

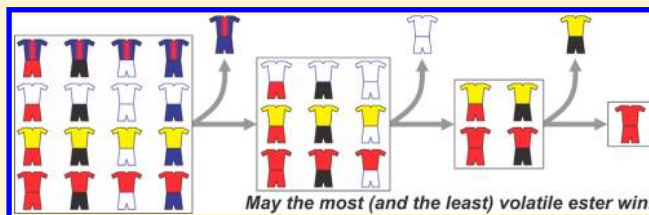
Distillative Self-Sorting of Dynamic Ester Libraries

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S Supporting Information

ABSTRACT: Metal alkoxides, such as NaOt-Bu or $\text{Ti}(\text{OBu})_4$, can initiate acyl exchange within complex ester libraries. Reactive distillation of such dynamic combinatorial libraries (DCLs) isolates the most volatile ester at the expense of the less volatile library members that share a constituent with it. This process can be iteratively repeated to yield up to four industrially relevant esters as pure products from a single reaction setup. An algorithm has been developed to predict reactive distillation products in DCLs of as many as 121 members.



INTRODUCTION

Living organisms have achieved an exquisite level of spatiotemporal control of synthetic chemistry. Within the highly complex chemical mixtures present in a typical cell, hundreds of simultaneous reactions occur without interference, creating dozens of products with absolute chemo-, regio-, and stereoselectivity. Replicating this synthetic prowess in unnatural systems would yield insights of relevance to prebiotic chemistry,¹ allow expedient discovery of new reactions, and possibly dramatically reduce construction and energy costs in the chemical industry, since multiple value-added chemicals could be concurrently produced in a single reactor.

In an effort to achieve analogous selective synthesis starting from “messy” precursor mixtures, our group has been studying how dynamic combinatorial libraries (DCLs),² complex equilibrating mixtures of structurally related compounds, simplify in response to external stimuli. We recently developed kinetic self-sorting³ protocols, in which selective and irreversible distillation,⁴ oxidation,⁵ or precipitation⁶ of imine-based DCLs reduces these mixtures in complexity from n^2 components into n products that can be isolated in high yields and purities. In this article, we derive general rules that guide these and other self-sorting processes in mixtures with an arbitrary number of components, present in any arbitrary stoichiometry. We then proceed to apply these rules to distillative self-sorting of dynamic ester libraries⁷ and demonstrate that as many as four pure and industrially relevant esters can be produced in a single reaction setup.

Esters were chosen as substrates because of their numerous uses as solvents, lubricants, fuels, fragrances, and food additives. Smaller esters are industrially produced through (trans)-esterification reactions, which are usually characterized by equilibrium constants close to unity. This fundamental obstacle is overcome by the use of reactive distillation (RD) processes, in which the chemical reactor doubles as a distillation setup.⁸ In these methods, the volatile component, either an ester or water, is continually removed from the reactor via controlled distillation until the equilibrium completely shifts in the

direction of the product and the starting materials are fully consumed.⁹ In eliminating the separate distillation step, RD yielded some of the chemical industry's most significant savings in energy, construction, and material costs during the past three decades. Several esters are produced through RD-based (trans)esterifications,¹⁰ and RD is attracting attention in the production of biodiesel through transesterification of fatty acids.¹¹ Despite this significant progress and huge practical relevance, virtually all RD-based (trans)esterifications generate just a single value-added ester as the product.¹²

We hypothesized that in the presence of a suitable acyl exchange catalyst, a multicomponent ester DCL could be used as a platform for an RD process that could generate multiple esters as pure products. Let us consider a general case of an ester library formally constructed by random esterification of n carboxylic acids (labeled as A, B, C, D, ..., in order of decreasing volatility) with m alcohols (labeled as 1, 2, 3, 4, ..., in order of decreasing volatility). The amounts of individual acids and alcohols may vary (and thus the resulting esters may be present in any ratio), but we set a limiting condition that the total number of moles of acids and alcohols is identical, so that the final mixture includes only esters and none of the unreacted carboxylic acids or alcohols.

Distillation of this mixture will isolate the most volatile ester **A1**, formed from the most volatile acid and the most volatile alcohol,¹³ as the first fraction. As **A1** is being removed from the library, equilibrium will shift so as to replenish it, until the mixture runs out of either A or 1 (or both). In the next step, two scenarios are possible. If A and 1 were exhausted simultaneously, then the next compound to distill out will be **B2**, consuming in the process all other esters that contain either carboxylic acid B or alcohol 2. However, if there was some of, for example, A left over in the mixture, then it will combine with the next most volatile alcohol 2, to yield **A2** as the second fraction, and this process will continue until the mixture runs

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out of either A or 2. Within the $[n \times m]$ matrix of compounds, distillation expresses the most volatile ester until one (or both) of its constituents are depleted, then moves to the next most volatile compound until its components are depleted and so on. Thus, a series of limiting reagent calculations allows the prediction of the distillation products and their amounts based on the composition of the starting library. We have developed a Microsoft Excel algorithm that automates these predictions for libraries with up to $[11 \times 11]$ members.¹⁴ Table 1 illustrates

Table 1. Calculated Compositions of Three Ester Libraries before and after Iterative Reactive Distillation: An Equimolar $[4 \times 4]$ Library (top), an Equimolar $[3 \times 5]$ Library (middle), and a Non-equimolar $[4 \times 4]$ Library (bottom)^a

| | 1 | 2 | 3 | 4 | | 1 | 2 | 3 | 4 | |
|---|-----|-----|-----|-----|---|---|-----|-----|-----|-----|
| A | 1.0 | 1.0 | 1.0 | 1.0 | → | A | 4.0 | 0.0 | 0.0 | 0.0 |
| B | 1.0 | 1.0 | 1.0 | 1.0 | | B | 0.0 | 4.0 | 0.0 | 0.0 |
| C | 1.0 | 1.0 | 1.0 | 1.0 | | C | 0.0 | 0.0 | 4.0 | 0.0 |
| D | 1.0 | 1.0 | 1.0 | 1.0 | | D | 0.0 | 0.0 | 0.0 | 4.0 |

| | 1 | 2 | 3 | | 1 | 2 | 3 | |
|---|-----|-----|-----|---|---|-----|-----|-----|
| A | 1.0 | 1.0 | 1.0 | → | A | 3.0 | 0.0 | 0.0 |
| B | 1.0 | 1.0 | 1.0 | | B | 2.0 | 1.0 | 0.0 |
| C | 1.0 | 1.0 | 1.0 | | C | 0.0 | 3.0 | 0.0 |
| D | 1.0 | 1.0 | 1.0 | | D | 0.0 | 1.0 | 2.0 |
| E | 1.0 | 1.0 | 1.0 | | E | 0.0 | 0.0 | 3.0 |

| | 1 | 2 | 3 | 4 | | 1 | 2 | 3 | 4 | |
|---|-----|-----|-----|-----|---|---|-----|-----|-----|-----|
| A | 1.0 | 1.0 | 1.0 | 1.0 | → | A | 4.0 | 0.0 | 0.0 | 0.0 |
| B | 1.0 | 1.0 | 1.0 | 1.0 | | B | 4.0 | 0.0 | 0.0 | 0.0 |
| C | 1.0 | 1.0 | 1.0 | 1.0 | | C | 4.0 | 0.0 | 0.0 | 0.0 |
| D | 9.0 | 1.0 | 1.0 | 1.0 | | D | 0.0 | 4.0 | 4.0 | 4.0 |

^aNumbers in the tables on the left indicate the hypothetical number of equivalents of the corresponding esters before the distillation and those on the right after the distillation.

three typical examples. In the first case (top), a hypothetical $[4 \times 4]$ mixture is constructed by combining equimolar amounts of four acids and four alcohols. Here, 4 equiv each of A1, B2, C3, and D4 are expected as products, because the balanced stoichiometry leaves no volatile alcohol or acid at the end of each step. Only the four diagonal members of the $[4 \times 4]$ matrix are expressed. In the second case (middle), five carboxylic acids are combined with three alcohols to produce equimolar amounts of 15 esters. In this $[3 \times 5]$ matrix, the distillation “zig-zags”, producing first 3 equiv of A1 (before it runs out of A), then 2 equiv of B1 (before it runs out of 1), then 1 equiv of B2 (when it runs out of B), and so on. While the simplification in this case is not great, since a 15-member

library reduces into seven final compounds, the isolated “pseudodiagonal” members are still symmetrically positioned within the matrix. The final case (bottom) examines a nonstoichiometric $[4 \times 4]$ library that contains 9 equiv of compound A4 and 1 equiv of each of the other compounds. In this case, distillation isolates 4 equiv each of compounds A1–A3 and B4–D4 (and, interestingly, no A4), meaning that excess of one DCL member “pulls” the normal diagonal distribution toward that component.

Guided by this theoretical insight, we proceeded to demonstrate ester self-sorting in practice. We analyzed the behavior of various mixtures of the 21 esters presented in Chart 1 during reactive distillation.

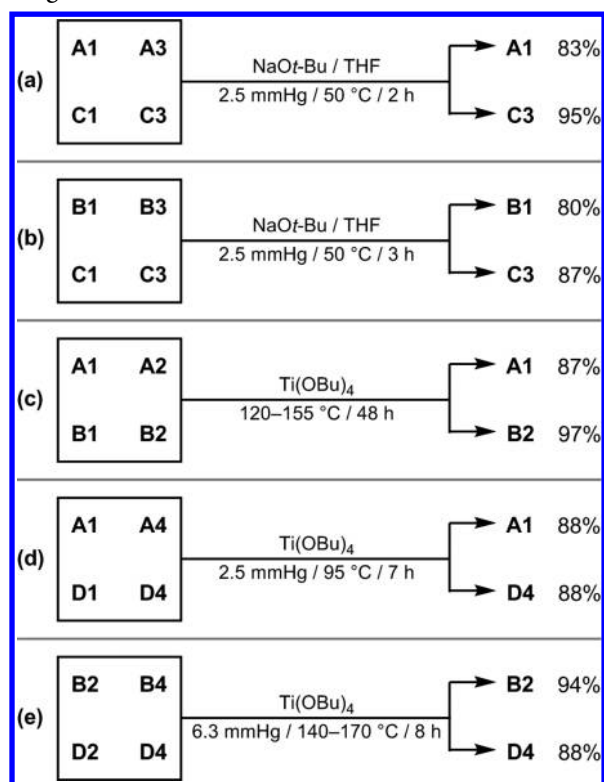
Chart 1. Compound Codes for Esters Examined in This Study

| | C ₂ H ₅ | <i>n</i> -C ₄ H ₉ | PhCH ₂ | <i>n</i> -C ₈ H ₁₇ | <i>n</i> -C ₁₆ H ₃₃ |
|---|-------------------------------|---|-------------------|--|---|
| CH ₃ | A1 | A2 | A3 | A4 | A5 |
| <i>n</i> -C ₃ H ₇ | B1 | B2 | B3 | B4 | B5 |
| Ph | C1 | C2 | C3 | — | — |
| <i>n</i> -C ₇ H ₁₅ | D1 | D2 | — | D4 | D5 |
| <i>n</i> -C ₁₅ H ₃₁ | E1 | E2 | — | E4 | E5 |

RESULTS AND DISCUSSION

In our first experiment (Scheme 1a), we utilized NaOt-Bu as the acyl exchange catalyst, previously reported by Gagné et al.¹⁵ An equimolar mixture¹⁶ of ethyl acetate (A1, Figure 1), benzyl acetate (A3), ethyl benzoate (C1), and benzyl benzoate (C3) was exposed to a catalytic amount of 1 M solution of NaOt-Bu in THF and then subjected to distillation in vacuo (2.50 mmHg) at 50 °C. After 2 h, the distillate was found to be pure A1, which was formed in 83% yield as quantified by ¹H NMR spectroscopy. Distillation residue contained ester C3 in 95% yield, and small amounts of the crossover esters A3 (5%) and C1 (4%). A similar experiment was successfully performed (Scheme 1b) with ethyl butyrate (B1), butyl butyrate (B2), C1, and C3. Again, the most volatile (B1, 80%) and the least volatile (C3, 87%) esters were isolated in high yields with small amounts of the esters of intermediate volatility (see Experimental Section and Supporting Information for details).

The NaOt-Bu catalyst proved nonoptimal in our attempts to perform distillative self-sorting of less volatile esters, for example, in protocols where benzyl or octyl esters were designed to be the more volatile components. Two potential explanations can be offered for this behavior. During the course of ester exchange, *t*-butyl esters are formed as intermediates; these esters are more volatile than, for example, octyl esters of the same acids and can thus be removed through distillation instead of the expected product. The stoichiometry of the alcohol and acid partners would thus be disturbed and lower purity of the resultant products would be expected, although not dramatically, as *t*-butoxide was used in catalytic amounts. The more significant obstacle was logistical: after the *t*-butyl esters were distilled, the effective role of the catalyst was turned over to a higher alkoxide, and these species were either insoluble or acted as gelling agents. In such a scenario,

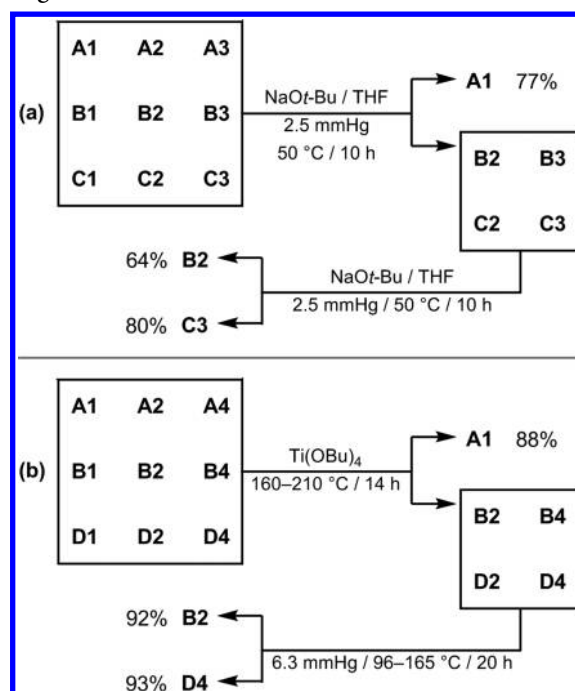
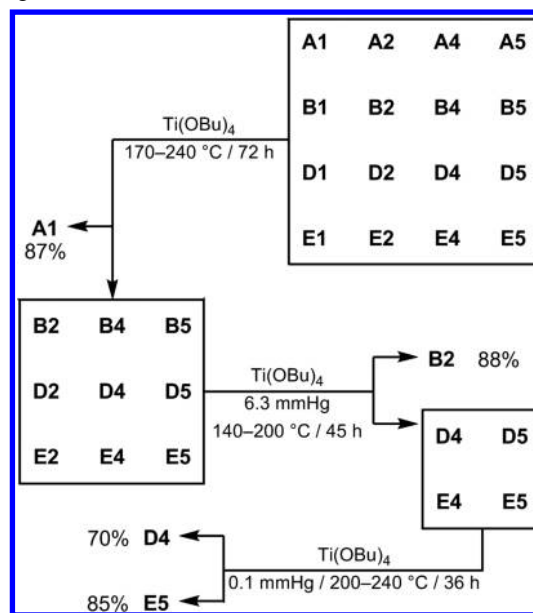
Scheme 1. Self-Sorting of Dynamic $[2 \times 2]$ Ester Libraries during Reactive Distillation^a^aAll of the starting esters were mixed in equimolar amounts.

distillations essentially shut down, and more forcing conditions caused significant decomposition of ester libraries.¹⁷

Forced to switch the acyl exchange catalyst, we turned to $\text{Ti}(\text{OBu})_4$,¹⁸ which was also reported to equilibrate esters in the absence of water or alcohols. With this new catalyst, a four-ester mixture A1–B2 could be self-sorted (Scheme 1c) during a distillation at atmospheric pressure into A1 (87%) and B2 (97%).¹⁹ Two subsequent experiments (Scheme 1d,e) successfully sorted $[2 \times 2]$ ester libraries that contained less volatile ester components, thus critically demonstrating the superiority of $\text{Ti}(\text{OBu})_4$ over NaOt-Bu , since the latter catalyst proved ineffective in these reactions because of gel formation.

The success of the $[2 \times 2]$ self-sorting experiments suggested that more complex mixtures could be similarly resolved. We next attempted distillative self-sorting of a nine-ester library A1–C3 (Scheme 2a) in the presence of NaOt-Bu . Upon vacuum distillation, ethyl acetate (A1) was isolated as the first fraction in 77% yield; continued distillation resulted in the production of B2 as the second distillate (64%), leaving C3 as the distillation residue (80%). Moderate yields of the three products, as well as the previously noticed gelation problems associated with the use of NaOt-Bu with less volatile esters, suggested that an alternative catalyst might perform better. Indeed, the use of $\text{Ti}(\text{OBu})_4$ on a $[3 \times 3]$ ester library composed of A1, A2, A4, B1, B2, B4, D1, D2, and D4 resulted in a rapidly equilibrating library, which upon two distillation steps yielded first A1 (88%) and then B2 (92%), leaving D4 (93%) as the distillation residue (Scheme 2b).

Our most complex experiment targeted a mixture of 16 esters shown in Scheme 3, top right. Upon subsection of this library to titanium catalysis and distillation at atmospheric pressure for 72 h, ethyl acetate (A1) was isolated as the first product in 87%

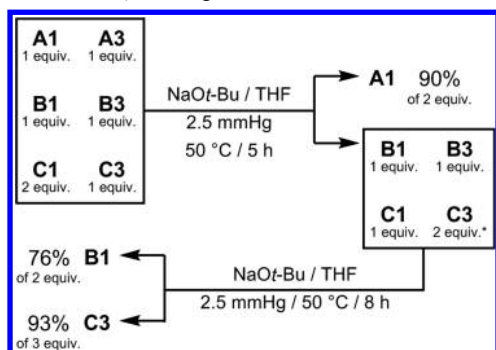
Scheme 2. Self-Sorting of Dynamic $[3 \times 3]$ Ester Libraries during Reactive Distillation^a^aAll of the starting esters were mixed in equimolar amounts.Scheme 3. Self-Sorting of a Dynamic $[4 \times 4]$ Ester Library during Reactive Distillation^a^aAll of the starting esters were mixed in equimolar amounts.

yield. At that point, all other acetates (A2, A4, and A5) and all other ethyl esters (B1, D1, and E1) were also removed from the mixture, because they shared either the acid or the alcohol component with A1. The second stage of this distillation required the use of a mild vacuum (6.3 mmHg) and an additional portion of the catalyst; after 45 h, this protocol yielded the second pure fraction consisting of B2, which was isolated in 88% yield. The final $[2 \times 2]$ library composed of D4–E5 was subjected to distillation in high vacuum (0.1

mmHg), producing **D4** (70%) as the distillate and **E5** (85%) as the distillation residue.

As mentioned previously, the applicability of these iterative self-sorting distillation protocols is not limited to just $[n \times n]$ mixtures, nor to strictly equimolar component compositions. To demonstrate this, we constructed a $[2 \times 3]$ mixture shown in Scheme 4, in which one component (**C1**) was added in 2-

Scheme 4. Self-Sorting of a Dynamic Nonstoichiometric $[2 \times 3]$ Ester Library during Reactive Distillation



fold excess relative to all other ester species, which were otherwise equimolar.²⁰ Upon distillation of such a library, **A1** is formed as the expected first product. Its isolated amount is close to twice the molar amount of **A1** originally added to the mixture; the second equivalent of **A1** comes from the extraction of all acetate (1 equiv from **A3**) and the equimolar amount of ethyl esters (1 equiv from either **B1** or **C1**). Once the distillation of **A1** is complete, the next most volatile fraction is **B1**, which extracts the remaining ethyl esters (1 equiv from **C1**) and butanoates (1 equiv from **B3**). Left over is approximately 3 equiv of **C3**, which is commensurate to the original amounts of benzoate (2 equiv in **C1** and 1 equiv in **C3**) and benzyl esters (1 equiv each in **A3**, **B3**, and **C3**) in the starting library.

CONCLUSION

Several important challenges remain associated with iterative self-sorting reactive distillation. Further expansion of this protocol to other compound classes of relevance to the chemical industry, such as ethers, alkylated aromatics, alkenes, and alkynes, would be of eminent interest. The simplifying aspects of this and related self-sorting protocols could be brought to the fore in the self-sorting of naturally occurring complex mixtures, such as those found in hydrolyzed lignin or in the naturally occurring oils and fats. If successful, self-sorting of such extremely abundant mixtures could result in new and facile routes to biomass-derived fuels and value-added chemicals. We are exploring these directions in our laboratory and will report our findings in due course.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed under nitrogen atmosphere in oven-dried glassware. All reagents and solvents were purchased from commercial suppliers. All commercially obtained esters were dried over CaH_2 prior to use. NMR spectra were obtained using working frequency of 500 MHz for ^1H nuclei and 125 MHz for ^{13}C nuclei. ^1H NMR chemical shifts are reported in ppm units relative to the residual signal of the solvent (CDCl_3 , 7.25 ppm). All NMR spectra were recorded at 25 °C, and ^{13}C NMR spectra were recorded with simultaneous decoupling of ^1H nuclei. Compound 1,3,5-trimethoxybenzene (Alfa Aesar, 99%) was utilized as the internal

standard for the calculations of yields of different esters on the basis of integration of ^1H NMR spectra of distillates and distillation residues.

Gas chromatography temperature program that was used for all characterizations started with (1) constant temperature of 50 °C for 1 min, followed by (2) monotonous temperature increase from 50 to 270 °C within 4 min, and finally (3) constant temperature of 270 °C for 10 min. Dodecane (Alfa Aesar, 99%) was utilized as an internal standard for the calculation of yields based on the integration of gas chromatograms.

Reactive Distillation of a $[2 \times 2]$ Ester Library: Ethyl Acetate (A1**) and Benzyl Benzoate (**C3**).** Equimolar amounts of ethyl acetate (**A1**, 445 mg, 5.00 mmol), ethyl benzoate (**C1**, 758 mg, 5.00 mmol), benzyl acetate (**A3**, 758 mg, 5.00 mmol), and benzyl benzoate (**C3**, 1.07 g, 5.00 mmol) were added to a 25 mL two-neck round-bottom flask. The reaction flask was equipped with a short path distillation head that connected it with a receiving flask placed in an *i*-PrOH/ CO_2 ice bath. The mixture was heated to 50 °C. A 1 M solution of NaOt-Bu in THF (0.5 mL) was injected into reaction flask in five 0.1 mL portions, with injections separated by 10 min. The distillation setup was placed under vacuum (2.5 mmHg) after the first loading of catalyst was added. After 2 h, the distillate (1.60 g) was collected as a colorless liquid. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture of **A1** (732 mg, 8.31 mmol, 83% yield) and THF (solvent, 720 mg, 9.98 mmol). Esters **A3**, **C1**, and **C3** could not be observed in the distillate. The residue (2.17 g) was identified by ^1H NMR spectroscopy as a mixture of **C3** (2.02 g, 9.51 mmol, 95% yield), **A3** (13.5 mg, 0.09 mmol, 5% yield), and **C1** (9.91 mg, 0.07 mmol, 4% yield). For detailed calculation of the yields of individual components, see Supporting Information.

A1: ^1H NMR (CDCl_3) 4.11 (q, $^3J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.20 (t, $^3J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 170.8, 60.1, 20.7, 13.9 ppm. Spectral data agree with a previous literature report.²¹

C3: ^1H NMR (CDCl_3) 8.10 (d, $^3J = 7.0$ Hz, 2H), 7.59 (t, $^3J = 7.5$ Hz, 1H), 7.37–7.50 (m, 7H), 5.40 (s, 2H) ppm; ^{13}C NMR (CDCl_3) 166.5, 136.3, 133.2, 130.3, 129.9, 128.8, 128.6, 128.4, 128.3, 66.8 ppm. Spectral data agree with a previous literature report.²²

Reactive Distillation of a $[2 \times 2]$ Ester Library: Ethyl Butyrate (B1**) and Benzyl Benzoate (**C3**).** Equimolar amounts of ethyl butyrate (**B1**, 587 mg, 5.00 mmol), ethyl benzoate (**C1**, 758 mg, 5.00 mmol), benzyl butyrate (**B3**, 900 mg, 5.00 mmol), and benzyl benzoate (**C3**, 1.07 g, 5.00 mmol) were added to a 25 mL two-neck pear-shaped flask. The reaction flask was equipped with a short path distillation head that connected it with a receiving flask placed in an *i*-PrOH/ CO_2 ice bath. The mixture was heated to 50 °C. A 1 M solution of NaOt-Bu in THF (0.5 mL) was injected into reaction flask in five 0.1 mL portions, with injections separated by 10 min. The distillation setup was placed under vacuum (2.5 mmHg) when the first loading of catalyst was added. After 3 h, the distillate (1.98 g) was collected as a colorless liquid. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture of **B1** (935 mg, 8.05 mmol, 80% yield) and THF (solvent, 917 mg, 12.7 mmol). Esters **B3**, **C1**, and **C3** were not observed in the distillate. The residue (2.35 g) was identified by ^1H NMR spectroscopy as a mixture of **C3** (1.84 g, 8.69 mmol, 87% yield), **B3** (216 mg, 1.21 mmol, 12% yield), and **C1** (118 mg, 0.78 mmol, 8% yield). For detailed calculation of the yields of individual components, see Supporting Information.

B1: ^1H NMR (CDCl_3) 4.13 (q, $^3J = 6.8$ Hz, 2H), 2.27 (t, $^3J = 7.4$ Hz, 2H), 1.65 (sextet, $^3J = 7.4$ Hz, 2H), 1.26 (t, $^3J = 6.8$ Hz, 3H), 0.96 (t, $^3J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 173.6, 60.1, 36.3, 18.6, 14.3, 13.7 ppm. Spectral data agree with a previous literature report.²³

C3: ^1H NMR (CDCl_3) 8.10 (d, $^3J = 7.0$ Hz, 2H), 7.59 (t, $^3J = 7.5$ Hz, 1H), 7.37–7.50 (m, 7H), 5.40 (s, 2H) ppm; ^{13}C NMR (CDCl_3) 166.5, 136.3, 133.2, 130.3, 129.9, 128.8, 128.6, 128.4, 128.3, 66.8 ppm. Spectral data agree with a previous literature report.²²

Reactive Distillation of a $[2 \times 2]$ Ester Library: Ethyl Acetate (A1**) and Butyl Butyrate (**B2**).** Titanium *n*-butoxide (413 mg, 1.20 mmol) and an equimolar mixture of **A1** (2.67 g, 30.0 mmol), **A2** (3.52 g, 30.0 mmol), **B1** (3.52 g, 30.0 mmol), and **B2** (4.37 g, 30.0 mmol) were placed in a 100 mL round-bottom flask. The flask was fitted with a short path distillation head, which connected it to a receiving flask that was placed in an *i*-PrOH/ CO_2 ice bath (−78 °C). This mixture was

heated from 120 to 155 °C for 48 h. The distillate (4.86 g) was collected as a colorless liquid. ^1H NMR spectroscopy confirmed the identity of this liquid as mostly **A1** (4.58 g, 52.1 mmol, 87% yield). ^1H NMR spectroscopic analysis of the residue (9.40 g) identified **B2** (8.41 g, 58.3 mmol, 97% yield) as the main component. For detailed calculation of the yields of individual components, see Supporting Information.

A1: ^1H NMR (CDCl_3) 4.11 (q, $^3J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.20 (t, $^3J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 170.8, 60.1, 20.7, 13.9 ppm. Spectral data agree with a previous literature report.²¹

B2: ^1H NMR (CDCl_3) 4.07 (t, $^3J = 6.8$ Hz, 2H), 2.27 (t, $^3J = 7.5$ Hz, 2H), 1.69–1.40 (m, 6H) 0.9 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 173.8, 64.1, 36.3, 30.7, 19.2, 18.5, 13.7, 13.6 ppm. Spectral data agree with a previous literature report.²⁴

Reactive Distillation of a [2 × 2] Ester Library: Ethyl Acetate (A1) and Octyl Octanoate (D4). Titanium *n*-butoxide (138 mg, 0.40 mmol) and an equimolar mixture of **A1** (0.89 g, 10.0 mmol), **A4** (1.74 g, 10.0 mmol), **D1** (1.74 g, 10.0 mmol), and **D4** (2.59 g, 10.0 mmol) were placed into a 100 mL round-bottom flask. The reaction flask was equipped with a 185 mm long Vigreux column that was cooled by an *i*-PrOH/ CO_2 cold trap (−30 °C). A short path distillation head was used to connect the top of the Vigreux column with a receiving flask, which was placed into a separate *i*-PrOH/ CO_2 ice bath (−78 °C). This reaction mixture was heated at 95 °C for 7 h under vacuum (2.5 mmHg). The distillate (1.56 g) was collected as a colorless liquid. ^1H NMR spectroscopy confirmed the identity of this liquid as **A1** (1.55 g, 17.6 mmol, 88% yield). The other three esters, **A4**, **D1**, and **D4**, could not be identified in the distillate. Using a combination of ^1H NMR spectroscopy and gas chromatography (see below), the residue (5.24 g) was identified as a mixture dominated by **D4** (4.61 g, 18.0 mmol, 90% yield) with minor contributions from **D1** (232 mg, 1.35 mmol, 7% yield) and **A4** (140 mg, 0.81 mmol, 4% yield). For detailed calculation of the yields of individual components, see Supporting Information.

A1: ^1H NMR (CDCl_3) 4.11 (q, $^3J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.20 (t, $^3J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 170.8, 60.1, 20.7, 13.9 ppm. Spectral data agree with a previous literature report.²¹

D4: ^1H NMR (CDCl_3) 4.04 (t, $^3J = 6.7$ Hz, 2H), 2.28 (t, $^3J = 7.5$ Hz, 1H), 1.60 (m, 4H), 1.29 (m, 18H), 0.86 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 174.1, 64.5, 34.5, 31.8 (2C), 29.3, 29.2, 29.0, 28.7 (2C), 25.1 (2C), 22.8, 22.7, 14.2 (2C) ppm. Spectral data agree with a previous literature report.²⁵

Reactive Distillation of a [2 × 2] Ester Library: Butyl Butyrate (B2) and Octyl Octanoate (D4). Titanium *n*-butoxide (138 mg, 0.40 mmol) and an equimolar mixture of **B2** (1.46 g, 10.0 mmol), **B4** (2.02 g, 10.0 mmol), **D2** (2.02 g, 10.0 mmol), and **D4** (2.59 g, 10.0 mmol) were added to a 100 mL round-bottom flask. The reaction flask was equipped with a short path distillation head, which connected it to a receiving flask that was placed in an *i*-PrOH/ CO_2 ice bath (−78 °C). This reaction was heated from 140 to 170 °C for 8 h under vacuum (6.3 mmHg). Using gas chromatography, the distilled liquid (2.85 g) was identified as **B2** (2.83 g, 19.6 mmol, 98% yield). The distillation residue (5.32 g) was analogously identified as a mixture dominated by **D4** (4.51 g, 17.6 mmol, 93% yield), with minor contributions from **D2** and **B4**, which could not be quantified individually because the peaks of these two compounds extensively overlap both in ^1H NMR spectra and in gas chromatograms. For detailed calculation of the yields of individual components, see Supporting Information.

B2: ^1H NMR (CDCl_3) 4.07 (t, $^3J = 6.8$ Hz, 2H), 2.27 (t, $^3J = 7.5$ Hz, 2H), 1.69–1.40 (m, 6H) 0.9 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 173.8, 64.1, 36.3, 30.7, 19.2, 18.5, 13.7, 13.6 ppm. Spectral data agree with a previous literature report.²⁴

D4: ^1H NMR (CDCl_3) 4.04 (t, $^3J = 6.7$ Hz, 2H), 2.28 (t, $^3J = 7.5$ Hz, 1H), 1.60 (m, 4H), 1.29 (m, 18H), 0.86 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 174.1, 64.5, 34.5, 31.8 (2C), 29.3, 29.2, 29.0, 28.7 (2C), 25.1 (2C), 22.8, 22.7, 14.2 (2C) ppm. Spectral data agree with a previous literature report.²⁵

Reactive Distillation of a [3 × 3] Ester Library: Ethyl Acetate (A1), Butyl Butyrate (B2), and Benzyl Benzoate (C3). An equimolar mixture of **A1** (890 mg, 10.0 mmol), **B1** (1.17 g, 10.0 mmol), **C1**

(1.56 g, 10.0 mmol), **A2** (1.17 g, 10.0 mmol), **B2** (1.46 g, 10.0 mmol), **C2** (1.80 g, 10.0 mmol), **A3** (1.52 g, 10.0 mmol), **B3** (1.80 g, 10.0 mmol), and **C3** (2.14 g, 10.0 mmol) was added to a 25 mL two-neck round-bottom flask. The reaction flask was equipped with a 185 mm long Vigreux column that was cooled by an *i*-PrOH/ CO_2 cold trap (−55 to −50 °C). A short path distillation head was placed on top of the Vigreux column, connecting it to a receiving flask, which was placed into a separate *i*-PrOH/ CO_2 ice bath (−78 °C). A 0.1 mL portion of a 1 M solution of NaOt-Bu in THF was injected into the reaction flask every 30 min for 10 h. Vacuum (2.5 mmHg) was started at the same time as the first loading of catalyst. The first step of this distillation was carried out at 50 °C over the course of 10 h. The first distillate was collected as a colorless liquid. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture of **A1** (2.03 g, 23.1 mmol, 77% yield), **A2** (41.4 mg, 0.36 mmol, 1% yield), **B1** (91.0 mg, 0.78 mmol, 3% yield), and THF (solvent, 2.59 g, 35.9 mmol). The second distillate was collected after another 10 h of distillation without the Vigreux column, during which time a 0.1 mL portion of a 1 M solution of NaOt-Bu in THF was injected into the reaction flask every 30 min. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture of **B2** (2.76 g, 19.2 mmol, 64% yield), **A2** (205 mg, 1.76 mmol, 6% yield), **B1** (37.5 mg, 0.32 mmol, 1% yield), **B3** (54.9 mg, 0.31 mmol, 1% yield), **C2** (47.9 mg, 0.27 mmol, 1% yield), and THF (solvent, 1.43 g, 19.9 mmol). The residue was identified by ^1H NMR spectroscopy as a mixture of **C3** (5.11 g, 24.1 mmol, 80% yield), **B3** (473 mg, 2.66 mmol, 9% yield), and **C2** (452 mg, 2.54 mmol, 8% yield). For detailed calculation of the yields of individual components, see Supporting Information.

A1: ^1H NMR (CDCl_3) 4.11 (q, $^3J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.20 (t, $^3J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 170.8, 60.1, 20.7, 13.9 ppm. Spectral data agree with a previous literature report.²¹

B2: ^1H NMR (CDCl_3) 4.07 (t, $^3J = 6.8$ Hz, 2H), 2.27 (t, $^3J = 7.5$ Hz, 2H), 1.69–1.40 (m, 6H) 0.9 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 173.8, 64.1, 36.3, 30.7, 19.2, 18.5, 13.7, 13.6 ppm. Spectral data agree with a previous literature report.²⁴

C3: ^1H NMR (CDCl_3) 8.10 (d, $^3J = 7.0$ Hz, 2H), 7.59 (t, $^3J = 7.5$ Hz, 1H), 7.37–7.50 (m, 7H), 5.40 (s, 2H) ppm; ^{13}C NMR (CDCl_3) 166.5, 136.3, 133.2, 130.3, 129.9, 128.8, 128.6, 128.4, 128.3, 66.8 ppm. Spectral data agree with a previous literature report.²²

Reactive Distillation of a [3 × 3] Ester Library: Ethyl Acetate (A1), Butyl Butyrate (B2), and Octyl Octanoate (D4). Titanium *n*-butoxide (0.93 g, 2.70 mmol) and an equimolar mixture of **A1** (2.7 g, 30.0 mmol), **A2** (3.5 g, 30.0 mmol), **A4** (5.2 g, 30.0 mmol), **B1** (3.5 g, 30.0 mmol), **B2** (4.4 g, 30.0 mmol), **B4** (6.1 g, 30.0 mmol), **D1** (5.2 g, 30.0 mmol), **D2** (6.1 g, 30.0 mmol), and **D4** (7.8 g, 30.0 mmol) was added to a 100 mL round-bottom flask. The flask was fitted with a Vigreux column, and a short path distillation head was used to connect it to a receiving flask, which was placed in an *i*-PrOH/ CO_2 ice bath (−78 °C). The first step of the distillation was carried out at atmospheric pressure for 14 h, with temperature slowly being raised from 160 to 210 °C. The first distillate (9.51 g) was collected as a colorless liquid. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture dominated by **A1** (7.01 g, 79.6 mmol, 88% yield) with contributions from **A2** and **B1**. The reaction flask was then equipped with a 185 mm long Vigreux column and placed under vacuum (6.3 mmHg) for the second step of the distillation. The second distillate (12.0 g) was collected after another 9.5 h. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture of **B2** (11.9 g, 82.8 mmol, 92% yield) and small amounts of **A2** and **B1**. Finally, the distillation residue (24.0 g) was identified by ^1H NMR spectroscopy and gas chromatography as a mixture of **D4** (21.5 g, 82.8 mmol, 93% yield) and small amounts of **D2** and **B4**. For detailed calculation of the yields of individual components, see Supporting Information.

A1: ^1H NMR (CDCl_3) 4.11 (q, $^3J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.20 (t, $^3J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 170.8, 60.1, 20.7, 13.9 ppm. Spectral data agree with a previous literature report.²¹

B2: ^1H NMR (CDCl_3) 4.07 (t, $^3J = 6.8$ Hz, 2H), 2.27 (t, $^3J = 7.5$ Hz, 2H), 1.69–1.40 (m, 6H) 0.9 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 173.8, 64.1, 36.3, 30.7, 19.2, 18.5, 13.7, 13.6 ppm. Spectral data agree with a previous literature report.²⁴

D4: ^1H NMR (CDCl_3) 4.04 (t, $^3J = 6.7$ Hz, 2H), 2.28 (t, $^3J = 7.5$ Hz, 1H), 1.60 (m, 4H), 1.29 (m, 18H), 0.86 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 174.1, 64.5, 34.5, 31.8 (2C), 29.3, 29.2, 29.0, 28.7 (2C), 25.1 (2C), 22.8, 22.7, 14.2 (2C) ppm. Spectral data agree with a previous literature report.²⁵

Reactive Distillation of a [4 × 4] Ester Library: Ethyl Acetate (A1), Butyl Butyrate (B2), Octyl Octanoate (D4), and Cetyl Palmitate (E5). Titanium *n*-butoxide (0.50 mL, 498 mg, 1.46 mmol) and an equimolar mixture of **A1** (0.9 g, 10.0 mmol), **A2** (1.2 g, 10.0 mmol), **A4** (1.7 g, 10.0 mmol), **A5** (2.9 g, 10.0 mmol), **B1** (1.2 g, 10.0 mmol), **B2** (1.5 g, 10.0 mmol), **B4** (2.0 g, 10.0 mmol), **B5** (3.2 g, 10.0 mmol), **D1** (1.7 g, 10.0 mmol), **D2** (2.0 g, 10.0 mmol), **D4** (2.6 g, 10.0 mmol), **D5** (3.8 g, 10.0 mmol), **E1** (2.9 g, 10.0 mmol), **E2** (3.2 g, 10.0 mmol), **E4** (3.8 g, 10.0 mmol), and **E5** (4.9 g, 10.0 mmol) were placed into a 100 mL round-bottom flask. A short path distillation head was used to connect the reaction flask with a receiving flask, which was placed in a liquid N_2 bath (-196°C). The first step of the distillation was performed at atmospheric pressure over 72 h, and the mixture was gradually heated from 170 to 240°C . The first distillate (3.50 g) was collected as a colorless liquid, and ^1H NMR spectroscopy of this liquid confirmed its identity as a mixture of **A1** (3.07 g, 34.9 mmol, 87% yield) and **A2** and **B1** as minor components. The reaction flask was then equipped with a 100 mm long Vigreux column and placed under vacuum (6.3 mmHg) for the second step of the distillation. The second distillate (7.00 g) was collected after the mixture was heated from 135 to 195°C during the course of additional 45 h. The temperature was slowly increased from 135 to 155°C in the first 4 h, and additional $\text{Ti}(\text{OBu})_4$ (0.10 mL, 99.6 mg, 0.29 mmol) was added to the reaction flask. Temperature was then increased from 155 to 165°C over 6 h and another portion of $\text{Ti}(\text{OBu})_4$ (0.10 mL, 99.6 mg, 0.29 mmol) was added to the reaction flask. Finally, temperature was increased from 165 to 190°C over the course of 19 h, and the final portion of $\text{Ti}(\text{OBu})_4$ (0.10 mL, 99.6 mg, 0.29 mmol) was added to the reaction flask. Temperature was brought from 190 to 195°C over the course of last 16 h. Using a combination of ^1H NMR spectroscopy and gas chromatography, the second distillate was identified as a mixture of **B2** (4.86 g, 33.7 mmol, 88% yield) and small amounts of **A2** and **B1**. The third distillate (9.70 g) was collected after high vacuum (0.10 mmHg) distillation at temperature from 200 to 240°C during the course of another 24 h. The temperature was slowly increased from 200 to 205°C in the first 4 h, followed by the addition of $\text{Ti}(\text{OBu})_4$ (0.10 mL, 99.6 mg, 0.29 mmol) to the reaction flask. The Vigreux column was removed, and the mixture was heated from 205 to 220°C for 4 h, followed by another portion of $\text{Ti}(\text{OBu})_4$ (0.10 mL, 99.6 mg, 0.29 mmol). Finally, the temperature was increased from 220 to 240°C over 4 h, and the temperature was kept at 240°C for 12 h. A combination of ^1H NMR spectroscopy and gas chromatography confirmed the identity of the third distillate liquid as a mixture of **D4** (7.40 g, 28.9 mmol, 70% yield) and small amounts of **B4** and **D2**. The residue (20.3 g) was identified by ^1H NMR spectroscopy and gas chromatography as a mixture of **E5** (17.2 g, 35.8 mmol, 85% yield) and small amounts of **D5** and **E4**. For detailed calculation of the yields of individual components, see Supporting Information.

A1: ^1H NMR (CDCl_3) 4.11 (q, $^3J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.20 (t, $^3J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 170.8, 60.1, 20.7, 13.9 ppm. Spectral data agree with a previous literature report.²¹

B2: ^1H NMR (CDCl_3) 4.07 (t, $^3J = 6.8$ Hz, 2H), 2.27 (t, $^3J = 7.5$ Hz, 2H), 1.69–1.40 (m, 6H) 0.9 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 173.8, 64.1, 36.3, 30.7, 19.2, 18.5, 13.7, 13.6 ppm. Spectral data agree with a previous literature report.²⁴

D4: ^1H NMR (CDCl_3) 4.04 (t, $^3J = 6.7$ Hz, 2H), 2.28 (t, $^3J = 7.5$ Hz, 1H), 1.60 (m, 4H), 1.29 (m, 18H), 0.86 (t, $^3J = 6.4$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3) 174.1, 64.5, 34.5, 31.8 (2C), 29.3, 29.2, 29.0, 28.7 (2C), 25.1 (2C), 22.8, 22.7, 14.2 (2C) ppm. Spectral data agree with a previous literature report.²⁵

E5: ^1H NMR (CDCl_3) 4.04 (t, $^3J = 6.7$ Hz, 2H), 2.28 (t, $^3J = 7.5$ Hz, 2H), 1.57–1.61 (m, 4H), 1.24–1.29 (m, 50H), 0.85–0.88 (m, 6H) ppm; ^{13}C NMR (CDCl_3) 174.2, 64.5, 34.6, 32.0, 29.8, 29.6, 29.5, 29.4, 28.7, 26.0, 25.1, 22.8, 14.2 ppm. Spectral data agree with a previous literature report.²⁶

Reactive Distillation of a [2 × 3] Ester Library: Ethyl Acetate (A1), Ethyl Butyrate (B1), and Benzyl Benzoate (C3). A mixture of **A1** (890 mg, 10.0 mmol), **B1** (1.17 g, 10.0 mmol), **C1** (3.03 g, 20.0 mmol), **A3** (1.52 g, 10.0 mmol), **B3** (1.80 g, 10.0 mmol), and **C3** (2.14 g, 10.0 mmol) was added to a 25 mL two-neck round-bottom flask. The reaction flask was equipped with a 185 mm long Vigreux column cooled by a *i*-PrOH/ CO_2 cold trap (-55 to -50°C). A short path distillation head was placed on top of the Vigreux column, connecting it to the receiving flask, which was placed in a separate *i*-PrOH/ CO_2 ice bath (-78°C). A 0.05 mL aliquot of a 1 M NaOt-Bu in THF solution was injected into the reaction flask every 30 min for 5 h. Vacuum (2.5 mmHg) was started at the same time as the first loading of catalyst was added. The first step of the distillation was performed at 50°C for 5 h, resulting in the first distillate, which was collected as a colorless liquid. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture of **A1** (1.58 g, 17.9 mmol, 90% yield), **B1** (106 mg, 0.91 mmol, 5% yield), and THF (solvent, 888 mg, 12.4 mmol). The second distillate was collected after another 8 h of distillation without the Vigreux column. A 0.05 mL aliquot of a 1 M sodium *tert*-butoxide in THF solution was injected into the reaction flask every 30 min for 8 h. ^1H NMR spectroscopy confirmed the identity of this liquid as a mixture of **A1** (35.9 mg, 0.41 mmol, 2% yield), **B1** (1.75 g, 15.1 mmol, 76% yield), and THF (solvent, 1.62 g, 22.5 mmol). Esters **A3**, **C1**, **B3**, and **C3** were not observed in either of the distillates. The remainder in the distillation flask was identified by ^1H NMR spectroscopy as a mixture of **C3** (5.90 g, 27.8 mmol, 93% yield), **B3** (209 mg, 1.18 mmol, 6% yield), and **C1** (199 mg, 1.33 mmol, 7% yield). For detailed calculation of the yields of individual components, see Supporting Information.

A1: ^1H NMR (CDCl_3) 4.11 (q, $^3J = 7.1$ Hz, 2H), 2.03 (s, 3H), 1.20 (t, $^3J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 170.8, 60.1, 20.7, 13.9 ppm. Spectral data agree with a previous literature report.²¹

B1: ^1H NMR (CDCl_3) 4.13 (q, $^3J = 6.8$ Hz, 2H), 2.27 (t, $^3J = 7.4$ Hz, 2H), 1.65 (sextet, $^3J = 7.4$ Hz, 2H), 1.26 (t, $^3J = 6.8$ Hz, 3H), 0.96 (t, $^3J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) 173.6, 60.1, 36.3, 18.6, 14.3, 13.7 ppm. Spectral data agree with a previous literature report.²³

C3: ^1H NMR (CDCl_3) 8.10 (d, $^3J = 7.0$ Hz, 2H), 7.59 (t, $^3J = 7.5$ Hz, 1H), 7.37–7.50 (m, 7H), 5.40 (s, 2H) ppm; ^{13}C NMR (CDCl_3) 166.5, 136.3, 133.2, 130.3, 129.9, 128.8, 128.6, 128.4, 128.3, 66.8 ppm. Spectral data agree with a previous literature report.²²

■ ASSOCIATED CONTENT

● Supporting Information

Detailed experimental procedures for reactive distillations and spectroscopic evidence of identities and purities of prepared esters. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (13) The volatilities of individual esters will determine the order in which they will be distilled out from the DCL. There is no explicit correlation between the volatility of a given ester and its constituent acids and alcohols. However, in this study, we found that esters formed from low boiling point alcohols and acids always had lower boiling points than those formed from alcohols and acids of higher boiling points. This behavior is probably a consequence of a sufficiently large difference in the molecular masses and boiling points of the chosen carboxylic acids and alcohols. The reader is advised that this may not be a general rule.
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- (16) It should be noted that ester libraries presented in Schemes 1–4 were not prepared through a random esterification of the corresponding alcohols and carboxylic acids. Instead, the commercial samples of the requisite esters (dried over CaH₂) were mixed in exactly equimolar ratios and then subjected to reactive distillation. The purpose of this strategy was (a) to ensure the most random ester distribution possible, that is, to prevent any potential biasing of the library during the esterification process, and (b) to avoid possible losses of highly volatile esters during the high-temperature esterification.
- (17) This hypothesis was indirectly confirmed through an experiment in which ester **A3** alone was exposed to a stoichiometric amount of NaOt-Bu and then subjected to distillation. *t*-Butyl acetate could be clearly identified in the distillate, although in low yield (~10%).
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- (20) Of course, as soon as the acyl exchange catalyst is added to this mixture, the excess amount of **C1** probably gets redistributed among other esters that share a component with it, that is, **A1**, **B1**, and **C3**. The same argument applies to the [2 × 2] library that results after the first distillation step; the 2 equiv amount of **C3** (marked with an * in Scheme 4) is only one of the several possible distributions of the excess of **C3**'s components.
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