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Kinetic Analysis as an Optimization Tool for Catalytic Esterification with a Moisture Tolerant Zirconium Complex

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Abstract: This work describes the use of kinetics as a tool for rational optimization of an esterification process with down to equimolar ratios of reagents using a recyclable commercially available zirconocene complex in catalytic amounts. In contrast to previously reported Group IV-catalyzed esterification protocols the herein presented work circumvents the use of water scavengers and PFOS ligands. Insights into the operating mechanism is presented.

Introduction: Esterification of an alcohol and a carboxylic acid with the release of water is one of the most fundamental organic reactions. In synthesis, the Brønsted acid-catalyzed Fischer esterification reaction has served the community well since 1895.[1] However, this equilibrium process typically requires high excess of one reagent and/or removal of water to drive the reaction to high yields, and is unsuitable for many applications. As a result, techniques that rely on

stoichiometric activation of the carboxylic acid are often utilized, such as Steglich esterification and the Schotten-Baumann reaction.[2] A breakthrough was seen in the early 2000's when Yamamoto and co-workers demonstrated that Lewis acids efficiently catalyze dehydrative esterification using equimolar ratios of the starting materials,[3] and the field expanded rapidly to include homogeneous, heterogeneous and micellar protocols.[4] The seminal papers by Yamamoto identified chloride and alkoxide complexes based on hafnium and zirconium as the most efficient catalysts in refluxing toluene with azeotropic water removal. The required use of a dehydration technique is a common feature for protocols using early transition metal catalysts with halide and alkoxide ligands, due to their tendency to undergo hydrolytic decomposition.[5] In contrast, analogous fluoroalkyl sulfonate complexes render moisture tolerant catalysts for a variety of applications.[6,7] Despite the benefits that water stable catalysts present, particularly in the context of dehydrative reactions, Lewis acidic fluoroalkyl sulfonate metal complexes remain a surprisingly understudied catalyst class with respect to (re)activity and mechanistic action.[8] While the use of the one-carbon trifluoromethane sulfonate (triflate) unit is unrestricted, its longer chain analogue perfluorooctane sulfonate (PFOS) displays bioaccumulative and toxic properties[9] and is regulated by *e.g.* the European Chemicals Regulation (REACH EC No. 1907/2006) and the United States Environmental Protection Agency's (EPA) PFOA Stewardship Program.[10] As a result, the use of PFOS in early transition metal catalysis is hampered despite its recently demonstrated efficiency as ligand in *e.g.* zirconium-catalyzed esterification.[11]

During the last decades, modern and user-friendly methods for intuitive visual kinetic analysis of organic reactions have been developed, starting with Blackmond's pioneering Reaction Progress Kinetic Analysis (RPKA)[12] and recently complemented with Burés' Variable Time Normalization Analysis (VTNA).[13] These methodologies enable facile extraction of kinetic data

by utilization of full reaction profiles for a minimal number of experiments under synthetically relevant conditions to generate in-depth understanding of a chemical system, and have been successfully employed for mechanistic elucidation of a wide variety of organic transformations.[14] While valuable from a fundamental perspective, mechanistic insights can also be converted into strategic modification of reaction conditions to improve yields and selectivities.[15] In this work, integrated use of kinetics enables rational optimization of zirconium-catalyzed esterification to provide more insight compared to traditional screening relying on single data points, typically yield at a specified time. In addition, insight into the operating mechanism is provided based on kinetics and NMR spectroscopy.

Results and discussion: Based on previous work using zirconocene triflate,[6i] we expected that the complex would display catalytic activity for dehydrative ester condensation in THF. Indeed, a first attempt using an equimolar ratio of benzyl alcohol and benzoic acid with a 2 mol% loading of the zirconium complex resulted in 6% benzyl benzoate after 24 hours at 80 °C. Taking off from this starting point an assessment of solvents was carried out (SI) that indicated by-product formation at high reactant concentrations. This prompted a switch to 2-phenylethanol as new benchmark alcohol and a lower reactant concentration for further screenings. By plotting product concentration as a function of time it became clear that aromatic hydrocarbons, and benzotrifluoride in particular,[16] were favorable for ester formation whereas the reaction rate decreased with increasing polarity and coordination capability of the solvent (Figure 1, left). Despite low to moderate yields after 24 hours in ethers and sulfolane continuous build-up of product indicated that decomposition or irreversible inhibition of the catalyst was not taking place, suggesting that these solvents may be used as co-solvents. As expected, the reaction rate was

shown to be temperature dependent, with virtually no reaction occurring at room temperature (Figure 1, right). At 60 °C a steady accumulation of product was observed, whereas reactions at 80 °C and 100 °C had increasingly faster rates. Approximately 70% yield of 2-phenylethyl benzoate (**3a**) for the 0.5 M equimolar reaction of **1a** and **2a** was reached at different reaction times depending on the temperature, whereas higher yields were not observed at any of the evaluated temperatures even with prolonged reaction times. For further assessments, a reaction temperature of 80 °C was chosen to allow for compatibility with a wider range of functionalized substrates.

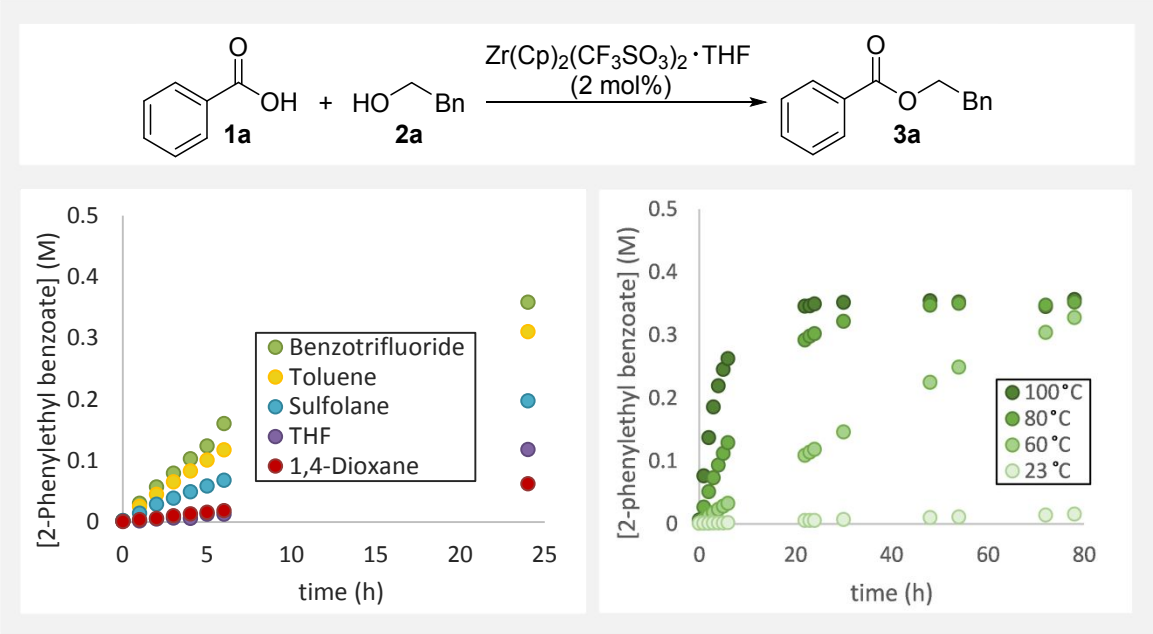


Figure 1. Left: Solvent evaluation at 80 ˚C. **Right:** Temperature evaluation. Conditions: 0.5 M benzoic acid **1a**, 0.5 M 2-phenylethanol **2a**, 2 mol% $Zr(Cp)_2(CF_3SO_3)_2$·THF, benzotrifluoride, ambient atmosphere.

The rate dependencies on reactant concentrations were assessed with *different excess* experiments[12] and determined to be close to zero by comparison with standard conditions (equimolar ratios of starting materials) (Figure 2, top). Furthermore, no reaction took place in the absence of zirconium. The order in [$Zr(Cp)_2(CF_3SO_3)_2$·THF] was estimated to 0.75 (Figure 2,

middle) for different global reaction concentrations.[13] The less than 1st order in [Zr] suggests that the zirconium is partitioned between catalytically active species and inactive forms of higher order, similar to what has previously been described for other catalytic systems.[17] The catalyst stability was probed with two *same excess* experiments (Figure 2, bottom),[12] where the equimolar esterification of **1a** and **2a** (0.5 M) (circles) was compared to two separate reactions simulating 25% conversion (0.375 M **1a** and **2a**) in the absence (squares) and presence (triangles) of the corresponding amount of water (0.125 M). As evident, the time-adjusted profile for the same excess experiments overlay very well with standard conditions, indicating that the catalyst does not undergo significant inhibition or decomposition under standard conditions.

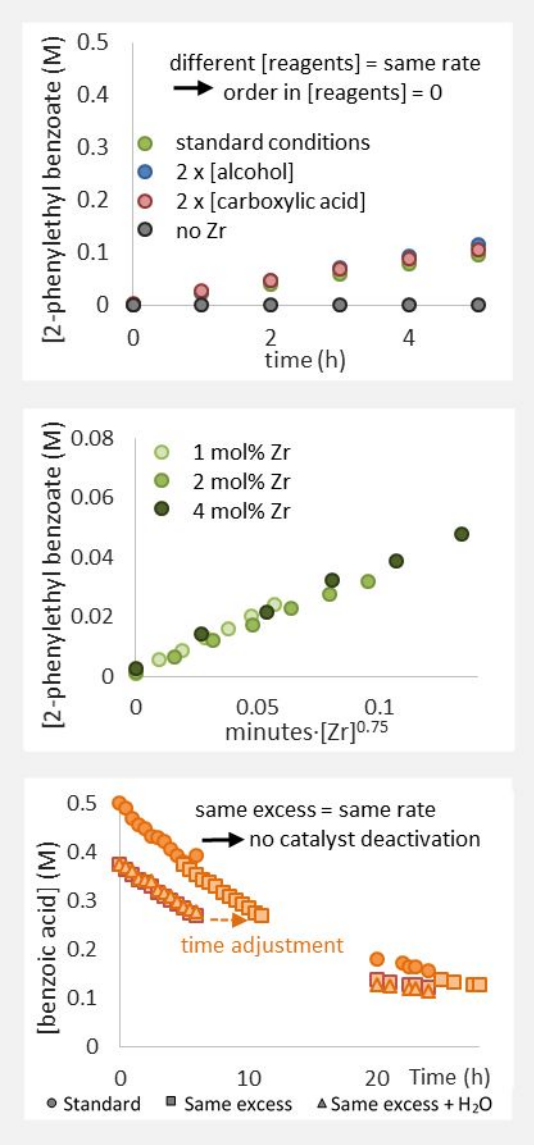


Figure 2. Top: *Different excess* experiments and blank experiments **Middle:** Determination of order in [Zr] (0.2 M equimolar substrate concentration) **Bottom:** *Same excess* experiments in the absence and presence of added water.

These results suggested that the reaction would tolerate an increase in zirconium and reactant concentrations by a decrease in solvent volume for the formation of ester **3a**, without the risk of catalyst deactivation. This was indeed found to be the case (SI) and concentrations of 1 M and 0.02 M for substrates and $Zr(Cp)_2(CF_3SO_3)_2$, respectively, were chosen as starting point for the substrate evaluation. Under these conditions, the turnover number (TON) for the first six hours of reaction time was estimated to 19.7, corresponding to a turnover frequency (TOF) around 3.3 h^{-1} (SI).[18]

The catalyst was found to be moisture stable, as assessed by the addition of water at the outset of the reaction (Figure 3, top left). Similar reaction rates compared to standard conditions were observed for reactions with 25 and 50 equivalents of water relative to zirconium, whereas addition of 250 molar equivalents of water quenched catalysis. It has previously been demonstrated that hydrolytic decomposition of titanocene triflate and other Lewis acidic trifluoromethane sulfonate complexes can occur under certain conditions to release triflic acid,[19] which can be used as a Brønsted acid catalyst for Fischer esterification.[20] To probe the nature of the active catalyst in our system, a set of experiments was performed using 2 mol% of either zirconocene triflate or triflic acid (Figure 3, top right). The use of the latter resulted in a slightly faster reaction compared to the zirconium complex, hence reaching a higher yield of **3a** over 24 hours under standard conditions at 0.5 M. The addition of 250 equivalents of water relative to catalyst resulted in 37% product in the presence of triflic acid after 24 hours whereas only traces of **3a** were observed in the presence of the zirconocene complex. Interestingly, addition of molecular sieves suppressed the reaction rate of the zirconium-containing reaction significantly and almost completely quenched triflic acid catalysis, resulting in only trace amounts of product **3a** after 24 hours (Figure 3, top right; for additional information see SI). This decelerating behavior stands in contrast to what is typically

observed for dehydrative transformations, where water removal shifts the equilibrium towards product formation.[6i] While the origin of catalytic inhibition by molecular sieves was not the subject of further investigations, the different responses from triflic acid and zirconocene triflate suggests that the esterification is indeed zirconium-catalyzed under our conditions.[21] Further support for zirconium catalysis was obtained by ^{13}C-NMR spectroscopy. While a sharp carbonyl peak was observed at 169.3 ppm for ^{13}C(1)-labeled benzoic acid, introduction of $Zr(Cp)_2(CF_3SO_3)_2 \cdot THF$ resulted in a downfield shift to 171.18 ppm and considerable broadening of the carbonyl peak (Figure 3, bottom), suggesting carbonyl coordination to zirconium in a fashion reminiscent of what has been observed for similar systems.[17a, 22] The line broadening indicates exchange between the free and coordinated carboxylic acid.

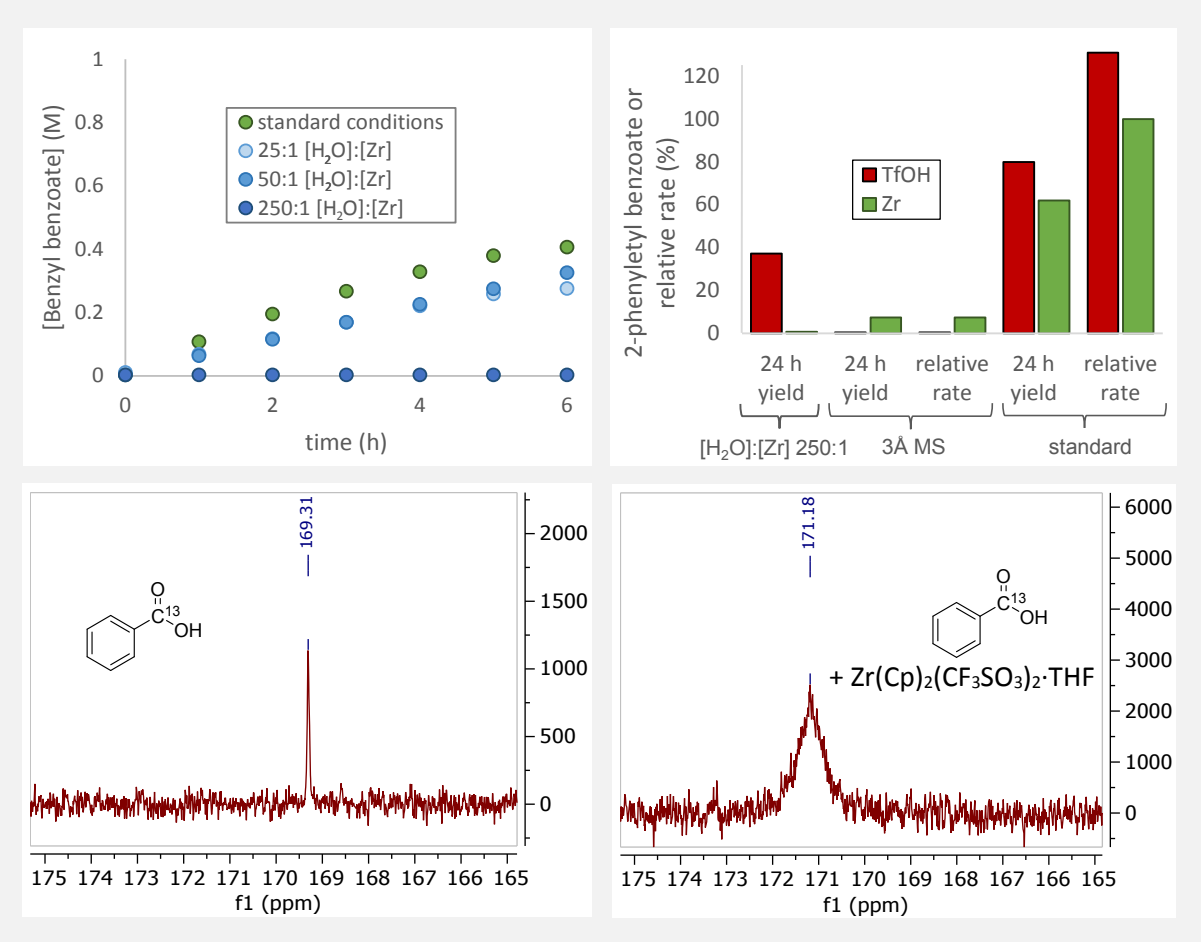


Figure 3. Top left: Assessment of the effect of water. Conditions: 2 mol% $Zr(Cp)_2(CF_3SO_3)_2 \cdot$ THF, 1 M benzoic acid, 1 M benzyl alcohol, 80 °C, toluene (dry, inert), N_2 atmosphere. **Top right:** Comparison between zirconium catalysis and triflic acid catalysis in the presence of water and molecular sieves. Conditions: 2 mol% $Zr(Cp)_2(CF_3SO_3)_2 \cdot$THF or 2 mol% TfOH, 0.5 M benzoic acid, 0.5 M 2-phenylethanol, H_2O (2.5 M) or 3 Å molecular sieves (MS) (0.1 g/1 mmol benzoic acid). Rates plotted as percent of Zr-catalyzed standard conditions. **Bottom:** The effect on carbonyl peak shift for $^{13}C(1)$-benzoic acid in the absence (left) and presence (right) of $Zr(Cp)_2(CF_3SO_3)_2 \cdot$ THF (d_8-toluene, 80 °C, 100 MHz).

A tentative catalytic cycle is depicted in Figure 4. The positive rate dependence on [Zr] and close to zero order in [benzoic acid] and [2-phenylethanol] suggest that the turnover limiting step is found late in the catalytic cycle. Since the *same excess* experiments indicated insignificant product inhibition, release of ester and water is likely not turnover limiting under the examined conditions. Hence, our data suggest that the slow step in the catalytic cycle may be the collapse of the tetrahedral intermediate resulting from nucleophilic attack by the alcohol on the coordinated carboxylic acid. This corresponds to a barrier of approximately 16.7 ± 0.5 kcal/mol (SI) and is of the same order of magnitude as what has previously been estimated by DFT calculations for collapse of the tetrahedral intermediate in zirconium-catalyzed amidation.[17a]

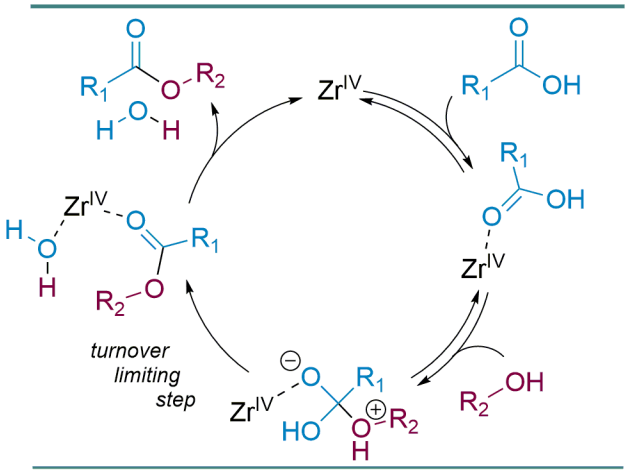


Figure 4. Proposed catalytic cycle

Using the optimized conditions, a range of carboxylic acids and alcohols were evaluated as substrates. Our model product, 2-phenylethyl benzoate (**3a**) was formed in 78% yield whereas

excess alcohol or carboxylic acid resulted in increased yields, as expected for an equilibrium process (Figure 5). Benzoic acid derivatives with electron withdrawing or electron-donating groups resulted in good to moderate yields (**3b** to **3i**), tolerating ketone and aldehyde substituents. Heteroaromatic carboxylic acids delivered the expected products **3j** and **3k** in moderate yields, whereas carboxylic acids with pyridine, imidazole and indazole backbones failed to form esters (*vide infra*). Aliphatic carboxylic acids were smoothly converted to their corresponding esters **3l** to **3u** in good to excellent yields using equimolar amounts of alcohol, including fatty acids **3m** and **3n**, sterically congested substrates **3o** and **3p** as well as diacids **3q** and **3r**. The anti-inflammatory drug Indomethacin was converted to its respective ester **3s** in good yield and we were pleased to see that the corresponding 2-phenethyl ester **3t** of Boc-protected L-Alanine retained >99% *ee*, similar to what has previously been described for zirconium-catalyzed amidation.[23] In contrast to the corresponding PFOS-complex,[11] zirconocene triflate in catalytic amounts preferentially mediates esterifications over transesterifications (SI). Gratifyingly, this differentiation in carbonyl activation allowed for selective synthesis of the unsymmetric diester **3u** from the corresponding methyl ester substituted phenylacetic acid without any transesterification product observed. The catalyst can be recycled and used for at least four consecutive cycles with negligible loss of activity for the formation of ester **3l** (SI).

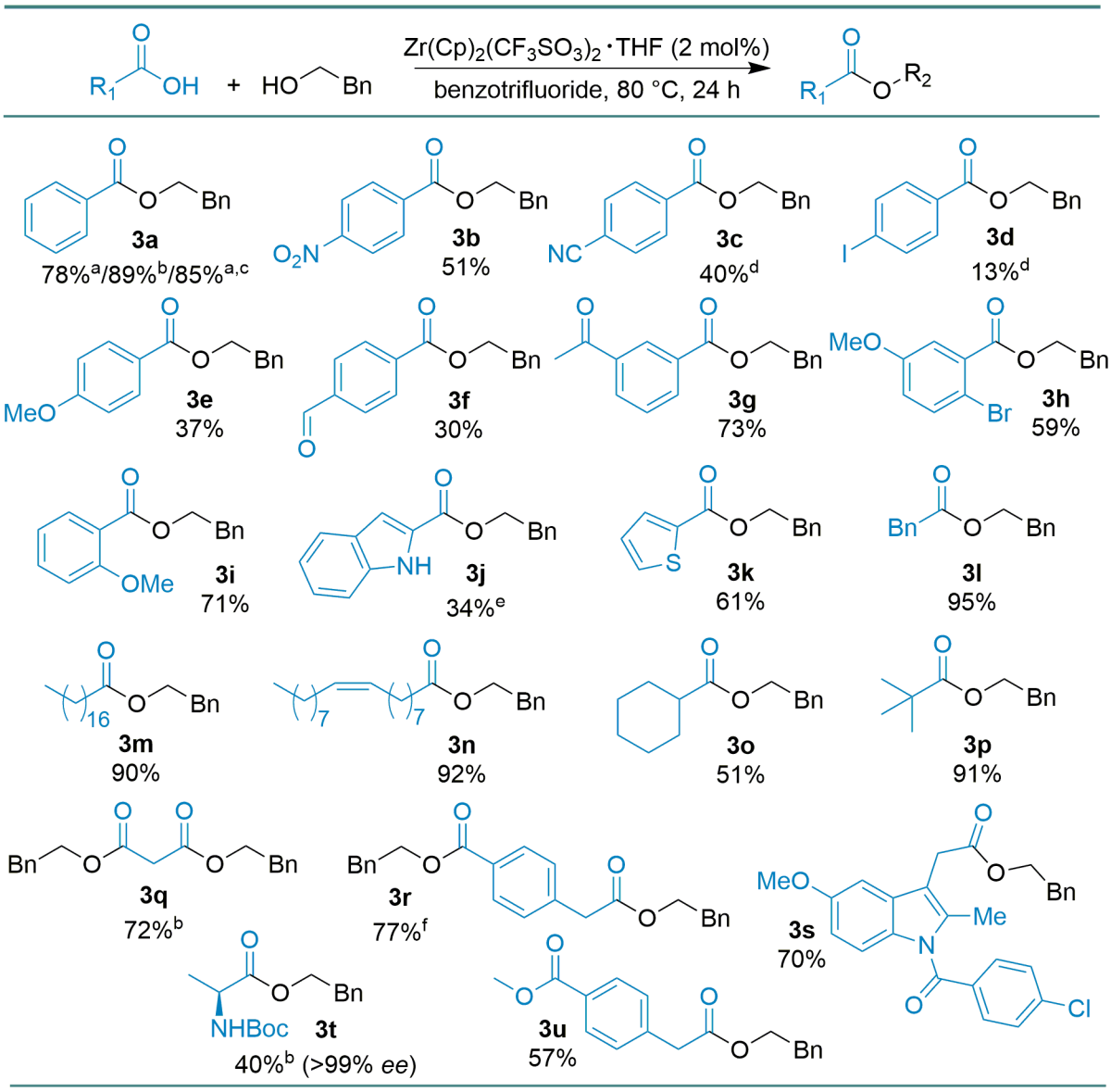


Figure 5. Carboxylic acid scope for esterification. Standard conditions: 2 mol% $Zr(Cp)_2(CF_3SO_3)_2 \cdot$ THF, 1 M carboxylic acid, 1 M alcohol, benzotrifluoride, 80 °C, 24 h, ambient atmosphere. [a] HPLC yield, [b] 2 equiv. alcohol, [c] 2 equiv. acid, [d] toluene as solvent, [e] 3 equiv. alcohol, [f] 1:2 ratio of alcohol to carboxylic acid moieties (1:1 molar ratio of starting materials).

A range of aliphatic alcohols proved to be suitable esterification coupling partners (Figure 6), including oleyl alcohol and allyl alcohol that smoothly yielded esters **3v** and **3w** with both aryl and

alkyl carboxylic acids. The electron-poor benzylic alcohol and the heteroaromatic 2-thiopheneethanol were smoothly acylated to form **3w** and **3y** in high yields. Trifluoroethanol formed the corresponding phenylacetate **3z** in moderate yield, as did the sterically hindered adamantly alcohol and cholesterol, rendering **3aa** and **3ab**, respectively. The corresponding benzoic and phenylacetic esters of 1-phenyl-2-propanol formed in different yields, giving benzoic ester **3ac** in moderate yield whereas the use of (*R*)-(-)-1-phenyl-2-propanol (>98% *ee*) furnished phenylacetic ester **3ad** in excellent yield and retained enantiomeric excess.

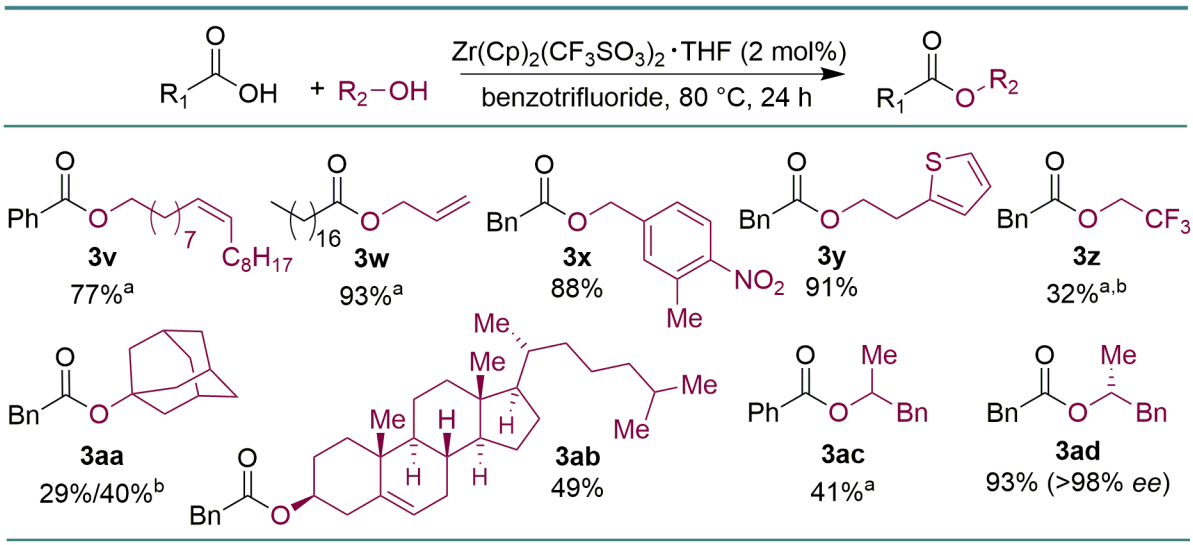


Figure 6. Alcohol scope for esterification. Standard conditions: 2 mol% $Zr(Cp)_2(CF_3SO_3)_2 \cdot THF$, 1 M carboxylic acid, 1 M alcohol, benzotrifluoride, 80 °C, 24 h, ambient atmosphere; [a] 2 equiv. alcohol, [b] 100 °C.

Aromatic alcohols and *N*-heterocyclic carboxylic acids and alcohols with a basic nitrogen failed to form esters, and the starting materials could be recovered in near quantitative amounts. To probe the origin of this observation, nicotinic acid and phenol were added separately to standard reactions after three hours of reaction time (Figure 7). Interestingly, whereas the effect of phenol addition on the formation rate of **3a** lies within the variability for the standard reaction (SI), addition of

nicotinic acid completely quenched the catalysis, indicating that the inability of aromatic alcohols and basic heteroaromatic compounds to form esters has different origins. The inhibiting effect of nicotinic acid, occurring already at near 1:1 ratio to zirconium (SI), may be explained by formation of catalytically inactive zirconium species that could form by N-coordination of the pyridine or by coordination of a negatively charged carboxylate species after deprotonation by pyridine. To the contrary, 2-phenylethyl benzoate **3a** continued to form with a similar rate after the addition of 50 equivalents of phenol relative to zirconium with only traces of phenyl ester formation (see SI). As secondary and tertiary alcohols perform well as coupling partners (Figure 6), the low reactivity of the phenol is likely not a function of steric hindrance, rather, its poor nucleophilicity under non-basic conditions is expected to be the main reason for the sluggish performance.

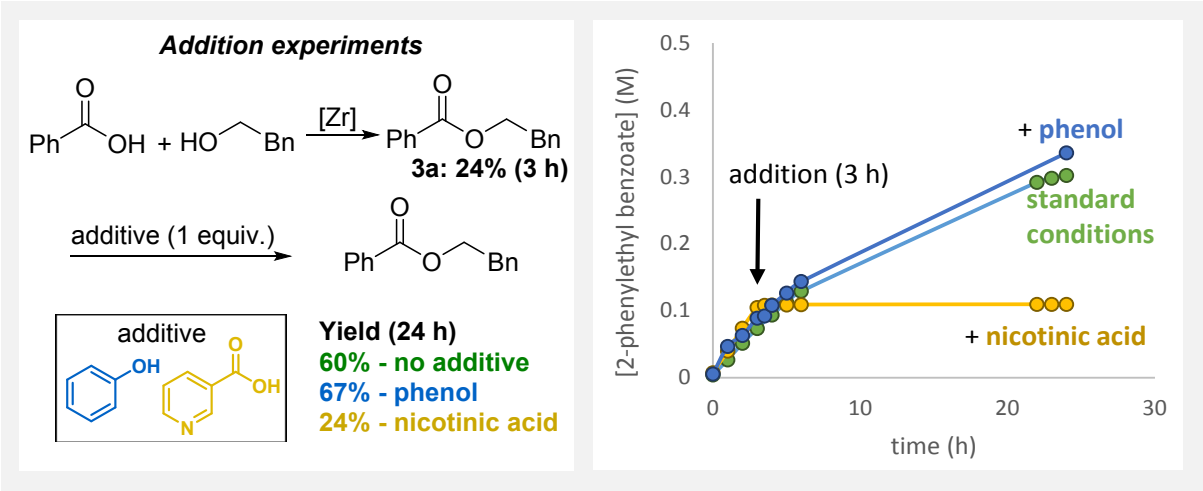
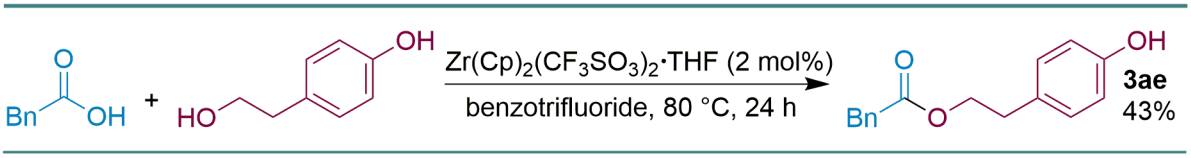


Figure 7. Addition of phenol/nicotinic acid to esterification of benzoic acid and 2-phenylethanol. Conditions: 2 mol% $Zr(Cp)_2(CF_3SO_3)_2$ · THF, 0.5 M carboxylic acid, 0.5 M alcohol, benzotrifluoride, 80 °C, ambient atmosphere. Addition of 1 equiv. phenol/nicotinic acid relative to carboxylic acid after 3 h. Yields obtained by HPLC analysis.

As suggested from Figure 7, the low reactivity of phenols under standard conditions would allow for esterification of substrates substituted with unprotected aromatic alcohols. Indeed, acylation of 2-(4-hydroxyphenyl)ethanol proceeded with full selectivity for the aliphatic over the aromatic alcohol to form ester **3ae** (Scheme 1).

Scheme 1. Selective monoacylation of a diol.



Conditions: 2 mol% $Zr(Cp)_2(CF_3SO_3)_2$ · THF, 1 M carboxylic acid, 1 M alcohol, benzotrifluoride, 80 °C, ambient atmosphere. Isolated yield.

In summary, this work demonstrates the use of kinetics as an integrated tool in the optimization of dehydrative esterification using a moisture-tolerant zirconium complex in catalytic amounts. The insights from the kinetic assessment of reaction parameters allowed for rational tuning of conditions and enabled an understanding of why certain substrate classes fail to form products. Furthermore, kinetics and spectroscopy were used to assess catalyst properties and provide support for the proposed mechanism. The present work adds to the general understanding of the reactivity of the understudied moisture-tolerant group (IV) metal complexes, a highly interesting compound class for use in future catalyzed dehydrative transformations.

Experimental Section

General Information. All reagents were purchased from commercial suppliers and used without further purification. Reactions were carried out in 4 mL screw neck glass vials furnished with screw caps equipped with PTFE/rubber septa, and stir bars under ambient atmosphere unless

otherwise noted. Silica gel 60 Å (40-60 μm, 230-400 mesh) was used for column chromatography. All NMR spectra were recorded in $CDCl_3$ using a Bruker AVANCE II 400 MHz or Bruker Avance 500 MHz. Chemical shifts are given in ppm relative to the residual solvent peak (^{1}H NMR: $CDCl_3$ δ 7.26, ^{13}C NMR: $CDCl_3$ δ 77.16) with multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (in Hz) and integration. Kinetic data was analyzed by Agilent 1260 Infinity Quaternary LC (Eclipse Plus 18C column, 3.5 μm, 4.6x100mm; UV detector, 265 nm) with a gradient of acetonitrile and 0.1% formic acid in Milli-Q water at a flow rate of 1 mL/min. The analytes were calibrated using a five-point calibration curve with three-fold dilution between each sample in the series. HPLC with a chiral stationary phase was performed on Agilent 1100 Series instrument. High resolution mass spectrometry analyses were obtained by Thermo Scientific Q Exactive HF Hybrid Quadrupole-Orbitrap HESI or Bruker microTOF ESI, low resolution mass analyses by Bruker Daltonic amaZon speed no 06052 ESI.

General esterification procedure A for kinetic analysis. For 1 M reaction mixture $Zr(Cp)_2(CF_3SO_3)_2$·THF (0.02 mmol, 11.8 mg), benzoic acid (1 mmol, 122.1 mg), internal standard 4,4'-di-*tert*-butylbiphenyl (0.02 mmol, 5.3 mg), benzotrifluoride (1 mL, non-dried) and 2-phenylethanol (1 mmol, 120 μL) were added into the reaction vessel under air atmosphere. The screw cap was tightened and the vial placed in an oil bath at 80 °C. At indicated times, 20 μL reaction mixture was removed with a microliter syringe and mixed with 0.5 mL 10% v/v aqueous acetonitrile (HPLC gradient grade), filtered in a filter vial (polypropylene housing, PTFE membrane) and subjected to HPLC analysis after which the analyte concentrations were integrated against the internal standard 4,4'-di-*tert*-butylbiphenyl.

Different excess experiments followed general esterification procedure A, where ***a)*** 0.5 M benzoic acid, 1 M 2-phenylethanol (0.5 M excess), 0.01 M (2 mol%) $Zr(Cp)_2(CF_3SO_3)_2$·THF,

benzotrifluoride, 80 °C, ambient atmosphere; ***b)*** 1 M benzoic acid (0.5 M excess), 0.5 M 2-phenylethanol, 0.01 M (2 mol%) $Zr(Cp)_2(CF_3SO_3)_2$·THF, benzotrifluoride, 80 °C, ambient atmosphere.

Same excess experiments followed general esterification procedure A, where *a)* standard conditions: 0.5 M benzoic acid, 0.5 M 2-phenylethanol, 0.01 M (2 mol%) $Zr(Cp)_2(CF_3SO_3)_2$·THF, benzotrifluoride, 80 °C, ambient atmosphere; *b)* same excess conditions mimicking 25% conversion of benzoic acid: 0.375 M benzoic acid, 0.375 M 2-phenylethanol, 0.01 M (2 mol%) $Zr(Cp)_2(CF_3SO_3)_2$·THF, benzotrifluoride, 80 °C, ambient atmosphere; *c)* same excess conditions mimicking 25% conversion of benzoic acid with addition of the corresponding amount of water at the outset of the reaction: 0.125 M Milli-Q water, 0.375 M benzoic acid, 0.375 M 2-phenylethanol, 0.01 M (2 mol%) $Zr(Cp)_2(CF_3SO_3)_2$·THF, benzotrifluoride, 80 °C, ambient atmosphere.

Addition reactions followed general esterification procedure A, where either *a)* water [25:1 H_2O:Zr (9 μL, 0.5 mmol H_2O), 50:1 H_2O:Zr (18 μL, 1.0 mmol H_2O), 250:1 H_2O:Zr (90 μL, 5.0 mmol H_2O) was added at the outset of three separate reactions (1 M equimolar reactants, 1 mmol scale); *b)* powdered molecular sieves (100 mg, 3 Å, flame-dried under high-vacuum) were added at the outset of the reaction (0.5 M equimolar reactants, 0.5 mmol scale); *c)* phenol (1 equiv., 0.5 mmol, 47 mg) was added 3 h after onset of reaction (0.5 M equimolar, 0.5 mmol scale); *d)* nicotinic acid (2 mol%, 3 mg, 0.02 mmol; 10 mol%, 14 mg, 0.1 mmol; 1 equiv., 123 mg, 1.0 mmol) was added 3 h after onset of three separate reactions (0.5 M equimolar reactants, 1.0 mmol scale).

TfOH catalyzed esterification followed general esterification procedure A for 0.5 M equimolar reaction in 0.5 mmol scale with TfOH (1 μL, 0.02 mmol) instead of $Zr(Cp)_2(CF_3SO_3)_2$. For TfOH catalyzed reaction in the presence of molecular sieves (0.5 M equimolar reaction, 0.5 mmol scale) was used MS (3 Å, 50 mg) and TfOH (1 μL, 0.02 mmol).

Recycling experiments were carried out as follows. Reaction was started in accordance with General esterification procedure B on a 0.5 mmol scale. After 24 hours the vial was removed from the heated oil bath and the solvent was evaporated. The reaction mixture was thereafter extracted with 1 mL petroleum ether (40-65 ^{o}C bp) and decanted. The opaque solution was injected into an Eppendorf tube (2 mL) and subjected to centrifugation (3000 rpm, 3 min), after which the yellow solution was removed from the black catalyst residue. This procedure was repeated for a total of 3 extractions. The combined product/substrate fractions were evaporated, weighed and subjected to ^{1}H-NMR analysis using d_4-MeOD as solvent. The black catalyst residue was dissolved in a minimal amount of dichloromethane and added to the original reaction vial and the solvent was evaporated. To the dried catalyst residue was then added phenylacetic acid, 2-phenylethanol and benzotrifluoride in accordance with General esterification procedure B and the reaction was stirred at 80 ^{o}C for another 24 hours, after which the recycling procedure was repeated.

General esterification procedure B for product isolation. For 1 M reaction mixture $Zr(Cp)_2(CF_3SO_3)_2 \cdot THF$ (0.02 mmol, 11.8 mg), carboxylic acid (1 mmol), benzotrifluoride (1 mL, non-dried) and alcohol (1 mmol) were added into the reaction vessel under air atmosphere. The screw cap was tightened and the vial placed in an oil bath at 80 °C (or the indicated temperature). After 24 h the reaction mixture was brought to room temperature and purified by column chromatography (silica gel 60, 2%–10% EtOAc/petroleum ether) unless otherwise stated.

2-Phenylethyl benzoate (3a) was synthesized according to the esterification procedure B in 1 mmol scale, using 2 equiv. of 2-phenylethanol (2 mmol, 240 µL). The product was isolated as a yellow oil in 89% (0.89 mmol, 200.7 mg). Analytical data matches with reported literature.[24, 25]

3a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.61–7.13 (m, 8H), 4.49 (m, 2H), 3.04 (m, 2H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.7, 138.0, 133.0, 130.4, 129.7, 129.1, 128.7, 128.5, 126.7, 65.6, 35.4.

2-Phenylethyl 4-nitrobenzoate (3b) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as yellow oil in 51% (0.511 mmol, 138 mg). Analytical data matches with reported literature.[26, 27] **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29–8.18 (m, 2H), 8.18–8.07 (m, 2H), 7.37–7.16 (m, 5H), 4.57 (t, J = 6.9 Hz, 2H), 3.08 (t, J = 6.9 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 164.7, 150.6, 137.5, 135.7, 130.7, 128.9, 128.7, 126.9, 123.6, 66.4, 35.2. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{13}NNaO_4$ 294.0737; Found 294.0761

2-Phenylethyl 4-cyanobenzoate (3c) was synthesized according to the general esterification procedure B in 0.5 mmol scale with toluene as solvent. The product was isolated as yellow solid in 40% (0.20 mmol, 50.8 mg). Analytical data matches with reported literature.[28] **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.04 (m, 2H), 7.79–7.68 (m, 2H), 7.41–7.21 (m, 5H), 4.57 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 164.9, 137.6, 134.2, 132.4, 130.2, 129.03, 128.8, 126.9, 118.1, 116.5, 66.3, 35.2.

2-Phenylethyl 4-iodobenzoate (3d) was synthesized according to the general esterification procedure B in 0.5 mmol scale with toluene as solvent. The product was isolated with minor inseparable impurities as a yellow liquid (28.8 mg). NMR-yield 13% for **3d** was determined by ^{1}H-NMR with 1,4-dimethoxybenzene as internal standard. Analytical data matches with reported literature.[27] **3d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.69 (m, 2H), 7.35–7.20 (m, 5H), 4.51 (t, J = 6.9 Hz, 2H), 3.06 (t, J = 6.9 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 137.8, 137.8, 131.1, 129.9, 129.1, 128.7, 126.8, 100.8, 65.8, 35.3.

2-Phenylethyl 4-methoxybenzoate (3e) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as a yellow oil in 37% (0.374 mmol, 96 mg). Analytical data matches with reported literature.[29] **3e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.30–7.09 (m, 5H), 6.82 (m, 2H), 4.42 (t, J = 7.0 Hz, 2H), 3.75 (s, 3H), 2.98 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3, 163.4, 138.1, 131.7, 129.1, 128.6, 126.6, 122.8, 113.7, 65.3, 55.5, 35.4.

2-Phenylethyl 4-formylbenzoate (3f) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated with minor by-products as a yellow waxy solid (110 mg). 30% NMR-yield for **3f** was obtained by ^{1}H-NMR analysis of a crude reaction mixture with 1,4-dimethoxybenzene as internal standard. After 24 h reaction time the reaction mixture was dried under vacuum to remove benzotrifluoride, then the internal standard (IS) was added (7.6 mg, 0.055 mmol), as well as $CDCl_3$. The resulting slurry was filtered through a cotton plug, followed by immediate recording of ^{1}H-NMR spectrum. Aromatic signals for **3f** and standard were used for NMR-yield calculation (SI). Further purification using preparative thin layer chromatography using an eluent of 1:15 ethyl acetate:petroleum ether (bp 40-65 ^{o}C) afforded the pure compound. **3f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.07 (m, 2H), 7.84 (m, 2H), 7.29–7.11 (m, 5H), 4.49 (t, J = 7.0 Hz, 2H), 3.01 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.7, 165.5, 139.2, 137.7, 135.2, 130.2, 129.5, 128.9, 128.6, 126.8, 66.1, 35.2. MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}NaO_3$ 277.08; Found 277.08.

2-Phenylethyl 3-acetylbenzoate (3g) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as yellow oil in 73% (0.728 mmol, 195 mg). **3g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (m, 1H), 8.15 (m, 1H), 8.10 (m, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.32–7.16 (m, 5H), 4.52 (t, J = 7.0 Hz, 2H), 3.06 (t, J = 7.0 Hz, 2H), 2.59 (s, 3H). ^{13}C{^{1}H}

NMR (126 MHz, $CDCl_3$) δ 197.2, 165.7, 137.8, 137.3, 133.9, 132.3, 130.9, 129.6, 129.0, 128.9, 128.6, 126.7, 65.9, 35.2, 26.7. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}NaO_3$ 291.0992; Found 291.0987.

2-Phenylethyl 2-bromo-5-methoxybenzoate (3h) was synthesized according to the general esterification procedure B in 0.5 mmol scale. The product was isolated as beige, waxy solid in 59% (0.297 mmol, 100 mg). **3h**: ^1H NMR (400 MHz, CDCl3) δ 7.44 (m, 1H), 7.34–7.11 (m, 6H), 6.80 (m, 1H), 4.50 (m, 2H), 3.70 (s, 3H), 3.03 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.9, 158.6, 137.7, 135.1, 132.8, 129.1, 128.6, 126.7, 119.2, 116.2, 112.0, 66.1, 55.7, 35.1. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{15}BrNaO_3$ 357.0097; Found 357.0093.

2-Phenylethyl 2-methoxybenzoate (3i) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as yellow oil in 71% (0.714 mmol, 183 mg). **3i**: ^1H NMR (500 MHz, CDCl3) δ 7.73 (dd, J = 7.9, 1.7 Hz, 1H), 7.42 (m, 1H), 7.32–7.25 (m, 4H), 7.24–7.19 (m, 1H), 6.97–6.90 (m, 2H), 4.50 (t, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.05 (t, J = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 166.1, 159.2, 138.1, 133.5, 131.6, 129.0, 128.5, 126.5, 120.1, 120.1, 112.0, 65.3, 55.9, 35.2. HRMS (HESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}O_3$ 257.1172; Found 257.1167.

2-Phenylethyl 1*H*-indole-2-carboxylate (3j) was synthesized according to the general esterification procedure B in 0.5 mmol scale using 3 equiv. of 2-phenylethanol (1.5 mmol, 180 µL). The product was isolated as pale yellow solid in 34% (0.17 mmol, 45.1 mg). **3j**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.55–7.19 (m, 9H), 4.65 (m, 2H), 3.18 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.0, 137.8, 136.9, 129.1, 128.7, 127.6, 127.4, 126.8, 125.6, 122.8, 120.9, 112.0, 108.9, 65.7, 35.4. HRMS (HESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}NO_2$ 266.1176; Found 266.1173.

2-Phenylethyl thiophene-2-carboxylate[27] (3k) was synthesized according to the general esterification procedure B in 0.5 mmol scale. The product was isolated as yellow oil in 61% (0.306 mmol, 71 mg). **3k**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.46 (m, 1H), 7.31–7.11 (m, 5H), 7.01 (m, 1H), 4.42 (t, J = 7.0 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.3, 137.9, 133.9, 133.6, 132.5, 129.2, 128.7, 127.8, 126.8, 65.7, 35.4. MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{12}NaO_2S$ 255.04; Found 255.04.

2-Phenylethyl 2-phenylacetate (3l) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as yellow liquid in 95% (0.949 mmol, 228 mg). Analytical data matches with reported literature.[30] **3l**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.29 (m, 8H), 7.23 (m, 2H), 4.40 (t, J = 7.0 Hz, 2H), 3.69 (s, 2H), 3.00 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.4, 137.7, 134.0, 129.3, 128.9, 128.5, 128.5, 127.1, 126.5, 65.3, 41.4, 35.0.

2-Phenylethyl octadecanoate (3m) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as pale yellow solid in 90% (0.90 mmol, 348.6 mg). **3m**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.17 (m, 5H), 4.29 (m, 2H), 2.94 (m, 2H), 2.28 (m, 2H), 1.64–1.50 (m, 2H), 1.26 (s, 28H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.9, 138.0, 129.0, 128.6, 126.7, 64.8, 35.3, 34.5, 32.1, 29.84–29.80 (overlapping signals, 7C), 29.75, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.3. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{44}NaO_2$ 411.3234; Found 411.3230.

2-Phenylethyl (*Z*)-octadec-9-enoate (3n) was synthesized according to the general esterification procedure B on a 0.5 mmol scale. The product was isolated as colourless oil in 92% (0.46 mmol, 177.7 mg). **3n**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.15 (m, 5H), 5.38 (m, 2H), 4.31 (t, J = 7.1 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H), 2.30 (t, J = 7.6 Hz, 2H), 2.04 (m, 4H), 1.60 (m, 2H), 1.48 – 1.22

(m, 20H), 0.91 (t, J = 6.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.9, 138.0, 130.2, 129.9, 129.0, 128.6, 126.7, 64.8, 35.3, 34.5, 32.1, 29.92–29.24 (overlapping signals, 8C), 27.4, 27.3, 25.1, 22.8, 14.3. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{42}NaO_2$ 409.3077; Found 409.3070.

2-Phenylethyl cyclohexanecarboxylate (3o) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as colourless oil in 51% (0.51 mmol, 118.8 mg). Analytical data matches with reported literature.[31] **3o**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.01 (m, 5H), 4.31 (t, J = 7.0 Hz, 3H), 2.96 (t, J = 7.0 Hz, 3H), 2.30 (m, 1H), 1.89 (m, 2H), 1.83–1.71 (m, 2H), 1.70–1.55 (m, 2H), 1.52–1.37 (m, 2H), 1.36–1.17 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 176.1, 138.1, 129.0, 128.5, 126.6, 64.7, 43.3, 35.3, 29.1, 25.9, 25.5.

2-Phenylethyl 2,2-dimethylpropanoate (3p) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as colourless oil in 91% (0.91 mmol, 187.6 mg). Analytical data matches with reported literature.[32] **3p**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.17 (m, 5H), 4.28 (t, J = 6.9 Hz, 2H), 2.94 (t, J = 6.9 Hz, 2H), 1.16 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 178.6, 138.2, 129.1, 128.5, 126.6, 64.9, 38.8, 35.3, 27.3.

Diphenethyl propanedioate (3q) was synthesized according to the general esterification procedure B in 1 mmol scale, using 2 equiv. of 2-phenylethanol (2 M, 2 mmol, 241 μL). The product was isolated as colourless oil in 72% (0.72 mmol, 225.1 mg). Analytical data matches with reported literature.[33] **3q**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.11 (m, 10H), 4.38 (m, 4H), 3.39 (s, 2H), 2.97 (m, 4H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.5, 137.6, 129.0, 128.7, 126.8, 66.1, 41.7, 35.0.

2-Phenethyl 4-(2-oxo-2-phenethoxyethyl)benzoate (3r) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as yellow oil in 77% (0.387 mmol, 150 mg). **3r**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.44–7.24 (m, 10H), 7.19

(m, 2H), 4.60 (t, J = 6.9 Hz, 2H), 4.38 (t, J = 6.9 Hz, 2H), 3.70 (s, 2H), 3.14 (t, J = 6.9 Hz, 2H), 2.97 (t, J = 6.9 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.7, 166.3, 139.2, 137.9, 137.6, 129.9, 129.4, 129.2, 129.0, 128.9, 128.6, 128.6, 126.7, 126.6, 65.6, 65.5, 41.4, 35.3, 35.0. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{24}NaO_4$ 411.1567; Found 411.1563.

Phenethyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (3s) was synthesized according to the general esterification procedure B in 0.5 mmol scale. The product was isolated as yellow oil in 70% (0.352 mmol, 163 mg). **3s**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 8.5, 2.2 Hz, 2H), 7.55 (dd, J = 8.5, 2.2 Hz, 2H), 7.31 (m, 3H), 7.21 (m, 2H), 7.08–6.95 (m, 2H), 6.78 (m, 1H), 4.43 (m, 2H), 3.91 (s, 3H), 3.74 (s, 2H), 3.01 (m, 2H), 2.42 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.8, 168.3, 156.1, 139.2, 137.7, 135.9, 134.0, 131.2, 130.9, 130.7, 129.2, 128.9, 128.5, 126.6, 115.0, 112.6, 111.7, 101.4, 65.5, 55.7, 35.1, 30.4, 13.4. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{24}ClNaNO_4$ 484.1286; Found 484.1281.

(*S*)-phenethyl 2-[(tert-butoxycarbonyl)amino]propanoate (3t) was synthesized according to the general esterification procedure B in 0.5 mmol scale with 2 equiv. of 2-phenylethanol (1 mmol, 120 µL). The product was isolated as white crystalline solid in 40% (0.20 mmol, 59 mg). **3t**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.05 (m, 5H), 5.00 (s, 1H), 4.46–4.24 (m, 3H), 2.96 (d, J = 7.0 Hz, 2H), 1.44 (s, 9H), 1.32 (d, J = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, MeOD) δ 174.89, 157.83, 139.19, 129.99, 129.49, 127.55, 80.47, 66.72, 50.64, 35.99, 28.71, 17.64. HRMS (HESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{24}NO_4$ 294.1699; Found 294.1696. HPLC analysis was used to determine *ee* >99% for **3t** (Chiralcel OD-H column 250x4.6 mm, 10% 2-propanol in hexane, 1.0 mL/min, λ=225 nm, 10 µL injection volume, *S* isomer t(1)= 5.8 min. Compared against racemic mixture: *S* isomer t(1)= 5.8 min, *R* isomer t(2)= 6.6 min).

Methyl 4-(2-oxo-2-phenethoxyethyl)benzoate (3u) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as colourless waxy solid in 57% (0.566 mmol, 169 mg) with two minor, unidentified impurities. **3u**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.25–7.12 (m, 5H), 7.07 (m, 2H), 4.26 (t, J = 6.9 Hz, 2H), 3.84 (s, 3H), 3.58 (s, 2H), 2.84 (t, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 167.0, 139.2, 137.7, 129.9, 129.5, 129.2, 129.0, 128.6, 126.7, 65.6, 52.2, 41.5, 35.1. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{18}NaO_4$ 321.1097; Found 321.1094.

[(*E*)-octadec-9-enyl] benzoate[34] (3v) was synthesized according to the general esterification procedure B in 0.5 mmol scale with 2 equiv. of oleyl alcohol (1 mmol, 316 µL). The product was isolated as colourless oil in 77% (0.385 mmol, 143.5 mg). **3v**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.55 (m, 1H), 7.44 (m, 2H), 5.36 (m, 2H), 4.32 (t, J = 6.9 Hz, 3H), 2.01 (m, 4H), 1.77 (m, 2H), 1.51–1.17 (m, 20H), 0.88 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.8, 132.9, 130.7, 130.1, 129.9, 129.7, 128.5, 65.3, 32.1 (overlapping signals, 2C), 29.8-29.4 (overlapping signals, 7C), 28.9, 27.4, 26.2, 22.8, 14.2. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{40}NaO_2$ 395.2921; Found 395.29205.

Prop-2-enyl octadecanoate[35] (3w) was synthesized according to the general esterification procedure B in 0.25 mmol scale, using 2 equiv. allyl alcohol (0.5 mmol, 34 µL). The product was isolated as white crystalline mass in 93% (0.25 mmol, 81.6 mg). **3w**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.27 (m, 2H), 4.57 (m, 2H), 2.33 (t, J = 7.6 Hz, 2H), 1.63 (m, 2H), 1.25 (s, 26H), 0.87 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.7, 132.5, 118.2, 65.1, 34.4, 32.1, 29.84–29.83 (overlapping signals, 4C), 29.82, 29.80, 29.79, 29.74, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.3. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{40}NaO_2$: 347.2921; Found 347.2903.

3-Methyl-4-nitrobenzyl 2-phenylacetate (3x) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as yellow oil in 88% (0.877 mmol, 250 mg). **3x**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.66–7.38 (m, 7H), 5.41 (s, 2H), 3.97 (s, 2H), 2.79 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.0, 148.6, 141.4, 133.9, 133.6, 131.5, 129.3, 128.6, 127.3, 125.7, 124.9, 64.9, 41.3, 20.4. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{15}NNaO_4$ $[M+Na]^+$ 308.0893; Found 308.0895.

2-(Thiophen-2-yl)ethyl 2-phenylacetate[36] (3y) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as clear, colourless liquid in 91% (0.914 mmol, 225 mg). **3y**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 5H), 7.15 (d, J = 5.2 Hz, 1H), 6.92 (m, 1H), 6.79 (m, 1H), 4.32 (m, 2H), 3.64 (s, 2H), 3.14 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.5, 139.9, 133.9, 129.4, 128.7, 127.2, 126.9, 125.7, 124.1, 65.1, 41.5, 29.3. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{14}NaO_2S$ 269.0607; Found 269.0603.

2,2,2-Trifluoroethyl 2-phenylacetate (3z) was synthesized according to the general esterification procedure B in 1 mmol scale with 2 equiv. of 2,2,2-trifluoroethanol (2 mmol, 145 μL) at 100 °C. The product was isolated as pale yellow oil in 32% (0.321 mmol, 70 mg). At 80 °C under the same conditions only traces of the product were isolated (*ca* 1%). Analytical data matches with reported literature.[37] **3z**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.07 (m, 5H), 4.37 (m, 2H), 3.62 (s, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.1, 132.9, 129.4, 128.9, 127.6, 123.0 (q, J = 277.2 Hz), 60.7 (q, J = 36.7 Hz), 40.7. ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.80 (t, J = 8.5 Hz).

(3s,5s,7s)-Adamantan-1-yl 2-phenylacetate (3aa) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as beige oil in 29% (0.291 mmol, 79 mg). When the reaction was carried out at 100 °C instead of 80 °C, the product was isolated in 40% (0.402 mmol, 109 mg). **3aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.18 (m, 5H),

3.54 (s, 2H), 2.26–2.03 (m, 9H), 1.66 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.6, 134.9, 129.3, 128.5, 126.9, 80.9, 42.9, 41.4, 36.3, 30.9. HRMS (HESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{23}O_2$ 271.1693; Found 271.1688.

Cholesterol phenylacetate (3ab) was synthesized according to the general esterification procedure B in 0.5 mmol scale. The product was isolated as yellow solid in 49% (0.244 mmol, 123 mg). **3ab**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.20 (m, 5H), 5.37 (d, J = 5.0 Hz, 1H), 4.64 (m, 1H), 3.60 (s, 2H), 2.32 (m, 2H), 2.08–1.91 (m, 2H), 1.85 (m, 3H), 1.67–1.22 (m, 10H), 1.23–0.80 (m, 23H), 0.68 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.1, 139.7, 134.5, 129.3, 128.6, 127.1, 122.8, 74.6, 56.8, 56.3, 50.1, 42.4, 41.8, 39.9, 39.7, 38.2, 37.1, 36.7, 36.3, 35.9, 32.0, 31.9, 28.4, 28.2, 27.9, 24.4, 23.9, 22.9, 22.7, 21.2, 19.5, 18.9, 11.9. HRMS (HESI) m/z: $[M+Na]^+$ Calcd for $C_{35}H_{52}NaO_2$ 527.3860; Found 527.3864.

1-Phenylpropan-2-yl benzoate (3ac) was synthesized according to the general esterification procedure B in 1 mmol scale with 2 equiv. of alcohol (138 μL, 1 mmol). The product was isolated as yellow oil in 41% (0.21 mmol, 49.4 mg). Analytical data matches with reported literature.[38] **3ac**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.92 (m, 2H), 7.63–7.49 (m, 1H), 7.50–7.38 (m, 2H), 7.38–7.14 (m, 5H), 5.37 (m, 1H), 3.08 (m, 1H), 2.90 (m, 1H), 1.35 (m, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2, 137.7, 132.9, 130.9, 129.7 (overlapping signals, 2C), 128.5, 128.4, 126.6, 72.3, 42.5, 19.6.

(*R*)-1-Phenylpropan-2-yl 2-phenylacetate (3ad) was synthesized according to the general esterification procedure B in 0.5 mmol scale. The product was isolated as beige oil in 93% (0.466 mmol, 119 mg). **3ad**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.09 (m, 10H), 5.21 (m, 1H), 3.62 (s, 2H), 2.96 (m, 1H), 2.81 (m, 1H), 1.29 (m, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.1, 137.5, 134.2, 129.5, 129.3, 128.6, 128.4, 127.0, 126.5, 77.5, 77.2, 76.8, 72.0, 42.2, 41.8, 19.5. HRMS

(HESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}NaO_2$ 277.1199; Found 277.1194. Er 99.18:0.82 (98.4% *ee*) for **3ad** was determined by HPLC analysis (ReproSil Chiral-NR 250x4.6 mm, 5% 2-propanol in hexane, 1.0 mL/min, λ=225 nm, 10 µL injection volume), *R* isomer t(1)= 10.2 min, *S* isomer t(2)= 11.4 min; compared against racemic mixture. Starting material (*R*)-(-)-1-phenyl-2-propanol 98.7% *ee* was confirmed by HPLC (Chiralcel OD-H column 250x4.6 mm, 0.5% 2-propanol in hexane, 0.5 mL/min, λ=225 nm, 10 µL injection volume, *S* isomer t(1)= 12.5 min, *R* isomer t(1)= 12.9 min; compared against racemic mixture.

4-Hydroxyphenethyl 2-phenylacetate (3ae) was synthesized according to the general esterification procedure B in 1 mmol scale. The product was isolated as colourless oil in 43% (0.434 mmol, 111 mg). Analytical data matches with reported literature.[39] **3ae**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H), 7.03–6.95 (m, 2H), 6.77–6.71 (m, 2H), 4.31 (t, J = 7.0 Hz, 2H), 3.65 (s, 2H), 2.86 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.5, 154.6, 133.7, 130.0, 129.32, 129.28, 128.6, 127.2, 115.5, 65.9, 41.5, 34.1.

Supporting Information Available: [PDF] This material is available free of charge at http://pubs.acs.org

^{1}H NMR and ^{13}C{^{1}H} NMR spectra of all new compounds, all known compounds made by a new route not reported in previous literature, and ^{13}C{^{1}H} NMR analysis of $Zr(Cp)_2(CF_3SO_3)_2\cdot$THF. HPLC chromatograms for esters **3t** and **3ac**. Additional data for the kinetic evaluation of solvents, reproducibility, VTNA analysis, concentration effects, addition of water and molecular sieves, transesterification with $Zr(Cp)_2(CF_3SO_3)_2\cdot$THF and incompatible substrates. Calculations for TON/TOF, Arrhenius equation and recycling experiments.

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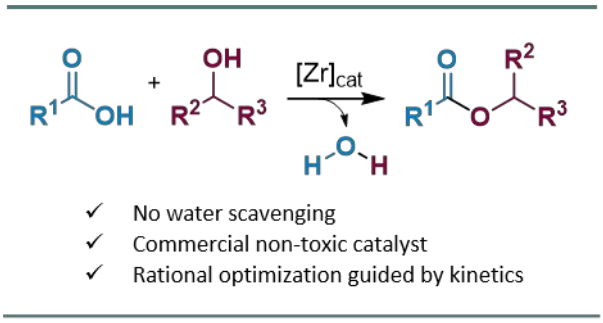

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