Electronic Supplementary Material (ESI) for Green Chemistry.

SUPPORTING INFORMATION

Why we might be misusing Process Mass Intensity (PMI) and a methodology to apply it effectively as a discovery level metric

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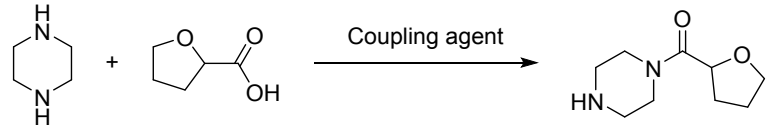
Table of Contents

1 Experimental for the synthesis of (oxolan-2-yl)(piperazin-1-yl)methanone (3)

The green credentials obtained via the Chem21 Metrics Toolkit of a reaction between piperazine (**1**) and tetrahydrofuran-2-carboxylic acid (**2**) via six different amide coupling reagents can be found in table 2 of the manuscript. Underneath the experimental procedures for the synthesis of synthesis of (oxolan-2-yl)(piperazin-1-yl)methanone (**3**) are provided. The characterisation of molecule **3** can be found in section 1.7.



1 **2** **3**

1.1 Silica as coupling agent

Tetrahydrofuran-2-carboxylic acid (5.0 mmol, 0.58 g, 1.0 equiv), piperazine (5.0 mmol, 0.43 g, 1.0 equiv) and K60 silica (0.1 g, activated at 700 °C) where heated at 110 °C. After 14 hours the mixture was cooled to room temperature and dissolved in acetone (20 mL). The silica catalyst was removed by filtration and solvent removed under reduced pressure. The crude material was purified by flash chromatography.

1.2 Immobilized novoenzyme 435 as coupling agent

To a solution of tetrahydrofuran-2-carboxylic acid (5.0 mmol, 0.58 g, 1.0 equiv) and piperazine (5.0 mmol, 0.43 g, 1.0 equiv) in heptane (20 mL) was added immobilized novoenzyme 435 (0.10 g) and the mixture stirred at room temperature. After 72 hours the solution was filtered and solvent removed under reduced pressure. The crude material was purified by flash chromatography.

1.3 Thionyl chloride as coupling agent

To a solution of tetrahydrofuran-2-carboxylic acid (5.0 mmol, 0.58 g, 1.0 equiv) and piperazine (5.0 mmol, 0.43 g, 1.0 equiv) in toluene (20 mL) was added thionyl chloride (15 mmol, 1.78 g, 1.5 equiv) and the mixture was refluxed. After 1 hour the mixture was cooled to room temperature and water (5 mL) added then the solvent removed under reduced pressure. The crude material was purified by flash chromatography.

1.4 Boric acid as coupling agent

To a solution of tetrahydrofuran-2-carboxylic acid (5.0 mmol, 0.58 g, 1.0 equiv) in toluene (20 mL) was added boric acid (0.5 mmol, 0.03 g, 10 mol%). To this mixture was added piperazine (5.0 mmol, 0.43 g, 1.0 equiv) and the mixture was refluxed. After 11 hours the mixture was cooled and solvent removed under reduced pressure. The crude material was purified by flash chromatography.

1.5 Triphenylphosphine and *N*-bromosuccinimide as coupling agent

A mixture of tetrahydrofuran-2-carboxylic acid (5.0 mmol, 0.58 g, 1.0 equiv) and triphenylphosphine (5.0 mmol, 1.31 g, 1.0 equiv) in dichloromethane (15 mL) was cooled to

5 °C. *N*-Bromosuccinimide (5.0 mmol, 0.89 g, 1.0 equiv) was added and the reaction mixture stirred for 15 min. Then a solution of piperazine (5.0 mmol, 0.43 g, 1.0 equiv) and pyridine (5.0 mmol, 0.40 g, 1.0 equiv) in dichloromethane (5 mL) was added dropwise to the above solution at room temperature. After 1 hour the solvent was removed under reduced pressure. The crude was dissolved in ethyl acetate (50 mL) and washed with saturated sodium bicarbonate solution (30 mL), water (30 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered and solvent removed under reduced pressure. The crude material was purified by flash chromatography.

1.6 Hexamethylsilazane as coupling agent

Tetrahydrofuran-2-carboxylic acid (5.0 mmol, 0.58 g, 1.0 equiv), piperazine (5.0 mmol, 0.43 g) and 1,1,1,3,3,3-hexamethyldisilazane (5.0 mmol, 0.81 g, 1.0 equiv) was heated at 110 °C. After 8 hours the mixture was cooled to room temperature and dissolved in ethyl acetate (50 mL) and washed with saturated sodium bicarbonate solution (30 mL), water (30 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered and solvent removed under reduced pressure. The crude material was purified by flash chromatography.

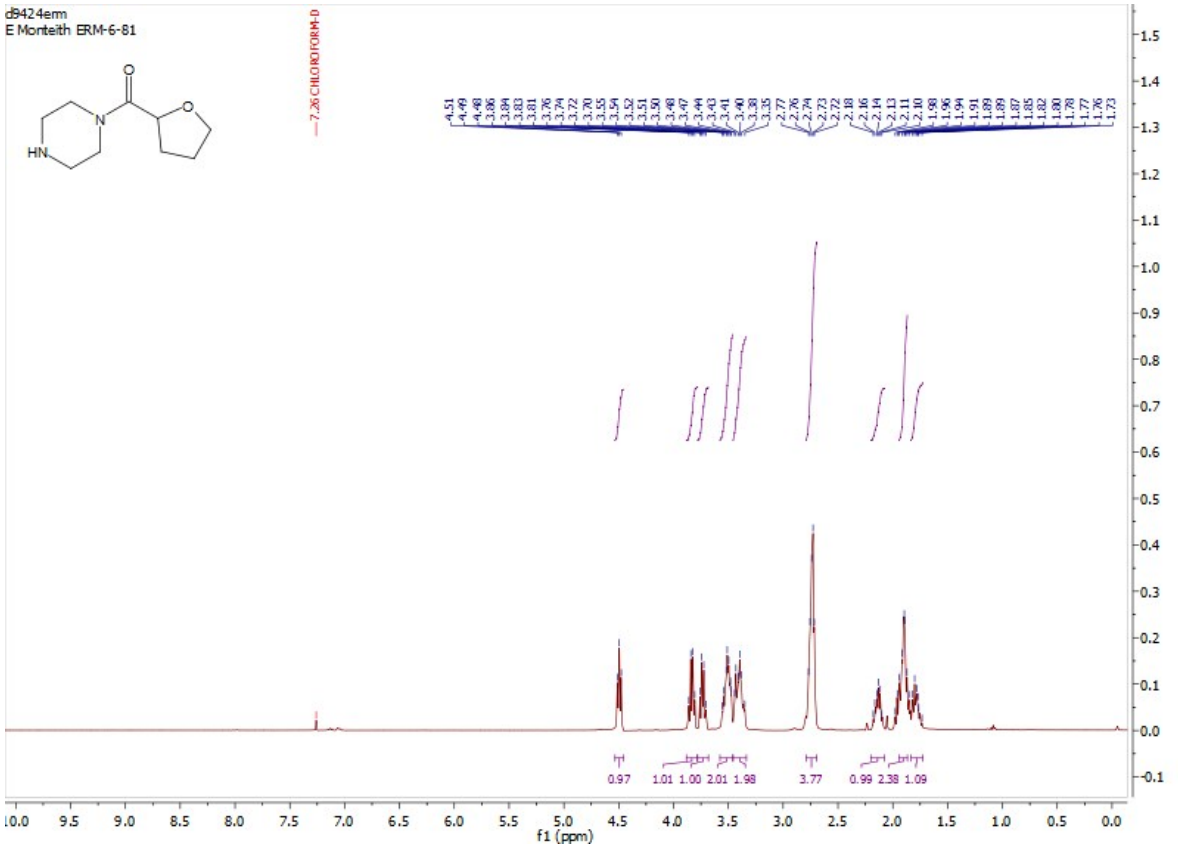
1.7 Characterization of (oxolan-2-yl)(piperazin-1-yl)methanone (3).

The compound was purified using EtOAc:MeOH:Et_3N (5:1:0.5, with R_f (**3**) = 0.26) as eluent system. All spectra are in agreement with the literature.[1]

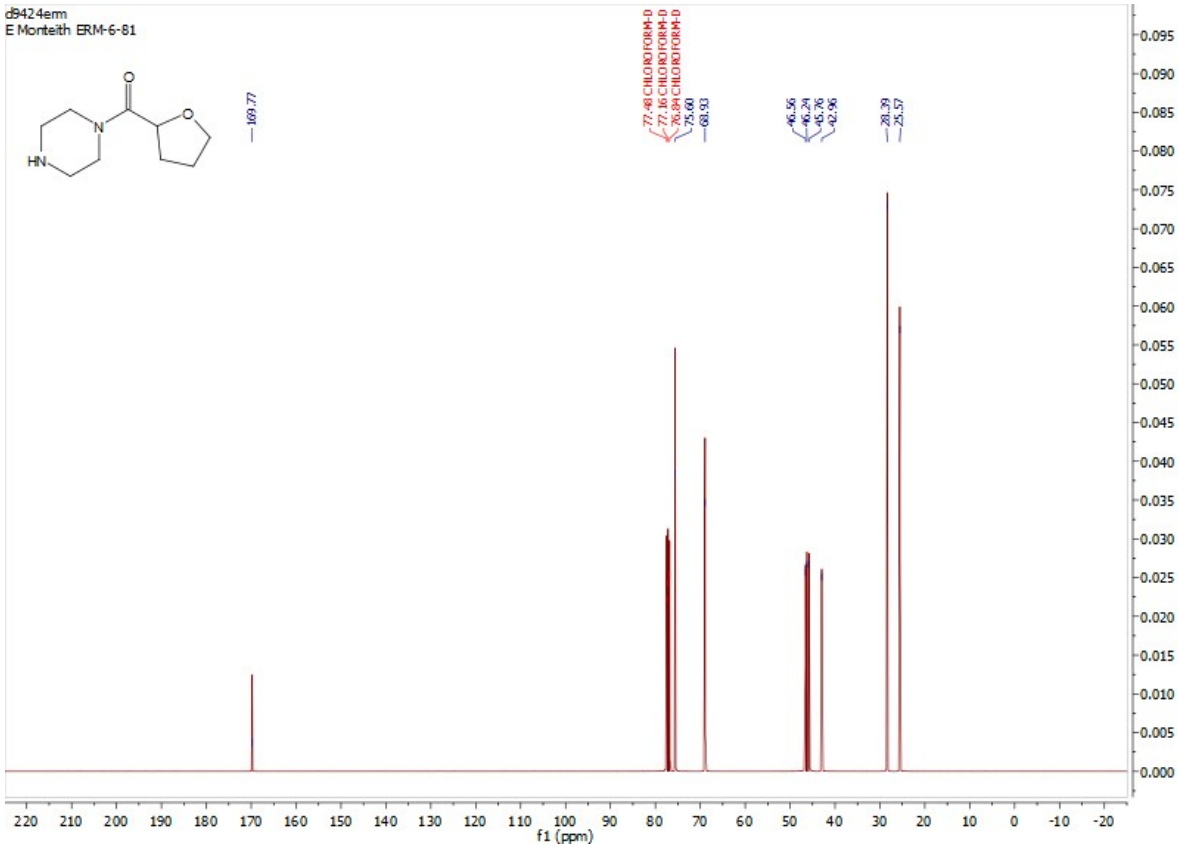
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (t, *J* = 6.9 Hz, 1H), 3.83 (q, *J* = 7.8, 7.3 Hz, 1H), 3.73 (q, *J* = 7.8, 7.0 Hz, 1H), 3.58 – 3.46 (m, 2H), 3.46 – 3.34 (m, 2H), 2.79 – 2.69 (m, 4H), 2.20 – 2.08 (m, 1H), 1.94 – 1.87 (m, 2H), 1.83 – 1.73 (m, 1H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 75.6, 68.9, 46.6, 46.2, 45.8, 43.0, 28.4, 25.6 ppm.
HRMS ESI (*m/z*): calculated for $C_9H_{17}N_2O_2$ $[M + H]^+$, 185.1285; found, 185.1285.
(*m/z*): calculated for $C_9H_{16}N_2NaO_2$ $[M + Na]^+$, 207.1104; found, 207.1103.

General information: All reagents were purchased from commercial sources and were used without further purification. Nuclear Magnetic Resonance (NMR) spectra were recorded on a JEOL ECX400 spectrometer at 295 K. ^{1}H NMR experiments were reported in δ units, parts per million (ppm), and were measured relative to residual chloroform (7.26 ppm) in the deuterated solvent. ^{13}C NMR spectra were reported in ppm relative to $CDCl_3$ (77.16 ppm) and the spectra were obtained with ^{1}H decoupling. All coupling constants *J* were reported in Hertz (Hz). The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quadruplet m = multiplet. All measurements were carried out at room temperature unless otherwise stated. High resolution mass-spectra were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) in positive mode on a Bruker Daltonics, Micro-tof spectrometer. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) or stained with a 10% solution of phosphomolybdic acid in ethanol. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm, 60 Å, under a positive pressure of air, eluting with the specified solvent system.

^{1}H NMR (400 MHz, $CDCl_3$):



^{13}C NMR (101 MHz, $CDCl_3$):



2 Amide synthesis

Amide bond formations is one of the most important reactions in organic synthesis. In this section we examined for several classical coupling reagents the effect of altering the reaction parameters on the green metrics parameters yield, atom economy (AE), reaction mass efficiency (RME), process mass intensity (PMI), process mass intensity reactants reagents and catalysts (PMI_{RRC}), process mass intensity solvents (PMI_{solv}).

In the following tables a green metric assessment of the reported literature procedures is determined as a benchmark. For every literature procedure also the molecular weight of the reactants and the acid concentration have been indicated. Subsequently, in simulations A-D the following parameters have been altered.

- Simulation A:
  - The acid concentration is changed to 0.4 M.
  - The equivalents of the reagents and reactants remain unaltered as well as the reported yield.

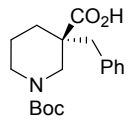
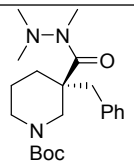
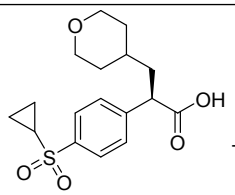
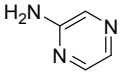
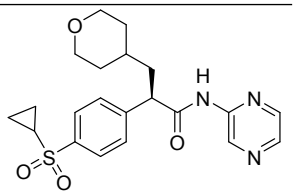
- Simulation B:
  - The acid concentration remains the same as reported.
  - The yield of the reaction is changed to 90%.

- Simulation C:
  - The acid concentration is changed to 0.4 M.
  - The yield of the reaction is changed to 90%.

- Simulation D:
  - The acid concentration is changed to 0.4 M.
  - The yield of the reaction is changed to 50%.

2.1 Oxalyl chloride $(COCl)_2$ as coupling reagent

Table S1. Literature and simulation A-D for oxalyl chloride[a]

Reaction 3	 319.40 g mol^{-1} (1.00 eq)	+  74.13 g mol^{-1} (1.50 eq)	i) $(COCl)_2$ (1.61 eq) DMF (10 mol%) NEt_3 (2.02 eq) DCM (0.3 M), -10 °C ii) MeHN-NHMe (1.50 eq) NEt_3 (2.02 eq) 1,4-dioxane (0.7 M), -20 °C	 375.51 g mol^{-1}
Reaction 4	 338.42 g mol^{-1} (1.00 eq)	+  95.11 g mol^{-1} (1.35 eq)	i) $(COCl_2)$ (1.29 eq) DMF (cat.) THF (0.3 M), < 30 °C ii) 2-aminopiperazine (1.35 eq) py (12.28 eq) THF (0.3 M), < 30 °C	 415.51 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Literature data reported						
Reaction 3: [Acid] = 0.2 M	95	79	20.3	3.2	17.1	91
Reaction 4: [Acid] = 0.3 M	96	70	15.0	4.4	10.5	74
Simulation A: [Acid] = 0.4 M, Literature yield						
Reaction 3	95	79	12.2	3.2	9.0	91
Reaction 4	96	70	11.6	4.4	7.2	74
Simulation B: [Acid] = Literature data, 90% Yield						
Reaction 3	95	78	20.4	3.2	17.2	90
Reaction 4	96	85	12.3	3.7	8.7	90
Simulation C: [Acid] = 0.4 M, 90% Yield						
Reaction 3	95	78	12.3	3.2	9.1	90
Reaction 4	96	85	9.5	3.7	5.9	90
Simulation D: [Acid] = 0.4 M, 50% Yield						
Reaction 3	95	44	22.1	5.7	16.4	50
Reaction 4	96	47	17.2	6.6	10.6	50

[a] Reactions refer to scheme 1 of the manuscript.

Reported Experimental procedures

Reaction 3:[2]

To a 72 L unjacketed reactor equipped with a temperature probe, reflux condenser, nitrogen sweep, cooling bath, and an overhead stirrer was charged *N*-Boc-3-benzylnipecotic acid (3 kg, 9.4 mol) followed by dichloromethane (30 L). The solution was cooled to -15 °C, and oxalyl chloride (1.3 L, 15.2 mol) was added over 15 min while the internal temperature was maintained below -10 °C. DMF (300 mL) was then charged to the mixture over 20 min followed by NEt_3 (2.7 L, 19 mol) over 1.75 h. The reaction mixture was stirred at -15 to -10 °C for 4.25 h until the conversion was complete. A solution of trimethylhydrazine in 1,4-dioxane (1.05 kg in 15 kg, 7% w/w, 14.1 mol) and NEt_3 (2.7 L, 19 mol) was added to the reaction mixture over 2 h using a fluid-metering pump, maintaining the internal temperature between -15 to -20 °C. The reaction

progress was monitored by HPLC analysis. The product was obtained as an oil (3.2 kg, 90% yield).

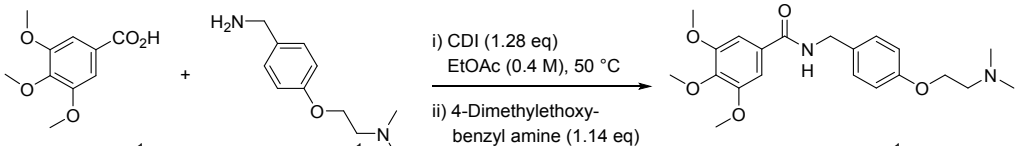
Reaction 4:[3]

At 20-25 °C, a reactor was charged with THF (100 L) followed by chiral acid (23.10 kg, 55.59 mol) which was rinsed into the reactor with THF (5 L). DMF (0.275 kg, 3.76 mol) was charged to the reactor followed by the addition of oxalyl chloride (9.125 kg, 71.89 mol) over 0.25 h, maintaining the temperature below 30 °C. The resulting mixture was held for 1.0 h, and a sample was quenched into MeOH for HPLC analysis, which indicated >99% conversion to the acid chloride via analysis of the methyl ester derivative. THF (116 L) was charged to a second reactor followed by 2-aminopyrazine (7.15 kg, 75.23 mol), which was rinsed into the reactor with THF (6 L). Pyridine (54 kg, 682.7 mol) was charged to the second reactor, and the temperature was maintained at 20−25 °C. The acid chloride mixture was transferred to the mixture of 10 in THF over 0.75 h while maintaining the temperature below 30 °C. THF (24 L) was used to rinse the acid chloride reactor into the second reactor. The resulting mixture was held for 1.0 h, and a sample was quenched into MeOH for HPLC analysis, which indicated <1% of the methyl ester derivative and production of (R)-1. The chiral amide was isolated as an off white solid with a weight of 21.06 kg and chiral purity of >99% ee (yield 73.6%).

2.2 *N*,*N*-carbonyldiimidazole (CDI) as coupling reagent

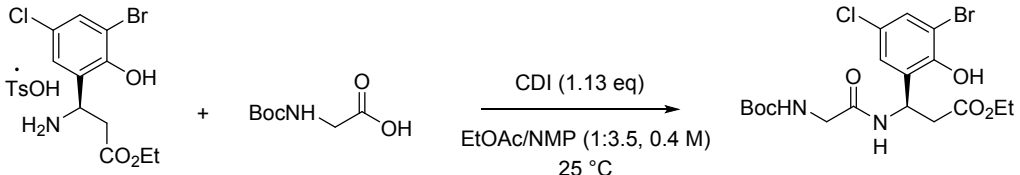
Table S2. Literature and simulation A-D for CDI[a]

Reaction 5



212.20 g mol^{-1} (1.00 eq) + 194.28 g mol^{-1} (1.14 eq) → 388.46 g mol^{-1}

Reaction 6



494.78 g mol^{-1} (1.00 eq) + 175.18 g mol^{-1} (1.13 eq) → 479.75 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Literature data reported						
Reaction 5: [Acid] = 0.4 M	96	81	8.8	2.2	6.6	89
Reaction 6: [Acid] = 0.2 M	72	56	8.1	2.2	5.9	87
Simulation A: [Acid] = 0.4 M, Literature yield						
Reaction 5	96	81	8.7	2.2	6.4	89
Reaction 6	72	56	7.8	2.2	5.6	87
Simulation B: [Acid] = Literature data, 90% Yield						
Reaction 5	96	82	8.7	2.2	6.5	90
Reaction 6	72	59	7.8	2.1	5.7	90
Simulation C: [Acid] = 0.4 M, 90% Yield						
Reaction 5	96	82	8.6	2.2	6.4	90
Reaction 6	72	59	7.5	2.1	5.4	90
Simulation D: [Acid] = 0.4 M, 50% Yield						
Reaction 5	96	46	15.6	4.0	11.6	50
Reaction 6	72	33	13.5	3.8	9.6	50

[a] Reactions refer to scheme 1 of the manuscript.

Reported experimental procedures

Reaction 5:[4]

3,4,5-Trimethoxybenzoic acid (63.0 kg; 0.29 mol), *N*,*N*-carbonyldiimidazole (60.65 kg; 0.37 mol) and ethyl acetate (378 L) were added to a flask and heated to a temperature of 50 - 55 °C for 2 h. After reaction completion, the mixture was cooled to 30 °C to 35 °C. 4-Dimethylaminoethoxy benzylamine (63.42 kg; 0.33 mol) and potassium carbonate (41.00 kg; 0.30 mol) were taken in ethyl acetate (378 L) at 25 °C to 30 °C under nitrogen atmosphere. A reaction mixture consisting of *N*-(3,4,5-trimethoxybenzoyl)imidazole was added to the above reaction mixture in drop wise manner so that the temperature is maintained below 10 °C. After completion of addition reaction mixture was stirred for 2.5 hours till completion of reaction. The title compound was obtained as a white solid. (Yield: 103 kg, 89%)

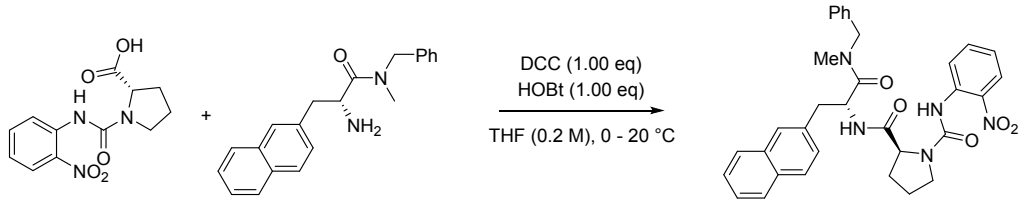
Reaction 6:[5]

A solution of *N*-*t*-Boc-glycine (81.2 kg, 464 mol) at 25 °C in ethyl acetate (428 L) in reactor 1 was transferred to a slurry of CDI (75.2 kg, 464 mol) at 25 °C in ethyl acetate (325 L) in reactor 2. Reactor 1 was rinsed with ethyl acetate (50 L), and the rinse was transferred to reactor 2. The clear yellow solution was stirred for 21 h at 25 °C. A solution of amine (221.6 kg, 410.3 mol) in NMP (239 L) was prepared in reactor 1 at 25 °C. The solution of the amine in reactor 2 was transferred to the solution of 2 in reactor 1 over 19 min. Reactor 2 was rinsed with ethyl acetate (50 L), and the rinse was transferred to reactor 1. The product was obtained in 87% yield (170.6 kg).

2.3 *N,N'*-dicycloheyxylcarbodiimide (DCC) as coupling reagent

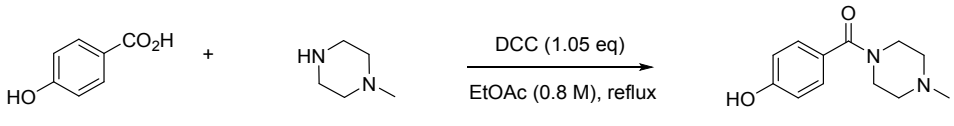
Table S3. Literature and simulation A-D for DCC[a]

Reaction 7



279.25 g mol^{-1} (1.00 eq) + 318.42 g mol^{-1} (1.05 eq) → 579.66 g mol^{-1}

Reaction 8



138.12 g mol^{-1} (1.00 eq) + 100.17 g mol^{-1} (1.02 eq) → 220.27 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Literature data reported						
Reaction 7: [Acid] = 0.2 M	97	77	14.1	2.1	12.0	77
Reaction 8: [Acid] = 0.8 M	92	79	8.1	2.4	5.7	86
Simulation A: [Acid] = 0.4 M, Literature yield						
Reaction 7	97	77	6.7	2.1	4.5	77
Reaction 8	92	79	14.2	2.4	11.8	86
Simulation B: [Acid] = Literature data, Yield = 90%						
Reaction 7	97	90	12.1	1.8	10.3	90
Reaction 8	92	83	7.7	2.3	5.4	90
Simulation C: [Acid] = 0.4 M, Yield = 90%						
Reaction 7	97	80	6.4	2.0	4.3	90
Reaction 8	92	83	13.6	2.3	11.3	90
Simulation D: [Acid] = 0.4 M, Yield = 50%						
Reaction 7	97	50	10.3	3.3	7.0	50
Reaction 8	92	46	24.5	4.1	20.3	50

[a] Reactions refer to scheme 1 of the manuscript.

Reported experimental procedures

Reaction 7:[6]

To a solution of 1-[(2-nitrophenylamino)carbonyl]-L-proline (11, 88.0 g, 0.315 mol) in THF (530 mL) was added a solution of (*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide free base in THF (200 mL) over 15 min while maintaining the internal temperature at 22 °C. THF (50 mL) was used to wash the addition funnel and added to the reaction mixture. 1-Hydroxybenzotriazole (40.54 g, 0.3 mol) was then added. The reaction mixture was stirred at 22 °C for 10 min to dissolve the solids and then cooled to 0 °C. A solution of 1,3-dicyclohexylcarbodiimide (62.53 g, 0.303 mol) in THF (100 mL) was added to the mixture over 15 min while maintaining the internal temperature at 0 °C. The mixture was warmed to 22 °C over 30 min and stirred at 22

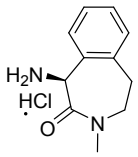
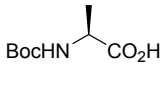
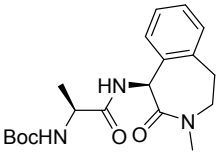
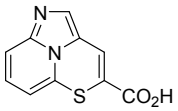
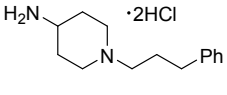
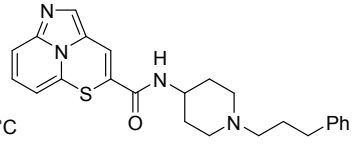
°C for 4 h. The product was distilled and the desired product was obtained in 86% (150 g) yield.

Reaction 8:[7]

N-methylpiperazine (226 mL, 2.0 mol) was added slowly (15 min) to a slurry of 4-hydroxybenzoic acid (229 g, 2.0 mol) in ethyl acetate (2 L) at 50 - 70 °C. A solution of dicyclohexylcarbodiimide (438 g, 2.1mol) in ethyl acetate (0.4 L) was added over 1.5 h to the salt slurry at 70 - 78 °C. The mixture was refluxed 1 h. The product was obtained in 84% (380 g).

2.4 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as coupling reagent

Table S4. Literature and simulation A-D for EDC[a]

Reaction 9	 226.71 g mol^{-1} (1.00 eq)	+	 189.21 g mol^{-1} (1.03 eq)	EDC (1.12 eq) HOBt (0.05 eq) NMM/EtOH (0.7 M), 25 °C	 361.44 g mol^{-1}		
Reaction 10	 218.23 g mol^{-1} (1.00 eq)	+	 291.26 g mol^{-1} (1.05 eq)	EDC (1.05 eq) HOBt (0.23 eq) NEt_3 (2.00 eq) DMF (0.6 M), 70 - 80 °C	 418.56 g mol^{-1}		
			AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Literature data reported								
	Reaction 9: [Acid] = 0.7 M		87	79	5.8	2.6	3.2	92
	Reaction 10: [Acid] = 0.6 M		82	61	8.3	3.0	5.3	76
Simulation A: [Acid] = 0.4 M, Literature yield								
	Reaction 9		87	79	8.5	2.6	5.9	92
	Reaction 10		82	61	10.4	3.0	7.4	76
Simulation B: [Acid] = Literature data, Yield 90%								
	Reaction 9		87	77	5.9	2.6	3.3	90
	Reaction 10		82	72	7.0	2.6	4.5	90
Simulation C: [Acid] = 0.4 M, Yield = 90%								
	Reaction 9		87	77	8.7	2.6	6.1	90
	Reaction 10		82	72	8.8	2.6	6.3	90
Simulation D: [Acid] = 0.4 M, Yield = 50%								
	Reaction 9		87	43	15.6	4.7	10.9	50
	Reaction 10		82	40	15.9	4.6	11.3	50

[a] Reactions refer to scheme 1 of the manuscript.

Reported experimental procedures

Reaction 9:[8]

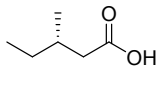
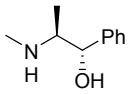
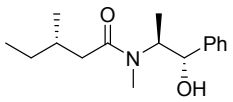
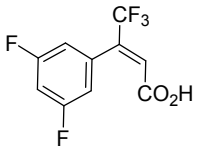
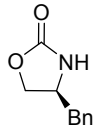
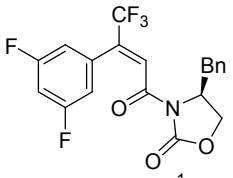
To a reaction vessel was charged ethanol (358 L), amine (59.94 kg, 264.4 mol), HOBt (2.04 kg, 13.32 mol), (*S*)-BocAla (51.28 kg, 271.0 mol), and NMM (57.30 kg, 566.5 mol) to form a solution. EDC (56.58 kg, 295.1 mol) was then charged, and the reaction mixture was stirred at 25 °C for 10 h followed by the slow addition of water (541 L) over 1 h. This provided the amide in 91% yield (88.16 kg).

Reaction 10:[9]

To a solution of amine.HCl (2.24 kg) in DMF (13 L) was added NEt_3 (2.15 L) dropwise at 20 - 30 °C. The mixture was stirred for 30 min at the same temperature. To the resulting mixture was added acid (1.595 kg), HOBt (225 g) and EDCI (1.47 kg), and the whole was stirred for 2 h at 70-80 °C. The product was obtained in 76% yield (2.33 kg) as a red crystalline powder.

2.5 Pivaloyl chloride (PivCl) as coupling reagent

Table S5. Literature and simulation A-D for PivCl[a]

Reaction 11		+ 	PivCl (1.00 eq) NEt_3 (1.05 eq) DCM (1.4 M), < -5 °C	
	116.16 g mol^{-1} (1.00 eq)	165.24 g mol^{-1} (1.00 eq)		263.38 g mol^{-1}
Reaction 12		+ 	LiCl (2.00 eq) PivCl (2.50 eq) NEt_3 (2.60 eq) THF (0.4 M), -20 °C	
	252.14 g mol^{-1} (1.00 eq)	177.20 g mol^{-1} (1.10 eq)		411.33 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Literature data reported						
Reaction 11: [Acid] = 1.4 M	94	94	5.9	2.3	3.5	100
Reaction 12: [Acid] = 0.4 M	96	86	8.6	2.9	5.7	93
Simulation A: [Acid] = 0.4 M, Literature yield						
Reaction 11	94	94	15.0	2.3	12.6	100
Reaction 12	96	86	8.6	2.9	5.8	93
Simulation B: [Acid] = Literature data, Yield = 90%						
Reaction 11	94	84	6.5	2.6	3.9	90
Reaction 12	96	83	8.9	3.0	5.9	90
Simulation C: [Acid] = 0.4 M, Yield = 90%						
Reaction 11	94	84	16.6	2.6	14.0	90
Reaction 12	96	83	8.9	3.0	6.0	90
Simulation D: [Acid] = 0.4 M, Yield = 50%						
Reaction 11	94	47	29.9	4.7	25.2	50
Reaction 12	96	46	16.1	5.3	10.7	50

[a] Reactions refer to scheme 1 of the manuscript.

Reported experimental procedures

Reaction 11:[10]

To a solution of the acid (2.32 kg, 20.00 mol) in CH_2Cl_2 (14 L) at -5 °C was added Et_3N (2.93 L, 2.12 kg, 21.00 mol, 1.05 equiv), followed by pivaloyl chloride (2.46 L, 2.41 kg, 20.00 mol, 1.00 equiv), while maintaining the internal temperature < 0 °C. The resultant slurry was stirred for 1 h, and then Et_3N (2.93 L, 2.12 kg, 21.00 mol, 1.05 equiv) was added. (1*S*,2*S*)-(+)-Pseudoephedrine (3.30 kg, 20.00 mol, 1.00 equiv) was added as a solid in portions, maintaining the internal temperature < 5 °C. The resultant slurry was stirred for 1 h, and water (14 L) was added. The amide was obtained in quantitative amount.

Reaction 12:[11]

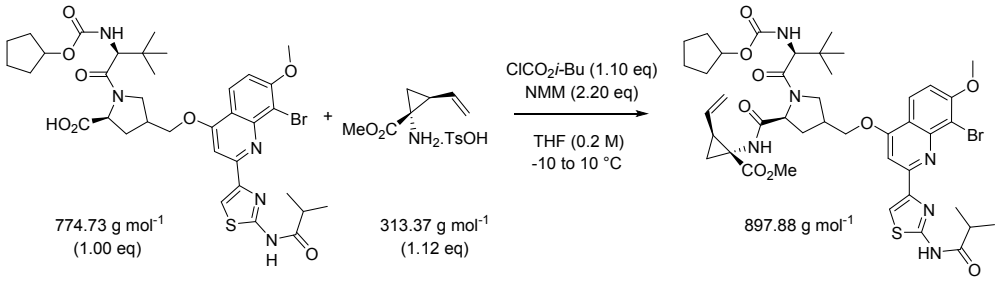
Acid (11 kg, 43.63 mol), (*S*)-(-)-4-benzyl-2-oxazolidinone (8.5 kg, 47.97 mol, 1.1 equiv) and LiCl (3.7 kg, 87.28 mol, 2.0 equiv) were added to THF (95.7 kg) cooled to

-15 °C. The temperature was adjusted to 20 °C, the mixture was stirred for 30 min and then cooled to -21 °C. Trimethyl acetyl chloride (13.1 kg, 108.54 mol, 2.5 equiv) was added over 30 min at -21 °C. Triethylamine (11.5 kg, 113.64 mol, 2.6 equiv) was added over 4.5 h at -22 to -20 °C. The mixture was stirred at -23 °C for 30 min. The reaction completion was confirmed by HPLC (no residual acid 9 was detected). The product was obtained in 93% yield (16.68 kg).

2.6 Isobutyl chloroformate (IBCF) as coupling reagent

Table S6. Literature and simulation A-D for IBCF[a]

Reaction 13



Scheme	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Literature data reported						
[Acid] = 1.4 M	83	67	8.3	2.0	6.3	84
Simulation A: [Acid] = 0.4 M, Literature yield						
	83	67	4.9	2.0	2.9	84
Simulation B: [Acid] = Literature data, Yield = 90%						
	83	72	7.8	1.9	5.9	90
Simulation C: [Acid] = 0.4 M, Yield = 90%						
	83	72	4.6	1.9	2.7	90
Simulation D: [Acid] = 0.4 M, Yield = 50%						
	83	40	8.3	3.4	4.9	50

[a] Reaction refers to scheme 1 of the manuscript.

Reported experimental procedure

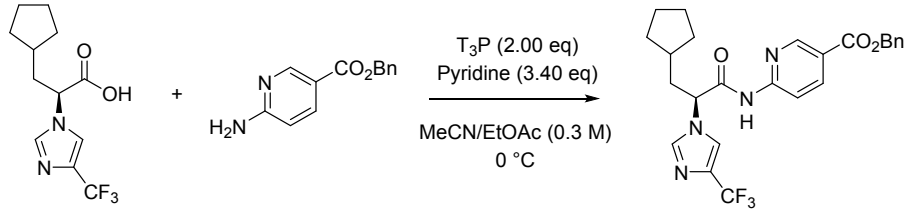
Reaction 13:[12]

A reactor was charged with the acid (15.7 kg, 20.6 mol, 1.0 equiv) and THF (110 L, dry). The mixture was agitated until a solution was formed, then the jacket was adjusted so that the internal temperature was approximately 158 °C. *N*-methylmorpholine (2.31 kg, 22.9 mol, 1.1 eq) was then slowly added at a rate that maintained the internal temperature at 108 °C. By using a pre-calibrated metering valve, isobutyl chloroformate (3.13 kg, 22.9 mol, 1.1 eq) was slowly added. On this scale the addition took 50 min. The internal temperature was adjusted to 108 °C and held for 90 min. Aminocyclopropane salt (7.12 kg, 22.9 mol, 1.1 eq) was then added through a solid-charging funnel and the internal temperature was maintained at 88 °C. A second charge of *N*-methylmorpholine (2.29 kg, 22.7 mol, 1.1 eq) was then added at a rate that maintained the internal temperature at 88 °C. The reaction was held at 108 °C for 2 h, then warmed to 108 °C, and held at that temperature until conversion was at least 95% by HPLC analysis (this batch required 12 h). The product was obtained in 85% (15.43 kg) yield.

2.7 Propylphosphonic anhydride (T_3P) as coupling reagent

Table S7. Literature and simulation A-D for T_3P[a]

Reaction 14



276.26 g mol^{-1} (1.00 eq) | 228.25 g mol^{-1} (1.10 eq) | 486.50 g mol^{-1}

Scheme	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Literature data reported						
[Acid] = 0.3 M	96	81	9.8	3.3	6.4	88
Simulation A: [Acid] = 0.4 M, Literature yield						
	96	81	8.1	3.3	4.7	88
Simulation B: [Acid] = Literature data, Yield = 90%						
	96	83	9.6	3.3	6.3	90
Simulation C: [Acid] = 0.4 M, Yield = 90%						
	96	83	7.9	3.3	4.6	90
Simulation D: [Acid] = 0.4 M, Yield = 50%						
	96	46	14.2	5.9	8.3	50

[a] Reaction refers to scheme 1 of the manuscript.

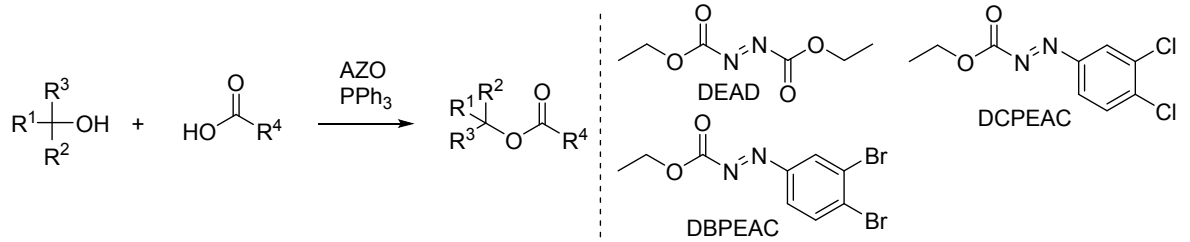
Reported experimental procedure

Reaction 14:[13]

A stirred mixture of the acid (22.00 kg, 79.64 mol), the amine (20.00 kg, 87.62 mol, 1.1 equiv), pyridine (22 L), MeCN (110 L), and EtOAc (57 L) was charged with T_3P solution (50 wt% MeCN, 101 kg, 104 L, 159 mol, 2.0 equiv) at -5 °C. The resulting homogeneous solution was held at 0 °C for 20 h as fine solids precipitated. The product was obtained in 88% yield (34.08 kg) as a white solid.

3 Mitsunobu reaction

The Mitsunobu reaction was selected as a second model reaction for our simulations in sections 3.1-3.4. The Mitsunobu reaction allows the conversion of primary and secondary alcohols to esters. Triphenylphosphine (PPh_3) is combined with an AZO-compound such as diethyl azodicarboxylate (DEAD), ethyl 2-(3,4-dichlorophenyl)diazene-1-carboxylate (DCPEAC) or ethyl 2-(3,4-dibromophenyl)diazene-1-carboxylate (DBPEAC) to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving leaving group. Subsequent nucleophilic substitution with the a carboxylate generates the desired ester together with triphenylphosphine oxide.



We applied in the following sections green metric simulations with DEAD, DCPEAC or DBPEAC as coupling reagent.

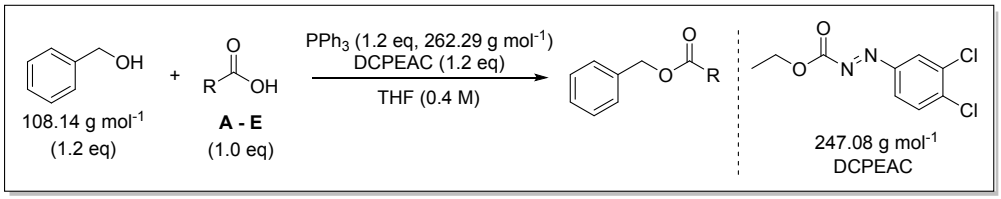
- Simulation 1:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - All other reactants are present in 1.2 equivalents.
  - A yield of 90% for the ester is assumed.
- Simulation 2:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - The other reactants are present in 1.2 equivalents.
  - A yield of 80% for the ester is assumed.
- Simulation 3:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - The other reactants are present in 1.2 equivalents.
  - A yield of 70% for the ester is assumed.
- Simulation 4:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - The other reactants are present in 1.2 equivalents.
  - A yield of 50% for the ester is assumed.
- Simulation 5:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - The other reactants are present in 1.2 equivalents.
  - A yield of 90% for the ester is assumed.
  - The scale of the reaction is multiplied by 5 compared to simulation A.
- Simulation 6:
  - The acid is the limiting reactant and is present in a 0.8 M solution.
  - The other reactants are present in 1.2 equivalents.
  - A yield of 90% for the ester is assumed.

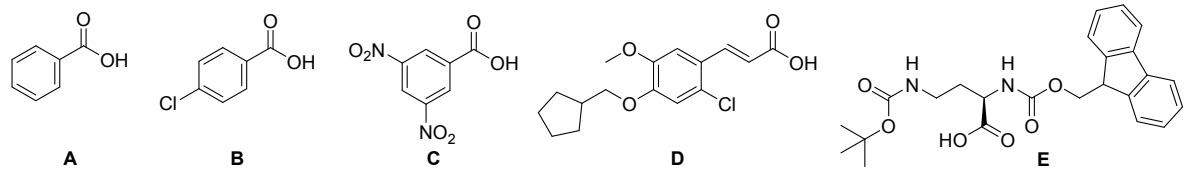
3.1 Diethyl azodicarboxylate (DEAD) as coupling reagent

These green metrics simulations have been incorporated in the manuscript and can be found in table 7.

3.2 Ethyl 2-(3,4-dichlorophenyl)diazene-1-carboxylate as coupling reagent

Table S8. Green metrics simulations applied on the Mitsunobu reaction with ethyl 2-(3,4-dichlorophenyl)diazene-1-carboxylate (DCPEAC) as coupling reagent.



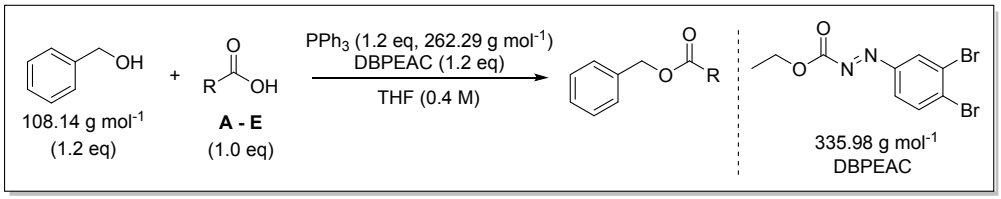


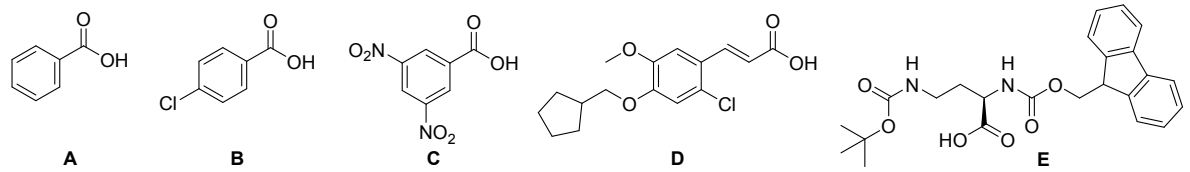
A 122.12 g mol^{-1} **B** 156.57 g mol^{-1} **C** 212.12 g mol^{-1} **D** 310.77 g mol^{-1} **E** 440.50 g mol^{-1}

Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.2	4.5	11.6	90
B	93	78	14.1	4.0	10.0	90
C	94	80	11.7	3.5	8.2	90
D	96	82	9.1	2.9	6.2	90
E	97	84	7.1	2.5	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	18.2	5.1	13.1	80
B	93	69	15.8	4.5	11.3	80
C	94	71	13.1	3.9	9.2	80
D	96	73	10.2	3.3	6.9	80
E	97	74	8.0	2.8	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	20.8	5.8	15.0	70
B	93	60	18.1	5.2	12.9	70
C	94	62	15.0	4.5	10.5	70
D	96	64	11.7	3.7	7.9	70
E	97	65	9.2	3.2	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	29.1	8.1	20.9	50
B	93	43	25.3	7.3	18.0	50
C	94	44	21.0	6.3	14.7	50
D	96	46	16.3	5.2	11.1	50
E	97	47	12.8	4.5	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.1	4.5	11.6	90
B	93	78	14.1	4.0	10.0	90
C	94	80	11.7	3.5	8.2	90
D	96	82	11.9	2.9	9.0	90
E	97	84	12.1	2.5	9.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	10.3	4.5	5.8	90
B	93	78	9.0	4.0	5.0	90
C	94	80	7.6	3.5	4.1	90
D	96	82	6.0	2.9	3.1	90
E	97	84	4.8	2.5	2.3	90

3.3 Ethyl 2-(3,4-dibromophenyl)diazene-1-carboxylate as coupling reagent

Table S9. Green metrics simulations applied on the Mitsunobu reaction with ethyl 2-(3,4-dibromophenyl)diazene-1-carboxylate (DBPEAC) as coupling reagent.





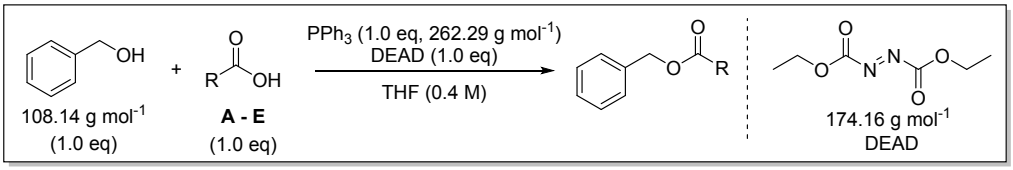
A 122.12 g mol^{-1} | **B** 156.57 g mol^{-1} | **C** 212.12 g mol^{-1} | **D** 310.77 g mol^{-1} | **E** 440.50 g mol^{-1}

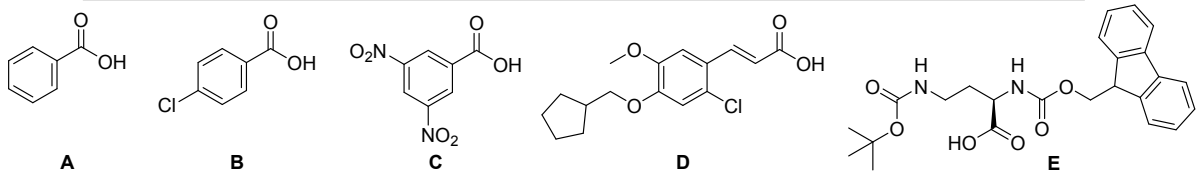
Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.7	5.1	11.6	90
B	93	78	14.5	4.5	10.0	90
C	94	80	12.1	3.9	8.2	90
D	96	82	9.4	3.2	6.2	90
E	97	84	7.4	2.7	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	18.8	5.7	13.1	80
B	93	69	16.4	5.1	11.3	80
C	94	71	13.6	4.4	9.2	80
D	96	73	10.5	3.6	6.9	80
E	97	74	8.3	3.0	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	21.5	6.5	15.0	70
B	93	60	18.7	5.8	12.9	70
C	94	62	15.5	5.0	10.5	70
D	96	64	12.0	4.1	7.9	70
E	97	65	9.5	3.5	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	30.1	9.1	20.9	50
B	93	43	26.2	8.1	18.0	50
C	94	44	21.7	7.0	14.7	50
D	96	46	16.9	5.8	11.1	50
E	97	47	13.2	4.9	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.7	5.1	11.6	90
B	93	78	14.5	4.5	10.0	90
C	94	80	12.1	3.9	8.2	90
D	96	82	12.2	3.2	9.0	90
E	97	84	12.4	2.7	9.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	10.9	5.1	5.8	90
B	93	78	9.5	4.5	5.0	90
C	94	80	8.0	3.9	4.1	90
D	96	82	6.3	3.2	3.1	90
E	97	84	5.0	2.7	2.3	90

3.4 Altering the acid concentration with DEAD as coupling partner

In this section the effect of altering the acid concentration on the Mitsunobu was examined. In Table S10 the reagents and reactants are added in equimolar amounts and a yield of 90% for the ester is assumed. The acid concentration is varied between 0.1 M and 2.0 M in simulations 1-4.

Table S10. Altering the acid concentration with DEAD as coupling reagent.



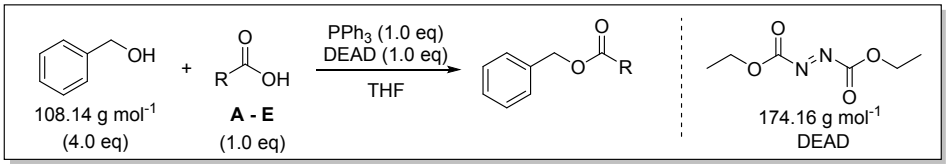


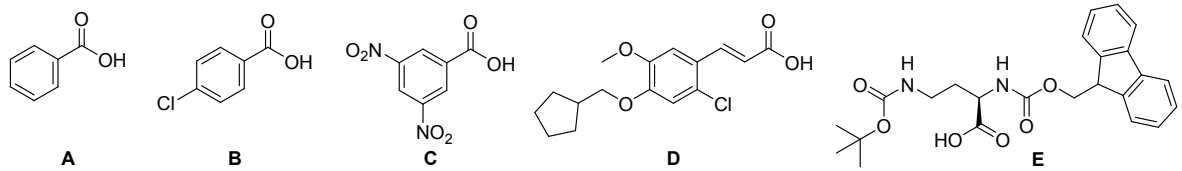
A 122.12 g mol^{-1} **B** 156.57 g mol^{-1} **C** 212.12 g mol^{-1} **D** 310.77 g mol^{-1} **E** 440.50 g mol^{-1}

Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.1 M						
A	92	83	49.8	3.5	46.3	90
B	93	84	43.0	3.2	39.9	90
C	94	85	35.3	2.8	32.5	90
D	96	86	26.9	2.4	24.5	90
E	97	87	20.6	2.1	18.5	90
Simulation 2: [Acid] = 0.5 M						
A	92	83	12.8	3.5	9.3	90
B	93	84	11.2	3.2	8.0	90
C	94	85	9.3	2.8	6.5	90
D	96	86	7.3	2.4	4.9	90
E	97	87	5.8	2.1	3.7	90
Simulation 3: [Acid] = 1.0 M						
A	92	83	8.1	3.5	4.7	90
B	93	84	7.2	3.2	4.0	90
C	94	85	6.1	2.8	3.3	90
D	96	86	4.8	2.4	2.5	90
E	97	87	3.9	2.1	1.9	90
Simulation 4: [Acid] = 2.0 M						
A	92	83	5.8	3.5	2.3	90
B	93	84	5.2	3.2	2.0	90
C	94	85	4.4	2.8	1.6	90
D	96	86	3.6	2.4	1.2	90
E	97	87	3.0	2.1	0.9	90

In Table S11 the benzyl alcohol is added in 4.0 equivalents while all other reactants and reagents are added in equimolar amounts. Moreover, a yield of 90% for the ester is assumed. The acid concentration is varied again between 0.1 M and 2.0 M in simulations 1-4.

Table S11. Altering the acid concentration with DEAD as coupling reagent with an excess of the alcohol.





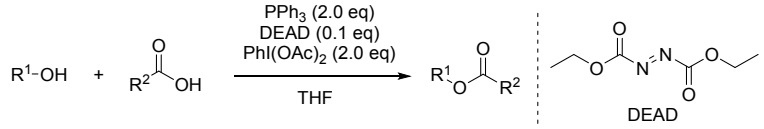
A 122.12 g mol^{-1} **B** 156.57 g mol^{-1} **C** 212.12 g mol^{-1} **D** 310.77 g mol^{-1} **E** 440.50 g mol^{-1}

Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.1 M						
A	92	34	58.4	12.0	46.3	90
B	93	38	50.4	10.5	39.9	90
C	94	42	41.3	8.8	32.5	90
D	96	49	31.4	6.9	24.5	90
E	97	55	24.0	5.5	18.5	90
Simulation 2: [Acid] = 0.5 M						
A	92	34	21.4	12.0	9.3	90
B	93	38	18.5	10.5	8.0	90
C	94	42	15.3	8.8	6.5	90
D	96	49	11.8	6.9	4.9	90
E	97	55	9.2	5.5	3.7	90
Simulation 3: [Acid] = 1.0 M						
A	92	34	16.7	12.0	4.7	90
B	93	38	14.5	10.5	4.0	90
C	94	42	12.1	8.8	3.3	90
D	96	49	9.4	6.9	2.5	90
E	97	55	7.3	5.5	1.9	90
Simulation 4: [Acid] = 2.0 M						
A	92	34	14.4	12.0	2.3	90
B	93	38	12.5	10.5	2.0	90
C	94	42	10.4	8.8	1.6	90
D	96	49	8.1	6.9	1.2	90
E	97	55	6.4	5.5	0.9	90

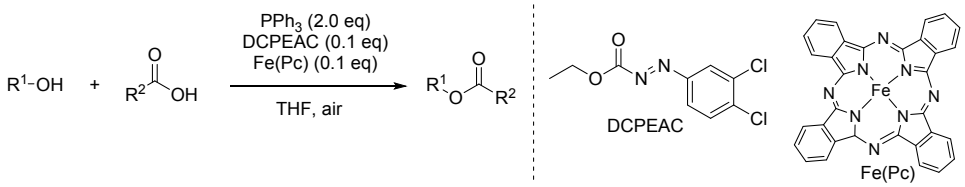
3.5 Catalytic Mitsunobu reaction

In this section the recent advances towards a catalytic Mitsunobu reaction were evaluated and compared with the classical alcohol activation with stoichiometric phosphine and azodicarboxylate. Four different catalytic conditions were evaluated:

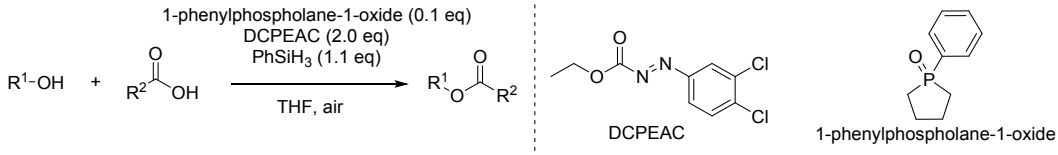
- The first example of a Mitsunobu protocol utilising a sub-stoichiometric azodicarboxylate reagent and di(acetoxy)iodobenzene as sacrificial oxidant, was reported by Toy in 2006.[14, 15]



  - *Representative experimental procedure:* To 4-nitrobenzoic acid (0.33 g, 1.98 mmol) and 2-phenylethanol (0.21 mL, 1.8 mmol) in anhydrous THF (15 mL), was added triphenylphosphine (0.94 g, 3.6 mmol), diethyl azodicarboxylate (0.028 mL, 0.18 mmol), and iodosobenzene diacetate (1.16 g, 3.6 mmol). The reaction was stirred at rt for 16 h and then the reaction mixture was diluted with diethyl ether (30 mL). The organic phase was washed with saturated aq. $NaHCO_3$ (2 x 20 mL) and brine (20 mL). The organic layer was dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to afford 2-phenylethyl 4-nitrobenzoate (90%) as yellow solid.
- Taniguchi and co-workers developed an alternative oxidation system for the *in situ* recycling of the azodicarboxylate, using an iron phthalocyanine co-catalyst, with oxygen as the terminal oxidant.[16]



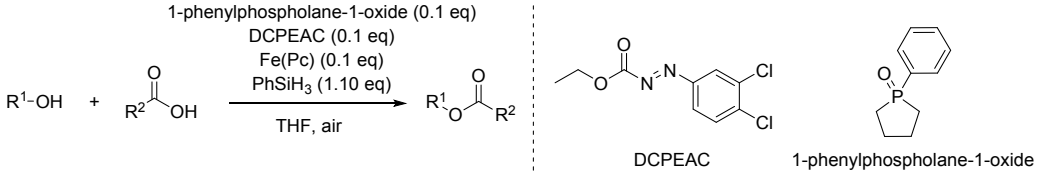
  - *Representative experimental procedure:* A mixture of (*S*)-ethyl lactate (100 mg, 0.850 mmol), 3,5-dinitrobenzoic acid (198 mg, 0.935 mmol), triphenylphosphine (446 mg, 1.70 mmol), hydrazine (21.2 mg, 0.0850 mmol), iron phthalocyanine (48.3 mg, 0.0850 mmol) and activated 5 Å MS (400 mg) in THF (1.7 mL) was heated at 65 °C under air (balloon). After the reaction mixture was cooled to room temperature and filtered, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (n-hexane/EtOAc, 6:1). The ester was isolated (209 mg, 79%, 98:2 e.r.) as a white solid.
- Buonomo and Aldrich proposed also disclosed a strategy where a substoichiometric phosphine oxide was used as a putative precatalyst in combination with phenyl silane and stoichiometric azodicarboxylate.[17]



  - *Representative experimental procedure:* To a 15 mL pressure tube equipped with a stir bar was added 1-phenylphospholane-1-oxide (18 mg, 0.10 equiv, 0.10 mmol) and 4-nitrobenzoic acid (250 mg, 1.5 equiv, 1.5 mmol). Then, THF (4 mL) was added followed by benzyl alcohol (103 mL, 1.0 equiv, 1.0 mmol), DIAD (216 mL, 1.1 equiv, 1.1 mmol), and phenylsilane (135 mL, 1.1 equiv, 1.1 mmol). The reaction vessel was sealed and heated to 80 °C for 18 h. The reaction was

cooled to 23 °C and concentrated under reduced pressure. The residue was purified by column chromatography. Benzyl 4-nitrobenzoate was isolated as an off-white solid (197 mg, 0.77 mmol, 77%).

- Aldrich and Taniguchi also proposed a fully catalytic procedure where they combined their phosphine recycling with azodicarboxylate recycling.[17, 18]



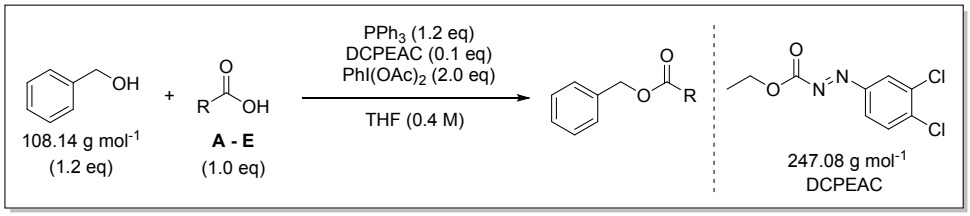
  - *Representative experimental procedure:* To a 35 mL pressure tube equipped with a stir bar was added 1-phenylphospholane-1-oxide (9.0 mg, 0.10 equiv, 0.05 mmol), DCPEAC (12.5 mg, 0.10 equiv, 0.05 mmol), Fe(Pc) (28.5 mg, 0.10 equiv, 0.05 mmol), 4-nitrobenzoic acid (125 mg, 1.5 equiv, 0.75 mmol), and 5 Å powdered molecular sieves (500 mg). THF (3 mL) was added followed by 4-methoxybenzyl alcohol (62 mL, 1.0 equiv, 0.50 mmol), and phenylsilane (68 mL, 1.1 equiv, 0.55 mmol). The vessel was purged with oxygen gas and sealed. The reaction was heated at 70 °C for 48 h. The reaction was cooled, filtered to remove the sieves and the filtrate was partitioned between EtOAc (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated and washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography. 4-Methoxybenzyl 4-nitrobenzoate was isolated as a yellow solid (90.5 mg, 0.32 mmol, 63%).

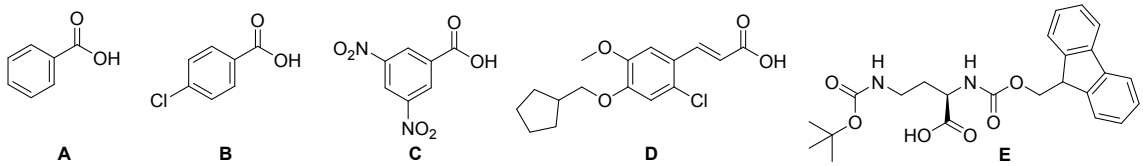
We applied the following simulations in the following sections:

- Simulation 1:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - A yield of 90% for the ester is assumed.
- Simulation 2:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - A yield of 80% for the ester is assumed.
- Simulation 3:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - A yield of 70% for the ester is assumed.
- Simulation 4:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - A yield of 50% for the ester is assumed.
- Simulation 5:
  - The acid is the limiting reactant and is present in a 0.4 M solution.
  - A yield of 90% for the ester is assumed.
  - The scale of the reaction is multiplied by 5 compared to simulation A.
- Simulation 6:
  - The acid is the limiting reactant and is present in a 0.8 M solution.
  - A yield of 90% for the ester is assumed.

3.5.1 Catalytic in the azo coupling reagent with di(acetoxy)iodobenzene as oxidant

Table S12. Green metrics simulations applied on the Mitsunobu reaction catalytic in azo reagent with iodosobenzene diacetate.



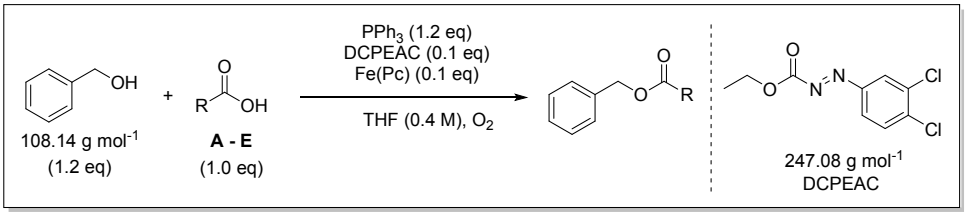


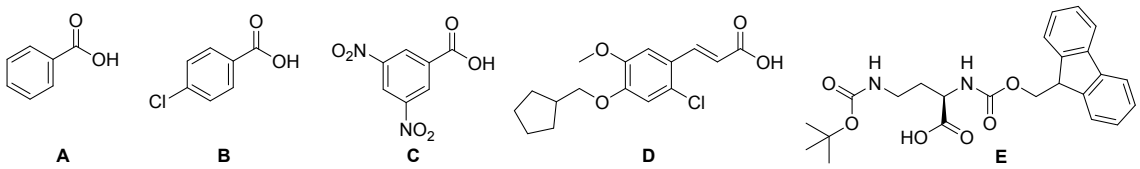
A 122.12 g mol^{-1} | **B** 156.57 g mol^{-1} | **C** 212.12 g mol^{-1} | **D** 310.77 g mol^{-1} | **E** 440.50 g mol^{-1}

Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	18.1	6.5	11.6	90
B	93	78	15.7	5.7	10.0	90
C	94	80	13.1	4.9	8.2	90
D	96	82	10.1	4.0	6.2	90
E	97	84	7.9	3.3	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	20.4	7.3	13.1	80
B	93	69	17.7	6.4	11.3	80
C	94	71	14.7	5.5	9.2	80
D	96	73	11.4	4.4	6.9	80
E	97	74	8.9	3.7	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	23.3	8.3	15.0	70
B	93	60	20.2	7.4	12.9	70
C	94	62	16.8	6.3	10.5	70
D	96	64	13.0	5.1	7.9	70
E	97	65	10.2	4.2	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	32.6	11.7	20.9	50
B	93	43	28.3	10.3	18.0	50
C	94	44	23.5	8.8	14.7	50
D	96	46	18.2	7.1	11.7	50
E	97	47	14.2	5.9	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	18.1	6.5	11.6	90
B	93	78	15.7	5.7	10.0	90
C	94	80	13.1	4.9	8.2	90
D	96	82	10.1	4.0	6.2	90
E	97	84	7.9	3.3	4.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	12.3	6.5	5.8	90
B	93	78	10.7	5.7	5.0	90
C	94	80	9.0	4.9	4.1	90
D	96	82	7.0	4.0	3.1	90
E	97	84	5.6	3.3	2.3	90

3.5.2 Catalytic in the azo coupling reagent with iron phthalocyanine and oxygen for reoxidation

Table S13. Green metrics simulations applied on the Mitsunobu reaction catalytic in azo reagent with phthalocyanine and O_2.



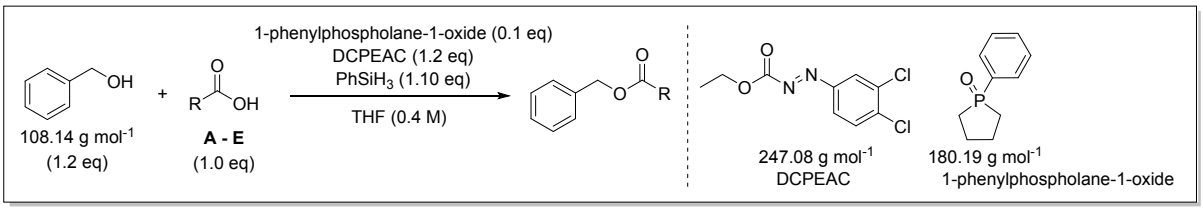


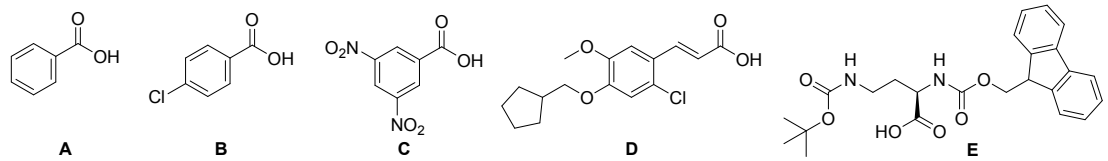
A 122.12 g mol^{-1} | **B** 156.57 g mol^{-1} | **C** 212.12 g mol^{-1} | **D** 310.77 g mol^{-1} | **E** 440.50 g mol^{-1}

Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	15.0	3.4	11.6	90
B	93	78	13.1	3.1	10.0	90
C	94	80	10.9	2.7	8.2	90
D	96	82	8.5	2.3	6.2	90
E	97	84	6.7	2.0	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	16.9	3.8	13.1	80
B	93	69	14.7	3.5	11.3	80
C	94	71	12.2	3.1	9.2	80
D	96	73	9.5	2.6	6.9	80
E	97	74	7.5	2.3	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	19.3	4.4	15.0	70
B	93	60	16.8	4.0	12.9	70
C	94	62	14.0	3.5	10.5	70
D	96	64	10.9	3..0	7.9	70
E	97	65	8.6	2.6	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	27.1	6.1	20.9	50
B	93	43	23.6	5.5	18.0	50
C	94	44	21.0	6.3	14.7	50
D	96	46	15.3	4.2	11.1	50
E	97	47	12.0	3.6	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	15.0	3.4	11.6	90
B	93	78	13.1	3.1	10.0	90
C	94	80	10.9	2.7	8.2	90
D	96	82	8.5	2.3	6.2	90
E	97	84	6.7	2.0	4.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	9.2	3.4	5.8	90
B	93	78	8.1	3.1	5.0	90
C	94	80	6.8	2.7	4.1	90
D	96	82	5.4	2.3	3.1	90
E	97	84	4.4	2.0	2.3	90

3.5.3 Catalytic in phosphine

Table S14. Green metrics simulations applied on the Mitsunobu reaction catalytic in phosphine.

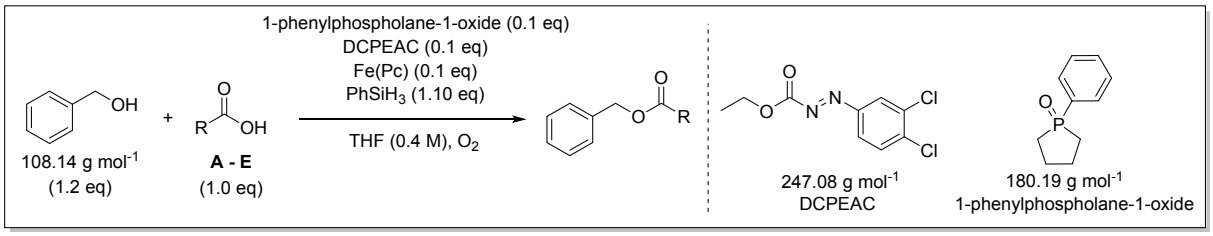


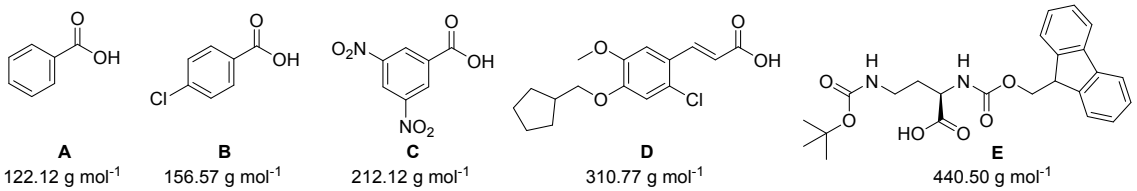


Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	15.2	3.6	11.6	90
B	93	78	13.3	3.3	10.0	90
C	94	80	11.0	2.9	8.2	90
D	96	82	8.6	2.4	6.2	90
E	97	84	6.8	2.1	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	10.6	4.1	6.5	80
B	93	69	9.3	3.7	5.6	80
C	94	71	7.8	3.2	4.6	80
D	96	73	6.2	2.7	3.5	80
E	97	74	5.0	2.4	2.6	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	19.6	4.6	15.0	70
B	93	60	17.1	4.2	12.9	70
C	94	62	14.2	3.7	10.5	70
D	96	64	11.0	3.1	7.9	70
E	97	65	8.7	2.7	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	27.4	6.5	20.9	50
B	93	43	23.9	5.9	18.0	50
C	94	44	19.9	5.1	14.7	50
D	96	46	15.5	4.4	11.1	50
E	97	47	12.2	3.8	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	15.2	3.6	11.6	90
B	93	78	13.3	3.3	10.0	90
C	94	80	11.0	2.9	8.2	90
D	96	82	8.6	2.4	6.2	90
E	97	84	6.8	2.1	4.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	9.4	3.6	5.8	90
B	93	78	8.3	3.3	5.0	90
C	94	80	6.9	2.9	4.1	90
D	96	82	5.5	2.4	3.1	90
E	97	84	4.4	2.1	2.3	90

3.5.4 "Fully catalytic" Mitsunobu reaction

Table S15. Green metrics simulations applied on the "fully catalytic" Mitsunobu reaction.





Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	14.1	2.5	11.6	90
B	93	78	12.3	2.3	10.0	90
C	94	80	10.2	2.1	8.2	90
D	96	82	8.0	1.8	6.2	90
E	97	84	6.3	1.7	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	15.9	2.8	13.1	80
B	93	69	13.8	2.6	11.3	80
C	94	71	11.5	2.3	9.2	80
D	96	73	9.0	2.1	6.9	80
E	97	74	7.1	1.9	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	18.1	3.2	15.0	70
B	93	60	15.8	2.9	12.9	70
C	94	62	13.2	2.7	10.5	70
D	96	64	10.3	2.3	7.9	70
E	97	65	8.1	2.1	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	25.4	4.4	20.9	50
B	93	43	22.1	4.1	18.0	50
C	94	44	18.4	3.7	14.7	50
D	96	46	14.4	3.3	11.1	50
E	97	47	11.4	3.0	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	14.1	2.5	11.6	90
B	93	78	12.3	2.3	10.0	90
C	94	80	10.2	2.1	8.2	90
D	96	82	8.0	1.8	6.2	90
E	97	84	6.3	1.7	4.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	8.3	2.5	5.8	90
B	93	78	7.3	2.3	5.0	90
C	94	80	6.1	2.1	4.1	90
D	96	82	4.9	1.8	3.1	90
E	97	84	4.0	1.7	2.3	90

4 References

1. W.-C. Chou, C.-W. Tan, S.-F. Chen and H. Ku, *J. Org. Chem.*, 1998, **63**, 10015-10017.
2. S. García-Rubio, C. D. Wilson, D. A. Renner, J. O. Rosser, D. Patra, J. G. Reid and S. H. Pines, *Org. Process Res. Dev.*, 2004, **8**, 360-362.
3. N. A. Magnus, T. M. Braden, J. Y. Buser, A. C. DeBaillie, P. C. Heath, C. P. Ley, J. R. Remacle, D. L. Varie and T. M. Wilson, *Org. Process Res. Dev.*, 2012, **16**, 830-835.
4. K. Neelakandan, H. Manikandan, N. Santosha and B. Prabhakaran, *Org. Process Res. Dev.*, 2013, **17**, 981-984.
5. G. A. Weisenburger, D. K. Anderson, J. D. Clark, A. D. Edney, P. S. Karbin, D. J. Gallagher, C. M. Knable and M. A. Pietz, *Org. Process Res. Dev.*, 2009, **13**, 60-63.
6. M. Prashad, K. Prasad, O. Repic, T. J. Blacklock and W. Prikoszovich, *Org. Process Res. Dev.*, 1999, **3**, 409-415.
7. L. Storace, L. Anzalone, P. N. Confalone, W. P. Davis, J. M. Fortunak, M. Giangiordano, J. J. Haley, K. Kamholz, H.-Y. Li, P. Ma, W. A. Nugent, R. L. Parsons, P. J. Sheeran, C. E. Silverman, R. E. Waltermire and C. C. Wood, *Org. Process Res. Dev.*, 2002, **6**, 54-63.
8. Y. J. Pu, R. K. Vaid, S. K. Boini, R. W. Towsley, C. W. Doecke and D. Mitchell, *Org. Process Res. Dev.*, 2009, **13**, 310-314.
9. T. Ito, T. Ikemoto, Y. Isogami, H. Wada, M. Sera, Y. Mizuno and M. Wakimasu, *Org. Process Res. Dev.*, 2002, **6**, 238-241.
10. B.-F. Li, R. M. Hughes, J. Le, K. McGee, D. J. Gallagher, R. S. Gross, D. Provencal, J. P. Reddy, P. Wang, L. Zegelman, Y. Zhao and S. E. Zook, *Org. Process Res. Dev.*, 2009, **13**, 463-467.
11. A. Alimardanov, A. Nikitenko, T. J. Connolly, G. Feigelson, A. W. Chan, Z. Ding, M. Ghosh, X. Shi, J. Ren, E. Hansen, R. Farr, M. MacEwan, S. Tadayon, D. M. Springer, A. F. Kreft, D. M. Ho and J. R. Potoski, *Org. Process Res. Dev.*, 2009, **13**, 1161-1168.
12. C. A. Busacca, X. Wei, N. Haddad, S. Kapadia, J. C. Lorenz, A. K. Saha, R. J. Varsolona, T. Berkenbusch, S. C. Campbell, V. Farina, X. Feng, N. C. Gonnella, N. Grinberg, P.-J. Jones, H. Lee, Z. Li, O. Niemeier, W. Samstag, M. Sarvestani, J. Schroeder, J. Smoliga, E. M. Spinelli, J. Vitous and C. H. Senanayake, *Asian J. Org. Chem.*, 2012, **1**, 80-89.
13. J. R. Dunetz, M. A. Berliner, Y. Xiang, T. L. Houck, F. H. Salingue, W. Chao, C. Yuandong, W. Shenghua, Y. Huang, D. Farrand, S. J. Boucher, D. B. Damon, T. W. Makowski, M. T. Barrila, R. Chen and I. Martínez, *Org. Process Res. Dev.*, 2012, **16**, 1635-1645.
14. T. Y. S. But and P. H. Toy, *J. Am. Chem. Soc.*, 2006, **128**, 9636-9637.
15. T. Y. S. But, J. Lu and P. H. Toy, *Synlett*, 2010, 1115-1117.
16. D. Hirose, T. Taniguchi and H. Ishibashi, *Angew. Chem. Int. Ed.*, 2013, **52**, 4613-4617.
17. J. A. Buonomo and C. C. Aldrich, *Angew. Chem. Int. Ed.*, 2015, **54**, 13041-13044.
18. D. Hirose, M. Gazvoda, J. Košmrlj and T. Taniguchi, *Org. Lett.*, 2016, **18**, 4036-4039.