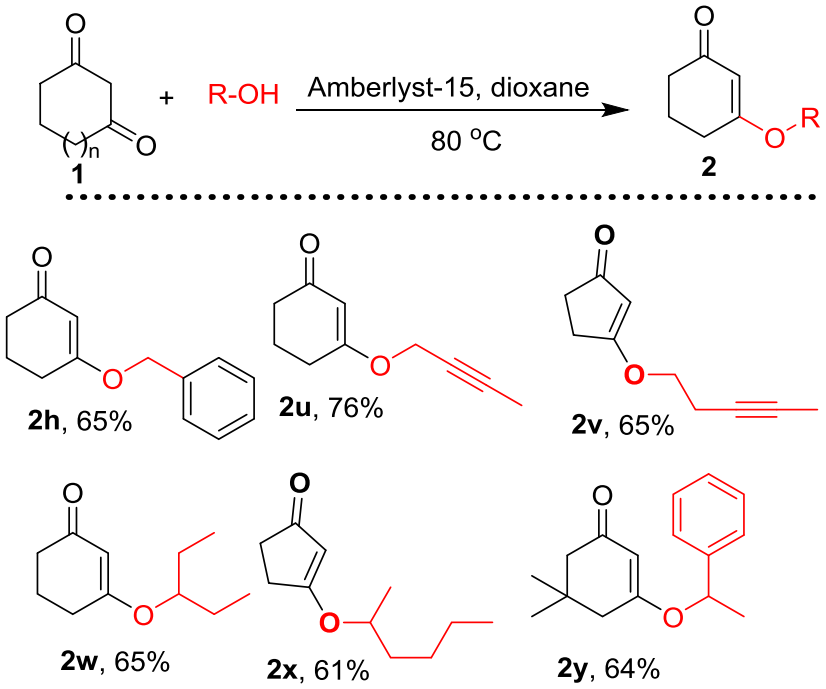


1a **2h**

entry	conc of **1a**	conc. of benzyl alcohol	solvent	flow rate in mL	time	yield (%)
Batch conditions (conc in mmole)[a]						
1	0.5	0.5	1,4-dioxane	-	1.5 hrs	80
2	0.5	0.5	Toluene	-	1.5 hrs	90
3	0.5	0.5	THF	-	1.5 hrs	75
Flow conditions (benzyl alcohol conc in molar)[b]						
4	1 mmol	0.1 M	1,4-dioxane	0.3	4.6 min	trace
5	1 mmol	0.3 M	1,4-dioxane	0.3	4.6 min	50
6	1 mmol	0.5 M	1,4-dioxane	0.3	4.6 min	65

Reaction conditions: [a]0.5 mmol of **1a** + 0.5 mmole of benzyl alcohol and 2ml solvent + amberlyst-15 (50 mg) were heated at 80 ^{o}C in a resealable tube for 2 hrs. [b]1 mmole of **1a** was dissolved in + 0.1 M, or 0.3 M or 0.5 M solution of benzyl alcohol were flown through the Omnifit® packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height, for residence time t_R, see table) (Vapourtec R-series) at 80 ^{o}C.

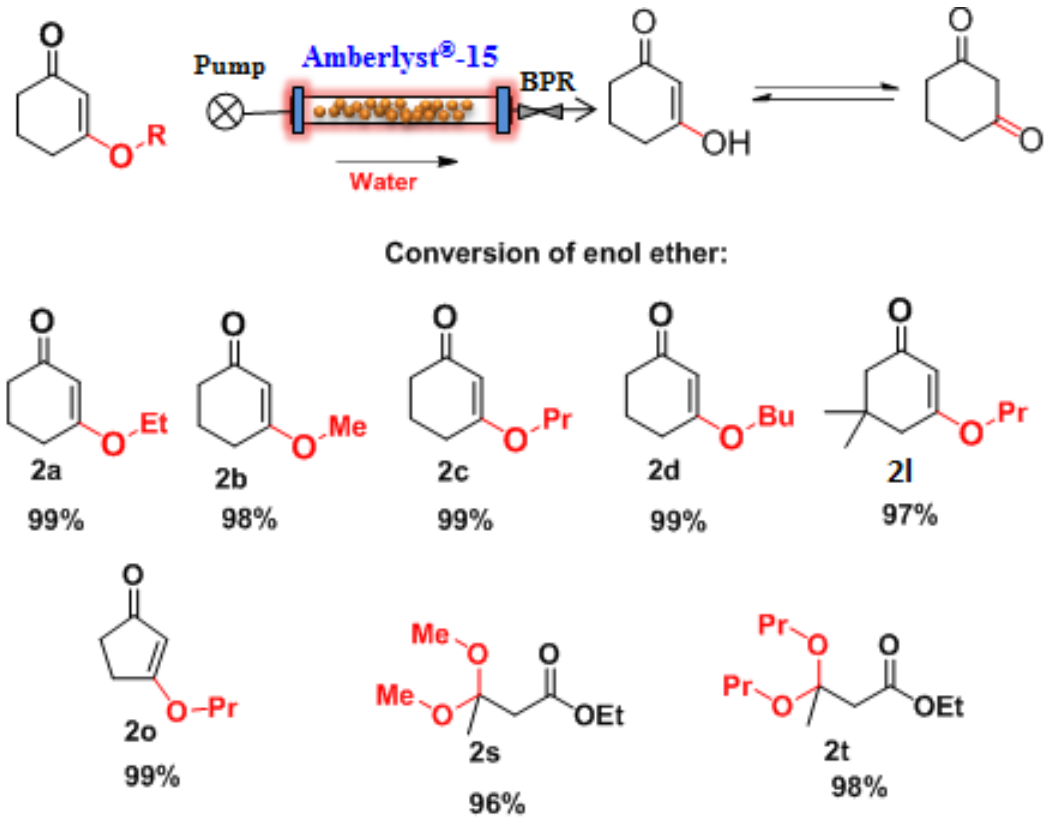
To avoid excess usage of special alcohols, further optimizations of the reaction especially for the highly viscous alcohols were performed using co-solvent and the optimised results are shown in Table 3. Under this optimized conditions, alcohol bearing sensitive alkyne functionality was worked efficiently to afford 3-(but-2-yn-1-yloxy)cyclohex-2-en-1-one **2u** in 76% yield (Scheme 5). Similar reaction with cyclopentane-1,3-dione afforded the respective vinylogous ester **2v** in 65% yield. Secondary alcohols such as 3-pentanol, 2-hexanol and 1-phenylethanol were also successfully reacted well to afford β-vinylogous esters **2w-y** in moderate yield (Scheme 5).



Scheme 5. Substrate scope for β-keto enol ether in continuous-flow. **Reaction condition**: 1 mmole of **1a** was dissolved in 0.1 M solution of alcohol in 1,4-dioxane (10 mL) and was flown through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height, residence time t_R = 4.6 min) at 80 °C.

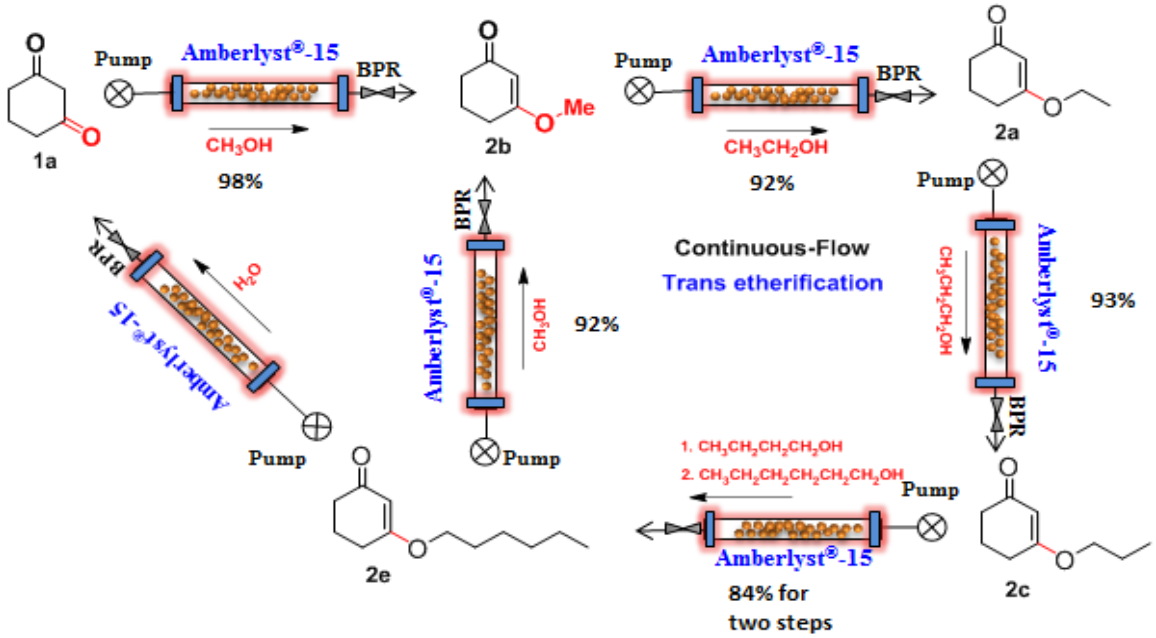
Use of water as a reagent as well as solvent for the chemical transformation is one of the attractive goals in green chemistry. In this aspect, the reversible transformation of vinylogous ester to the dicarbonyl compounds is one of the important transformation catalysed by acid.[13] Therefore, we sought to achieve the reversible transformation i.e. selective and milder hydrolysis of vinylogous ester under environmentally benign continuous flow approach. To achieve hydrolysis of vinylogous ester under continuous flow, a set reaction was attempted (Scheme 6). Thus, vinylogous ester **2a** was allowed to hydrolysis in the presence of water, led 10% yield after 4 hrs under batch condition. Addition of stoichiometry Amberlyst-15 in the same reaction, a complete conversion of **2a** was observed in to ketone **1a** after 3 hours. Interestingly, vinylogous esters **2a** and **2b** are highly soluble in water, which were flown (0.1M, 0.1 mL/min, tr = 13.6 min) in to the Omnifit column reactor prepacked with the Amberlyst-15, results in >98%

conversion to ketone (Scheme 6). However, compounds **2c, d, l** and **o** were not soluble in water. As a result of vinylogous ester insoluble in water, these compounds were dissolved 1:1 mixture of water and ACN, flown into the reactor afforded the 48-52% conversion of the ketone under continuous flow (Scheme 6). Interestingly, water suspension of these compounds was flown into the Omnifit column reactor prepacked with the Amberlyst-15, which led rapid hydrolysis to afford the1,3-diketone in >95% yield. Similarly, ketal derivatives **2s** and **2t** were also flown into the column reactor for the hydrolysis to give the respective dicarbonyl compounds in >98% yield.



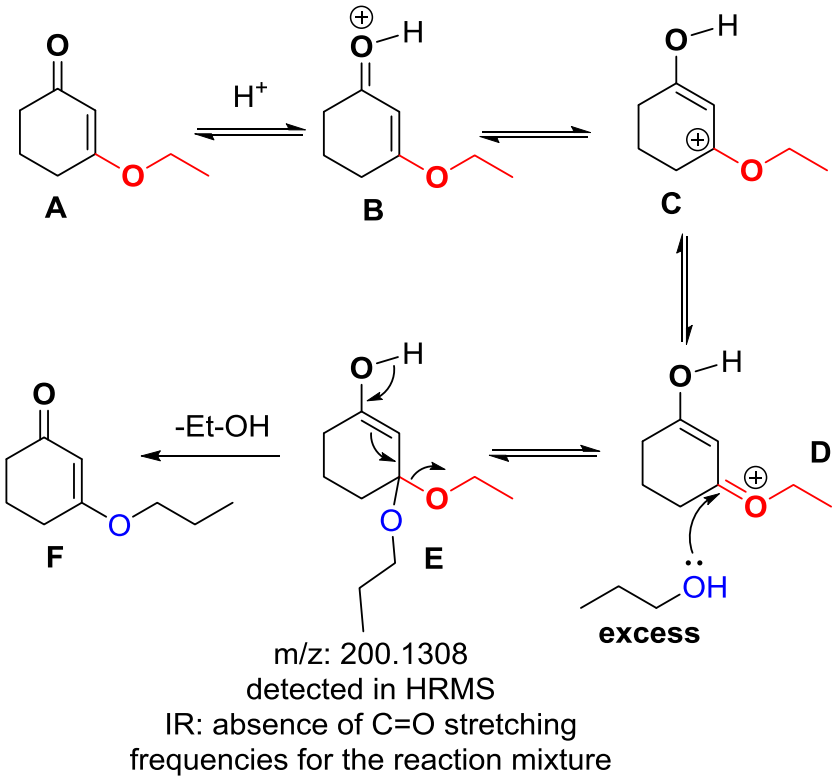
Scheme 6. Continuous-flow hydrolysis of vinylogous ester using water and Amberlyst-15. Reaction condition: 0.1 M solution of **2** in water was flown (0.1 mL/min) through the 6.6 x 150 mm Omnifit® packed bed reactor (628 mg of Amberlyst-15, 4 cm bed height) at room temperature (Residence time t_R = 13.6 min).

Transetherification[14] is an important transformation in organic synthesis due to its reactivity and easy accessibility. Developing environmentally benign approach for the transetherification is important aspect in chemical process. Thus, transetherification using vinylogous ester under continuous flow mode was investigated (Scheme 7). For this study, vinylogous ester **2b** was chosen as a model substrate and set of conditions were attempted. The optimised condition for the trans-etherification was established by flowing 0.3 mL/min of the 0.1 M solution of vinylogous ester in ethanol to the Omnifit column reactor prepacked with the Amberlyst-15 and heated at 80 ^{o}C to afford the vinylogous ester **2a** in 92% yield (Scheme 7). Under similar experimental condition and flow rate, vinylogous ester **2b** was transetherified using propanol solvent to give the vinylogous ester **2c** in 93% yield (Scheme 7). Similarly, continuous transetherification was carried to the vinylogous ester **2e** in 84% yield (for two consecutive transetherification steps) in continuous flow mode. Finally, hexyl group exchanged with the methyl via transetherification of vinylogous ester **2e** in methanol under continuous flow process to afford the corresponding vinylogous ester **2b** in 92% yield (Scheme 7). Furthermore, these transetherification of vinylogous ester was performed in gram under continuous flow.



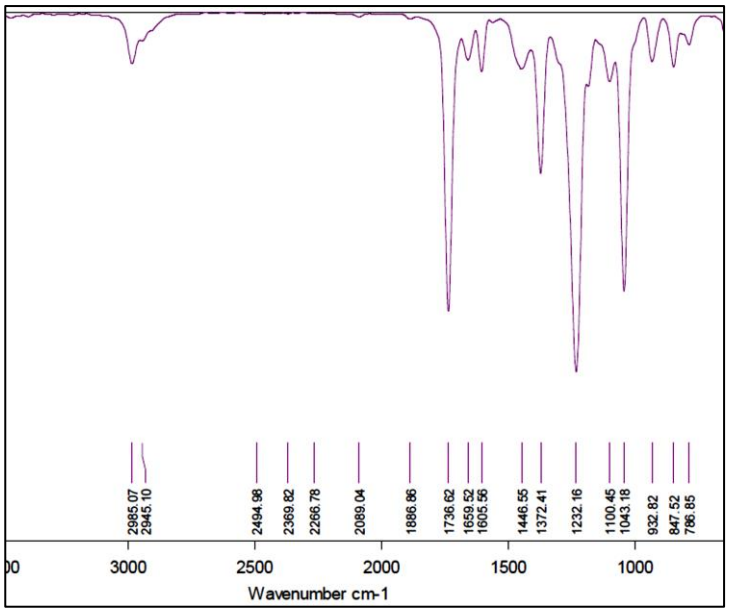
Scheme 7. Transetherification of vinylogous ester using alcohols under continuous-flow

The mechanism of the amberlyst-15 mediated transetherification of vinylogous ester is proposed in Scheme 8. Initially protonation of the C=O of the cyclic vinylogous ester **A** to give the intermediate **B**. The absence of the C=O functional group of the reaction mixture in the IR-spectra clearly indicate the formation of the intermediate **B** (Figure 4 (ii)). The interemediate **B** is resonance stabilised to generate the intermediates **C** and **D**. Further, the oxonium intermediate **D** is attacked by the alcohol to afford the ketal intermediate **E**. The HRMS spectra of the amberlyst-15 mediated reaction of **A** and *n*-propanol shows peak at *m/z* 200.1308 confirms the formation of the intermediate **E** (Figure 4 (iii)). Finally, the keto-enol taumerism assisted elimination of ethanol from the the intermediate **E** to form the transetherified product **F**.

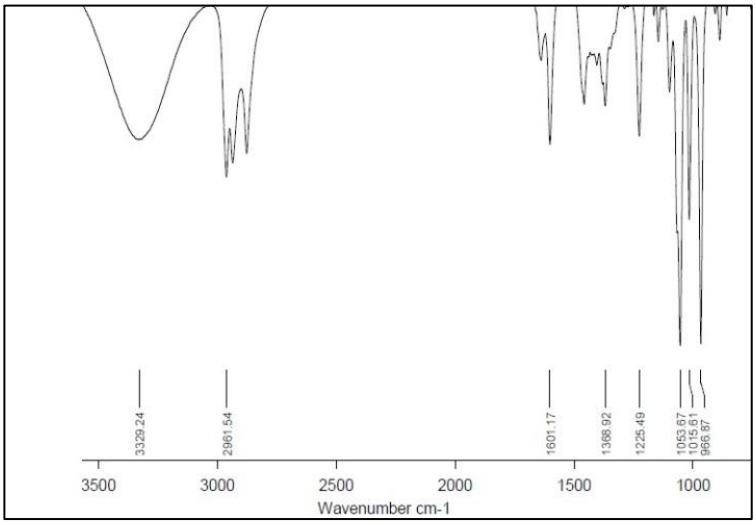


Scheme 8. Plausible mechanism for the transetherification of vinylogous ester using alcohol

i)



ii)



(iii)

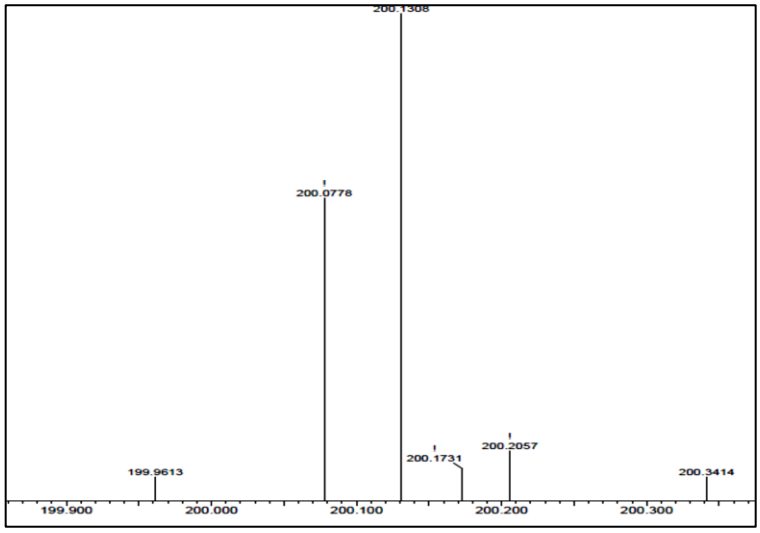


Figure 4. Mechanistic evidences; (i) IR spectra of **2a**; (ii) IR spectra of transetherification reaction mixture; (iii) HR-MS spectra of reaction mixture.

CONCLUSIONS

In conclusion, we have developed environmentally benign approach for the synthesis of vinylogous ester from commercially available 1,3-diketone using Amberlyst-15 under continuous flow mode. This process has been generalised with variety of vinylogous esters tethered by aliphatic, alkene, alkyne and aromatic substituents with rapid access (t_R = 4.6 min) in excellent yield with high selectivity. The long-time studies in a continuous-flow up to 40 hrs

revealed the efficiency of the Amberlyst-15 catalyst with TON= 28.6 and TOF= 0.715 h^{-1}, which generated 8 g of vinylogous ester in 40 hrs continuous synthesis. This methodology was also extended for continuous transetherification of vinylogous ester to another vinylogous ester in higher yield under continuous flow mode. Interestingly, the possible reverse reaction of vinylogous esters to ketones (hydrolysis of vinylogous ester) was achieved effectively under continuous flow process. Mechanism for the transetherification was also proposed with the experimental evidences.

EXPERIMENTAL SECTION

General information and data collection:

All the chemicals were purchased from Sigma Aldrich and SD Fine Chemicals and used without further modification. All solvents were purchased from Rankem and Finar Chemicals. Deuterated solvents were used as received. Column chromatographic separations performed over 100-200 Silica-gel. Visualization was accomplished with UV light and/or PMA stain followed by heating. The flow chemistry experiments were carried on Vapourtec R-series with glass column (Omntifit, 6.6 x 150 mm). ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker 400 MHz or JEOL 400 MHz spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-E Fourier transform infrared spectrometer.

A) General procedure for preparation of vinylogous esters ether compounds by using Amberlyst-15 under batch reaction:

In a 20 mL glass tube, 1,3-cyclohexadione (56 mg, 0.5 mmol) and Amberlyst-15 (50 mg) were added to alcohol (2 mL) and the tube was sealed using a crimper. The reaction mixture was stirred at 80 °C for 5 hrs. After cooling to room temperature, the reaction mixture was filtered and washed with DCM. The organic layer was concentrated under reduced pressure and the residue was subjected to column chromatography purification (EtOAc : *n*-hexane = 25:75) afforded cyclic vinylogous esters ether as a pure compound **2**. Similar reaction protocol was followed for the synthesis of other cyclic vinylogous ester derivatives by taking 1,3-cyclic diketone (0.5 mmol) and 50 mg of Amberlyst-15 (50 mg).

B) General procedure for preparation of vinylogous esters by using Amberlyst-15 under continuous flow:

0.1 M solution of the 1,3-cyclodiketone (1 mmol in 10 mL alcohol) was flown through the packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 ^{o}C temperature at 3.3 bar pressure. The organic layer was concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc : *n*-hexane = 25:75) purification afforded corresponding vinylogous esters compounds.

C) General procedure for preparation of vinylogous esters using alcohol and 1,3-diketone in the presence of Amberlyst-15 under continuous flow:

0.5 M solution of alcohol was made with 1,4-dioxane. 0.1 M solution of the 1,3-cyclodiketone (1 mmol in 10 mL of 0.5 M alcohol solution) was flown through the packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst-15 up to 4 cm (628 mg, swollen up to 5.5cm after passing solvent) of bed heated at 80 ^{o}C temperature at 3.3 bar pressure. The organic

layer was concentrated under reduced pressure followed by column chromatography (EtOAc : *n*-hexane = 10:90) purification afforded corresponding vinylogous esters.

D) General procedure for transetherification of vinylogous esters using alcohol in the presence of Amberlyst-15 under continuous flow:

0.1 M solution of 3-ethoxycyclohex-2-en-1-one (**2a**, 4mmol) was prepared in *n*-propanol (30 mL) and flown (0.3 mL/min) through the packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 ^{o}C temperature at 3.3 bar pressure. The organic layer was concentrated under reduced pressure to get the vinylogous ester product. Further, the residue was made 0.1 M solution in *n*-butanol and the above procedure was repeated to afford corresponding vinylogous esters. In a similar manner, sequential transetherification of vinylogous esters has been achieved using solvent *n*-hexanol, methanol and ethanol. In all the reactions, the starting material of vinylogous ester was completely converted to other vinylogous esters.

E) General procedure for hydrolysis of vinylogous esters under continuous flow:

0.1 M solution vinylogous esters or ketal (0.5 mmol) was prepared in water (5 mL) and flown through packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.2 bar pressure having flow rate 0.1 mL/min. The reaction was monitored by TLC and the reaction fraction was concentrated in rotary evaporator to afford 1,3-cyclohexadione.

F) Study of life time of catalyst and gram scale synthesis of vinylogous esters:

The gram scale synthesis of vinylogous esters was prepared by using general procedure B. 0.1 M solution of 1,3-cyclohexadione (8.085 g in 720 mL ethanol) was prepared and flown through packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) loaded with amberlyst-15 up to 4

cm (628 mg, swollen up to 6 cm after passing solvent) of bed heated at 80 ^{o}C temperature at 3.3 bar pressure for 40 hrs. The reaction mixture was monitored periodically by ^{1}H-NMR analysis. All the reaction fraction was concentrated in rotary evaporator to afford 8.112 gm of vinylogous esters **2a** as a yellowish oil.

G) Experimental procedure for detection of intermediate in transetherification reaction:

In a 20 mL of glass tube, 3-ethoxycyclohex-2-en-1-one (**2a**, 0.5 mmol) was taken in n-propanol (2 mL) followed by amberlyst-15 and the tube was sealed using a crimper. The reaction mixture was stirred for 1 hr at room temperature. The reaction mixture was directly taken in syringe and the IR and HRMS analysis for the reaction mixture was recorded.

H) Analytical data for the product:

3-ethoxycyclohex-2-en-1-one (2a)[16] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL ethanol) afforded 99% (138.5 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.28 (s, 1H), 3.84 (q, *J* = 6.8 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.27 (t, *J* = 6.8 Hz, 2H) 1.94-1.88 (m, 2H), 1.30 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.78, 177.90, 102.67, 64.15, 36.75, 29.08, 21.25, 14.12; **FT-IR**: 2954.24, 1728.68, 1598.77, 1412.65, 1314, 1222.42, 1125.60, 1091.52, 769.23 568.24 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_8H_{12}O_2$ $(M+H)^+$: 141.0916, found: 141.0925.

3-methoxycyclohex-2-en-1-one (2b)[17] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1M solution in 10 mL methanol) afforded 99% (124.8 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.69 (s, 3H), 2.40 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.4 Hz 2H), 2.01-1.94 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_{3,}$) δ 199.99, 178.90, 102.48, 55.75, 36.86, 28.96, 21.36; **FT-IR** (neat): 2953.87, 2315.29, 1724.89, 1590.46, 1458.78, 1369.83, 1226.41, 1179.69 1060.78, 753.04, 601.90 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_7H_{10}O_2$ $(M+H)^+$: 127.0759, found: 127.0762.

3-propoxycyclohex-2-en-1-one (2c)[18] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL propanol) afforded 97% (149.3 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.78 (t, *J* = 6.4 Hz, 2H),

2.39 (t, *J* = 6.4 Hz, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 2.00-1.93 (m, 2H), 1.78-1.70 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.04, 178.27, 102.81, 70.13, 36.87, 29.16, 22.02, 21.37, 10.52; **FT-IR**: 2952.28, 1727.07, 1601.11, 1453.93, 1380, 1232.65, 1183.99, 1001.03, 758.03, 597.32 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_9H_{14}O_2$ $(M+H)^+$: 155.1072, found: 155.1078.

3-butoxycyclohex-2-en-1-one (2d) was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1 M solution in 10 mL *n*-butanol), afforded 85% (142.4 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 3.79 (t, *J* = 6.4 Hz, 2H), 2.36 (t, *J* = 6.4 Hz, 2H), 2.30 (t, *J* = 6 Hz, 2H), 1.97-1.90 (m, 2H), 1.70-1.63 (m, 2H), 1.43-1.34 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.84, 178.14, 102.73, 68.33, 36.81, 30.58, 29.11, 21.31, 19.19, 13.75; **FT-IR** (neat): 2954.40, 2879.20, 2313.28, 1724.37, 1593.24, 1461.02, 1222.62, 1181.79, 1065.22, 748.22, 667.12 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{10}H_{16}O_2$ $(M+H)^+$:169.1229 found: 169.1238.

3-(hexyloxy)cyclohex-2-en-1-one (2e) was synthesized by following the experimental procedure of trans etherification using 3-butoxycyclohex-2-en-1-one (2d) in (0.1 M solution in 25 mL of *n*-hexanol) afforded 95% (462.5 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, CDCl3) δ 5.34 (s, 1H), 3.82 (t, *J* = 6.4 Hz, 2H), 2.40 (t, *J* = 6.4Hz, 2H), 2.34 (t, *J* = 6Hz, 2H), 2.01-1.94 (m, 2H), 1.75-1.68 (m,2H), 1.42-1.29 (m, 6H), 0.9 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl3) δ 200.03, 178.27, 102.84, 68.75, 36.90, 31.57, 29.20, 28.63, 25.74, 22.67, 21.39, 14.13; **FT-IR**: 2944.26, 2834.76, 2310.19, 1718.52, 1589.98, 1465.80, 1298.50, 1110.66, 1034.34, 786.44, 610.97 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{12}H_{20}O_2$ $(M+H)^+$: 197.1463, found: 197.1469.

3-(octyloxy)cyclohex-2-en-1-one (2f) was synthesized by using syringe pump. Due to high viscosity of octanol, Vapourtec R-series pump was not able to flow the *n*-octanol. 1,3-cyclohexadione (0.1 M solution in 10 mL octanol) was taken in syringe and flown through reactor bed at 0.3 mL /min, at 80 ^{o}C temperature, afforded 94% (210.3 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 3.80 (t, *J* = 6.8 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.33 (t, *J* = 6 Hz, 2H), 1.99-1.93 (m, 2H), 1.74-1.64 (m, 2H), 1.37-1.22 (m, 10H), 0.87 (t, *J* =7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.23, 178.21, 102.78, 68.69, 36.84, 31.83, 29.29, 29.23, 29.14, 28.59, 26.00, 22.71, 21.33, 14.16; **FT-IR** (neat): 2929.90, 2862.30, 2314.45,

1727.50, 1592.35, 1461.24, 1233.15, 1184.78, 1090.23, 756.55, 607.87 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{14}H_{24}O_2$ $(M+H)^+$: 225.1855, found: 225.1861.

3-isopropoxycyclohex-2-en-1-one (2g)[19] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1M solution in 10 mL propan-2-ol), afforded 87% (134.1 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.45-4.36 (m, 1H), 2.34 (t, *J* = 6.4Hz, 2H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.97-1.91 (m, 2H), 1.27 (d, *J* = 6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.02, 177.10, 103.09, 71.26, 36.79, 29.66, 21.57, 21.31; **FT-IR** (neat): 2978.67, 2310.65, 1730.60, 1641.95, 1595.51, 1461.11, 1230.90, 1187.26, 1000.27, 757.95, 608.98 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_9H_{14}O_2$ $(M+H)^+$: 155.1072, found:155.1078.

3-(benzyloxy)cyclohex-2-en-1-one (2h)[20] was synthesized by following the experimental procedure B using 1,3-cyclohexadione (0.1M solution in 10 mL benzylalcohol), afforded 80% (161.8 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.39-7.38 (m, 3H), 7.37-7.32 (m, 2H), 5.51 (s, 1H), 5.00 (s, 2H), 2.52 (t, *J* = 6.4Hz, 2H), 2.35 (t, *J* = 6Hz, 2H), 2.04-1.97 (m, 2H); **^{13}C NMR** (100 MHz, MeOH-d_4) δ 203.14, 181.17, 136.81, 129.65, 129.44, 128.95, 103.72, 71.85, 37.46, 30.02, 22.34; **FT-IR:** 3029.14, 2947.04, 2947.04, 2881.89, 2315.54, 1734.79, 1648.08, 1597.17, 1359.34, 1221.55, 1175.66, 863.08, 743.15 cm-^{1}; **HRMS** (ESI) m/z calculated for $C_{13}H_{14}O_2$ $(M+H)^+$: 203.1072, found: 203.1079.

3-(allyloxy)cyclohex-2-en-1-one (2i)[11g] was synthesized by following the experimental procedure B, using 1,3-cyclopentadione (0.1 M solution in 10 mL allyl alcohol), afforded 88% (133.6mg) as a yellowish liquid compound. **^{1}H NMR** (400 MHz, $CDCl_3$+CCl_4) δ 6.00-5.90 (m, 1H), 5.39-5.28 (m, 3H), 4.37 (d, *J* = 5.6Hz, 2H), 2.43 (t, *J* = 6.4Hz, 2H), 2.33 (t, *J* = 6.4 Hz, 2Hz), 2.02-1.95 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$ + CCl_4) δ 199.30, 177.17, 131.59, 119.10, 103.41, 62.24, 36.91, 29.20, 21.43; **FT-IR** : 2947.30, 2896.91, 2213.25, 2166.25, 1589.46, 1345.83, 1222.23, 1179.43, 1135.53, 988.73, 761.04 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_9H_{12}O_2$ $(M+Na)^+$: 175.0735, found: 175.0739.

3-methoxy-5,5-dimethylcyclohex-2-en-1-one (2j)[21] was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL methanol), afforded 99% (152.4 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$)

δ 5.35 (s, 1H), 3.67 (s, 3H), 2.25 (s, 2H), 2.19 (s, 2H), 1.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.77, 177.14, 101.20, 55.77, 50.80, 42.75, 32.61, 28.34; **FT-IR** (neat): 2956.40, 2312.12, 1649.43, 1601.68, 1456.82, 1373.03, 1221.59, 1147.82, 1013.68, 754.09, 602.35 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_9H_{14}O_2$ $(M+H)^+$: 155.1072, found: 155.1080.

3-ethoxy-5,5-dimethylcyclohex-2-en-1-one (2k)[22] was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL ethanol), afforded 99% (163.1 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 3.87 (q, *J* =7.2 Hz, 2H), 2.24 (s, 2H), 2.17 (s, 2H), 1.33 (t, *J*=7.2Hz, 3H), 1.03 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.77, 176.32, 101.55, 64.30, 50.79, 43.01, 32.54, 28.54, 14.18; **FT-IR** (neat):2956.43, 2884.89, 2312.03, 1723.53, 1649.47, 1599.53, 1464.58, 1368.81, 1216.68, 1149.36, 1031.43, 752.88, 628.50 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{10}H_{16}O_2$ $(M+H)^+$: 169.1229, found: 169.1235.

5,5-dimethyl-3-propoxycyclohex-2-en-1-one (2l)[22] was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL propanol), afforded 95% (191.1 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.32 (S, 1H), 3.77 (t, *J* = 6.4Hz, 2H), 2.26 (s, 2H), 2.19 (s, 2H), 1.72 (m, 2H), 1.05 (s, 6H), 0.96 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.80, 176.53, 101.57, 70.16, 50.84, 43.01, 32.56, 28.39, 22.01, 10.48; **FT-IR:** 2959.17**,** 2881.44**,** 2310.50, 1722.54, 1598.80, 1463.91, 1367.11, 1218.58, 1147.97; **HRMS** (ESI) m/z calculated for $C_{11}H_{18}O_2$ $(M+H)^+$: 183.1385, found: 183.1390.

3-isopropoxy-5,5-dimethylcyclohex-2-en-1-one (2m) was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL propan-2-ol), afforded 99% (180.3 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.41 (m, 1H), 2.21 (s, 2H), 2.19 (s, 2H), 1.27 (d, *J* = 6Hz 6H), 1.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.80, 175.25, 101.90, 71.02, 50.78, 43.49, 32.50, 28.33, 21.55; **FT-IR**: 2966.01, 2881.94, 2310.43, 1726.02, 1650.87, 1600.63, 1464.21, 1380.26, 1226.90, 1152.05, 1054.82, 758.78, 639.20 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{11}H_{18}O_2$ $(M+H)^+$: 183.1385, found: 183.1389.

3-(2-methoxyethoxy)-5,5-dimethylcyclohex-2-en-1-one (2n) was synthesized by following the experimental procedure B using 5,5-dimethyl-1,3-cyclohexadione (0.1 M solution in 10 mL 2-methoxyethanol), afforded 94% (186.3 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 3.98-3.95 (m, 2H), 3.69-3.67 (m, 2H), 3.41 (s, 3H), 2.32 (s, 2H), 2.20 (s,2H), 1.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.77, 176.23, 101.81, 70.22, 67.82, 59.30, 50.79, 42.79, 32.57, 28.36; **FT-IR** (neat): 2959.92, 2311.92, 2170.72, 1729.73, 1650.26, 1607.76, 1463.70, 1376.35, 1228.08, 1136.64, 1041.23, 751.46, 659.57 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{11}H_{18}O_3$ $(M+H)^+$: 199.1334, found: 199.1343.

3-propoxycyclopent-2-en-1-one (2o) was synthesized by following the experimental procedure B, using 1,3-cyclopentadione (0.1 M solution in 10 mL *n*-propanol), afforded 73% (102.5 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.27 (m, 1H), 3.92 (t, J = 6.8Hz, 2H), 2.61-2.59 (m, 2H), 2.44-2.41 (m, 2H), 1.83-1.74 (m, 2H), 1.00 (t, J = 7.2Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.30, 190.59, 104.78, 73.60, 34.08, 28.64, 22.06, 10.42; **FT-IR**: 2967.17, 2934.64, 2246.12 1676.46, 1584.73, 1411.72, 1344.25, 1289.43, 1183.57, 724.32, 651.14 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_8H_{12}O_2$ $(M+Na)^+$: 163.0735, found: 163.0739.

3-(2-methoxyethoxy)cyclopent-2-en-1-one (2p) was synthesized by following the experimental procedure B, using 1,3-cyclopentadione (0.1 M solution in 10 mL 2-methoxyethanol), afforded 83% (130.2 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.31 (m, 1H), 4.13-4.11 (m, 2H), 3.73-3.71 (m, 2H), 3.43 (s, 3H), 2.67-2.61 (m, 2H), 2.46-2.44 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.15, 190.24, 105.17, 71.12, 70.21, 59.37, 34.24, 28.63; **FT-IR**: 2964.77, 2251.33, 1738.96, 1590.97, 1345.35, 1189.58, 1126.01, 1039.62, 719.60, 649.78 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_8H_{12}O_3$ $(M+Na)^+$: 179.0684, found: 179.0692.

3,3-diethoxyindolin-2-one (2q) was synthesized by following the experimental procedure B, using isatin (0.1M solution in 10 mL ethanol), afforded 80% (177.2 mg) as a yellowish solid compound. **Melting point**: 69 ^{o}C – 72 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.40 (d, J = 7.6Hz, 1H), 7.29(td, J = 7.6Hz, 1.2Hz, 1H), 7.06 (td, J = 7.6 Hz, 0.8Hz, 1H), 3.98-3.90 (m, 2H), 3.84-3.77 (m, 2H), 1.24 (t, J = 7.2Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.22, 140.41, 130.64, 126.17, 125.32, 122.87, 110.76, 97.22, 59.04, 15.43; **FT-IR** (neat): 3198.45, 2978.91, 2922.69, 2309.47, 1727.33, 1615.39, 1466.95, 1259.02, 1054.35, 751.51, 659.57 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{12}H_{15}NO_3$ $(M+Na)^+$: 244.0950, found: 244.0956.

3,3-dipropoxyindolin-2-one (2r) was synthesized by following the experimental procedure B using isatin (0.1 M solution in 10 mL propanol), afforded 76% (211.9 mg) as a yellowish solid compound. **Melting point:** 79 ^{o}C- 83 ^{o}C; **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.36 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 3.77-3.72 (m, 2H), 3.65-3.61 (m, 2H), 1.62-1.53 (m, 4H), 0.91 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR** (100 MHz, MeOH-d_4) δ 175.02, 142.69, 131.67, 127.26, 126.29, 123.39, 111.66, 90.74, 65.88, 65.88, 24.09, 10.95; **FT-IR**: 2967.60, 2882.16, 2312.22, 1734.96, 1617.66, 1467.37, 1201.92, 1059.91, 757.02 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{14}H_{19}NO_3$ $(M+Na)^+$: 272.1263, found: 272.1266.

ethyl 3,3-dimethoxybutanoate (**2s**) was synthesized by 0.1 M solution of the ethyl acetoacetate (1 mmol in 10 mL methanol) was flown through the packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) at flow rate 0.3 mL / min, loaded with amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.3 bar pressure. The organic layer was concentrated under reduced pressure and the residue was subjected to column chromatography using *n*-hexane purification afforded 86% (151.5 mg) ethyl 3,3-dimethoxybutanoate compounds. **^{1}H NMR** (400 MHz, $CDCl_3$+CCl_4) δ 4.15 (q, *J* = 7.2 Hz, 2H), 3.21 (s, 6H), 2.64 (s, 2H), 1.45 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$+ CCl_4) δ 169.68, 99.99, 60.60, 48.53, 42.47, 22.00, 14.37; **FT-IR**: 2983.81, 2942.16, 2832.30, 1735.06, 1626.09, 1462.19, 1380.78, 1227.42, 1139.80, 1096.74, 931.19, 762.90, 649.42 cm^{-1} ; **HRMS** (ESI) m/z calculated for $C_8H_{16}O_4$ $(M+Na)^+$: 199.0946, found: 199.0948.

ethyl 3,3-dipropoxybutanoate (2t) was synthesized by 0.1 M solution of the ethyl acetoacetate (1 mmol in 10 mL propanol) was flown through the packed bed reactor (Omnifit®, 6.6 mm i.d. × 150.0 mm length) at flow rate 0.3 mL / min, loaded with amberlyst-15 up to 4 cm (628 mg, swollen up to 6 cm after passing solvent) of bed at room temperature at 1.3 bar pressure. The organic layer was concentrated under reduced pressure and the residue was subjected to column chromatography using *n*-hexane purification afforded 95% (220 mg) ethyl 3,3-dipropoxybutanoate compounds. **^{1}H NMR** (400 MHz, $CDCl_3$+CCl_4) δ 4.13 (q, *J* = 6.8Hz, 2H), 3.43-3.34 (m, 4H), 2.66 (s, 2H), 1.59-1.50 (m, 4H), 1.48 (s, 3H), 1.25 (t, *J* = 6.8 Hz, 3H), 0.9 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$+ CCl_4) δ 169.92, 99.54, 62.39, 60.46, 43.36, 23.28, 23.12, 14.41, 11.00; **FT-IR** : 2984.61, 2934.43, 1737.43, 1712.73, 1627.17, 1391.98, 1315.37,

1149.57, 1065.52, 915.12, 754.28 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{12}H_{24}O_2$ $(M+Na)^+$: 255.1572, found: 255.1579.

3-(but-2-yn-1-yloxy)cyclohex-2-en-1-one (2u) was synthesized by following the experimental procedure C, using 1,3-cyclohexadione (1 mmol) in 0.5 M solution of but-2-yn-1-ol in 1,4-dioxane, afforded 76% (121.1mg) as a yellowish solid compound. **Melting point:** 57 ^oC – 65 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.44 (s, 1H), 4.50 (q, *J* = 2.4Hz, 2H), 2.43 (t, *J* = 6Hz, 2H), 2.35 (t, *J* = 6.4Hz, 2H), 2.02-1.96 (m, 2H), 1.86 (dt, *J* = 2.8 Hz, 0.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.88, 176.79, 103.71, 85.36, 72.27, 57.03, 36.83, 28.97, 21.29, 3.86; **FT-IR**: 2954.22, 2313.21, 2240.62, 1731.10, 1650.10, 1603.87, 1358.40, 1222.68, 1180.52, 1069.84, 907.60, 762.26, 600.72 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{10}H_{12}O_2$ $(M+H)^+$: 165.0916, found: 165.0921.

3-(pent-3-yn-1-yloxy)cyclopent-2-en-1-one (2v) was synthesized by following the experimental procedure C, using 1,3-cyclopentadione (1 mmol) in 0.5 M solution of pent-3-yn-1-ol in 1,4-dioxane, afforded 64% (105.3 mg) as a yellowish solid compound. **Melting point :** 50 ^oC – 51 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.31 (m, 1H), 4.03 (t, *J* = 7.2 Hz, 2H), 2.65-2.62 (m, 2H), 2.46-2.43 (m, 2H), 1.79 (t, *J* = 2.8 Hz, 2H), 1.64 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.77, 176.23, 101.81, 70.22, 67.82, 59.30, 50.79, 42.79, 32.57, 28.36; **FT-IR**: 2927.29, 2243.55, 1702.41, 1591.31, 1439.77, 1347.61, 1184.29, 1059.36, 954.63, 705.52, 599.66 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{10}H_{12}O_2$ $(M+Na)^+$: 187.0735, found: 187.0739.

3-(pentan-3-yloxy)cyclohex-2-en-1-one (2w) was synthesized by following the experimental procedure C using 1,3-cyclohexadione (1 mmol) in 0.5 M solution of pentane-3-ol in 1,4-dioxane, afforded 65% (118.5 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.06-4.00 (m, 1H), 2.39 (t, *J* = 6.4Hz, 2H), 2.34 (t, *J* = 6Hz, 2H), 2.00-1.94 (m,2H), 1.66-1.59 (m,4H), 0.89 (t, J = 6Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.73, 177.86, 103.06, 80.94, 36.84, 29.58, 25.72, 21.35, 9.59; **FT-IR** (neat): 2959.92, 2311.92, 2170.72, 1729.73, 1650.26, 1607.76, 1463.70, 1376.35, 1228.08, 1136.64, 1041.23, 751.46, 659.57 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{11}H_{18}O_2$ $(M+Na)^+$: 205.1204, found: 205.1212.

3-(hexan-2-yloxy)-cyclopent-2-en-1-one (2x) was synthesized by following the experimental procedure C, using 1,3-cyclopentadione (1 mmol) in 0.5 M solution of hexan-2-ol in 1,4-

dioxane, afforded 61% (111.4 mg) as a yellowish liquid compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.25 (m, 1H), 4.27-4.19 (m, 1H), 2.60-2.57 (m, 2H), 2.43-2.41 (m, 2H), 1.73-1.52 (m, 4H), 1.31 (d, *J* = 6Hz, 5H), .90 (t, *J* = 6.8Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.47, 189.69, 104.72, 79.27, 35.66, 33.84, 29.13, 27.60, 22.65, 19.35, 14.12; **FT-IR** : 2934.77, 2824.34, 2234.22 1712.66, 1565.73, 1423.82, 1355.55, 1278.64, 1182.57, 745.23, 661.14 cm-1; **HRMS** (ESI) m/z calculated for $C_{11}H_{18}O_2$ $(M+Na)^+$: 205.1204; found: 205.1210.

5,5-dimethyl-3-(1-phenylethoxy)cyclohex-2-en-1-one (2y) was synthesized by following the experimental procedure C, using 5,5-dimethyl-1,3-cyclohexadione (1 mmol) in 0.5 M solution of 1-phenylethan-1-ol in 1,4-dioxane, afforded 64% (140 mg) as a yellowish oil compound. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.39-7.34 (m, 3H), 7.32-7.29 (m, 2H), 5.37 (q, *J* = 6.4 Hz,1H), 5.27 (s, 1H), 2.41 (dd, *J* = 27.6Hz, 17.6 Hz, 2H), 2.16 (dd, *J* = 25.6 Hz, 16.4 Hz, 2H), 1.59 (d, *J* = 6.4 Hz, 3H), 1.08 (s, 3H), 1.01 (s, 3H); **^{13}C NMR** (100 MHz, MeOH-d_4) δ 202.65, 178.32, 143.01, 129.84, 120.02, 126.40, 104.16, 78.37, 51.19, 44.01, 33.53, 28.41, 28.10, 24.19; **FT-IR**: 3022.63, 2964.80, 2313.47, 1725.35, 1601.88, 1457.35, 1216.51, 753.31, 667.96 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{14}H_{16}O_2$ $(M+H)^+$: 245.1542, found: 245.1544.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website

Copy of the NMR spectra for the synthesized products (PDF)

AUTHOR INFORMATION

Corresponding Author

*Email: gnanaprakasam@iiserpune.ac.in

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was supported by the SERB, (EMR/2014/000700), India. N.M. and M.B.C thanks IISER-Pune for a research fellowship.

REFERENCES

(1) (a) Wuts, P. G. M.; Green, T. W. Protective Groups in Organic Synthesis. John Wiley and Sons: New York, **2006.** (b) Kocienski, P. J. Protecting Groups; Thieme: Stuttgart, **2003**.

(2) (a) Demir, A. S.; Sesenoglu, O. A New and Efficient Chemoenzymatic Route to Both Enantiomers of 4-Hydroxycyclohex-2-en-1-one. *Org. Lett.* **2002,** *4,* 2021-2023. (b) Chen, X.; Martinez, J. S.; Mohr, J. T. Regiodivergent Halogenation of Vinylogous Esters: One-Pot, Transition-Metal-Free Access to Differentiated Haloresorcinols. *Org. Lett*. **2015**, *17*, 378−381. (c) Dai, W.; Katzenellenbogen, J. A. New Approaches to the Synthesis of Alkyl-Substituted Enol Lactone systems, Inhibitors of the Serine Protease Elastase. *J. Org. Chem*. **1993**, *58*, 1900-1908. (d) Wu, Y.; He, H.; Bertekap, R., Westphal, R.; Lelas, S.; Newton, A.; Wallace, T.; Taber, M.; Davis, C.; Macor, J. E.; Bronson, J. Discovery of Disubstituted Piperidines and Homopiperidines as Potent Dual NK1 Receptor Antagonists–Serotonin Reuptake Transporter Inhibitors for the Treatment of Depression. *Bioorg. Med. Chem.* **2013**, *21*, 2217-2228. (e) House, H. 0.; Rasmusson, G. H. Perhydroindanone Derivatives. I. Applicability of the Diels-Alder Reaction. *J. Org. Chem.* **1963**, *28,* 27-30.

(3) (a) Maity, S.; Sar, S.; Ghorai, P. Primary Aminothiourea-Catalyzed Enantioselective Synthesis of Rauhut–Currier Adducts of 3-Arylcyclohexenone with a Tethered Enone on the Aryl Moiety at the Ortho-Position. *Org. Lett*., **2018**, *20*, 1707−1711. (b) Zimmerman, H. E.;

Nesterov, E. E. An Experimental and Theoretical Study of the Type C Enone Rearrangement: Mechanistic and Exploratory Organic Photochemistry. *J. Am. Chem. Soc.* **2003**, *125*, 5422-5430. (c) Woods, G. F.; Reed, F. T. *m*-Diarylbenzenes. *J. Am. Chem. Soc.* **1949**, *71*, 1348-1350. (d) d'Augustin, M.; Palais, L.; Alexakis, A. Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers. *Angew. Chem. Int. Ed*., **2005**, *44*, 1376–1378.

(4) Fisk, J. S.; Tepe, J. J. Intermolecular Ene Reactions Utilizing Oxazolones and Enol Ethers. *J. Am. Chem. Soc.* **2007**, *129*, 3058-3059.

(5) (a) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions. *Chem. Rev*. **2016**, *116*, 9748−9815. (b) Kurdyumov, A. V.; Lin, N.; Hsung, R. P.; Gullickson, G. C. Cole, K. P.; Sydorenko, N.; Swidorski, J. J. A Lewis Acid-Catalyzed Formal [3 + 3] Cycloaddition of *α, β*-Unsaturated Aldehydes with 4-Hydroxy-2-Pyrone, Diketones, and Vinylogous Esters. *Org. Lett.* **2006**, *8*, 191–193.

(6) (a) Effenberger, F. The Chemistry of Enol Ether. *Angew. Chem. Int. Ed*. **1969**, *8*, 295-400. (b) Lin, M.-H.; Hung, S.-F.; Lin, L.-Z.; Tsai, W.-S.; Chuang, T.-H.; Tin Mediated Allylation Reactions of Enol Ethers in Water. *Org. Lett.* **2011**, *13*, 332-335. (c) Ondet, P.; Joffrin, A.; Diaf, I.; Lemière, G.; Duñach, E. Cycloisomerization of Allene–Enol Ethers under $Bi(OTf)_3$ Catalysis. *Org. Lett.* **2015**, *17,* 1002-1005. (d) Hart, D. J.; Bennett, C. E. Acid-Promoted Prins Cyclizations of Enol Ethers to Form Tetrahydropyrans. *Org. Lett.* **2003**, *5*, 1499-1502. (e) Johnson, T.; Pultar, F.; Menke, F.; Lautens, M. Palladium-Catalyzed α-Arylation of Vinylogous Esters for the Synthesis of γ,γ-Disubstituted Cyclohexenones. *Org. Lett.* **2016**, 18, 6488–6491.

(7) Badham, N. F. Homologation of ketones into carboxylic acids. *Tetrahedron* **2004**, *60,* 11–42.

(8) (a) Wang, H.-S.; Li, H.-J.; Wang, J.-L.; Wu, Y.C. Protecting-Group-Free Synthesis of Haterumadienone- and Puupehenone-Type Marine Natural Products. *Green Chem.* **2017**, *19*, 2140-2144. (b) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. The Catalytic Asymmetric Total Synthesis of Elatol. *J. Am. Chem. Soc*. **2008**, *130,* 810-811. (c) Nicolaou, K. C.; Stepan, A. F.; Lister, T.; Li, A.; Montero, A.; Tria, G. S.; Turner, C. I.; Tang, Y.; Wang, J.; Denton, R. M.; Edmonds, D. J. Design, Synthesis, and Biological Evaluation of Platensimycin Analogues with Varying Degrees of Molecular Complexity. *J. Am. Chem. Soc*. **2008**, *130,* 13110–13119. (d) Schuppe, A. W.; Huang, D.; Chen, Y.; Newhouse, T. R. Total Synthesis of (−)-Xylogranatopyridine B via a Palladium-Catalyzed Oxidative Stannylation of Enones. *J. Am. Chem. Soc.* **2018**, *140*, 2062−2066. (e) Bisai, A.; West, S. P.; Sarpong, R. Unified Strategy for the Synthesis of the "Miscellaneous" *Lycopodium* Alkaloids: Total Synthesis of (±)-Lyconadin A. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223 (f) Hou, W-Y.; Wu, Y-K. Palladium-Catalyzed α-Arylation of Cyclic Vinylogous Esters for the Synthesis of γ-Arylcyclohexenones and Total Synthesis of Aromatic Podocarpane Diterpenoids. *Org. Lett.* **2017**, *19*, 1220–1223.

(9) Leonard, S. E.; Reddie, K. G.; Carroll, K. S. Mining the Thiol Proteome for Sulfenic Acid Modifications Reveals New Targets for Oxidation in Cells. *ACS Chem. Biol*. **2009**, *4,* 783−799.

(10) (a) Börgardts, M.; Verlinden, K.; Neidhardt, M.; Wöhrle, T.; Herbst, A.; Laschat, S.; Janiakb, C.; Müller, T. J. J. Synthesis and Optical Properties of Covalently Bound Nile Red in Mesoporous Silica Hybrids – Comparison of Dye Distribution of Materials Prepared by Facile Grafting and by Co-condensation Routes. *RSC Adv.* **2016**, *6*, 6209–6222. (b) Jose, J.; Ueno, Y.; Castro, J. C.; Li, L.; Burgess, K. Energy transfer dyads based on Nile Red. *Tetrahedron Lett.*

2009, *50,* 6442–6445. (c) Pinkert, T.; Furkert, D.; Korte, T.; Herrmann, A.; Arenz, C. Amplification of a FRET Probe by Lipid–Water Partition for the Detection of Acid Sphingomyelinase in Live Cells. *Angew. Chem. Int. Ed*. **2017**, *56*, 2790 –2794.

(11) Synthesis of vinylogous esters: (a) Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F. Gold Catalysis in the Reactions of 1,3-Dicarbonyls With Nucleophiles. *Green Chem*. **2003**, *5*, 64–67. (b) Johnson, T.; Pultar, F.; Menke, F.; Lautens, M. Palladium-Catalyzed α-Arylation of Vinylogous Esters for the Synthesis of γ,γ-Disubstituted Cyclohexenones. *Org. Lett.* **2016**, *18,* 6488–6491. (c) Palframan, M. J.; Pattenden, G. The versatility of furfuryl alcohols and furanoxonium ions in synthesis. *Chem. Commun.* **2014**, *50*, 7223-7242. (d) Aggarwal, V. K.; Daly, A. M. Extension of ring closing metathesis methodology to the synthesis of carbocyclic methyl and silyl enol ethers. *Chem. Commun.* **2002**, *0*, 2490–2491. (e) Zirimwabagabo, J.-O.; Harrity, J. P. A. Pd-Catalyzed Kinetic Resolution of Cyclic Enol Ethers. An Enantioselective Route to Functionalised Pyrans. *Chem. Commun.* **2014**, *50*, 2735-2737. (f) Curini, M.; Epifanob, F.; Genovese, S. Ytterbium Triflate Catalyzed Synthesis of *β*-keto Enol Ethers. *Tetrahedron Lett.*, 2006, *47*, 4697–4700. (g) Das, B.; Laxminarayana, K.; Ravikanth, B. Application of Heterogeneous Catalysts for an Efficient Synthesis of *β*-Keto Enol Ethers. *J. Mol. Catal. A: Chem.* **2007**, *271*, 131–133. (h) Li, P.-H.; Li, B.-L.; Hu, H.-C.; Zhao, X.-N.; Zhang, Z.-H. Ionic liquid Supported on Magnetic Nanoparticles as Highly Efficient and Recyclable Catalyst for the Synthesis of *β*-Keto Enol Ethers. *Catal. Commun.* **2014**, *46*, 118–122. (i) Banerjee, B.; Mandal, S. K.; Roy, S. C. Cerium(IV) Ammonium Nitrate-catalyzed Synthesis of β-Keto Enol Ethers from Cyclic *β*-Diketones and Their Deprotection. *Chem. Lett.*, **2006**, *35*, 16-17. (j) Fuwa, H.; Sasaki, M. An Efficient Method for the Synthesis of Enol Ethers and Enecarbamates. Total Syntheses of Isoindolobenzazepine Alkaloids, Lennoxamine and Chilenine. *Org. Biomol. Chem.*,

2007, *5*, 1849–1853. (k) Chandrasekhar, S.; Rao, Y. S.; Reddy, N. R. $B(C_6F_5)_3$-Catalyzed Synthesis of β-Keto Enol Ethers from β-Diketones. *Synlett* **2005**, *9,* 1471-1473. (l) De, S.; Kinthada, L. K.; Bisai, A. Base-Promoted Michael Reaction Concomitant with Alkylation of Cyclic-1,3-diones, an Efficient Approach to 2-Substituted Vinylogous Esters. *Synlett* **2012**, *23*, 2785–2788. (m) Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. Formal Total Syntheses of Classic Natural Product Target Molecules via Palladium-Catalyzed Enantioselective Alkylation. *Beilstein J. Org. Chem.* **2014**, *10*, 2501–2512. (n) Fadel, S.; Hajbi, Y.; Rakib, E. M.; Khouili, M.; Pujol, M. D.; Guillaumet, G. Condensation of 2-Pyrone with 3-Aminopyrazolone. A Novel Synthesis of Pyrazolo[3,4-*b*]pyridines. *Synth. Commun*. **2004**, *34*, 2195-2204.

(12) Review for flow chemistry related work, see: (a) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016**, *116*, 10276–10341. (b) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892-4928; (c) McQuade, D. T.; Seeberger, P. H. Applying Flow Chemistry: Methods, Materials, and Multistep Synthesis. *J. Org. Chem.* **2013**, *78***,** 6384-6389. (c) Watts, P.; Haswell S. J. The Application of Micro Reactors For Organic Synthesis. *Chem. Soc. Rev.* **2005**, *34***,** 235-246. (d) Plutschack, M. B.; Pieber, B.; Gilmore, K. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017,** *117*, 11796–11893. (e) Wegner, J.; Ceylan, S.; Kirschning, A. Flow Chemistry – A Key Enabling Technology for (Multistep) Organic Synthesis *Adv. Synth. Catal.* **2012,** *354*, 17–57.

(13) Selected paper for hydrolysis of vinylogous esters: (a) Aoyama, H.; Tokunaga, M.; Hiraiwa, S-i.; Shirogane, Y.; Obora, Y.; Tsuji, Y. Hydrolysis of Alkenyl Esters and Ethers Catalyzed by Metal Complexes. *Org. Lett.* **2004**, *6*, 509-512. (b) Fife, T. H. Vinyl Ether Hydrolysis. The Facile General Acid Catalyzed Conversion of 2-Ethoxy-1-Cyclopentene-1-Carboxylic Acid to Cyclopentanone. *J. Am. Chem. Soc*. **1965,** *87,* 1084-1089. (c) Cheon, C. H.; Kanno, O.; Toste, F. D. Chiral Brønsted Acid from a Cationic Gold(I) Complex: Catalytic Enantioselective Protonation of Silyl Enol Ethers of Ketones. *J. Am. Chem. Soc.* **2011**, *133*, 13248–13251. (d) Kirby, A. J.; Williams, N. H. Efficient Intramolecular General Acid Catalysis of Enol Ether Hydrolysis. Hydrogen-bonding stabilisation of the transition state for Proton Transfer to Carbon. *J. Chem. Soc., Perkin Trans. 2*, **1994**, 0, 643-648; e) Lou, M.; Gilpin, M. E.; Burger, S. K.; Malik, A. M.; Gawuga, V.; Popović, V.; Capretta, A.; Berti, P. J. Transition State Analysis of Acid-Catalyzed Hydrolysis of an Enol Ether, Enolpyruvylshikimate 3-Phosphate (EPSP). *J. Am. Chem. Soc.* **2012**, 134, 12947-12957. (f) Noyce, D. S.; Pollack, R. M. Two Mechanisms for the Acid-Catalyzed Hydrolysis of Enol Acetates. *J. Am. Chem. Soc.* **1969**, 91, 119-124.

(14) Selected paper for transetherification: (a) Sahoo, P. K.; Gawali, S. S.; Gunanathan, C. Iron-Catalyzed Selective Etherification and Transetherification Reactions Using Alcohols. *ACS Omega* **2018,** *3,* 124−136. (b) Li, X.; Liu, B.; Xu, X.; Chmielewski, P. J. DDQ-Supported Alkoxylation of 2-Aza-21-carbaporphyrin and Noncatalyzed Transetherification of Its 3,21-Dialkoxy Derivatives. *J. Org. Chem.,* **2012**, 77, 8206–8219. (c) Kihara, N.; Kidoba, K. Dynamic Covalent Chemistry of the Nicholas Ether-Exchange Reaction. *Org. Lett.* **2009**, *11*, 1313–1316. (d) Thompson, D. S.; Markoski, L. J.; Moore, J. S.; Sendijarevic, I.; Lee, A.; McHugh, A. J. Synthesis and Characterization of Hyperbranched Aromatic Poly(ether imide)s with Varying

Degrees of Branching. *Macromolecules* **2000**, *33*, 6412–6415. (e) Zoltewicz, J. A.; Sale, A. A. Cleavage of Pyridyl Methyl Ethers and Reactions of 3-Halopyridines with Sodium Methoxide. *J. Org. Chem.* **1970**, *35*, 3462–3467. (f) Čorić, I.; Kim, J. H.; Vlaar, T.; Patil, M. W.; List, B. Brønsted Acid Catalyzed Asymmetric S_N2-Type O-Alkylations. *Angew. Chem. Int. Ed.* **2013**, *52*, 3490-3493. (h) Yang, L. Seshan, K. Li, Y. Transetherification of Guaiacol to O-ethoxyphenol with Gamma Al_2O_3 as a Catalyst in Supercritical Ethanol. *Catal. Commun.* **2013**, *30*, 36–39.

(15) Sampath, G.; Kannan, S. Fructose dehydration to 5-hydroxymethylfurfural: Remarkable solvent influence on recyclability of Amberlyst-15 Catalyst and Regeneration Studies. *Catal. Commun.* **2013**, *37*, 41–44.

(16) Findley, T. J. K.; Sucunza, D.; Miller, L. C.; Davies, D. T.; Procter, D. J. A Flexible, Stereoselective Approach to the Decorated cis-Hydrindane Skeleton: Synthesis of the ProposedStructu re of Faurinone. *Chem. Eur. J.* **2008**, *14*, 6862 – 6865

(17) Winkler, C. K.; Stueckler, C.; Mueller, N. J.; Pressnitz, D.; Faber, K. Asymmetric Synthesis of O-Protected Acyloins Using Enoate Reductases: Stereochemical Control through Protecting Group Modification. *Eur. J. Org. Chem.* **2010**, 6354–6358.

(18) Moriya, O.; Urata, Y.; Ikeda, Y.; Ueno, Y.; Endo, T. Synthesis of Tetrahydrofurans from Active Methylene Compounds via Radical Cyclization. *J. Org. Chem.* **1986**, *51*, 4708-4709.

(19) Toshio, K.; Masaru, S.; Itaru, K.; Makoto, W.; Oyo, M. Stereospecific and Stereoselective Reactions. V. Alkylation of Active Methylene Compounds by the Use of Alcohols, Diethyl Azodicarboxylate, and Triphenylphosphine. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 2107-2112.

(20) Theobald, D.W. The Reaction of Some Dibromocyclohexanediones with Bases. *Tetrahedron* **1978**, *34*, 1567-1569.

(21) Yoshino, T.; Ng, F.; Danishefsky, S. J. A Total Synthesis of Xestodecalactone A and Proof of Its Absolute Stereochemistry: Interesting Observations on Dienophilic Control with 1,3-Disubstituted Nonequivalent Allenes. *J. Am. Chem. Soc.* **2006**, *128*, 14185-14191.

(22) Frank, R. L.; Hall, H. K. Monocyclic Terpenes from Cyclic 1,3-Diketones. *J. Am. Chem. Soc.* **1950**, *72*, 1645-1648.