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ARTICLE

Reversible Chemoselective Transetherification of Vinylogous Ester Using Fe-Catalyst under Additive Free Condition

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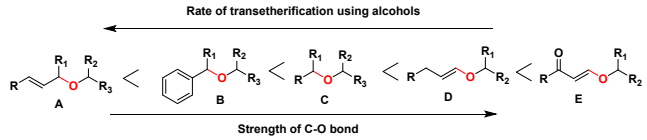
An additive/Bronsted acid/base free, highly efficient and chemoselective transetherification of electron deficient vinylogous esters and water mediated de-alkylation using earth-abundant Fe-catalyst under very mild reaction condition is described. This reaction is highly selective to primary alcohols over the secondary alcohols, well functional group tolerant, scalable to the gram and demonstrated a purification free sequential transetherification in continuous flow mode.

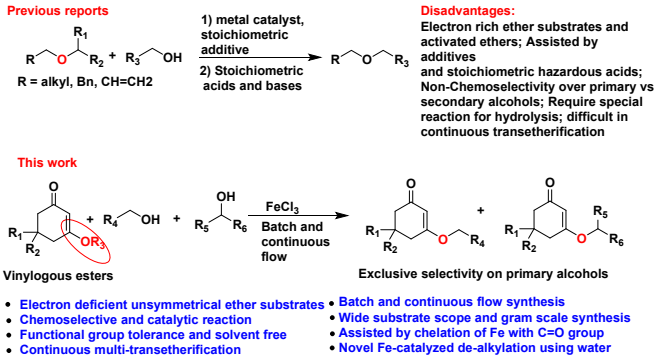
Introduction

Ethers are prevalent motifs in a various range of natural products, pharmaceuticals, agrochemicals, polymers, fragrances, and materials.[1] Traditionally, Williamson etherification employs stochiometric sodium alkoxide and alkyl halides to generate symmetrical and unsymmetrical ethers[2] involves few drawbacks; a requirement of stochiometric strong bases, generation of stoichiometric amount of inorganic waste, toxic and expensive genotoxic organohalides derived from alcohols, making the ether synthesis an eventual multistep process.[3] During the past decades, several approaches utilizing homogeneous catalysts such as Brønsted acid or Lewis acid were developed for the synthesis of ethers from diverse functional groups to avoid these shortcomings.[4] Nevertheless these methods have advantages, but suffers from poor atom economy, need of stochiometric additives, limited substrate scope, absence of chemoselectivity and a special stochiometric reagent for the hydrolysis/ethereal C-O bond cleavage. Alternatively, it has been synthesized *via* transetherification reactions by using a metal catalyst with additives and also promoted by a stoichiometric amount of bases and acids[5] which encompasses only electronically rich substrates having benzyl and allyl groups. In general, syntheses of ethers *via* transetherification reactions are reversible in nature; hence the excess amount of alcohol is used to shift the equilibrium in the forward direction in the presence of the catalyst. The relative strength of the C-O bond in various ethers and their reactivities towards various alcohols is shown in Scheme 1.

Ethers having allyl, benzyl and alkyl group facilitated the C-O bond dissociation *via* the resonance stabilization and thus



Scheme 1. Relative strength and ease of substitution on ethers



Scheme 2. State of art for the transetherification reaction

assisted easy substitution of the alkoxy group by the alcohols. On the other hand, this transformation was more difficult with electron deficient ethers such as vinylogous esters due to the conjugated C=O group which makes stronger alkenyl C-O bond. Hence, the activation of alkenyl C–O bond and concomitant substitution reaction by various nucleophile is one of the challenges in synthetic organic chemistry, where it is often used to form C-C and C-N bond in cross-coupling reactions.[6] Moreover, vinylogous esters are electron deficient ethers and become an attractive feedstock in several chemical transformations such as coupling reaction,[7] ene reactions,[8] photocycloaddition reaction,[9] and many other organic transformations.[10]

Development of metal catalyzed chemoselective transetherification is one of the challenges in synthetic

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[c] Electronic Supplementary Information (ESI) available: [copies of ^{1}H NMR and ^{13}C NMR]. See DOI: 10.1039/x0xx00000x

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methodology.[11] While transetherification of ethers having alkyl, allyl, and benzyl substituent were reported Scheme 2, the metal-catalyzed transetherification of electron deficient vinylogous ester and chemoselective transetherification were not studied in the literature.

Besides, continuous flow organic reactions are immensely attracted by synthetic chemist since it has several advantages over the conventional batch reactions that include improved safety, great efficiency, reproducibility, precise control of reaction conditions, and easy scale-up.[12] Furthermore, vinylogous esters are highly reversible in nature in the presence of the acid/catalyst, which requires shorter reaction time to avoid the exposure of the reaction mixture under prolonged acidic or catalytic reaction condition. Hence, continuous flow approach can overcome the existing problems associated with the transetherification reaction.

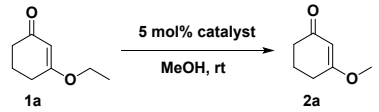
Herein, we report additive free, highly efficient and chemoselective transetherification of vinylogous ester using Fe-catalyst in the absence of stochiometric strong acids or bases. Advantages of this novel approach include easily and rapidly integrable into continuous flow mode, purification free continuous flow sequential transetherification and scalable in grams in short duration. In addition, a novel approach for the reversible reaction of this vinylogous ester and water-mediated de-alkylation under a very mild reaction condition is also demonstrated.

Results and discussion

To examine the optimal condition for transetherification of vinylogous ester, 3-ethoxycyclohex-2-en-1-one (**1a**) was used as a model substrate in the presence of catalytic amounts of various metals. The results are listed in table 1. In a controlled experiment, in the absence of a catalyst, no transetherification product **2a** was observed (Table 1, entry 1). A subsequent survey of the reaction by addition of 5 mol% of $RuCl_3.6H_2O$ and $[Ru(p\text{-cymene})Cl_2]_2$ catalysts significantly proceeded to yield **2a** in 95% and 93% yield respectively (Table 1, entries 2 and 3). However, this reaction was less efficient with Ru-complexes such as $Ru(bpy)_3Cl_2.6H_2O$ in acetonitrile (ACN) and Ru-MACHO (Table 1, entries 4-6). To identify an earth-abundant catalyst, this reaction was investigated with Mn, Fe, Co, Ni, and Cu-precursor. No reaction was notified while using Mn-salts such as $MnCl_2{\cdot}2H_2O$, $(CH_3COO)_3Mn{\cdot}2H_2O$ as a catalyst (Table 1, entries 9-10). Other transition metal salts *viz* Co, Ni, and Cu give a poor yield of **2a** (Table 1, entries 11-13). Interestingly, a best-optimized condition was obtained by 5 mol% $FeCl_3.6H_2O$ catalyst in methanol as a solvent to afford **2a** in 98% yield (Table 1, entry 12).

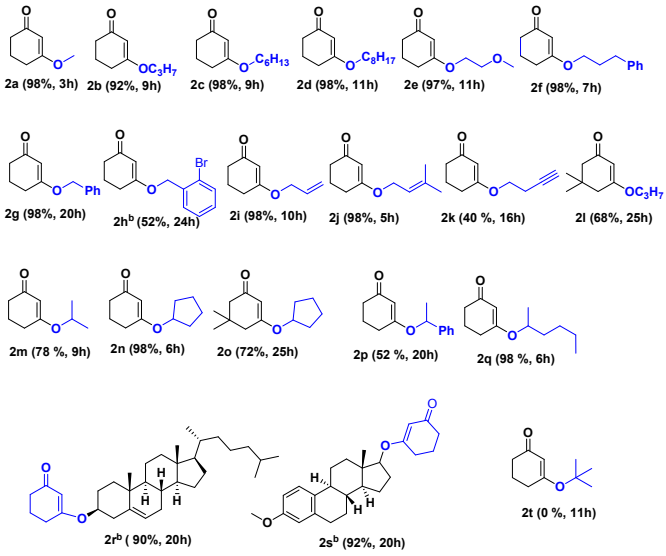
With the optimized conditions in hand, the substrate scope of this reaction was explored further by using a variety of vinylogous ester with various aliphatic or aromatic alcohols. Thus, the reaction of vinylogous ester **1a** with various aliphatic alcohols such as *n*-propanol, *n*-hexanol, and *n*-octanol in the presence of 5 mol% of $FeCl_3$ afforded the respective

Table 1. Optimization for transetherification reaction in batch[a]



entry	catalyst	MeOH	solvent	time (h)	yield (%)
1	-	10	-	21	-
2	$Ru(bpy)_3Cl_2.6H_2O$	10	ACN	21	40
3	$Ru(bpy)_3Cl_2.6H_2O$	excess	-	11	90
4	$RuCl_3.6H_2O$	excess	-	3	95
5	$[Ru(p\text{-cymene})Cl_2]_2$	excess	-	6	93
6	Ru-MACHO	excess	-	40	-
7	$FeCl_3.6H_2O$	excess	-	3	98
8	Fe-zeolite	excess	-	3	95
9	$(CH_3COO)_3Mn{\cdot}2H_2O$	excess	-	3	-
10	$MnCl_2{\cdot}2H_2O$	excess	-	3	-
11	$NiBr_2.2H_2O$	excess	-	3	30
12	$CuCl_2{\cdot}2H_2O$	excess	-	3	25
13	$CoCl_3{\cdot}2H_2O$	excess	-	3	40

[a]**Reaction condition**: **1a** (1 mmol), catalyst (5 mol%), and methanol (2 mL) were stirred at room temperature.



[a]**Reaction conditions:** Vinylogous ester (1 mmol), $FeCl_3.6H_2O$ (5 mol %), alcohols (2 mL), were stirred at room temperature. [b]vinylogous ester (1 mmol), alcohols (3 mmol), $FeCl_3.6H_2O$ (5 mol %), 1,2-dichloroethane (2 mL) were stirred at 80 °C for 20 h.

Scheme 3. Substrates scope under batch condition[a]

transetherification product **2b-d** in excellent yield (Scheme 3). Other substituted primary alcohols; 2-methoxy ethanol, 3-phenylpropan-1-ol, benzyl alcohol, and 2-bromo benzylalcohol were also reacted well with **1a** to afford the corresponding products **2e-h** in very good yield (Scheme 3). Interestingly, this reaction is well tolerant to olefin and alkyne functional groups; for example, allyl alcohol, 3-methylbut-2-en-1-ol, and but-3-yn-1-ol reacted smoothly to afford the transetherified products **2i** and **2j** in 98% except for **2k** (40%) (Scheme 3).

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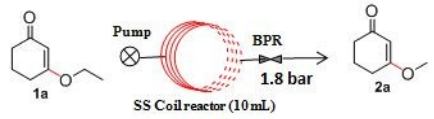
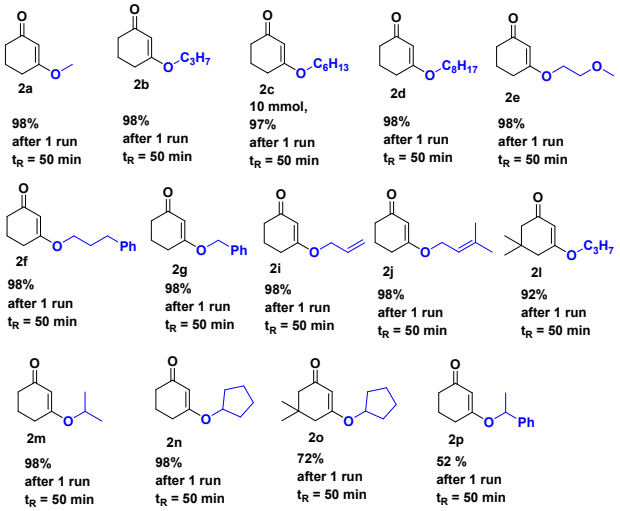
Substituted vinylogous ester, 3-ethoxy-5,5-dimethylcyclohex-2-en-1-one was also reacted well with the *n*-propanol to afford the product **2l** in 68% yield. Fascinatingly, this reaction was effective for sterically hindered secondary alcohols (iso-propyl alcohol, cyclopentanol, 1-phenylethanol, 2-hexanol, cholesterol, and esterol) to afford the corresponding products **2m-s** in good to excellent yield (Scheme 3). Unfortunately, sterically hindered tertiary butanol was incompatible in this reaction and did not generate the desired product **2t** (Scheme 3).

To examine our hypothesis in continuous-flow, a flow set up was assembled (Figure S1, ESI) by using the pump, coil reactor and BPR. Initial reactions of 0.1 M, 3-ethoxycyclohex-2-en-1-one (**1a**) with methanol in continuous flow at 60 °C without any catalyst were unsuccessful (Table 2, entry 1). However, flowing the reactants and 3 mol % $FeCl_3.6H_2O$ catalyst with 0.2 mL/min flow rate at room temperature providing 3-methoxycyclohex-2-en-1-one (**2a**) in 65% isolated yield (Table 2, entry 2). We continued to evaluate the effect of catalyst loading, temperature, and residence time (Table 2).

Table 2. Optimization in a continuous flow



entry	$FeCl_3.6H_2O$ (mol%)	temp. (°C)	Flow rate (mL/min.)	t_R (min.)	yield (%)
1	-	60	0.2	50	-
2	3	rt	0.2	50	65
3	3	60	0.2	50	82
4	3	80	0.2	50	85
5	5	60	0.2	50	92
6	5	80	0.2	50	98
7	5	100	0.2	50	98



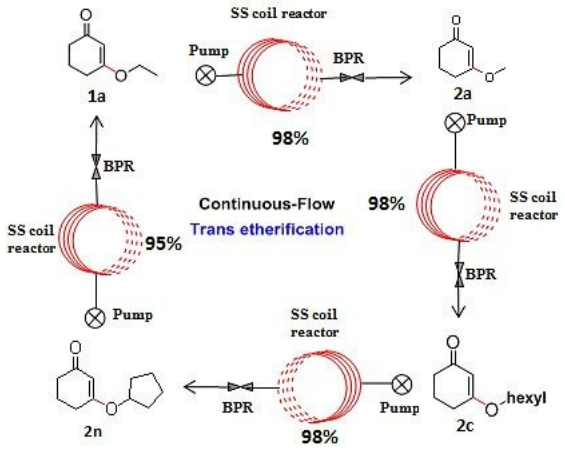
Reaction conditions: [a]All reactions were run on a 0.1 M scale in 10 mL of alcohol using 5 mol% of $FeCl_3.6H_2O$ catalyst at 80 °C and maintained at a pressure of 1.2 bar using a BPR.

Scheme 4. Substrates scope under continuous flow [a]

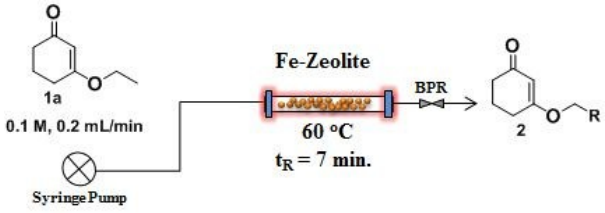
Increasing both the catalyst loading (5 mol %) and temperature (80 °C) with residence time 50 minutes resulted in the best yield of **2a** around 98% (Table 2, entry 6). There was no improvement in the yield of the reaction while increasing the temperature to 100 °C (Table 2, entry 7).

With optimized conditions in hand, we set out to investigate a range of substrates in a continuous flow and the results are shown in Scheme 4. The yields were generall comparable to the batch reaction, but reactions are completed in a shorter duration of time (Scheme 4). A slight decrease in yield of **2o** and **2p** was observed when the reaction was carried out with cyclopentanol and 1-phenylethanol. To demonstrate gram scale synthetic utility of this strategy, we also conducted in 10 mmol scales transetherification reaction with hexanol, which provided **2c** in 1.9 g (97 %).

Subsequently, a sequential transetherification of vinylogous ester was investigated under continuous flow condition (Scheme 5). Hence, the vinylogous ester **1a** and $FeCl_3$ in methanol were flown (0.2 mL/min) into the coil reactor at 80 °C afforded the product **2a** in 98% yield. The product **2a** in hexanol was further flown into the SS coil reactor to afford the **2c** in 98% yield. Further, the product **2c** was continuously transformed into **2n** and subsequently, the product **2n** was transformed into **1a** in excellent yield under continuous transetherification condition. In addition, the catalyst recyclability for this transformation was demonstrated by flowing the vinylogous ester **1a** in methanol to the column packed with Fe-supported on zeolite[13] using syringe addition pump and heated at 60 °C to afford the product **2a** in 99% yield with residence time t_R = 7 min. (Scheme 6).



Scheme 5. Sequential transetherification under continuous flow



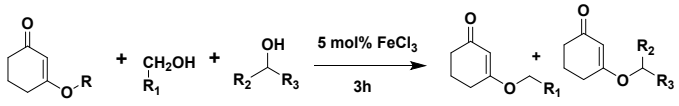
Scheme 6. Recyclable Fe-Zeolite catalyzed transetherification under continuous flow mode

To study the chemoselectivity of alcohols, we have investigated intermolecular transetherification of vinylogous ester using primary and secondary alcohols (Table 3). Thus, an equivalent amount of methanol and IPA was reacted with vinylogous ester **1a** in the presence of 5 mol% of $FeCl_3$ afforded the products **2b** and **2e** in the ratio 75:25% (Table 3, entry 1). Interestingly, selectivity was increased to 95:5% in case of MeOH/1-phenylethanol mixture (Table 3, entry 2). Excellent selectivity (100%) and exclusive reactivity of the primary alcohols was observed while using diphenylmethanol, bis(4-methoxyphenyl)methanol and phenyl(3-(trifluoromethyl)phenyl)methanol (Table 3, entries 3-5). Similarly, higher selectivity (90:10) with the aliphatic and less substituted methanol was observed (Table 3, entry 6).

To probe the ether cleavage, Fe-catalysed water-mediated hydrolysis of vinylogous ester was investigated (Scheme 7). A solution of vinylogous ester **1a** and $FeCl_3$ in water was allowed to stir at room temperature for 5-12 hrs results in complete deprotection of vinylogous ester to cyclohexane-1,3-dione (Scheme 7). Under similar reaction condition other vinylogous esters **2c**, **2i**, **2o**, **2p,** and **2q** were easily hydrolyzed to respective 1,3-diketone in >99% conversion using 5 mol % $FeCl_3$ under a very mild and environmentally benign condition in 5-12 hrs.

Next, we have explored the synthetic application of the vinylogous ester (Scheme 8). Thus, the vinylogous ester **2a** was reacted I_2 in methanol at 60 °C to afford the corresponding 1,3-dimethoxy benzene **3** in 85% yield.

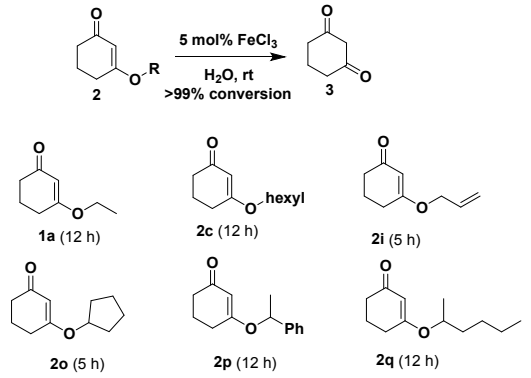
Table 3. Chemoselective transetherification



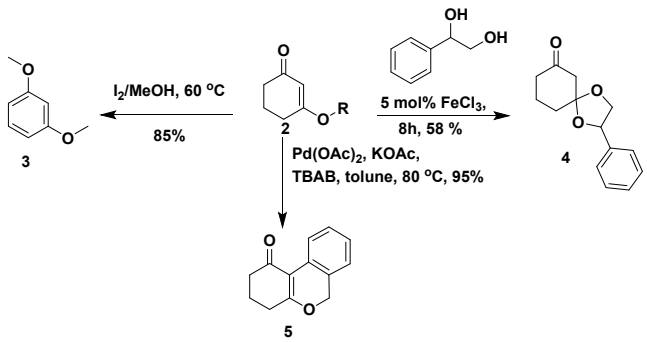
entry	vinylog-ous ester	primary alcohol	secondary alcohols	Selectivity based on GC-MS and ^{1}H-NMR
1	**1a**	methanol	IPA	75:25
2	**1a**	methanol	1-phenylethanol	95:5
3	**1a**	methanol	diphenylmethanol	100:0
4	**1a**	*n*-propanol	bis(4-methoxyphenyl)methanol	100:0
5	**1a**	*n*-hexanol	phenyl(3-(trifluoromethyl)phenyl)methanol	100:0
6	**1a**	methanol:benzyl alcohol	-	90:10

Interestingly, the reaction of vinylogous ester **2a** and 1-phenylethane-1,2-diol afforded the spiro product 2-phenyl-1,4-dioxaspiro[4.5]decan-7-one **4** in 58% yield *via* tandem transetherification and 1,4-addition with a conjugated ketone. Furthermore, the vinylogous ester **2h** was easily converted into 2,3,4,6-tetrahydro-1H-benzo[c]chromen-1-one **5** *via* Pd-catalysed intramolecular Heck reaction (95%).[7c]

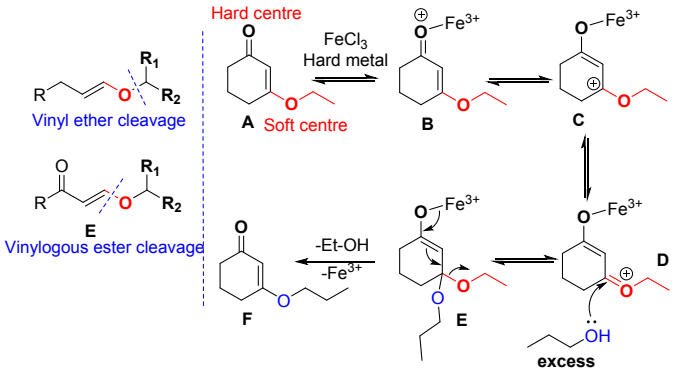
The mechanism for the Fe-catalysed transetherification of a vinylogous ester is proposed in Scheme 9. Vinyl ether is known to cleave a C-O bond in the presence of the metal catalyst or acid. In contrast to this, vinylogous ester C-O bond



Scheme 7. Fe-catalysed hydrolysis of the vinylogous ester



Scheme 8. Synthetic utility of vinylogous esters



Scheme 9. Plausible mechanism for transetherification

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cleavage proceeds as shown in Scheme 9 due to the activation of the hard C=O center which is in conjugation with the vinyl ethers. Initially hard Fe^{3+} coordinate to the hard C=O centre of the cyclic vinylogous ester **A** to form the intermediate **B**. The intermediate **B** is resonance stabilized to generate the intermediates **C** and **D**. Further, an addition of alcohol to the oxonium intermediate **D** to afford the ketal intermediate **E**. Finally, the keto-enol tautomerism assisted elimination of ethanol from the intermediate **E** to form the transetherified product **F**.

Experimental

General information and data collection:

Materials and methods: All the chemicals are purchased Sigma Aldrich or Alfa-Aesar. Deuterated solvents were used as received. All the solvents used were dry grade and stored over 4 Å molecular sieves. Column chromatographic separations performed over 100–200 Silica-gel. Visualization was accomplished with UV light and PMA, CAM stain followed by heating. The iron (III) chloride (product number: 44939) was purchased from Sigma Aldrich. All the experiments were carried out without maintaining the inert condition. The flow chemistry experiments were carried on Vaportec R-series. 1H and 13C 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 recorded with Waters-synapt G2 using electrospray ionization (ESI-TOF). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-E Fourier transform infrared spectrometer.

General procedure for the transetherification of enol ether in Batch reaction (2a-2p):

Vinylogous ester (1mmol), $FeCl_3.6H_20$ (5 mol%) and 2 mL of alcohol was added to a 10 mL round bottom flask with a magnetic bar and stirred at room temperature (25 ^{0}C) in open air for respective time (Scheme 2, main manuscript). After completion of the reaction, alcohol was removed using a vacuum and the crude reaction mixture was purified by column chromatography affording the pure transetherification product.

General procedure for the transetherification of compounds 2h, 2r and 2s in batch reaction:

Vinylogous ester (1 mmol), $FeCl_3.6H_20$ (5 mol%) was added to a solution of alcohols (1mmol) in Dichloroethane (10 mL). The solution was heated at 80 °C for 20 h. The reaction was allowed to cool to room temperature. The solvent was removed using a vacuum and the crude reaction mixture was purified by column chromatography on silica gel with eluent afforded respective products.

General procedure for the transetherification of enolether in a continuous flow:

Transetherification reactions were performed in a Vapourtec R-series continuous flow system equipped with high-temperature SS coil reactor (10 mL, stainless steel, 1.00 mm i.d.). 0.1 M solution of vinylogous ester in different alcohols is passed through tube reactors at 0.2 mL/min. flow rate, 1.8 bar pressure and at 80 °C. After completion of the reaction, alcohol was removed using vacuum pressure and the crude reaction mixture was purified by column chromatography to afford the pure transetherification product.

General procedure for Iodine catalyzed aromatization of vinylogous ester (3)

To a solution of compound 1a (1 mmol, 0.140 g) in methanol, Iodine 0.508g (2 equiv.) was added and the resulting mixture was stirred at 60 °C temperature for 2 hrs. Once TLC confirms complete consumption of the starting material, the reaction mixture was quenched with cold sodium thiosulfate and extracted with ethyl acetate. The organic layer was evaporated and purified through column chromatography (10-90% EtOAc in hexane) to obtain the desired compounds 3.

Representative procedure for coupling reactions: synthesis of 2,3,4,6-tetrahydro-1H-benzo[c]chromen-1-one (5):

3-((2-bromobenzyl)oxy)cyclohex-2-en-1-one (280 mg, 1 equiv.), TBAB (1 equiv.), KOAc (2.5 equiv.), $Pd(OAc)_2$ (0.02 equiv.) and toluene (7 mL) were added in sequence to a Schlenk tube and stirred under N_2 at 130 °C. After 3.5 h, water (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (2 ×10 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried and the solvents evaporated. The crude material obtained was purified by column chromatography (silica, 1:1 hexane/EtOAc) to afford the product 5 in 95% yield.

Fe catalyzed the hydrolysis of vinylogous esters:

To a solution of vinylogous ester in water, $FeCl_3.6H_20$ (5 mol %) was added and the reaction mixture was stirred at room temperature for respective time (Scheme 7, main manuscript). After completion, the reaction mixture was diluted with ethyl acetate and extracted 3 times with ethyl acetate. Organic layers were dried on sodium sulfate and concentrated in vacuum affording quantitative yields of 1, 3-diketone.

Analytical data for the product:

3-methoxycyclohex-2-en-1-one (2a): Yellowish oil (Batch-0.123 g, 98%; Continuous flow-0.123 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 3.68 (s, 3H), 2.40 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.01 – 1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 178.9, 102.4, 55.7, 36.8, 28.9, 21.4. FTIR (neat): 2952.28, 2311.97, 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 $C_7H_{11}O_2$ $(M+H)^+$: 127.0759, found: 127.0762

3-propoxycyclohex-2-en-1-one (2b): Yellowish oil (Batch-0.141 g, 92%; Continuous flow-0.150 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.78 (t, *J* = 6.5 Hz, 2H), 2.40 (t, *J* =

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6.4 Hz, 2H), 2.34 (t, *J* = 6.0 Hz, 2H), 2.03 – 1.92 (m, 2H), 1.80-1.68 (m, 2H), 0.98 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (s), 178.3, 102.8, 77.5, 76.8, 70.1, 36.9, 29.2, 22.0, 21.4, 10.5. FTIR: 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 $C_9H_{15}O_2$ $(M+H)^+$: 155.1072, found: 155.1078.

3-(hexyloxy)cyclohex-2-en-1-one (2c): Yellowish oil (Batch-0.192 g, 98%; Continuous flow-0.950 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.81 (t, *J* = 6.8 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.01 – 1.93 (m, 2H), 1.71 (p, *J* = 6.7 Hz, 3H), 1.43-1.36 (m, 2H), 1.13-1.28 (m, 2), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 178.3, 102.8, 68.7, 36.9, 31.6, 29.2, 28.6, 25.7, 22.7, 21.4, 14.1. FTIR: 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 $C_{12}H_{21}O_2$ $(M+H)^+$: 197.1463, found: 197.1469.

3-(octyloxy)cyclohex-2-en-1-one (2d): Yellowish oil (Batch-0.219 g, 98%; Continuous flow-0.219 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.81 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.0 Hz, 2H), 2.01 – 1.93 (m, 2H), 1.77 – 1.65 (m, 3H), 1.33 – 1.26 (m, 9H), 0.89 (t, *J* = 6.8 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 178.3, 102.8, 68.8, 36.9, 31.9, 29.4, 29.3, 29.1, 28.7, 26.1, 22.8, 21.4, 14.2. FTIR (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 $C_{14}H_{25}O_2$ $(M+H)^+$: 225.1854, found: 225.1861.

3-(2-methoxyethoxy)cyclohex-2-en-1-one (2e): Yellowish oil (Batch- 0.164 g, 97%; Continuous flow-0.166 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.99 – 3.94 (dt, *J* = 8.8 Hz, 1.6 Hz, 2H), 3.72 – 3.66 (dt, *J* = 9.5 Hz, 2 Hz, 2H), 3.42 (s, 3H), 2.45 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.02 – 1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.9, 103.1, 70.3, 67.8, 59.3, 36.8, 29.1, 21.3. FTIR (neat): 3023.28, 2401.97, 1730.21, 1602.11, 1464.39, 1217.26, 1188.16, 1001.03 cm^{-1}.HRMS (ESI) m/z calculated for $C_9H_{15}O_3$ $(M+H)^+$: 171.1021, found:171.1031.

3-(3-phenylpropoxy)cyclohex-2-en-1-one (2f): Yellowish oil (Batch- 0.225 g, 98%; Continuous flow-0.225 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.15 (m, 3H), 5.32 (s, 1H), 3.83 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.0 Hz, 2H), 2.09 – 2.03 (m, 2H), 2.02 – 1.94 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 178.1, 141.0, 128.6, 128.5, 126.3, 102.9, 67.7, 36.9, 32.2, 30.2, 29.1, 21.4. FTIR: 3023.67, 2847.54, 2875.98, 2365.45, 1723.13, 1663.91, 1547.80, 1379.97, 1221.50, 1198.80cm^{-1}. HRMS (ESI) m/z calculated for $C_{15}H_{19}O_2$ $(M+H)^+$: 231.1385, found:231.1387.

3-(benzyloxy)cyclohex-2-en-1-one (2g): Yellowish oil (Batch-0.197 g, 98%; Continuous flow-0.197 g, 98%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 5H), 5.48 (s, 1H), 4.89 (s, 2H), 2.47 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 6.4 Hz, 2H), 2.05 – 1.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.7, 135.1, 128.8, 128.7, 128.0, 103.5, 70.5, 36.9, 29.2, 21.3. FTIR: 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 $C_{13}H_{15}O_2$ $(M+H)^+$: 203.1072, found: 203.1079.

3-((2-bromobenzyl)oxy)cyclohex-2-en-1-one (2h): Yellowish oil (Batch- 0.146 g, 52%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.22 (td, *J* = 7.9, 1.8 Hz, 1H), 5.50 (s, 1H), 4.97 (s, 2H), 2.51 (t, *J* = 6.3 Hz, 2H), 2.43 – 2.35 (m, 2H), 2.08 – 2.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 177.3, 134.5, 133.1, 130.1, 129.4, 127.8, 103.8, 69.9, 36.9, 29.0, 21.4. FTIR: 3056.27, 3016.68, 2984.66, 2298.97, 1731.92, 1643.92, 1594.96, 1401.18, 1270.41, 1216.91, 1179.39 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{14}BrO_2$ $(M+H)^+$: 281.0177, found: 281.0177.

3-(allyloxy)cyclohex-2-en-1-one (2i): Yellowish oil (Batch-0.149 g, 98%; Continuous flow-0.149 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 – 5.90 (m, 1H), 5.36 (qt, *J* = 1.5, 1.4 Hz, 1H), 5.36 (s, 2H), 5.30 (ddd, *J* = 10.5, 2.4, 1.3 Hz, 2H), 4.37 (dt, *J* = 5.6, 1.3 Hz, 2H), 2.43 (t, *J* = 6.3 Hz, 2H), 2.34 (dd, *J* = 7.3, 6.0 Hz, 2H), 1.98 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.6, 131.5, 119.1, 103.3, 69.2, 36.9, 29.1, 21.3. FTIR: 3016.17, 2981.44, 2316.54, 1716.45, 1640.31, 1555.80, 1463.91, 1366.11, 1218.94, 1140.12 cm^{-1}. HRMS (ESI) m/z calculated for $C_9H_{13}O_2$ $(M+H)^+$: 153.0915, found:153.0916.

3-((3-methylbut-2-en-1-yl)oxy)cyclohex-2-en-1-one (2j): Yellowish oil (Batch- 0.176 g, 98%; Continuous flow-0.176 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41-5.38 (m, 1H)5.38 (s, 1H), 4.37 (d, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 6.4 Hz, 2H), 2.35 (t, *J* = 6.4 Hz, 2H), 1.98 (dd, *J* = 13.0, 6.5 Hz, 2H), 1.78 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 178.1, 139.7, 118.0, 103.1, 65.6, 36.9, 29.3, 25.9, 21.4, 18.3. FTIR (neat): 2953.38, 2311.97, 1720.17, 1601.11, 1553.93, 1380.22, 1242.55, 1173.79 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{17}O_2$ $(M+H)^+$: 181.1228, found:181.1236.

3-(but-3-yn-1-yloxy)cyclohex-2-en-1-one (2k): Yellowish oil (Batch- 0.065 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.94 (t, *J* = 6.7 Hz, 2H), 2.63 (td, *J* = 6.7, 2.7 Hz, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 1.98 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.5, 103.1, 79.7, 70.4, 66.3, 36.8, 28.9, 21.3, 19.1. FTIR (neat): 2929.90, 2862.30, 2314.45, 2140.17, 1722.50, 1600.35, 1561.24, 1237.15, 1184.78, 1090.23 cm^{-1}. HRMS (ESI) m/z calculated for $C_{10}H_{13}O_2$ $(M+H)^+$: 165.0915, found:165.0727.

5,5-dimethyl-3-propoxycyclohex-2-en-1-one (2l): Yellowish oil (Batch- 0.123 g, 68%; Continuous flow-0.167 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.79 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 2H), 2.20 (s, 2H), 1.81 – 1.70 (m, 2H), 1.07 (s, 6H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 176.5, 101.6, 70.2, 50.9, 43.0, 32.6, 28.4, 22.0, 10.5. FTIR: 2959.17, 2881.44, 2310.50, 1722.54, 1598.80, 1463.91, 1367.11, 1218.58, 1147.97 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{19}O_2$ $(M+H)^+$: 183.1385, found: 183.1392.

3-isopropoxycyclohex-2-en-1-one (2m): Yellowish oil Yellowish oil (Batch- 0.120 g, 78%; Continuous flow-0.150 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.43 (dt, *J* = 12.2, 5.9 Hz, 1H), 2.40-2.31 (m, 4H), 2.01 -1.92 (m, 2H), 1.30 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 177.0, 103.1, 70.1, 36.8, 29.6, 21.5, 21.3. FTIR (neat): 2978.67, 2310.65, 1730.60, 1641.95, 1595.51, 1461.11, 1230.90, 1187.26, 1000.27, 757.95,

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608.98 cm^{-1}. HRMS (ESI) m/z calculated for $C_9H_{15}O_2$ $(M+H)^+$: 155.1072, found:155.1078.

3-(cyclopentyloxy)cyclohex-2-en-1-one (2n): Yellowish oil (Batch- 0.176 g, 98%; Continuous flow-0.176 g, 98%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.64 – 4.57 (m, 1H), 2.34 (dd, *J* = 12.5, 6.3 Hz, 4H), 1.95 (dt, *J* = 9.0, 6.5 Hz, 2H), 1.90 – 1.82 (m, 2H), 1.82 – 1.77 (m, 2H), 1.76-1.71 (m, 2H), 1.65 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 177.3, 103.8, 80.7, 36.8, 32.8, 29.5, 24.2, 21.4. FTIR: 2995.15, 2910.56, 2344.50, 1734.64, 1599.78, 1499.91, 1304.68, 1211.78, 1122.97 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{17}O_2$ $(M+H)^+$: 181.1228, found:181.1225.

3-(cyclopentyloxy)-5,5-dimethylcyclohex-2-en-1-one (2o): Yellowish oil (Batch- 0.149 g, 72%; Continuous flow-0.149 g, 72%).^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.60 (m, 1H), 2.21 (s, 2H), 2.19 (s, 2H), 1.90 – 1.56 (m, 8H), 1.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 175.5, 102.6, 80.7, 50.8, 43.3, 32.8, 32.60, 28.4, 24.2. FTIR: 3012.15, 2988.66, 2388.57, 1712.54, 1488.98, 1412.81, 1356.12, 1226.88, 1182.27 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{21}O_2$ $(M+H)^+$: 209.1524, found:209.1545.

3-(1-phenylethoxy)cyclohex-2-en-1-one (2p): Yellowish oil (Batch- 0.112 g, 52%; Continuous flow-0.112 g, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.29 – 7.23 (m, 3H), 5.26 (s, 1H), 5.19 (q, *J* = 6.4 Hz, 1H), 2.46-2.41 (m, 2H), 2.30-2.24 (m, 2H), 1.98-1.89 (m, 2H), 1.56 (d, *J* = 6.4 Hz, 2H), 0.91 – 0.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 176.7, 141.4, 128.9, 128.2, 125.5, 104.7, 76.8, 36.8, 29.5, 23.8, 21.3. FTIR: 3029.14, 2947.04, 2947.04, 2881.89, 2315.54, 1724.79, 1658.08, 1587.17, 1449.34, 1266.11, 1199.44 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{17}O_2$ $(M+H)^+$: 217.1228, found:217.1227.

3-(hexan-2-yloxy)cyclohex-2-en-1-one (2q): Colourless oil (Batch- 0.193 g, 92 %). ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 4.23 (h, *J* = 6.2 Hz, 1H), 2.36 – 2.29 (m, 4H), 1.99 – 1.89 (m, 2H), 1.69-1.61 (m, 1H), 1.55 – 1.42 (m, 1H), 1.34 – 1.24 (m, 4H), 1.21 (s, 2H), 0.87 (t, *J* = 7.0 Hz, 3H). ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 4.23 (h, *J* = 6.2 Hz, 1H), 2.37-2.28 (m, 4H), 1.99 - 1.90 (m, 2H), 1.69 - 1.60 (m 1H), 1.55 - 1.43 (m, 1H), 1.34-1.24 (m, 4H), 1.22 (d, *J* = 2.4 Hz, 2H), 0.90-0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 177.3, 102.9, 74.8, 36.8, 35.6, 29.5, 27.5, 22.6, 21.3, 19.2, 14.1. FTIR (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 $C_{12}H_{21}O_2$ $(M+H)^+$: 197.1541, found:197.1549.

3-(((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[α]phenanthren-3-yl)oxy)-5,5-dimethylcyclohex-2-en-1-one (2r): White solid (Batch- 0.349 g, 92 %). ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (m, 2H), 4.07-3.46 (m, 1H), 2.40 – 2.31 (m, 3H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.93- 0.90 (m, 3H), 0.87 (d, *J* = 1.2 Hz, 3H), 0.85 (d, *J* = 1.2 Hz, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 176.9, 140.9, 139.3, 123.3, 121.8, 103.2, 77.8, 71.9, 56.9, 56.8, 56.3, 56.3, 50.3, 50.2, 42. 5, 39.9, 39.8, 39.7, 37.9, 37.4, 37.0, 36.8, 36.6, 36.3, 35.9, 32.0, 31.9, 31.8, 29.8, 29.7, 28.4, 28.1, 27.6, 24.4, 23.9, 22.9, 22.7, 21.3, 21.2, 21.1, 19.6, 19.5, 18.9, 12.0. FTIR (neat): 3023.79, 2954.91, 2852.40, 2387.87, 1718.30, 1629.40, 1593.84, 1524.58, 1467.16, 1429.53, 1378.29, 1328.47 1001.03, 758.03, 597.32 cm^{-1}. HRMS (ESI) m/z calculated for $C_{33}H_{52}O_2$ $(M+H)^+$: 480.3967, found: 480.3967.

3-(((8R,9S,13S,14S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[α]phenanthren-17-yl)oxy)cyclohex-2-en-1-one (2s): White solid (Batch- 0.349 g, 92 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 5.37 (s, 1H), 4.09 (dd, *J* = 8.7, 7.2 Hz, 1H), 3.78 (s, 3H), 2.91 – 2.82 (m, 2H), 2.39 (dd, *J* = 6.2, 3.0 Hz, 2H), 2.34 (dd, *J* = 7.4, 5.8 Hz, 2H), 2.03 – 1.93 (m, 3H), 0.88 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 178.1, 157.6, 138.0, 132.5, 126.5, 113.96, 111. 7, 103.8, 55.4, 49.8, 43.9, 43.7, 38.6, 37.5, 36.9, 29.9, 29.4, 17.9, 26.4, 23.7, 21.4, 12.3. . FTIR (neat): 3016.59, 2966.53, 2874.26, 2437.37, 2378.87, 1724.53, 1629.40, 1593.84, 1524.58, 1467.16, 1429.53, 1378.29, 1328.74, 1101.03 cm^{-1}. HRMS (ESI) m/z calculated for $C_{25}H_{33}O_3$ $(M+H)^+$: 381.2429, found: 381.2430.

1,3-dimethoxybenzene (3): Colourless liquid (0.117 g, 85%) ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.2 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.48 (t, *J* = 2.4 Hz, 1H), 3.80 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 130.0, 106.2, 100.6, 77.5, 76.8, 55.4. FTIR: 3095.15, 2910.56, 1599.78, 1554.91, 1304.68, 1211.78, 1122.97 cm^{-1}. HRMS (ESI) m/z calculated for $C_8H_{11}O_2$ $(M+H)^+$: 139.0761, found: 139.0761.

2-phenyl-1,4-dioxaspiro[4.5]decan-7-one (4): Colourless liquid (0.134 g, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.09 (ddd, *J* = 10.9, 8.2, 6.1 Hz, 1H), 4.32 (ddd, *J* = 10.2, 8.3, 6.1 Hz, 1H), 3.72 (td, *J* = 8.3, 2.9 Hz, 1H), 2.77 (dd, *J* = 23.2, 14.2 Hz, 2H), 2.37 (t, *J* = 6.7 Hz, 2H), 2.15-2.01 (m, 2H), 2.00-1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5 (d, *J* = 8.4 Hz), 138.4 (s), 138.1 (s), 128.7 (d, *J* = 4.3 Hz), 128.4 (d, *J* = 3.4 Hz), 126.3 (d, *J* = 2.5 Hz), 111.1 (s), 78.32 (d, *J* = 29.4 Hz), 71.8 (d, *J* = 4.3 Hz), 52.6 (s), 52.1 (s), 40.4 (s), 35.2 (s), 34.6 (s), 20.2 (d, *J* = 11.5 Hz). FTIR: 3023.79, 2962.12, 2873.22, 2312.25, 1711.09, 2594.96, 1465.21 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{17}O_3$ $(M+H)^+$: 233.3070, found: 233.3075.

2,3,4,6-tetrahydro-1H-benzo[c]chromen-1-one (5): Yellow solid (0.190 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.20 (td, *J* = 7.5, 1.2 Hz, 1H), 7.02 (dd, *J* = 7.5, 0.7 Hz, 1H), 5.12 (s, 2H), 2.59 -2.51 (m, 4H), 2.00 (dt, *J* = 12.6, 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 174.1, 128.7, 127. 9, 127.0, 124.9, 123.8, 113.2, 69.6, 38.4, 29.0, 20.2. FTIR: 3329.14, 2947.04, 2947.04, 2881.89, 2315.54, 1664.08 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{13}O_2$ $(M+H)^+$: 201.0915, found:201.0919.

Conclusions

In conclusion, we have developed a novel, highly efficient and chemoselective catalytic method for transetherification of a variety of vinylogous ester with various primary and secondary alcohols to afford the substituted vinylogous ester in high yield. Furthermore, this approach was sustainable to all the functional groups and easily integrated into continuous flow mode to produce a variety of vinylogous ester in large scale.

Interestingly, a novel method for de-alkylation of vinylogous ester was also developed by using an environmentally benign water and Fe-catalyst. A plausible mechanism was proposed for transetherification involves remote C=O group chelation and followed by an alcohol attack on the double bond.

Conflicts of interest

"There are no conflicts to declare".

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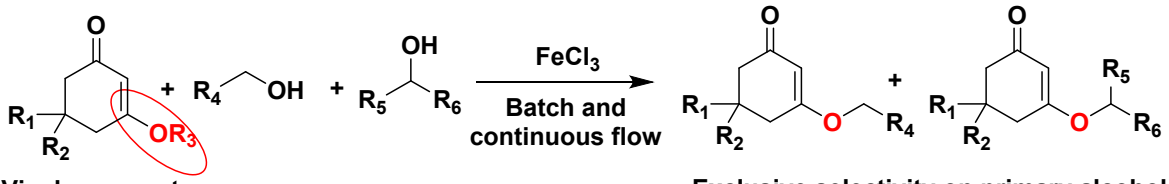

Vinylogous esters **Exclusive selectivity on primary alcohols**

- **Electron deficient unsymmetrical ether substrates**
- **Chemoselective and catalytic reaction**
- **Functional group tolerance and solvent free**
- **Continuous multi-transetherification**
- **Batch and continuous flow synthesis**
- **Wide substrate scope and gram scale synthesis**
- **Assisted by chelation of Fe with C=O group**
- **Novel Fe-catalyzed de-alkylation using water**

An additive/Bronsted acid/base free, highly efficient and chemoselective transetherification of vinylogous esters and water mediated de-alkylation using Fe-catalyst is described.