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

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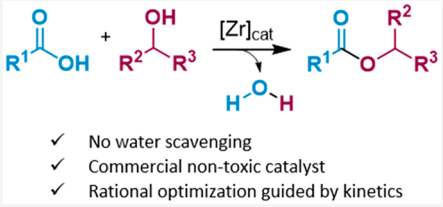
ABSTRACT: This work describes the use of kinetics as a tool for rational optimization of an esterification process with down to equimolar ratios of reagents using a recyclable commercially available zirconocene complex in catalytic amounts. In contrast to previously reported group IV metal-catalyzed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



INTRODUCTION:

Esterification of alcohol and 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 2000s 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 a 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 the utilization of full reaction profiles for a minimal number of experiments under synthetically relevant conditions to generate an in-depth understanding of a chemical system, and have been successfully employed for the mechanistic elucidation of a wide variety of organic transformations.[14] While valuable from a fundamental perspective, mechanistic insights can also be converted into strategic modifications 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 tetrahydrofuran (THF). Indeed, a first attempt using an equimolar ratio of benzyl alcohol and benzoic acid with a 2 mol % loading of the

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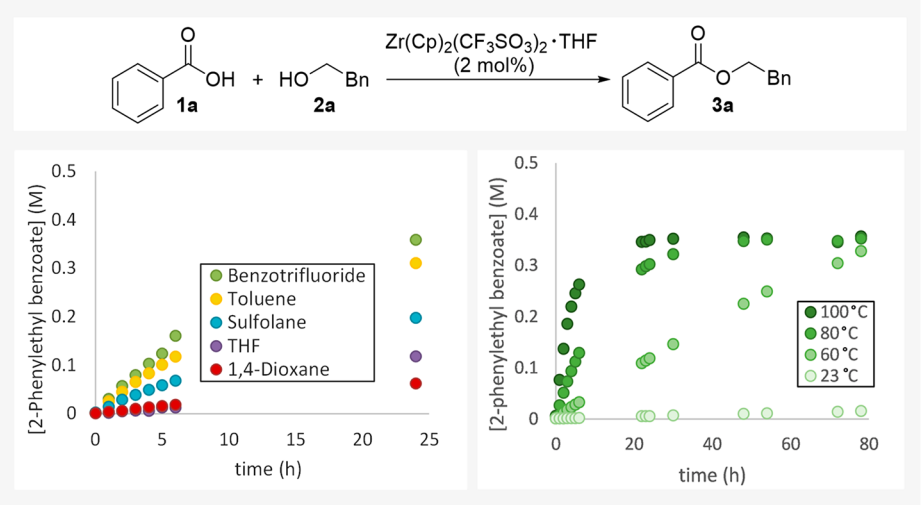

Figure 1. Left: solvent evaluation at 80 °C. Right: temperature evaluation. Conditions: 0.5 M benzoic acid **1a**, 0.5 M 2-phenylethanol **2a**, 2 mol % $Zr(Cp)_2(CF_3SO_3)_2$·THF, benzotrifluoride, and ambient atmosphere.

zirconium complex resulted in 6% benzyl benzoate after 24 h at 80 °C. Taking off from this starting point, an assessment of solvents was carried out (Supporting Information (SI)) that indicated byproduct formation at high reactant concentrations. This prompted a switch to 2-phenylethanol as the 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 h 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 and 100 °C had increasingly faster rates. An approximate 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.

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 be 0.75 (Figure 2, middle) for different global reaction concentrations.[13] The less than first 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

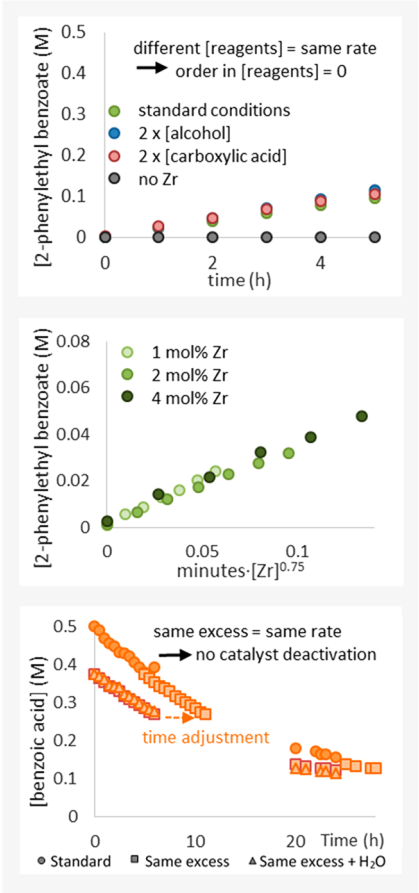

Figure 2. Top: different excess experiments and blank experiments. Middle: determination of order in [Zr] (0.2 M equimolar substrate concentration). Bottom: same excess experiments in the absence and presence of added water.

the absence (squares) and presence (triangles) of the corresponding amount of water (0.125 M). As evident, the time-adjusted profiles for the same excess experiments overlay very well with that of standard conditions, indicating that the catalyst does not undergo significant inhibition or decomposition under standard conditions.

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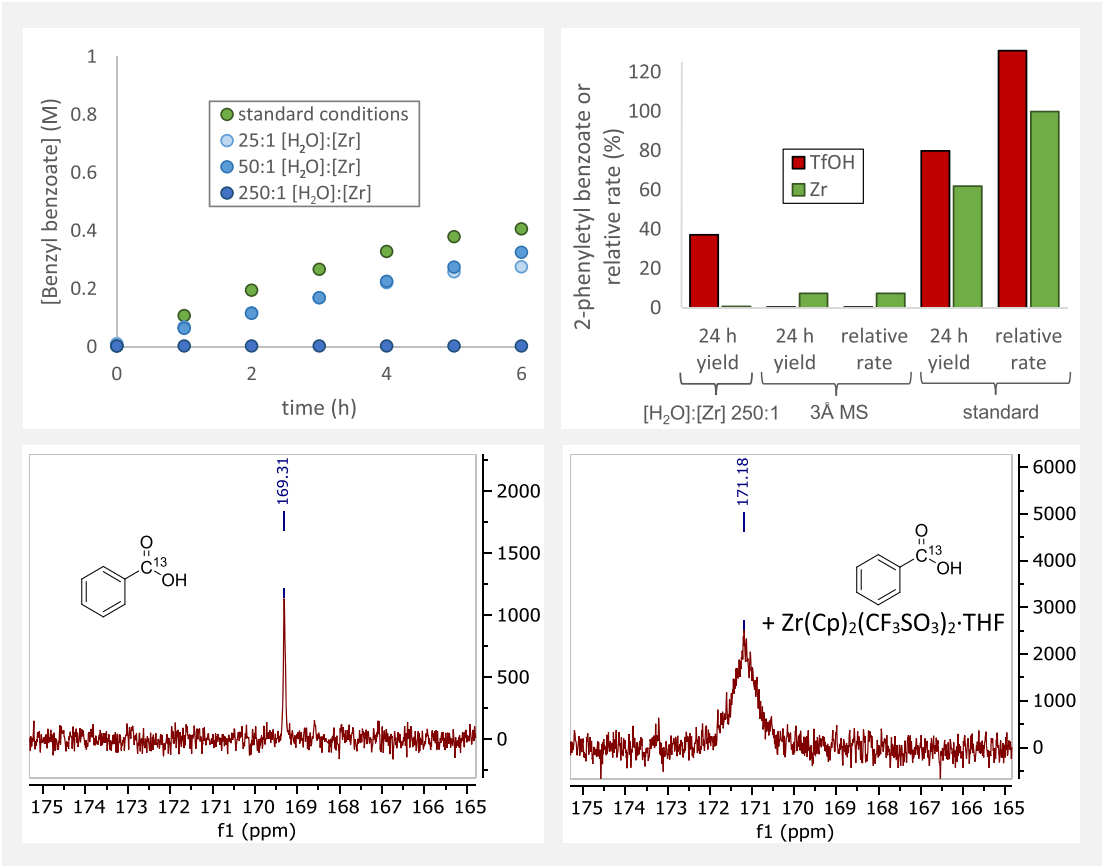

Figure 3. Top left: assessment of the effect of water. Conditions: 2 mol % $Zr(Cp)_2(CF_3SO_3)_2$·THF, 1 M benzoic acid, 1 M benzyl alcohol, 80 °C, toluene (dry, inert), and N_2 atmosphere. Top right: comparison between zirconium catalysis and triflic acid catalysis in the presence of water and molecular sieves. Conditions: 2 mol % $Zr(Cp)_2(CF_3SO_3)_2$·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 are plotted as percent of Zr-catalyzed standard conditions. Bottom: effect on carbonyl peak shift for $^{13}C(1)$-benzoic acid in the absence (left) and presence (right) of $Zr(Cp)_2(CF_3SO_3)_2$·THF (toluene-d_8, 80 °C, 100 MHz).

The combined kinetic 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 $Zr(Cp)_2(CF_3SO_3)_2$·THF, respectively, were chosen as the starting points for the substrate evaluation. Under these conditions, the turnover number (TON) for the first 6 h of the reaction time was estimated to be 19.7, corresponding to a turnover frequency (TOF) of 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 equiv of water relative to zirconium, whereas the addition of 250 molar equiv 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 h under standard conditions at 0.5 M. The addition of 250 equiv of water relative to the catalyst resulted in the product in 37% yield in the presence of triflic acid after 24 h, whereas only traces of **3a** were observed in the presence of the zirconocene complex. Interestingly, the addition of molecular sieves (MS) 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 h (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 toward 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 suggest 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 $Zr(Cp)_2(CF_3SO_3)_2$·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.

A tentative catalytic cycle is depicted in Figure 4. The positive rate dependence on [Zr] and close to zero order in [benzoic

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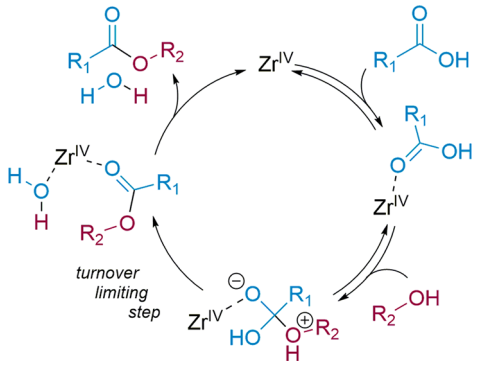

Figure 4. Proposed catalytic cycle.

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, the 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 is 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 density functional theory (DFT) calculations for collapse of the tetrahedral intermediate in zirconium-catalyzed amidation.[17a]

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 a 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**–**i**), 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 into their corresponding esters **3l**–**u** 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 into its respective ester **3s** in a good yield, and we were pleased to see that the corresponding 2-phenethyl ester **3t** of Boc-protected L-alanine retained >99% enantiomeric excess (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**

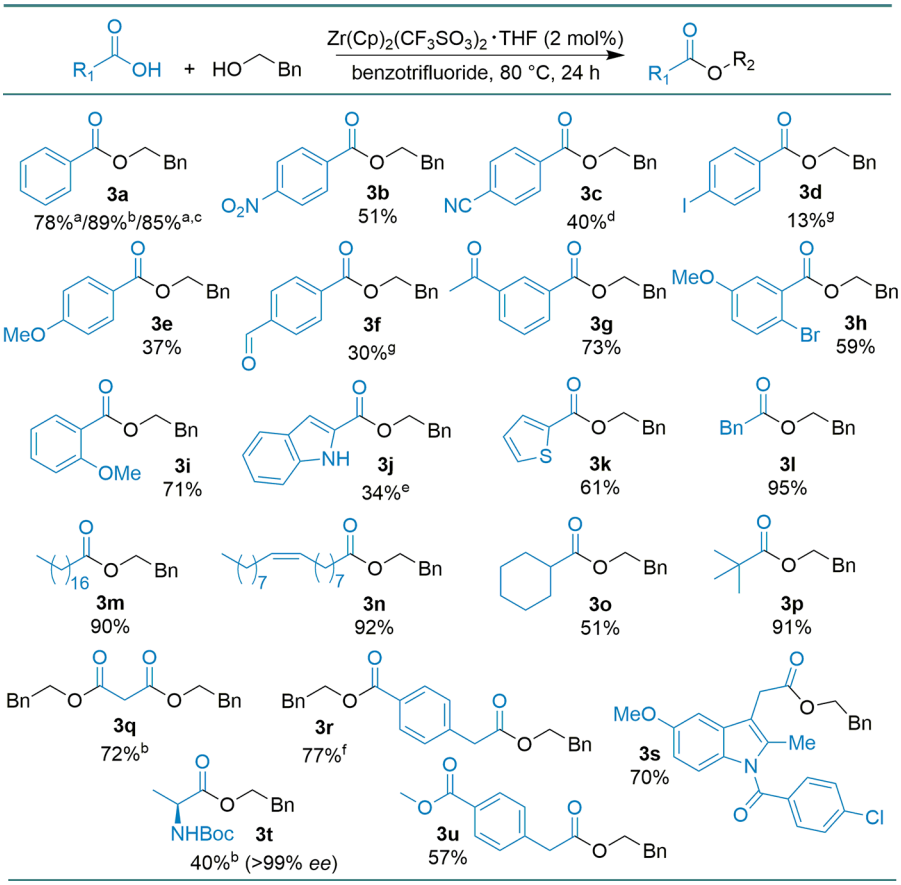

Figure 5. Carboxylic acid scope for esterification. Standard conditions: 2 mol % $Zr(Cp)_2(CF_3SO_3)_2$·THF, 1 M carboxylic acid, 1 M alcohol, benzotrifluoride, 80 °C, 24 h, and ambient atmosphere. [a]High-performance liquid chromatography (HPLC) yield, [b]2 equiv of alcohol, [c]2 equiv of acid, [d]toluene as solvent, [e]3 equiv of alcohol, and [f]1:2 ratio of alcohol to carboxylic acid moieties (1:1 molar ratio of starting materials). [g]^{1}H-NMR yield.

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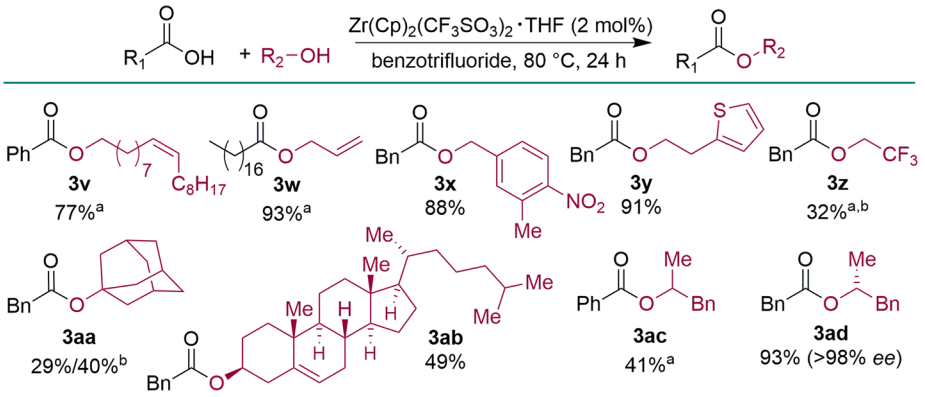


Figure 6. Alcohol scope for esterification. Standard conditions: 2 mol % $Zr(Cp)_2(CF_3SO_3)_2$·THF, 1 M carboxylic acid, 1 M alcohol, benzotrifluoride, 80 °C, 24 h, and ambient atmosphere; [a]2 equiv of alcohol, [b]100 °C.

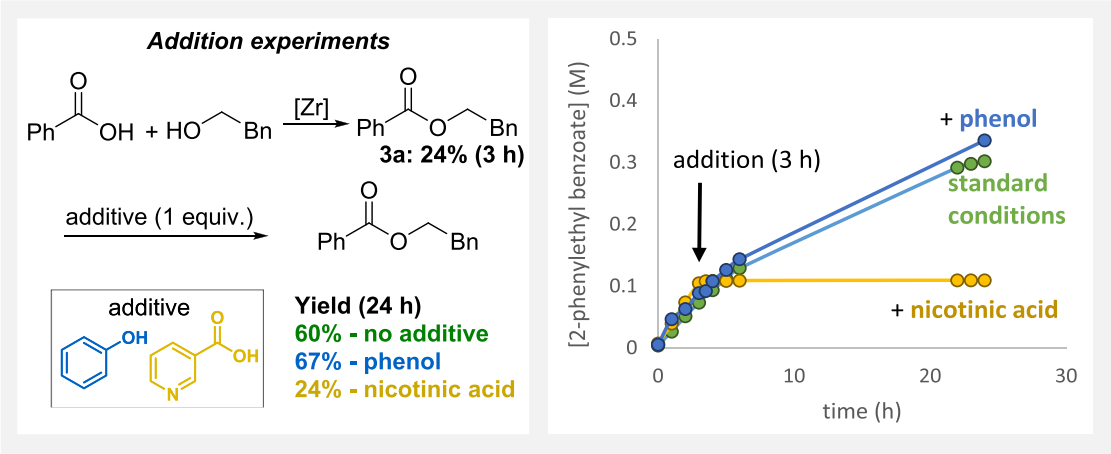
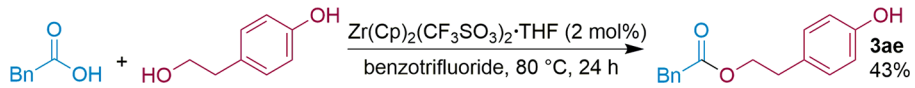


Figure 7. Addition of phenol/nicotinic acid to esterification of benzoic acid and 2-phenylethanol. Conditions: 2 mol % $Zr(Cp)_2(CF_3SO_3)_2$·THF, 0.5 M carboxylic acid, 0.5 M alcohol, benzotrifluoride, 80 °C, and ambient atmosphere. Addition of 1 equiv of phenol/nicotinic acid relative to carboxylic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

Scheme 1. Selective Monoacylation of a Diol[a]



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

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).

A range of aliphatic alcohols proved to be suitable esterification coupling partners (Figure 6), including oleyl alcohol and allyl alcohol, which smoothly yielded esters **3v** and **3w** with both aryl and alkyl carboxylic acids. The electron-poor benzylic alcohol and the heteroaromatic 2-thiophene ethanol were acylated to form **3x** and **3y** in high yields. Trifluoroethanol formed the corresponding phenylacetate **3z** in moderate yield, as did the sterically hindered adamantyl 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 a moderate yield, whereas the use of (*R*)-(−)-1-phenyl-2-propanol (>98% ee) furnished phenylacetic ester **3ad** in an excellent yield and retained enantiomeric excess.

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 3 h 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), the 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 a nearly 1:1 ratio to zirconium (SI), may be explained by the 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. On the contrary, 2-phenylethyl benzoate **3a** continued to form at a similar rate after the addition of 50 equiv of phenol relative to zirconium with only traces of phenyl ester formation (see SI).

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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.

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).

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 future use in dehydrative catalyzed reactions.

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 poly(tetrafluoroethylene) (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 hertz), and integration. Kinetic data was analyzed by Agilent 1260 Infinity Quaternary LC (Eclipse Plus 18C column, 3.5 μm, 4.6 × 100 mm^2; 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 threefold dilution between each sample in the series. HPLC with a chiral stationary phase was performed on an Agilent 1100 series instrument. High-resolution mass spectrometry analyses were performed by Thermo Scientific Q Exactive HF Hybrid Quadrupole-Orbitrap HESI or Bruker microTOF ESI, and low-resolution mass analyses by Bruker Daltonics 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 (IS) 4,4′-di-*tert*-butylbiphenyl (0.02 mmol, 5.3 mg), benzotrifluoride (1 mL, nondried), and 2-phenylethanol (1 mmol, 120 μL) were added into the reaction vessel under an air atmosphere. The screw cap was tightened and the vial was placed in an oil bath at 80 °C. At indicated times, 20 μL of the reaction mixture was removed with a microliter syringe and mixed with 0.5 mL of 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. 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. 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, and 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, and ambient atmosphere; and (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, and ambient atmosphere.

Addition Reactions. 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), or 250:1 H_2O/Zr (90 μL, 5.0 mmol H_2O) was added at the outset of three separate reactions (1 M equimolar ratios of benzyl alcohol and 2-phenylethanol, 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 the onset of the reaction (0.5 M equimolar, 0.5 mmol scale); and (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 the onset of three separate reactions (0.5 M equimolar reactants, 1.0 mmol scale).

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

Recycling Experiments. Recycling experiments were carried out as follows. The reaction was started in accordance with general esterification procedure B on a 0.5 mmol scale. After 24 h, the vial was removed from the heated oil bath and the solvent was evaporated. The reaction mixture was thereafter extracted with 1 mL of petroleum ether (40−65 °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 three extractions. The combined product/substrate fractions were evaporated, weighed, and subjected to ^{1}H NMR analysis using MeOD-d_4 as the 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, phenylacetic acid, 2-phenylethanol, and benzotrifluoride were then added in accordance with general esterification procedure B and the reaction was stirred at 80 °C for another 24 h, after which the recycling procedure was repeated.

General Esterification Procedure B for Product Isolation. For 1 M reaction mixture, $Zr(Cp)_2(CF_3SO_3)_2$·THF (0.02 mmol, 11.8 mg), carboxylic acid (1 mmol), benzotrifluoride (1 mL, nondried), and alcohol (1 mmol) were added into the reaction vessel under an air atmosphere. The screw cap was tightened and the vial was 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**).* **3a** was synthesized according to the esterification procedure B on a 1 mmol scale using 2 equiv of 2-phenylethanol (2 mmol, 240 μL). The product was isolated as a yellow oil in 89% yield (0.89 mmol, 200.7 mg). Analytical data matches with the 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.

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*2-Phenylethyl 4-Nitrobenzoate (**3b**).* **3b** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a yellow oil in 51% yield (0.511 mmol, 138 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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. High-resolution mass spectrometry (HRMS) (heated electrospray ionization (HESI)) m/z: $[M + Na]^+$ calcd for $C_{15}H_{13}NNaO_4$ 294.0737; found 294.0761.

*2-Phenylethyl 4-Cyanobenzoate (**3c**).* **3c** was synthesized according to the general esterification procedure B on a 0.5 mmol scale with toluene as the solvent. The product was isolated as a yellow solid in 40% yield (0.20 mmol, 50.8 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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**).* **3d** was synthesized according to the general esterification procedure B on a 0.5 mmol scale with toluene as the 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 the internal standard. Analytical data matches with the 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). $^{13}C\{^1H\}$ 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**).* **3e** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a yellow oil in 37% yield (0.374 mmol, 96 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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**).* **3f** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated with minor byproducts 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 the internal standard. After a 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 the ^{1}H NMR spectrum. Aromatic signals for **3f** and the standard were used for the NMR-yield calculation (SI). Further purification using preparative thin-layer chromatography using an eluent of 1:15 ethyl acetate/petroleum ether (bp 40−65 °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). $^{13}C\{^1H\}$ 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 (electrospray ionization (ESI)) m/z: $[M + Na]^+$ calcd for $C_{16}H_{14}NaO_3$ 277.08; found 277.08.

*2-Phenylethyl 3-Acetylbenzoate (**3g**).* **3g** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a yellow oil in 73% yield (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). $^{13}C\{^1H\}$ 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**).* **3h** was synthesized according to the general esterification procedure B on a 0.5 mmol scale. The product was isolated as a beige, waxy solid in 59% yield (0.297 mmol, 100 mg). **3h**: ^{1}H NMR (400 MHz, $CDCl_3$) 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**).* **3i** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a yellow oil in 71% yield (0.714 mmol, 183 mg). **3i**: ^{1}H NMR (500 MHz, $CDCl_3$) 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 1H-Indole-2-carboxylate (**3j**).* **3j** was synthesized according to the general esterification procedure B on a 0.5 mmol scale using 3 equiv of 2-phenylethanol (1.5 mmol, 180 μL). The product was isolated as a pale yellow solid in 34% yield (0.17 mmol, 45.1 mg). **3j**: ^{1}H 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**).* **3k** was synthesized according to the general esterification procedure B on a 0.5 mmol scale. The product was isolated as a yellow oil in 61% yield (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). $^{13}C\{^1H\}$ 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**).* **3l** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a yellow liquid in 95% yield (0.949 mmol, 228 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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**).* **3m** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a pale yellow solid in 90% yield (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). $^{13}C\{^1H\}$ 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**).* **3n** was synthesized according to the general esterification procedure B on a 0.5 mmol scale. The product was isolated as a colorless oil in 92% yield (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). $^{13}C\{^1H\}$ 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**).* **3o** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a colorless oil in 51% yield (0.51 mmol, 118.8 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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.

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*2-Phenylethyl 2,2-Dimethylpropanoate (**3p**).* **3p** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a colorless oil in 91% yield (0.91 mmol, 187.6 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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**).* **3q** was synthesized according to the general esterification procedure B on a 1 mmol scale using 2 equiv of 2-phenylethanol (2 M, 2 mmol, 241 μL). The product was isolated as a colorless oil in 72% yield (0.72 mmol, 225.1 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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**).* **3r** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a yellow oil in 77% yield (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). $^{13}C\{^1H\}$ 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**).* **3s** was synthesized according to the general esterification procedure B on a 0.5 mmol scale. The product was isolated as a yellow oil in 70% yield (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). $^{13}C\{^1H\}$ 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**).* **3t** was synthesized according to the general esterification procedure B on a 0.5 mmol scale with 2 equiv of 2-phenylethanol (1 mmol, 120 μL). The product was isolated as a white crystalline solid in 40% yield (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). $^{13}C\{^1H\}$ 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 250 × 4.6 mm^2, 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**).* **3u** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a colorless waxy solid in 57% yield (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). $^{13}C\{^1H\}$ 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**).* **3v** was synthesized according to the general esterification procedure B on a 0.5 mmol scale with 2 equiv of oleyl alcohol (1 mmol, 316 μL). The product was isolated as a colorless oil in 77% yield (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). $^{13}C\{^1H\}$ 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**).* **3w** was synthesized according to the general esterification procedure B on a 0.25 mmol scale using 2 equiv of allyl alcohol (0.5 mmol, 34 μL). The product was isolated as a white crystalline mass in 93% yield (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). $^{13}C\{^1H\}$ 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**).* **3x** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a yellow oil in 88% yield (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). $^{13}C\{^1H\}$ 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**).* **3y** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a clear, colorless liquid in 91% yield (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). $^{13}C\{^1H\}$ 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**).* **3z** was synthesized according to the general esterification procedure B on a 1 mmol scale with 2 equiv of 2,2,2-trifluoroethanol (2 mmol, 145 μL) at 100 °C. The product was isolated as a pale yellow oil in 32% yield (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 the 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). $^{13}C\{^1H\}$ 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**).* **3aa** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a beige oil in 29% yield (0.291 mmol, 79 mg). When the reaction was carried out at 100 °C instead of 80 °C, the product was isolated in 40% yield (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). $^{13}C\{^1H\}$ 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**).* **3ab** was synthesized according to the general esterification procedure B on a 0.5 mmol scale. The product was isolated as a yellow solid in 49% yield (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). $^{13}C\{^1H\}$ 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**).* **3ac** was synthesized according to the general esterification procedure B on a 1 mmol scale with 2 equiv of alcohol (138 μL, 1 mmol). The product was isolated as a yellow oil in 41% yield (0.21 mmol, 49.4 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2, 137.7,

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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**).* **3ad** was synthesized according to the general esterification procedure B on a 0.5 mmol scale. The product was isolated as a beige oil in 93% yield (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). $^{13}C\{^1H\}$ 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. Enantiomeric ratio (er) 99.18:0.82 (98.4% ee) for **3ad** was determined by HPLC analysis (ReproSil Chiral-NR 250 × 4.6 mm^2, 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 and $t(2)$ = 11.4 min, compared against the racemic mixture. Starting material (*R*)-(−)-1-phenyl-2-propanol 98.7% ee was confirmed by HPLC (Chiralcel OD-H column 250 × 4.6 mm^2, 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 the racemic mixture).

*4-Hydroxyphenethyl 2-Phenylacetate (**3ae**).* **3ae** was synthesized according to the general esterification procedure B on a 1 mmol scale. The product was isolated as a colorless oil in 43% yield (0.434 mmol, 111 mg). Analytical data matches with the 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). $^{13}C\{^1H\}$ 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00235.

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

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Notes

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■ REFERENCES

(1) Fischer, E.; Speier, A. Darstellung der Ester. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3252−3258.

(2) (a) Neises, B.; Steglich, W. Simple Method for the Esterification of Carboxylic Acids. *Angew. Chem., Int. Ed.* **1978**, *17*, 522−524. (b) Schotten, C. Ueber die Oxydation des Piperidins. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2544−2547. (c) Baumann, E. Ueber eine einfache Methode der Darstellung von Benzoësäureäthern. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 3218−3222.

(3) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. Direct Condensation of Carboxylic Acids with Alcohols Catalyzed by Hafnium(IV) Salts. *Science* **2000**, *290*, 1140−1142. (b) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. Direct ester condensation from a 1:1 mixture of carboxylic acids and alcohols catalyzed by hafnium(IV) or zirconium-(IV) salts. *Tetrahedron* **2002**, *58*, 8179−8188.

(4) (a) Ishihara, K. Dehydrative condensation catalyses. *Tetrahedron* **2009**, *65*, 1085−1109. (b) Matsumoto, K.; Yanagi, R.; Oe, Y. Recent Advances in the Synthesis of Carboxylic Acid Esters. In *Carboxylic Acid—Key Role in Life Sciences*;Georgiana Ileana, B.; Gabriel Lucian, R., Eds.; InTechOpen, 2018.

(5) Fang, Z.; Dixon, D. A. Hydrolysis of $ZrCl_4$ and $HfCl_4$: The Initial Steps in the High-Temperature Oxidation of Metal Chlorides to Produce ZrO_2 and HfO_2. *J. Phys. Chem. C* **2013**, *117*, 7459−7474.

(6) (a) Hollis, T. K.; Robinson, N. P.; Bosnich, B. Homogeneous catalysis. Titanium complex $[Ti(Cp)_2(CF_3SO_3)_2]$ and zirconium complex $[Zr(Cp)_2(CF_3SO_3)_2THF]$, efficient catalysts for the Diels-Alder reaction. *Organometallics* **1992**, *11*, 2745−2748. (b) Hollis, T. K.; Robinson, N. P.; Bosnich, B. Homogeneous catalysis. $[TiCp_2(CF_3SO_3)_2]$ and $[ZrCp_2(CF_3SO_3)_2THF]$, fast and efficient catalysts for the Mukaiyama cross-aldol reaction. *Tetrahedron Lett.* **1992**, *33*, 6423−6426. (c) Kobayashi, S. Rare earth metal trifluoromethanesulfonates as water-tolerant Lewis acid catalysts in organic synthesis. *Synlett* **1994**, 689−701. (d) Waller, F. J.; Barrett, A. G. M.; Braddock, D. C.; Ramprasad, D. Hafnium(IV) and zirconium-(IV) triflates as superior recyclable catalysts for the atom economic nitration of o-nitrotoluene. *Tetrahedron Lett.* **1998**, *39*, 1641−1642. (e) Lin, S.; Bondar, G. V.; Levy, C. J.; Collins, S. Mukaiyama Aldol Reactions Catalyzed by Zirconocene Bis(triflate) Complexes: Stereochemistry and Mechanisms for C−C Bond Formation. *J. Org. Chem.* **1998**, *63*, 1885−1892. (f) Kobayashi, S.; Ogawa, C. New Entries to Water-Compatible Lewis Acids. *Chem. − Eur. J.* **2006**, *12*, 5954−5960. (g) Ishitani, H.; Suzuki, H.; Saito, Y.; Yamashita, Y.; Kobayashi, S. Hafnium Trifluoromethanesulfonate $[Hf(OTf)_4]$ as a Unique Lewis Acid in Organic Synthesis. *Eur. J. Org. Chem.* **2015**, 5485−5499. (h) de Léséleuc, M.; Collins, S. K. Direct Macrolactonization of Seco Acids via Hafnium(IV) Catalysis. *ACS Catal.* **2015**, 1462−1467. (i) Lundberg, H.; Tinnis, F.; Adolfsson, H. Zirconium catalyzed amide formation without water scavenging. *Appl. Organomet. Chem.* **2019**, *33*, No. e5062.

(7) (a) Qiu, R.; Xu, X.; Peng, L.; Zhao, Y.; Li, N.; Yin, S. Strong Lewis Acids of Air-Stable Metallocene Bis(perfluorooctanesulfonate)s as High-Efficiency Catalysts for Carbonyl-Group Transformation Reactions. *Chem. − Eur. J.* **2012**, *18*, 6172−6182. (b) Li, N.; Wang, L.; Zhang, L.; Zhao, W.; Qiao, J.; Xu, X.; Liang, Z. Air-stable Bis(pentamethylcyclopentadienyl) Zirconium Perfluorooctanesulfonate as an Efficient and Recyclable Catalyst for the Synthesis of N-

substituted Amides. *ChemCatChem* **2018**, *10*, 3532−3538. (c) Li, N.; Wang, L.; Wang, H.; Qiao, J.; Zhao, W.; Xu, X.; Liang, Z. Synthesis and structure of an air-stable bis(pentamethylcyclopentadienyl) zirconium pentafluorbezenesulfonate and its application in catalytic epoxide ring-opening reactions. *Tetrahedron* **2018**, *74*, 1033−1039. (d) Li, N.; Wang, Y.; Liu, F.; Zhao, X.; Xu, X.; An, Q.; Yun, K. Air-stable zirconium (IV)-salophen perfluorooctanesulfonate as a highly efficient and reusable catalyst for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones under solvent-free conditions. *Appl. Organomet. Chem.* **2020**, *34*, No. e5454.

(8) (a) Kobayashi, S.; Nagayama, S.; Busujima, T. Lewis Acid Catalysts Stable in Water. Correlation between Catalytic Activity in Water and Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands. *J. Am. Chem. Soc.* **1998**, *120*, 8287−8288. (b) Koito, Y.; Nakajima, K.; Kobayashi, H.; Hasegawa, R.; Kitano, M.; Hara, M. Slow Reactant-Water Exchange and High Catalytic Performance of Water-Tolerant Lewis Acids. *Chem. − Eur. J.* **2014**, *20*, 8068−8075. (c) Tripodi, G. L.; Correra, T. C.; Angolini, C. F. F.; Ferreira, B. R. V.; Maître, P.; Eberlin, M. N.; Roithová, J. The Intermediates in Lewis Acid Catalysis with Lanthanide Triflates. *Eur. J. Org. Chem.* **2019**, 3560−3566.

(9) (a) Renner, R. Growing Concern Over Perfluorinated Chemicals. *Environ. Sci. Technol.* **2001**, *35*, 154A−160A. (b) Brendel, S.; Fetter, É.; Staude, C.; Vierke, L.; Biegel-Engler, A. Short-chain perfluoroalkyl acids: environmental concerns and a regulatory strategy under REACH. *Environ. Sci. Eur.* **2018**, *30*, No. 9.

(10) U.S. EPA. *Risk Management for Per- and Polyfluoroalkyl Substances (PFASs) under TSCA*; U.S. EPA, 2019; [online] Available at: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-and-polyfluoroalkyl-substances-pfass#tab-3 (accessed 11 Nov, 2019).

(11) (a) Tang, Z.; Jiang, Q.; Peng, L.; Xu, X.; Li, J.; Qiu, R.; Au, C.-T. Zirconocene-catalyzed direct (trans)esterification of acyl acids (esters) and alcohols in a strict 1: 1 ratio under solvent-free conditions. *Green Chem.* **2017**, *19*, 5396−5402. (b) Deng, Y.; Hu, X.; Cheng, L.; Wang, H.; Duan, L.; Qiu, R. Zirconocene-catalysed biodiesel synthesis from vegetable oil with high free fatty acid contents. *J. Organomet. Chem.* **2018**, *870*, 116−120.

(12) (a) Blackmond, D. G. Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302−4320. (b) Blackmond, D. G. Kinetic Profiling of Catalytic Organic Reactions as a Mechanistic Tool. *J. Am. Chem. Soc.* **2015**, *137*, 10852−10866.

(13) (a) Burés, J. What is the Order of a Reaction? *Top. Catal.* **2017**, *60*, 631−633. (b) Nielsen, C. D. T.; Burés, J. Visual kinetic analysis. *Chem. Sci.* **2019**, *10*, 348−353.

(14) (a) Hill, D. E.; Bay, K. L.; Yang, Y.-F.; Plata, R. E.; Takise, R.; Houk, K. N.; Yu, J.-Q.; Blackmond, D. G. Dynamic Ligand Exchange as a Mechanistic Probe in Pd-Catalyzed Enantioselective C−H Functionalization Reactions Using Monoprotected Amino Acid Ligands. *J. Am. Chem. Soc.* **2017**, *139*, 18500−18503. (c) O'Brien, A. G.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. Radical C-H functionalization of heteroarenes under electrochemical control. *Angew. Chem., Int. Ed.* **2014**, *53*, 11868−11871. (d) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. Mechanistic Rationalization of Unusual Kinetics in Pd-Catalyzed C−H Olefination. *J. Am. Chem. Soc.* **2012**, *134*, 4600−4606. (e) Nielsen, C. D. T.; Mooij, W. J.; Sale, D.; Rzepa, H. S.; Burés, J.; Spivey, A. C. Reversibility and reactivity in an acid catalyzed cyclocondensation to give furanochromanes − a reaction at the 'oxonium-Prins' vs. 'ortho-quinone methide cycloaddition' mechanistic nexus. *Chem. Sci.* **2019**, *10*, 406−412.

(15) (a) Blackmond, D. G.; Rosner, T.; Pfaltz, A. Comprehensive Kinetic Screening of Catalysts Using Reaction Calorimetry. *Org. Process Res. Dev.* **1999**, *3*, 275−280. (b) Zotova, N.; Valera, F.; Blackmond, D. G. Reaction Progress Kinetic Analysis: A Powerful Methodology for Streamlining Mechanistic Analysis of Complex Organic Reactions. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K., Braish, T. Eds.; CRC Press: Boca Raton, 2008; Vol. 2, pp 455−444. (c) Companyó, X.; Burés, J. Distribution of Catalytic Species as an Indicator To Overcome Reproducibility Problems. *J. Am. Chem. Soc.* **2017**, *139*, 8432−8435. (d) Colletto, C.; Burés, J.; Larrosa, I. Reaction monitoring reveals poisoning mechanism of $Pd_2(dba)_3$ and guides catalyst selection. *Chem. Commun.* **2017**, *53*, 12890−12893. (e) Wang, J.; Lundberg, H.; Asai, S.; Martín-Acosta, P.; Chen, J. S.; Brown, S.; Farrell, W.; Dushin, R. G.; O'Donnell, C. J.; Ratnayake, A. S.; Richardson, P.; Liu, Z.; Qin, T.; Blackmond, D. G.; Baran, P. S. Kinetically guided radical-based synthesis of $C(sp^3)−C(sp^3)$ linkages on DNA. *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *115*, E6404−E6410.

(16) Ogawa, A.; Curran, D. P. Benzotrifluoride: A Useful Alternative Solvent for Organic Reactions Currently Conducted in Dichloromethane and Related Solvents. *J. Org. Chem.* **1997**, *62*, 450−451.

(17) (a) Lundberg, H.; Tinnis, F.; Zhang, J.; Algarra, A. G.; Himo, F.; Adolfsson, H. Mechanistic Elucidation of Zirconium-Catalyzed Direct Amidation. *J. Am. Chem. Soc.* **2017**, *139*, 2286−2295. (b) Rosner, T.; LeBars, J.; Pfaltz, A.; Blackmond, D. G. Observation of Unusual Kinetics in Heck Reactions of Aryl Halides: The Role of Non-Steady-State Catalyst Concentration. *J. Am. Chem. Soc.* **2001**, *123*, 1848−1855. (c) van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; deVries, J. G.; van Leeuwen, P. W. N. M. Fast Palladium Catalyzed Arylation of Alkenes Using Bulky Monodentate Phosphorus Ligands. *Eur. J. Inorg. Chem.* **1999**, 1073−1076.

(18) Arno, B.; Neuberth, P. *Applied Homogeneous Catalysis*, 1st ed.; Wiley-VCH Verlag GmbH: Weinheim, 2012.

(19) Hollis, T. K.; Bosnich, B. Mechanisms of the Catalytic Mukaiyama Aldol and Sakurai Allylation Reactions. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581.

(20) (a) Xu, X.-H.; Azuma, A.; Taniguchi, M.; Tokunaga, E.; Shibata, N. Efficient direct ester condensation between equimolar amounts of carboxylic acids and alcohols catalyzed by trifluoromethanesulfonic acid (TfOH) in Solkane365mfc. *RSC Adv.* **2013**, *3*, 3848−3852. (b) Kwie, F. H. A.; Baudoin-Dehoux, C.; Blonski, C.; Lherbet, C. Bismuth(III) Triflate: A Safe and Easily Handled Precursor for Triflic Acid: Application to the Esterification Reaction. *Synth. Commun.* **2010**, *40*, 1082−1087.

(21) It has previously been demonstrated that zirconocene with fluorinated sulfonate ligands form dimers in the presence of water (ref 21a). Furthermore, titanocene triflate is reported to readily form aqua complexes (ref 21b). In this context, the observed decelerating effect of molecular sieves on catalysis may suggest that dimers and/or aqua complexes of zirconocene triflate are involved in the catalysis. The need for a sufficient amount of water for efficient catalysis to occur has previously been reported for different types of Lewis acid catalysts (refs 21c−e). (a) Qiu, R.; Xu, X.; Li, Y.; Zhang, G.; Shao, L.; An, D.; Yin, S. Synthesis and structure of air-stable Lewis acidic binuclear complex of zirconocene pentafluorophenylsulfonate and its catalytic application in the allylation of carbonyl compounds with tetraallyltin. *Chem. Commun.* **2009**, 1679−1681. (b) Hollis, T. K.; Robinson, N. P.; Bosnich, B. Homogeneous catalysis. $[Ti(Cp^*)_2(H_2O)_2]^{2+}$: an air-stable, water-tolerant Diels-Alder catalyst. *J. Am. Chem. Soc.* **1992**, *114*, 5464−5466. (c) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. Direct and waste-free amidations and cycloadditions by organocatalytic activation of carboxylic acids at room temperature. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876−2879. (d) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. Direct Amidation of Carboxylic Acids Catalyzed by ortho-Iodo Arylboronic Acids: Catalyst Optimization, Scope, and Preliminary Mechanistic Study Supporting a Peculiar Halogen Acceleration Effect. *J. Org. Chem.* **2012**, *77*, 8386−8400. (e) Lundberg, H.; Adolfsson, H. Hafnium-Catalyzed Direct Amide Formation at Room Temperature. *ACS Catal.* **2015**, *5*, 3271−3277.

(22) Cutler, A.; Raja, M.; Todaro, A. Chlorozirconocene carboxylate complexes $Cp_2ClZr(OCOR)$ (R = H, CH_3, tert-Bu, Ph) and their reactions with zirconium hydride reagents. Metal hydride reduction of ligated carboxylate. *Inorg. Chem.* **1987**, *26*, 2877−2881.

(23) Lundberg, H.; Tinnis, F.; Adolfsson, H. Direct Amide Coupling of Non-activated Carboxylic Acids and Amines Catalysed by Zirconium(IV) Chloride. *Chem. − Eur. J.* **2012**, *18*, 3822−3826.

https://dx.doi.org/10.1021/acs.joc.0c00235
J. Org. Chem. 2020, 85, 6959−6969

(24) Yamada, K.; Liu, J.; Kunishima, M. Development of triazine-based esterifying reagents containing pyridines as a nucleophilic catalyst. *Org. Biomol. Chem.* **2018**, *16*, 6569−6575.
(25) McNulty, J.; Nair, J. J.; Cheekoori, S.; Larichev, V.; Capretta, A.; Robertson, A. J. Scope and Mechanistic Insights into the Use of Tetradecyl(trihexyl)phosphonium Bistriflimide: A Remarkably Selective Ionic Liquid Solvent for Substitution Reactions. *Chem. − Eur. J.* **2006**, *12*, 9314−9322.
(26) (a) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. Dimethylmalonyltrialkylphosphoranes: New General Reagents for Esterification Reactions Allowing Controlled Inversion or Retention of Configuration on Chiral Alcohols. *J. Org. Chem.* **2003**, *68*, 1597−1600. (b) But, T. Y. S.; Lu, J.; Toy, P. H. Organocatalytic Mitsunobu Reactions with 3,5-Dinitrobenzoic Acid. *Synlett* **2010**, *7*, 1115−1117.
(27) Huang, X.; Li, X.; Zou, M.; Song, S.; Tang, C.; Yuan, Y.; Jiao, N. From Ketones to Esters by a Cu-Catalyzed Highly Selective C(CO)−C(alkyl) Bond Cleavage: Aerobic Oxidation and Oxygenation with Air. *J. Am. Chem. Soc.* **2014**, *136*, 14858−14865.
(28) Chighine, A.; Crosignani, S.; Arnal, M.-C.; Bradley, M.; Linclau, B. Microwave-Assisted Ester Formation Using O-Alkylisoureas: A Convenient Method for the Synthesis of Esters with Inversion of Configuration. *J. Org. Chem.* **2009**, *74*, 4753−4762.
(29) Zhang, C.; Feng, P.; Jiao, N. Cu-Catalyzed Esterification Reaction via Aerobic Oxygenation and C−C Bond Cleavage: An Approach to α-Ketoesters. *J. Am. Chem. Soc.* **2013**, *135*, 15257−15262.
(30) Dam, J. H.; Osztrovszky, G.; Nordstrom, L. U.; Madsen, R. Amide Synthesis from Alcohols and Amines Catalyzed by Ruthenium N-Heterocyclic Carbene Complexes. *Chem. − Eur. J.* **2010**, *16*, 6820−6827.
(31) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. Ruthenium-catalyzed alkoxycarbonylation of alkenes using carbon monoxide. *Org. Chem. Front.* **2015**, *2*, 771−774.
(32) Weng, S.-S.; Ke, C.-S.; Chen, F.-K.; Lyu, Y.-F.; Lin, G.-Y. Transesterification catalyzed by iron(III) β-diketonate species. *Tetrahedron* **2011**, *67*, 1640−1648.
(33) Yamada, K.; Liu, J.; Kunishima, M. Development of triazine-based esterifying reagents containing pyridines as a nucleophilic catalyst. *Org. Biomol. Chem.* **2018**, *16*, 6569−6575.
(34) (a) Bernhard, K.; Gloor, U. Beiträge zum biologischen Abbau der Ölsäure. *Helv. Chim. Acta* **1952**, *35*, 608−616. (b) Posner, G. H.; Oda, M. Organic reactions at alumina surfaces. An extremely simple, convenient and selective method for acetylating primary alcohols in the presence of secondary alcohols. *Tetrahedron Lett.* **1981**, *22*, 5003−5006.
(35) (a) Boucher-Jacobs, C.; Nicholas, K. M. Catalytic Deoxydehydration of Glycols with Alcohol Reductants. *ChemSusChem* **2013**, *6*, 597−599. (b) Gangadhar, A.; Subbarao, R.; Lakshminarayana, G. A Facile Synthesis of 1(3)-Acylglycerols. *Synth. Commun.* **1989**, *19*, 2505−2514. (c) Klán, P.; Beňovský, P. Phase-Transfer Catalyzed Synthesis of 2-Propenyl Esters of Carboxylic Acids. *Monatsh. Chem.* **1992**, *123*, 469−471.
(36) Li, Y.; Wang, Z.; Wu, X.-F. A sustainable procedure toward alkyl arylacetates: palladium-catalysed direct carbonylation of benzyl alcohols in organic carbonates. *Green Chem.* **2018**, *20*, 969−972.
(37) Duggan, P. J.; Humphrey, D. G.; McCarl, V. Lipase-Catalyzed 1,6-Acylation of D-Mannitol. *Aust. J. Chem.* **2004**, *57*, 741−745.
(38) Kleman, P.; González-Liste, P. J.; García-Garrido, S. E.; Cadierno, V.; Pizzano, A. Highly Enantioselective Hydrogenation of 1-Alkylvinyl Benzoates: A Simple, Nonenzymatic Access to Chiral 2-Alkanols. *Chem. − Eur. J.* **2013**, *19*, 16209−16212.
(39) Pfaff, D.; Nemecek, G.; Podlech, J. A Lewis acid-promoted Pinner reaction. *Beilstein J. Org. Chem.* **2013**, *9*, 1572−1577.

https://dx.doi.org/10.1021/acs.joc.0c00235
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