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Application of divergent multi-component reactions in the synthesis of a library of peptidomimetics based on γ-amino-α,β-cyclopropyl acids

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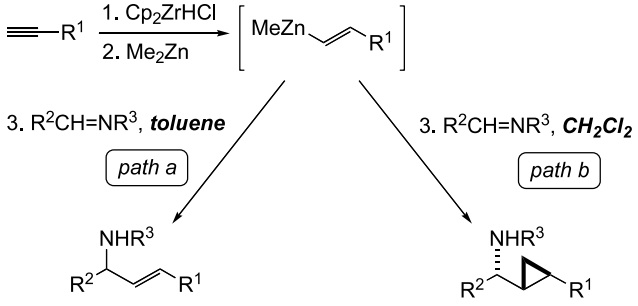
Abstract—The multi-component condensation of organozirconocene, aldimine and zinc carbenoid was applied to the stereoselective synthesis of cyclopropane amino acid derivatives. These compounds served as scaffolds for the preparation of a 46-member library. The C- and N-termini of the cyclopropane amino acid derivatives were diversified by condensations with ten amines and ten acylating agents, respectively. To improve yields and accelerate library synthesis, most products were prepared under microwave irradiation and purified by polymer-bound scavengers and SPE methodology. All compounds were analyzed by LC–MS and a representative selection was fully characterized.

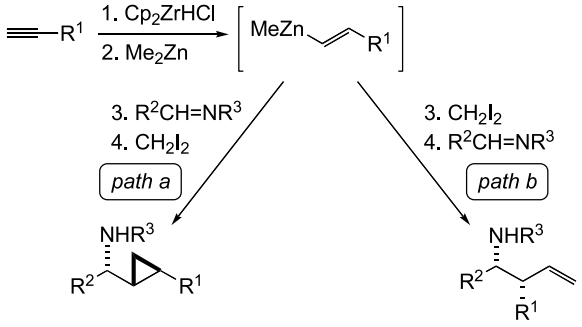
1. Introduction

Multi-component reactions such as the Ugi and Passerini reactions have had a significant influence on industrial structure–activity relationship (SAR) analyses and pharmaceutical library syntheses.[1] The Ugi four-component condensation provides amino acid analogs from readily available aldehydes, carboxylic acids, and amines, and less easily accessible isocyanides,[2] but only a single product structure is obtained from a given set of starting materials. We have recently introduced the concept of divergent multi-component reactions (DMCRs),[3] whereby reaction conditions such as the choice of solvent[4] or the order of addition of reagents[5] influence the reaction pathway and thus provide a rapid access to different scaffolds (Schemes 1 and 2).[6]

In addition to the discovery of new *C*,*C*-bond forming cascade reactions,[7] we have directed our DMCR methodology toward the synthesis of peptidomimetics[8] such as (*E*)-alkene peptide isosteres (ψ[RC=CH], δ-amino-β,γ-unsaturated amino acids, with R = alkyl, aryl, H, F, and CF_3),[9] cyclopropane dipeptide isosteres (ψ[RCp], δ-amino-β,γ-cyclopropyl amino acids),[9a,c] and, in an extension of the



Scheme 1. Choice of solvent influences product formation.



Scheme 2. Order of reagent addition influences product formation.

Keywords: Indexed library; Microwave irradiation; Polymer-bound scavengers.
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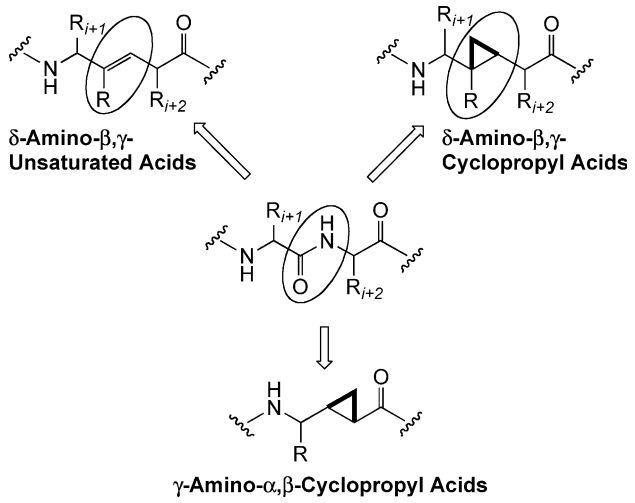


Figure 1. Peptidomimetics based on isosteric amide bond replacements or amino acid backbone chain extensions.

principle of vinylogy for α-amino acids,[10] backbone-modified γ-amino-α,β-cyclopropyl acids (Fig. 1).[11]

The scissile peptide bond is in part responsible for poor pharmacokinetic properties, low oral bioavailability and rapid proteolytic degradation of oligopeptides composed of natural amino acid residues. Peptidomimetics have the potential to provide increased metabolic stability and better oral bioavailability.[12] The replacement of peptide bonds with transition-state analogs such as hydroxyethylene,[13] hydroxyethylamine,[14] dihydroxyethylene[15] or ketomethylene[16] groups has produced chimeric molecules that combine improved pharmacokinetic properties and higher potency. Isosteric replacements such as (*E*)- or (*Z*)-alkenes,[17] (*E*)- or (*Z*)-methylalkenes,[9,18] (*Z*)-fluoroalkenes,[19] cyclopropyl rings[9,11,20] or larger ring systems[21] do not only prevent hydrolytic cleavage but also incorporate conformational constraints into the peptide backbone. This may allow for a tighter binding to a target enzyme or receptor leading to increased potency. We recently introduced the cyclopropane amino acid derivative ΔPhg (Fig. 2).[11] In contrast to alkenes which have the potential to undergo isomerization or oxidation, cyclopropanes display an increased chemical and metabolic stability.[22] X-ray and solution structural analyses have shown that cyclopropane-containing peptides occupy biologically relevant conformational space.[9,11]

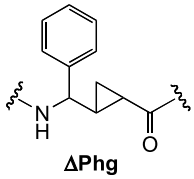


Figure 2. Phenylglycine derived cyclopropane amino acid residue; the Δ-prefix is used for amino acids that have a cyclopropane ring inserted into the backbone chain between carbonyl-C and α-C.

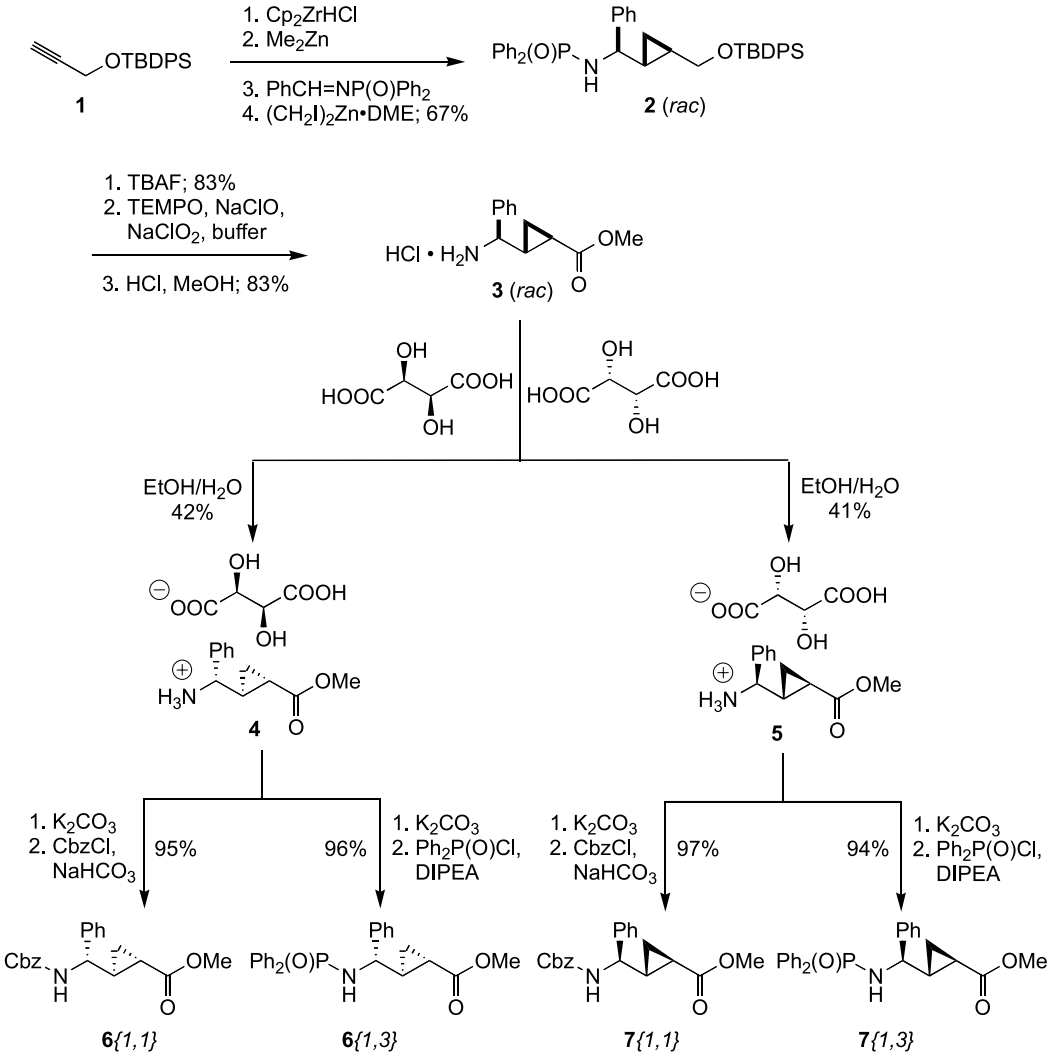
The ΔPhg residue can be accessed stereoselectively by the three component condensation of an alkenylzirconocene,[23] an aldimine and a dihalomethane-derived zinc carbenoid species. As a starting point for further investigation of the biological properties of these peptidomimetics,[4e] we now report a new, more expedient synthesis of ΔPhg as well as the synthesis of a 46-member library of ΔPhg derivatives.

2. Results and discussion

Synthetic methodology. In our recent approach to γ-amino-α,β-cyclopropyl acids,[11] we described a 9-step (including resolution) sequence relying upon sequential Grieco elimination–alkene oxidation to introduce the C-terminal carboxylate function. This strategy introduced several steps that complicated the scale up for preparative purposes. We have now been able to optimize this sequence to allow the multi-gram synthesis of the enantiomerically pure cyclopropyl amino acid derivatives **6** and **7** in a more efficient fashion (Scheme 3). Addition of Cp_2ZrHCl[24] to TBDPS-protected propargyl alcohol **1**, followed by sequential transmetallation to dimethylzinc, addition to *N*-diphenylphosphinylimine and treatment with bis(iodomethyl)-zinc·DME complex[25] afforded the desired amide **2** in an overall yield of 67% and in high diastereomeric ratio (>19:1). Removal of the TBDPS group with TBAF and oxidation of the resulting alcohol afforded the carboxylic acid which could be converted into the methyl ester hydrochloride salt **3** under acidic conditions (HCl in MeOH). The racemate **3** was resolved by formation of the diastereomeric salts with L- and D-tartaric acid. The hydrochloride salts **3** were first converted to the free amines that were co-crystallized with tartaric acid in an ethanol–water mixture affording **5**. The corresponding diastereomeric salt (recovered from the filtrate) was an amorphous solid, which was not easily crystallized. Formation of the D-tartaric acid salt facilitated its crystallization. Indeed, after only three crystallizations, over 80% of the initial amine could be recovered in the form of enantiomerically pure salts. Pure γ-amino-α,β-cyclopropyl acids (ee >95%) could be obtained by washing the crystalline salts **4** and **5** with an aqueous solution of K_2CO_3 at 0 °C in chloroform. X-ray structure analysis of a diastereomeric derivative was used to assign the absolute configuration of **4** and **5**.[11] The free amines were transformed into the Cbz-protected amino acid methyl esters **6**{*1,1*} and **7**{*1,1*} or the *N*-diphenylphosphinyl amides **6**{*1,3*} and **7**{*1,3*}.

Library design. For the generation of a focused library, both C- and N-termini of the cyclopropane peptidomimetics were modified. Instead of synthesizing a complete 12×12 matrix for **6** and **7**, i.e., 288 compounds, an indexed library design was chosen.[26] In an indexed library, only one substituent is varied at a time while all other substituents remain unchanged. Accordingly, a two-dimensional matrix is divided into two one-dimensional matrices (Fig. 3). In the present example, two 12×12 matrices were transformed into four 12×1 matrices, i.e., 48 compounds. Since two compounds appear in two matrices, only 46 compounds were synthesized to encompass a similar chemical space as two 12×12 matrices. If compounds **A**{*1,4*} and **A**{*3,1*} in Figure 3 show activity in an initial screen, compound **A**{*3,4*} can be synthesized and evaluated in a subsequent screen.

For an efficient library synthesis, polymer- or silica-bound



Scheme 3. Preparation of cyclopropane amino acid derivatives ΔPhg **6**{*1,1*}, **6**{*1,3*}, **7**{*1,1*} and **7**{*1,3*}.

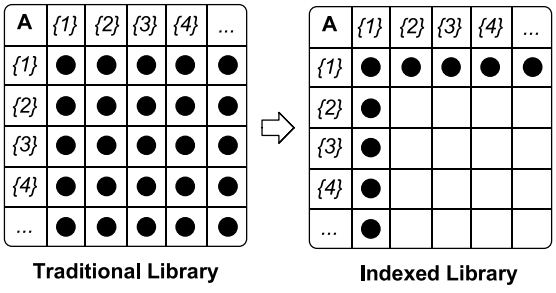


Figure 3. Traditional versus indexed library.

reagents and SPE scavenging and separation techniques were applied.[27] To further accelerate the library workflow, most reactions were carried out in an automated Emrys Optimizer single-mode microwave reactor.

C-Terminal functionalizations. The two esters **6**{*1,3*} and **7**{*1,3*} were hydrolyzed in parallel and the free acids were extracted using an ALLEXis system.[28] Each batch was divided into eleven parts; the free acid was added directly to the library, and the remaining 10 parts were transformed into amides. In order to obtain a broad distribution of

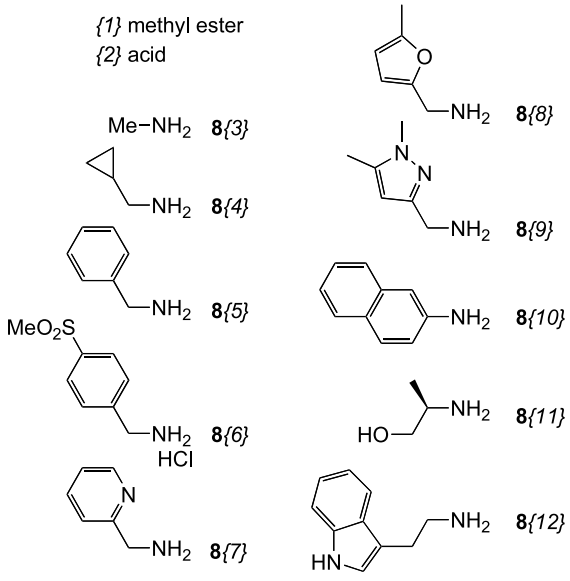
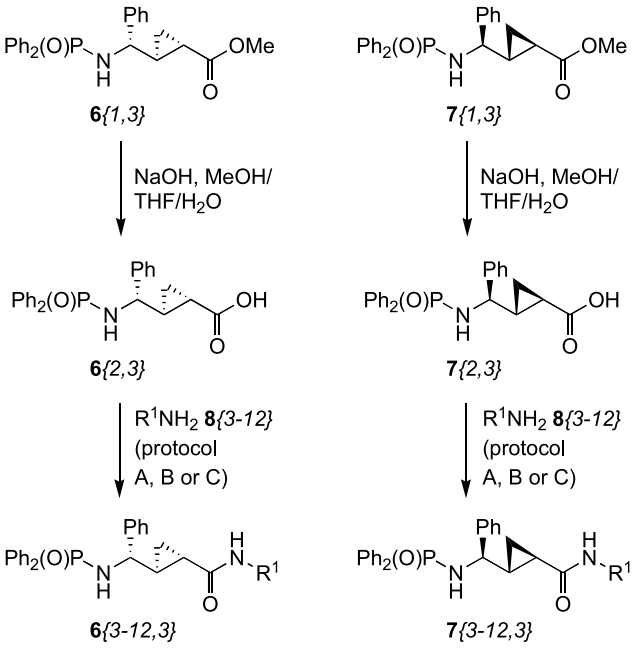


Figure 4. Building blocks **8**{*3–12*} for C-terminal functionalizations.

pharmacokinetic properties for the library,[29] a diverse set of 10 amines was chosen (Fig. 4). While methylamine (**8**{*3*}) was selected due to its small size, cyclopropanemethylamine (**8**{*4*}) was chosen due to its chain branching as well as its lipophilic character. Several aromatic and heteroaromatic amines (**8**{*5–10*}) that can act as hydrogen bond donors were also selected. Polar functions were represented by alaninol (**8**{*11*}) and tryptamine (**8**{*12*}).

The drawback of this diverse set of building blocks **8**{*3–12*} was that three different protocols for amide coupling were required (Scheme 4). The most efficient protocol (protocol A)[30] involved polymer-bound carbodiimide and 1-hydroxybenzotriazole as coupling reagents. These reagents were added in excess to a solution of the acid in chlorobenzene and stirred for 5 min before an equimolar amount of amine was added. Microwave irradiation at 100 °C for 5 min afforded the corresponding amides. In order to drive reactions to completion, volatile amines were added in excess and the reaction mixture was irradiated at 60 °C for



protocol A:
1. PS-DCC, HOBt
2. R^1NH_2, μW 100 °C, 5 min
workup: Si-CO_3^{2-} SPE
estimated time needed for 10 reactions: 2-3 h
scope: limited

protocol B:
1. EDCI, HOBt
2. R^1NH_2, r.t., 12 h
workup: ChemElut extraction and chromatography
estimated time needed for 10 reactions: ca. 15 h
scope: good

protocol C:
DEPBT, NEt_3, R^1NH_2, r.t., 12 h
workup: aq. extraction and chromatography
estimated time needed for 10 reactions: ca. 24 h
scope: broad

Scheme 4. C-Terminal functionalizations.

30 min. The reagents and polymer beads were removed by filtration of the reaction mixture through a silica-bound carbonate cartridge. This protocol was fast and allowed the synthesis of 10 library members in 2–3 h. Methylamine (**8**{*3*}), cyclopropanemethylamine (**8**{*4*}), benzylamine (**8**{*5*}), 4-methylsulfonylbenzylamine (**8**{*6*}), 2-aminomethylpyridine (**8**{*7*}), 5-methyl-2-furanmethanamine (**8**{*8*}) and (1,5-dimethyl-1*H*-pyrazol-3-yl)methylamine (**8**{*9*}) afforded the corresponding amides in moderate to good yields and high purities (Table 1). Subsequent purification was not necessary.

While protocol A worked well for most amines, for the syntheses of **6**{*10,3*} and **7**{*10,3*} the use of EDCI as the coupling reagent in the presence of HOBt was found to be advantageous, and the reaction mixture was stirred for 12 h at room temperature (protocol B). All water-soluble components were removed by ChemElut extraction. Since this extract contained a significant amount of impurities, automated parallel chromatography on SiO_2 with the ISCO Optix 10 system was necessary to afford the library members in high purity.

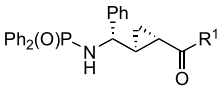
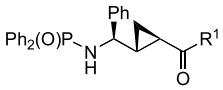
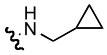
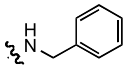
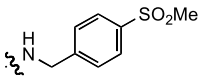
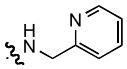
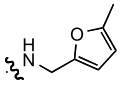
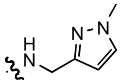
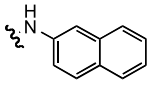
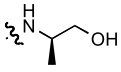
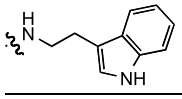
When the coupling protocols A or B were applied to the amidation with tryptamine (**8**{*12*}), the product was obtained in low yield, and with (*R*)-(−)-2-amino-1-propanol (**8**{*11*}) no product was formed. A more efficient coupling reagent such as 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT)[31] had to be used (protocol C). This method provided the desired amides in moderate yields and high purities, but it involved time-consuming additional aqueous extractions by the ALLEXis system and parallel chromatography on SiO_2 with the ISCO Optix 10 instrumentation.

Applying the three protocols A–C, a sublibrary of 20 C-terminal derivatized cyclopropyl carboxamides was successfully prepared. The use of polymer-bound reagents and scavenging techniques for most substrates significantly decreased the time needed for the library synthesis.

N-Terminal functionalizations. In addition to the C-terminal functionalizations of ΔPhg derivatives, *N*-phosphinylation, *N*-sulfonylation, *N*-carbamoylation and *N*-acylation further expanded the compound collection. The building blocks **6**{*1,2*} and **7**{*1,2*} were prepared by hydrogenolysis of **6**{*1,1*} and **7**{*1,1*}, followed by immediate conversion to the corresponding ammonium salts (Scheme 5). Compounds **6**{*1,2*} and **7**{*1,2*} were treated with 10 structurally diverse acylating reagents **9**{*3–12*} (Fig. 5), including one phosphinyl chloride, one chloroformate, two sulfonyl chlorides and six acyl chlorides to afford the 20 *N*-acyl derivatives **6**{*1,3–12*} and **7**{*1,3–12*}.

In a typical *N*-acylation procedure, microwave irradiation of a suspension of the ammonium salts **6**{*1,2*} or **7**{*1,2*} (1.0 equiv), PS-DMAP (1.2 equiv), triethylamine (2.0 equiv) and the corresponding acylating agent **9**{*3–12*} at 100 °C for 10 min in CH_2Cl_2 afforded the crude *N*-acylated products. Resin-bound scavengers were found to be ideal for purification because of ease, speed (avoiding chromatography) and the ability to proceed in parallel fashion. Upon cooling to room temperature, the reaction vial

Table 1. C-Terminal functionalizations, isolated yields (purity by LC–MS with ELS detection)

R^1	Protocol		
		**6**{*1*,*3*}, (95)	**7**{*1*,*3*}, (95)
		**6**{*2*,*3*}, (94)	**7**{*2*,*3*}, (94)
	**A**	**6**{*3*,*3*}, 23 (97)	**7**{*3*,*3*}, 30 (98)
	**A**	**6**{*4*,*3*}, 35 (91)	**7**{*4*,*3*}, 44 (>99)
	**A**	**6**{*5*,*3*}, 81 (92)	**7**{*5*,*3*}, 92 (98)
	**A**	**6**{*6*,*3*}, 82 (94)	**7**{*6*,*3*}, 98 (95)
	**A**	**6**{*7*,*3*}, 66 (>99)	**7**{*7*,*3*}, 77 (96)
	**A**	**6**{*8*,*3*},[a] 72 (94)	**7**{*8*,*3*},[a] 84 (91)
	**A**	**6**{*9*,*3*},[a] 73 (>99)	**7**{*9*,*3*},[a] 72 (98)
	**B**	**6**{*10*,*3*}, 69 (91)	**7**{*10*,*3*}, 72 (95)
	**C**	**6**{*11*,*3*}, 46 (98)	**7**{*11*,*3*}, 44 (97)
	**C**	**6**{*12*,*3*}, 53 (98)	**7**{*12*,*3*},[b] 68 (97)

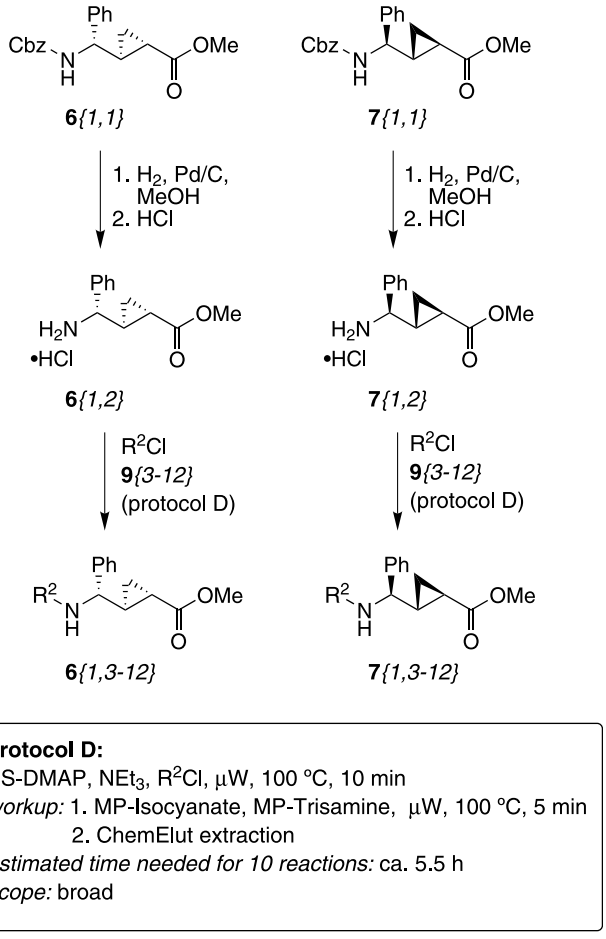
[a] Traces of amine were removed by product precipitation in diethylether.
[b] With protocol B, **7**{*12*,*3*} was obtained in 23% yield.

containing the crude product was charged with MP-trisamine[32,33] (1.0 equiv) and MP-isocyanate[33] (1.0 equiv), and microwave irradiation in the automated Emrys Optimizer microwave reactor was resumed at 100 °C for 5 min. Finally, the reaction mixture was subjected to an aqueous work-up by passage through a ChemElut SPE cartridge preconditioned with saturated aqueous $NaHCO_3$ solution to remove the resin-bound reagents and the triethylammonium chloride salt. The eluant was collected and concentrated to dryness using a centrifugal vacuum evaporator (Genevac HT-4) to provide the desired amides (Table 2).

Library analysis. The purity of all 46 library members was determined by reversed-phase HPLC with ELS and MS detection. Twelve library members (26%) were analyzed by ^{1}H NMR and five library members (11%) were fully characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, MS, HRMS and mp. All library members were obtained in >85% purity by ELS detection and none had to be repurified by chromatography on SiO_2. The C-terminal functionalized amides **6**{*3–12*,*3*} and **7**{*3–12*,*3*} were isolated in an average yield of 64% and in an average purity of 96% (Table 1). The *N*-functionalized amides **6**{*1*,*3–12*} and **7**{*1*,*3–12*} were obtained in an average yield of 91% and in an average purity of 95% (Table 2).

3. Conclusions

We have optimized our DMCR approach to ΔPhg and applied it toward the preparation of a diverse indexed library of backbone-extended cyclopropane amino acid derivatives. Modern parallel synthesis techniques were used for the synthesis of 46 library members in an average purity of 95% after resin-based scavenging and SPE purification. Product yields varied depending on the reactant structure, but in most cases, the desired products were generated in good to excellent yields. The library members were obtained in an average yield of 78% and in an average amount of 24 mg. This study represents a further demonstration of the utility of multi-component reactions for diversity-oriented small molecule library synthesis.[34] Biological evaluation of this library will be reported in due course.



Scheme 5. N-Terminal functionalizations.

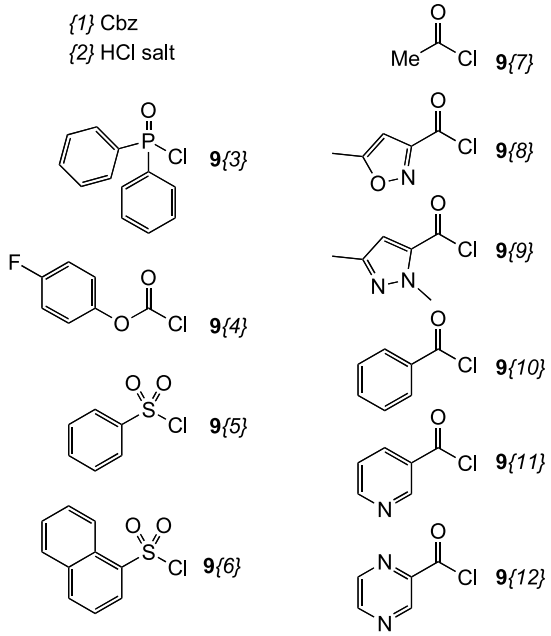


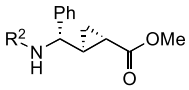
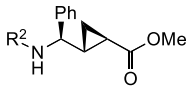
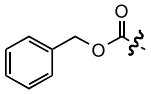
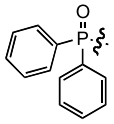
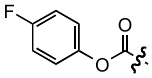
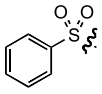
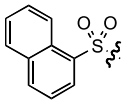
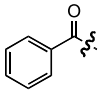
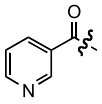
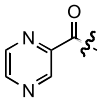
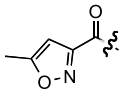
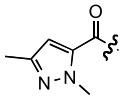
Figure 5. Building blocks **9**{*3–12*} for N-terminal functionalizations.

4. Experimental

4.1. General

All moisture-sensitive reactions were performed under an atmosphere of N_2 and glassware was flame dried under vacuum prior to use. DME and THF were dried by distillation over Na/benzophenone, Et_3N was dried by distillation over CaH_2. Toluene and CH_2Cl_2 were purified by filtration through activated alumina. Me_2Zn (2.0 M in toluene) and Et_2Zn (neat) were purchased from the Aldrich Chemical Company. Cp_2ZrHCl,[35] $PhCH{=}NP(O)Ph_2$[36] and alkyne **1**[37] were prepared according to literature protocols. PS-Carbodiimide, PS-DMAP, MP-isocyanate and MP-trisamine were purchased from Argonaut, silica-bound carbonate SPE cartridges from Silicycle and ChemElut 1003 cartridges from Varian. Unless stated otherwise, solvents or reagents were used without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040–0.055 mm, 230–400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.20 g of $Ce(SO_4)_2$ in 100 mL of 3.5 N H_2SO_4 solution). NMR spectra were recorded in $CDCl_3$ (298 K) at either 300.1 MHz (^1H), 75.5 MHz (^{13}C) or 121.5 MHz (^{31}P) using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are reported in parts per million (ppm) with the

Table 2. N-Terminal functionalizations, isolated yields (purity by LC–MS with ELS detection)

R^2	Protocol		
		**6**{*1,1*}, (99)	**7**{*1,1*}, (>99)
HCl•H		**6**{*1,2*},[a] (93)	**7**{*1,2*},[a] (90)
	**D**	**6**{*1,3*}, 97 (96)	**7**{*1,3*}, >99 (90)
	**D**	**6**{*1,4*}, >99 (92)	**7**{*1,4*}, 98 (96)
	**D**	**6**{*1,5*}, >99 (96)	**7**{*1,5*}, >99 (>99)
	**D**	**6**{*1,6*}, >99 (99)	**7**{*1,6*}, 87 (93)
	**D**	**6**{*1,7*}, >99 (88)	**7**{*1,7*}, 97 (92)
	**D**	**6**{*1,8*}, 95 (>99)	**7**{*1,8*}, 92 (99)
	**D**	**6**{*1,9*}, >99 (92)	**7**{*1,9*}, >99 (99)
	**D**	**6**{*1,10*}, 89 (97)	**7**{*1,10*}, 83 (97)
	**D**	**6**{*1,11*}, 85 (97)	**7**{*1,11*}, 76 (95)
	**D**	**6**{*1,12*}, 52 (92)	**7**{*1,12*}, 97 (92)

[a] Purity by UV with detection at 240 nm.

residual solvent peak used as an internal standard. For ^{31}P NMR, Ph_3P (δ −5.5) was used as an external standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, bs=broad singlet, bd=broad dublet, bt=broad triplet, app.=apparent), coupling constants and integration. IR spectra were obtained on a Nicolet AVATAR 360 FTIR E.S.P. Spectrometer. Mass spectra were obtained on a Waters QTof API US. Melting points were obtained on a MelTemp melting point apparatus with digital temperature reading and are reported uncorrected. Optical rotations were obtained on a Perkin–Elmer 241 polarimeter. All microwave assisted reactions were performed in an Emrys Optimizer single mode microwave reactor (Biotage) using 2–5 mL Emrys process vials.

4.1.1. *N*-(*R)-(((1*R**,2*R**)-2-(*tert*-Butyldiphenylsilyloxymethyl)cyclopropyl)(phenyl)-methyl)-*P*,*P*-diphenylphosphinamide (2).** In a cooled flask (0 °C), Cp_2ZrHCl (12.7 g, 49.1 mmol) was suspended in dry CH_2Cl_2 (125 mL) and alkyne **1** (14.5 g, 49.1 mmol) was added immediately. The reaction mixture was warmed to room temperature, stirred for 30 min and the resultant light yellow solution was cooled to −78 °C and treated with Me_2Zn (24.6 mL, 49.1 mmol, 2.0 M in toluene). The reaction mixture was warmed to 0 °C and *N*-diphenylphosphinylimine (5.00 g, 16.4 mmol) was added. The mixture was heated under reflux for 30 h, cooled to 0 °C and treated with a solution of $(CH_2I)_2Zn\cdot DME$ (81.9 mmol) in CH_2Cl_2 (20.0 mL). This zinc carbenoid complex was prepared by dropwise addition of CH_2I_2 (13.2 mL, 164 mmol) to a solution of Et_2Zn (neat, 10.1 g,

81.9 mmol) in CH_2Cl_2 (20.0 mL) and DME (8.51 mL, 81.9 mmol) at −30 °C. After stirring for 10 min at −30 °C, the resultant solution was transferred via cannula. After warming to room temperature, the reaction mixture was stirred for 12 h, cooled to 0 °C, carefully quenched with satd NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc 3/2) to give **2** (6.80 g, 67%) as a colorless foam: IR (neat) 3189, 3070, 3028, 2930, 2857, 1590, 1471, 1455, 1438, 1428, 1190, 1111 cm^{-1}; ^1H NMR δ 7.93–7.86 (m, 2H), 7.75–7.62 (m, 7H), 7.47–7.33 (m, 12H), 7.31–7.24 (m, 4H), 3.80 (dt, J=10.0, 7.9 Hz, 1H), 3.63 (dd, J=10.6, 5.4 Hz, 1H), 3.42 (dd, J=10.6, 6.2 Hz, 1H), 3.32–3.28 (m, 1H), 1.23–1.08 (m, 2H), 1.01 (s, 9H), 0.51 (dt, J=8.5, 5.1 Hz, 1H), 0.42 (dt, J=8.5, 5.2 Hz, 1H); ^{13}C NMR δ 143.32 (d, J_{CP}=4.5 Hz), 135.52 (d, J_{CP}=8.0 Hz), 133.82, 132.24 (d, J_{CP}=9.6 Hz), 131.91 (d, J_{CP}=9.3 Hz), 131.61 (d, J_{CP}=8.6 Hz), 131.41, 129.48, 128.37, 128.20, 128.13, 127.96, 127.53, 126.96, 126.79, 66.15, 58.16, 26.83, 24.72 (d, J_{CP}=5.7 Hz), 20.33, 19.09, 8.45; MS (ESI) *m/z* (intensity) 1253 ($[2M+Na]^+$, 23), 1231 ($[2M+H]^+$, 20), 638 ($[M+Na]^+$, 35), 616 ($[M+H]^+$, 100), 538 (29); HRMS (ESI) *m/z* calculated for $C_{39}H_{43}NO_2PSi$ (M+H) 616.2801, found 616.2799.

4.1.2. (1*R,2*R**)-2-((*R**)-1-Amino-1-phenylmethyl)cyclopropane carboxylic acid methyl ester hydrochloride salt (3).** Amide **2** (6.80 g, 11.0 mmol) was dissolved in THF (100 mL), cooled to 0 °C and treated with TBAF (13.8 mL, 13.8 mmol, 1.0 M in THF). The solution was warmed to room temperature, stirred for 10 h, quenched with sat. NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/acetone 2/3) to afford the corresponding alcohol (3.45 g, 83%) as a colorless solid. Mp 170.3–172.0 °C; IR (KBr) 3422, 3231, 2850, 1654, 1637, 1458, 1439 cm^{-1}; ^1H NMR δ 8.11–8.06 (m, 2H), 7.91–7.87 (m, 2H), 7.56–7.32 (m, 11H), 5.01 (bs, 1H), 4.08 (dd, J=11.1, 3.8 Hz, 1H), 3.53 (bs, 1H), 3.29 (bs, 1H), 2.86 (t, J=10.7 Hz, 1H), 1.44–1.32 (m, 1H), 1.10–0.99 (m, 1H), 0.41 (dt, J=8.5, 5.3 Hz, 1H), 0.26 (dt, J=8.7, 5.3 Hz, 1H); ^{13}C NMR δ 143.00 (d, J_{CP}=10.4 Hz), 133.67, 133.13 (d, J_{CP}=9.4 Hz), 131.69 (d, J_{CP}=9.4 Hz), 131.17, 129.43, 128.95, 128.84, 128.65, 128.48, 127.68, 126.67, 66.37, 61.43, 26.71, 23.04, 9.16; MS (EI) *m/z* (intensity) 377 (M^+, 3), 359 (4), 347 (6), 306 (67), 356 (10), 201 (100), 176 (9); HRMS (EI) *m/z* calculated for $C_{19}H_{12}NOP$ $[M-C_4H_7O]^+$306.1034, found 306.1048.

This alcohol (3.25 g, 8.61 mmol) was suspended in acetonitrile (100 mL) and pH 6.7 phosphate buffer (100 mL). The biphasic mixture was warmed to 45 °C and treated with TEMPO (135 mg, 0.861 mmol), $NaClO_2$ (1.95 g, 21.5 mmol) and NaClO (2.46 mL, 1.72 mmol, 0.7 M aqueous solution). After 12 h, the reaction mixture was cooled to room temperature, treated with methanol (5.0 mL), 10% HCl (300 mL) and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The resultant foam was dissolved in methanol (50.0 mL), cooled to 0 °C and HCl gas was bubbled through the solution for 5 min. After 6 h, the solution was poured into dry diethyl ether (350 mL), cooled to −20 °C and filtered to afford the methyl ester **3**[11] (1.72 g, 83%).

4.1.3. (1*S*,2*S*)-2-((*S*)-1-Amino-1-phenylmethyl)cyclopropane carboxylic acid methyl ester D-tartrate salt (4) and (1*R*,2*R*)-2-((*R*)-1-amino-1-phenylmethyl)cyclopropane carboxylic acid methyl ester L-tartrate salt (5). A solution of the methyl ester **3** (1.04 g, 4.30 mmol) in ice (10 g) and chloroform (75 mL) was treated with 1 M K_2CO_3 (25.0 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3×) and EtOAc (2×). The combined organic layers were dried (Na_2SO_4) and evaporated and the resulting free amine (850 mg, 96%) was dissolved in ethanol (15.0 mL) and treated with L-tartaric acid (622 mg, 4.14 mmol). The reaction mixture was heated at reflux for 10 min (white suspension formed), and water was added until the solid material dissolved. Ethanol (10.0 mL) was added and the mixture was allowed to stand for 24 h at room temperature. The mixture was filtered to give a colorless solid (725 mg) which was recrystallized from ethanol/water (20:1) to afford **5**[11] (604 mg, 41%) as a crystalline solid. The filtrates from two crystallizations were combined, concentrated and dissolved in water. Ice was added, followed by chloroform and 1 M K_2CO_3 (25.0 mL). The aqueous layer was extracted with $CHCl_3$ (3×) and EtOAc (2×) and the combined organic layers were dried and evaporated. The free amine was dissolved in a mixture of ethanol (10.0 mL) and water (1.5 mL) and D-tartaric acid (368 mg, 2.45 mmol) was added. The mixture was heated until all solid materials dissolved, treated with ethanol (10.0 mL), and slowly cooled to room temperature. Filtration afforded **4**[11] (614 mg, 42%) as a colorless crystalline solid.

4.1.4. (1*S*,2*S*)-2-((*S*)-(Benzyloxycarbonylamino)phenylmethyl)cyclopropane carboxylic acid methyl ester (6{*1,1*}) and (1*R*,2*R*)-2-((*R*)-(benzyloxycarbonylamino)-phenyl-methyl)cyclopropane carboxylic acid methyl ester (7{*1,1*}). The tartrate salt **4** (0.48 g, 1.34 mmol) was dissolved in EtOAc (5.0 mL) and water (5.0 mL), cooled to 0 °C followed by $NaHCO_3$ (0.56 g, 6.68 mmol) and benzyl chloroformate (0.22 mL, 1.60 mmol). The mixture was stirred at 0 °C for 2 h, diluted with water, extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc 17/3) afforded **6**{*1,1*}[11] (0.43 g, 95%): $[\alpha]_D$+51.5 (*c* 1.1, $CHCl_3$). According to the same protocol, tartrate salt **5** (0.57 g, 1.60 mmol), $NaHCO_3$ (0.67 g, 8.00 mmol), benzyl chloroformate (0.28 mL, 1.92 mmol) in EtOAc (5.0 mL) and water (5.0 mL) afforded **7**{*1,1*}[11] (0.53 g, 97%): $[\alpha]_D$ −48.6 (*c* 1.0, $CHCl_3$).

4.1.5. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid methyl ester (6{*1,3*}) and (1*R*,2*R*)-2-((*R*)-(diphenylphosphinylamino)-phenylmethyl)cyclopropane carboxylic acid methyl ester (7{*1,3*}). The tartrate salt **4** (608 mg, 1.71 mmol) was dissolved in water (15.0 mL) and placed in a separatory funnel. Ice was added and the cold mixture was treated with 1 M K_2CO_3 solution (15.0 mL) and extracted with $CHCl_3$ (3×) and EtOAc (2×). The combined organic layers were

dried (Na_2SO_4) and evaporated to afford the free amine as a colorless oil. The residue was dissolved in dry CH_2Cl_2 (15.0 mL), cooled to 0 °C and treated with $Ph_2P(O)Cl$ (809 mg, 3.42 mmol) followed by DIPEA (1.18 mL, 6.75 mmol). The reaction mixture was warmed to room temperature, stirred for 10 h, diluted with EtOAc, washed with 10% HCl, water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/acetone 4/1, containing 1% v/v Et_3N) to afford **6**{*1*,*3*}[11] (664 mg, 96%) as a colorless solid: $[\alpha]_D+34.2$ (*c* 0.8, $CHCl_3$). According to the same protocol, **5** (600 mg, 1.69 mmol), $Ph_2P(O)Cl$ (800 mg, 3.38 mmol) and DIPEA (1.18 mL, 6.75 mmol) in dry CH_2Cl_2 (15.0 mL) afforded **7**{*1*,*3*}[11] (644 mg, 94%) as a colorless solid: $[\alpha]_D$ −34.8 (*c* 0.8, $CHCl_3$).

4.2. C-Terminal functionalizations

A solution of the cyclopropyl amino acid methyl esters **6**{*1*,*3*} and **7**{*1*,*3*} (0.935 mmol), respectively, in a mixture of methanol (10.0 mL) and THF (2.0 mL) was treated at room temperature with 1.0 M NaOH (10.0 mL). The resulting suspension was stirred until a clear solution was obtained (6 h). The resulting free acids **6**{*2*,*3*} and **7**{*2*,*3*} were extracted using an automated liquid–liquid extraction system (ALLEXis:[28] add 1.0 M HCl (20.0 mL), add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add saturated aqueous NaCl solution (15.0 mL), mix three times, extract lighter phase). The organic phases were dried ($MgSO_4$) and all volatile components were removed in vacuo. The free acids were obtained in an average yield of 88% as colorless crystals (0.83 mmol). Each acid was dissolved in chlorobenzene (22.0 mL) and divided into eleven 2–5 mL Emrys process vials (0.0750 mmol each). Compounds **6**{*2*,*3*} and **7**{*2*,*3*} dissolved only upon heating to 60 °C in a water bath. Twenty vials (ten vials of each acid) were used to synthesize the corresponding amides according to the general protocols A–C, the remaining two vials contained the two free acids **6**{*2*,*3*} and **7**{*2*,*3*} as part of the desired library and all volatile components were removed in vacuo from these vials.

General protocol A.[30] PS-carbodiimide (loading 1.20 mmol/g, 125 mg, 0.150 mmol, 2 equiv) and 1-hydroxybenzotriazole (15.3 mg, 0.113 mmol, 1.5 equiv) were added to the acid in chlorobenzene. The reaction mixture was stirred for 5 min at room temperature before addition of the amine. Volatile amines such as methylamine (**8**{*3*}) (33 wt% in ethanol, 143 μL, 1.88 mmol, 25.0 equiv) and cyclopropanemethylamine (**8**{*4*}) (30.2 mg, 0.375 mmol, 5.0 equiv) were added in excess. Benzylamine (**8**{*5*}), 2-aminomethylpyridine (**8**{*7*}), 5-methyl-2-furanmethanamine (**8**{*8*}) and (1,5-dimethyl-1*H*-pyrazol-3-yl)methylamine (**8**{*9*}) were added as 0.4 M solution in chlorobenzene (188 μL, 0.0750 mmol, 1.0 equiv). 4-Methylsulfonylbenzylamine hydrochloride (**8**{*6*}) (8.9 mg, 0.075 mmol, 1.0 equiv) was added neat, followed by triethylamine (15.2 mg, 0.150 mmol, 2.0 equiv). After addition of the amines, the microwave tubes were sealed and irradiated for 5 min (hold time) at 100 °C (applying an initial power of 200 W). Reactions involving volatile amines (**8**{*3*} and **8**{*4*}) were irradiated for 30 min at 60 °C. After cooling to room temperature, the microwave tubes were uncapped and the reaction mixtures (including the resin) were loaded onto SPE-cartridges (prepacked with 500 mg silica-bound carbonate and preconditioned with CH_2Cl_2 (1.0 mL)). The SPE-cartridges were washed three times with CH_2Cl_2 (2.0 mL each). The eluants were collected via gravity filtration. Evaporation of all volatile components in a centrifugal vacuum evaporator (Genevac HT-4) provided the desired amides in yields of 23–98% (Table 1).

General protocol B. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28.8 mg, 0.150 mmol, 2.0 equiv) and 1-hydroxybenzotriazole (15.3 mg, 0.113 mmol, 1.5 equiv) were added to a solution of the acid in chlorobenzene. The reaction mixture was stirred for 5 min at room temperature before 2-aminonaphthalene (**8**{*10*}) (188 μL of a 0.4 M solution in chlorobenzene, 0.075 mmol, 1.0 equiv) was added. The vials were sealed, purged with argon and stirred at room temperature for 12 h. The reaction mixtures were loaded onto ChemElut cartridges (3.0 mL cartridges, preconditioned for 5 min with 2.0 mL water) and washed with CH_2Cl_2 (2×2.0 mL). The eluants were collected via gravity filtration and all volatile components were removed in vacuo. Automated parallel chromatography on SiO_2 (ISCO Optix 10 System, 4 g cartridges, hexanes to hexanes/EtOAc, 1:1), followed by evaporation of all volatile components in a centrifugal vacuum evaporator (Genevac HT-4) provided the desired amides in yields of 69–72% (Table 1).

General protocol C.[31] 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (44.9 mg, 0.150 mmol, 2.0 equiv) and the corresponding amine were added to a solution of the acid in chlorobenzene. (*R*)-(−)-2-Amino-1-propanol (**8**{*11*}) was added as 0.4 M solution in chlorobenzene (281 μL, 0.113 mmol, 1.5 equiv), whereas tryptamine (**8**{*12*}) (18.1 mg, 0.113 mmol, 1.5 equiv) was added neat. After treating the reaction mixture with triethylamine (30.4 mg, 0.300 mmol, 4.0 equiv) the tube was sealed, purged with argon and stirred at room temperature for 12 h. The crude products were extracted using an automated liquid–liquid extraction system (ALLEXis:[28] add aqueous saturated NaCl solution (15.0 mL), add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add aqueous 1 M HCl (15.0 mL), mix three times, extract lighter phase, add saturated $NaHCO_3$ solution (15.0 mL), mix three times, extract lighter phase, add saturated NaCl solution (15.0 mL), mix three times, extract lighter phase). The combined organic layers were dried ($MgSO_4$) and all volatile components were removed in vacuo. Automated parallel chromatography on SiO_2 (ISCO Optix 10 System, 4 g cartridges, hexanes to EtOAc), followed by evaporation of all volatile components in a centrifugal vacuum evaporator (Genevac HT-4) provided the desired amides in yields of 44–68% (Table 1).

4.2.1. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid cyclopropylmethyl amide (6{*4*,*3*}). According to the general protocol A,

(**6**{*4*,*3*}) (11.8 mg, 35%) was obtained as colorless crystals. Mp 198 °C; IR (KBr) 3400, 3151, 2859, 1645, 1529, 1436 cm^{-1}; ^1H NMR δ 7.92–7.78 (m, 4H), 7.55–7.26 (m, 12H), 3.54 (dd, $J=10.2$, 6.0 Hz, 1H), 3.39 (app. q, $J=$ 9.9 Hz, 1H), 3.20–3.02 (m, 2H), 2.04–1.96 (m, 1H), 1.65–1.55 (m, 1H), 1.38–1.32 (m, 1H), 1.05–0.97 (m, 1H), 0.72–0.66 (m, 1H), 0.53–0.47 (m, 2H), 0.27–0.22 (m, 2H); ^{13}C NMR δ 172.1, 142.6 (d, $J_{CP}=8.7$ Hz), 133.1 (d, $J_{CP}=$ 129.0 Hz), 132.7 (d, $J_{CP}=9.5$ Hz), 132.1 (2 signals overlapping), 131.7 (d, $J_{CP}=9.5$ Hz), 130.3, 128.8, 128.7, 128.5, 127.6, 126.3, 60.3, 44.3, 29.0, 23.5, 12.5, 10.8, 3.4, 3.3; ^{31}P NMR δ 22.9; MS (ESI) *m*/*z* (rel. intensity) 467 ($[M+Na]^+$, 100), 445 ($[M+H]^+$, 27); HRMS (ESI) *m*/*z* calculated for $C_{27}H_{30}N_2O_2P$ (M+H) 445.2045, found 445.2024.

4.2.2. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid 4-methanesulfonylbenzylamide (6{*6*,*3*}). According to the general protocol A, (**6**{*6*,*3*}) (34.4 mg, 82%) was obtained as colorless crystals: ^1H NMR δ 8.66 (app. t, $J=5.6$ Hz, 1H), 7.88–7.77 (m, 6H), 7.56 (d, $J=8.2$ Hz, 2H), 7.51–7.26 (m, 11H), 4.58 (dd, $J=15.9$, 6.7 Hz, 1H), 4.50–4.43 (m, 1H), 3.73 (dd, $J=10.8$, 6.1 Hz, 1H), 3.31 (app. q, $J=9.7$ Hz, 1H), 3.00 (s, 3H), 2.16–2.07 (m, 1H), 1.62–1.54 (m, 1H), 1.45–1.39 (m, 1H), 0.74–0.68 (m, 1H).

4.2.3. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid (pyridin-2-ylmethyl)amide (6{*7*,*3*}). According to the general protocol A (**6**{*7*,*3*}) (23.8 mg, 66%) was obtained as colorless crystals: ^1H NMR δ 8.53 (d, $J=4.2$ Hz, 1H), 8.13 (app. t, $J=5.3$ Hz, 1H), 7.89–7.77 (m, 4H), 7.60 (app. td, $J=7.7$, 1.6 Hz, 1H), 7.50–7.29 (m, 12H), 7.15 (dd, $J=6.6$, 5.3 Hz, 1H), 4.60, 4.56 (d of AB, $J=16.2$, 5.6 Hz, 2H), 3.63 (dd, $J=9.9$, 6.1 Hz, 1H), 3.46 (app. q, $J=9.7$ Hz, 1H), 2.10–2.04 (m, 1H), 1.74–1.65 (m, 1H), 1.41–1.34 (m, 1H), 0.77–0.71 (m, 1H).

4.2.4. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid naphthalen-2-ylamide (6{*10*,*3*}). According to the general protocol B (**6**{*10*,*3*}) (26.9 mg, 69%) was obtained as colorless crystals: ^1H NMR δ 10.74 (s, 1H), 8.41 (s, 1H), 7.99–7.95 (m, 4H), 7.81–7.76 (m, 4H), 7.60–7.33 (m, 13H), 3.54 (dd, $J=10.5$, 5.4 Hz, 1H), 3.37 (app. q, $J=9.4$ Hz, 1H), 2.30–2.20 (m, 1H), 1.70–1.50 (m, 2H), 1.80–1.74 (m, 1H).

4.2.5. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino) phenylmethyl)cyclopropane carboxylic acid methylamide (7{*3*,*3*}). According to the general protocol A, (**7**{*3*,*3*}) (9.1 mg, 30%) was obtained as colorless crystals: ^1H NMR δ 7.91–7.77 (m, 4H), 7.54–7.30 (m, 12H), 3.62 (dd, $J=9.9$, 5.8 Hz, 1H), 3.34 (app. q, $J=9.6$ Hz, 1H), 2.78 (d, $J=4.7$ Hz, 3H), 1.98–1.88 (m, 1H), 1.65–1.57 (m, 1H), 1.39–1.33 (m, 1H), 0.68–0.62 (m, 1H).

4.2.6. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino) (phenyl)methyl)cyclopropane carboxylic acid cyclopropylmethylamide (7{*4*,*3*}). According to the general protocol A, (**7**{*4*,*3*}) (14.7 mg, 44%) was obtained as colorless crystals: ^1H NMR δ 7.92–7.78 (m, 4H), 7.55–7.26 (m, 12H), 3.54 (dd, $J=10.2$, 6.1 Hz, 1H), 3.38 (app. q, $J=$ 9.9 Hz, 1H), 3.20–3.02 (m, 2H), 2.04–1.96 (m, 1H), 1.65–1.55 (m, 1H), 1.38–1.32 (m, 1H), 1.05–0.97 (m, 1H), 0.72–0.66 (m, 1H), 0.53–0.47 (m, 2H), 0.27–0.22 (m, 2H).

4.2.7. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino)-phenylmethyl)cyclopropane carboxylic acid (5-methylfuran-2-ylmethyl)amide (7{*8*,*3*}). According to the general protocol A, (**7**{*8*,*3*}) (30.4 mg, 84%) was obtained as colorless crystals. Mp 170 °C; IR (KBr) 3165, 3058, 2920, 1653, 1541, 1437, 1186 cm^{-1}; ^1H NMR δ 7.86–7.78 (m, 4H), 7.71 (app. t, $J=4.1$ Hz, 1H), 7.51–7.28 (m, 11H), 6.14 (d, $J=2.6$ Hz, 1H), 5.88 (bs, 1H), 4.43–4.30 (m, 2H), 3.50 (dd, $J=10.1$, 4.1 Hz, 1H), 3.38 (app. q, $J=9.6$ Hz, 1H), 2.26 (s, 3H), 2.02–1.96 (m, 1H), 1.64–1.58 (m, 1H), 1.41–1.35 (m, 1H), 0.72–0.66 (m, 1H); ^{13}C NMR δ 172.0, 150.8 (d, $J_{CP}=87.7$ Hz), 142.5 (d, $J_{CP}=8.9$ Hz), 133.9, 132.7 (d, $J_{CP}=9.5$ Hz), 132.2 (d, $J_{CP}=7.0$ Hz), 132.0 (d, $J_{CP}=$ 2.8 Hz), 131.9 (d, $J_{CP}=2.8$ Hz), 131.6 (d, $J_{CP}=9.5$ Hz), 130.4, 128.7, 128.6 (d, $J_{CP}=4.7$ Hz), 128.5 (d, $J_{CP}=$ 4.5 Hz), 127.6, 126.3, 107.7, 106.1, 60.3, 36.8, 29.0, 23.5, 13.6, 12.5; ^{31}P NMR δ 22.9; MS (ESI) *m*/*z* (rel. intensity) 507 ($[M+Na]^+$, 100), 485 ($[M+H]^+$, 22); HRMS (ESI) *m*/*z* calculated for $C_{29}H_{29}N_2O_3PNa$ (M+Na) 507.1814, found 507.1798.

4.2.8. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino)-phenylmethyl)cyclopropane carboxylic acid (1,5-dimethyl-1*H*-pyrazol-3-ylmethyl)amide (7{*9*,*3*}). According to the general protocol A, (**7**{*9*,*3*}) (26.0 mg, 72%) was obtained as colorless crystals: ^1H NMR δ 7.90–7.75 (m, 4H), 7.52–7.23 (m, 12H), 6.01 (s, 1H), 4.45 (dd, $J=15.1$, 5.6 Hz, 1H), 4.30 (dd, $J=15.1$, 5.3 Hz, 1H), 3.72 (s, 3H), 3.52 (dd, $J=5.8$, 3.8 Hz, 1H), 3.45 (app. q, $J=8.9$ Hz, 1H), 2.21 (s, 3H), 1.98–1.92 (m, 1H), 1.70–1.65 (m, 1H), 1.38–1.31 (m, 1H), 0.73–0.66 (m, 1H).

4.3. N-Terminal functionalizations

General protocol D. A 5 mL microwave tube was charged with PS-DMAP (loading 1.6 mmol/g, 0.046–0.13 mmol, 1.2 equiv), ammonium salt **6**{*1*,*2*} or **7**{*1*,*2*} (0.038–0.11 mmol, 1.0 equiv), respectively, and the solids were suspended in dry CH_2Cl_2 (0.75–2.0 mL). The suspension was treated with triethylamine (0.076–0.22 mmol, 2.0 equiv) and the acylating reagent **9**{*3–12*} (0.046–0.13 mmol, 1.2 equiv). The tube was capped and irradiated in the microwave for 10 min (hold time) at 100 °C (applying an initial power of 200 W). After cooling to room temperature, MP-trisamine[33] (loading 3.0 mmol/g, 0.038–0.11 mmol, 1.0 equiv) and MP-isocyanate[32,33] (loading 1.54 mmol/g, 0.038–0.11 mmol, 1.0 equiv) were added to the crude reaction mixture and the microwave irradiation was resumed for 5 min (hold time) at 100 °C (applying an initial power of 200 W). Upon cooling, the reaction mixture was transferred to a ChemElut SPE-cartridge (preconditioned with saturated aqueous $NaHCO_3$, 2.0 mL) and washed five times with CH_2Cl_2 (1.0 mL each). The CH_2Cl_2 eluant was collected and concentrated (Genevac HT-4) to afford the pure products.

4.3.1. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid methyl ester (6{*1*,*3*}). According to the general protocol D, **6**{*1*,*2*}

(25 mg, 0.10 mmol), PS-DMAP (80 mg, 0.12 mmol), triethylamine (30 μL, 0.20 mmol), diphenyl phosphinic chloride (24 μL, 0.12 mmol), MP-isocyanate (70 mg, 0.10 mmol) and MP-trisamine (35 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) afforded **6**{*1,3*} (37 mg, 87%) as a colorless solid: ^{1}H NMR δ 7.94–7.87 (m, 2H), 7.75–7.68 (m, 2H), 7.56–7.42 (m, 5H), 7.36–7.30 (m, 6H), 3.88 (app. q, J=8.8 Hz, 1H), 3.62 (s, 3H), 3.34 (bt, J=7.7 Hz, 1H), 1.99–1.88 (m, 1H), 1.81–1.75 (m, 1H), 1.17–1.11 (m, 1H), 0.90–0.85 (m, 1H).

4.3.2. (1*S*,2*S*)-Methyl-2-((*S*)-phenyl(naphthalene-sulfonylamido)methyl)cyclopropanecarboxylate (6{*1,6*}). According to the general protocol D, **6**{*1,2*} (10 mg, 0.041 mmol), PS-DMAP (31 mg, 0.049 mmol), triethylamine (11 μL, 0.082 mmol), 1-naphthalene sulfonylchloride (12 mg, 0.049 mmol), MP-isocyanate (25 mg, 0.041 mmol) and MP-trisamine (13 mg, 0.041 mmol) in CH_2Cl_2 (1 mL) afforded **6**{*1,6*} (16 mg, 97%) as a pale yellow solid: ^{1}H NMR δ 8.55 (d, J=8.4 Hz, 1H), 8.02 (d, J=7.6 Hz, 1H), 7.95 (d, J=8.2 Hz, 1H), 7.88 (d, J=8.2 Hz, 1H), 7.66–7.55 (m, 2H), 7.35 (dd, J=7.8, 7.6 Hz, 1H), 7.03 (t, J=7.2 Hz, 1H), 6.95 (app. t, J=7.2 Hz, 2H), 6.86 (d, J=7.2 Hz, 2H), 5.25 (bd, J=6.2 Hz, 1H), 3.82 (app. t, J=6.4 Hz, 1H), 3.59 (s, 3H), 1.81–1.72 (m, 1H), 1.58–1.52 (m, 1H), 1.12–1.06 (m, 1H), 0.89–0.80 (m, 1H).

4.3.3. (1*S*,2*S*)-Methyl 2-((*S*)-(nicotinamido)(phenyl) methyl)cyclopropanecarboxylate (6{*1,9*}). According to the general protocol D, **6**{*1,2*} (25 mg, 0.10 mmol), PS-DMAP (80 mg, 0.12 mmol), triethylamine (30 μL, 0.20 mmol), 2-pyridinecarbonyl chloride (22 mg, 0.12 mmol), MP-isocyanate (70 mg, 0.10 mmol) and MP-trisamine (35 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) afforded **6**{*1,9*} (35 mg, >99%) as an off white solid. Mp 143–144 °C; IR (KBr) 3367, 3090, 3028, 3003, 2952, 1722, 1639 cm^{-1}; ^{1}H NMR δ 8.98 (d, J=1.8 Hz, 1H), 8.69 (dd, J=1.9, 4.8 Hz, 1H), 8.13 (ddd, J=1.8, 1.9, 8.1 Hz, 1H), 7.43–7.28 (m, 6H), 7.08 (bd, J=7.8 Hz, 1H), 4.78 (app. t, J=8.5 Hz, 1H), 3.64 (s, 3H), 2.05–1.84 (m, 2H), 1.36–1.30 (m, 1H), 1.08–1.02 (m, 1H); ^{13}C NMR δ 174.21, 164.93, 152.00, 147.91, 140.62, 135.48, 130.01, 128.67, 127.73, 126.64, 123.41, 56.02, 51.85, 26.80, 19.20, 14.46; MS (EI) *m/z* (rel. intensity) 310 (M^+, 3), 279 (9), 250 (11), 224 (70), 204 (74), 195 (23), 129 (31), 106 (87), 78 (100); HRMS (EI) *m/z* calculated for $C_{18}H_{18}N_2O_3$ (M) 310.1317, found 310.1306.

4.3.4. (1*S*,2*S*)-Methyl 2-((*S*)-(5-methylisoxazole-3-carboxamido)(phenyl)methyl)cyclopropanecarboxylate (6{*1,11*}). According to the general protocol D, **6**{*1,2*} (25 mg, 0.10 mmol), PS-DMAP (80 mg, 0.12 mmol), triethylamine (30 μL, 0.20 mmol), 5-methyl-isoxazole-3-carbonyl chloride (18 mg, 0.12 mmol), MP-isocyanate (70 mg, 0.10 mmol) and MP-trisamine (35 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) afforded **6**{*1,11*} (30 mg, 95%) as an off white solid: ^{1}H NMR δ 7.44–7.31 (m, 5H), 7.21 (bd, J=7.7 Hz, 1H), 6.45 (s, 1H), 4.74 (app. t, J=8.6 Hz, 1H), 3.69 (s, 3H), 2.49 (s, 3H), 2.02–1.90 (m, 2H), 1.38–1.27 (m, 1H), 1.04–0.98 (m, 1H).

4.3.5. (1*R*,2*R*)-Methyl 2-((*R*)-phenyl(benzenesulfonyl-amido)methyl)cyclopropanecarboxylate (7{*1,5*}). According to the general protocol D, **7**{*1,2*} (15 mg, 0.062 mmol), PS-DMAP (50 mg, 0.074 mmol), triethylamine (20 μL, 0.12 mmol), benzenesulfonyl chloride (11 mg, 0.074 mmol), MP-isocyanate (40 mg, 0.062 mmol) and MP-trisamine (21 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,5*} (23 mg, >99%) as a pale yellow solid: ^{1}H NMR δ 7.67 (d, J=7.7 Hz, 2H), 7.48 (t, J=7.5 Hz, 1H), 7.36 (dd, J=7.5, 7.7 Hz, 2H), 7.21–7.16 (m, 3H), 7.09–7.05 (m, 2H), 5.16 (bd, J=6.2 Hz, 1H), 3.92 (app. t, J=7.1 Hz, 1H), 3.66 (s, 3H), 1.87–1.78 (m, 1H), 1.72–1.66 (m, 1H), 1.19–1.13 (m, 1H), 0.93–0.87 (m, 1H).

4.3.6. (1*R*,2*R*)-Methyl 2-((*R*)-(benzamido)(phenyl) methyl)cyclopropanecarboxylate (7{*1,8*}). According to the general protocol D, **7**{*1,2*} (20 mg, 0.082 mmol), PS-DMAP (63 mg, 0.098 mmol), triethylamine (23 μL, 0.16 mmol), benzoylchloride (11 μL, 0.098 mmol), MP-isocyanate (55 mg, 0.082 mmol) and MP-trisamine (28 mg, 0.082 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,8*} (24 mg, 92%) as a colorless solid. Mp 160–161 °C; IR (KBr) 3362, 3030, 2949, 1725, 1635 cm^{-1}; ^{1}H NMR δ 7.80–7.77 (m, 2H), 7.55–7.31 (m, 8H), 6.49 (bd, J=8.4 Hz, 1H), 4.85 (app. t, J=8.4 Hz, 1H), 3.69 (s, 3H), 2.04–1.93 (m, 2H), 1.37–1.31 (m, 1H), 1.08–1.01 (m, 1H); ^{13}C NMR δ 174.04, 166.71, 140.73, 134.27, 131.50, 128.71, 128.47, 127.71, 126.98, 126.70, 55.56, 51.75. 26.82, 18.99, 14.13; MS (EI) *m/z* (rel. intensity) 309 (M^+, 14), 278 (15), 222 (46), 204 (48), 129 (60), 105 (73), 77 (100); HRMS (EI) *m/z* calculated for $C_{19}H_{19}NO_3$ 309.1365, found 309.1368.

4.3.7. (1*R*,2*R*)-Methyl 2-((*R*)-(nicotinamido)(phenyl) methyl)cyclopropanecarboxylate (7{*1,9*}). According to the general protocol D, **7**{*1,2*} (15 mg, 0.062 mmol), PS-DMAP (50 mg, 0.074 mmol), triethylamine (20 μL, 0.12 mmol), nicotinoyl chloride (11 mg, 0.074 mmol), MP-isocyanate (40 mg, 0.062 mmol) and MP-trisamine (21 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,9*} (20 mg, >99%) as an off white solid: ^{1}H NMR δ 8.99 (d, J=1.9 Hz, 1H), 8.71 (dd, J=4.8, 1.8 Hz, 1H), 8.13 (ddd, J=8.0, 1.9, 1.8 Hz, 1H), 7.44–7.29 (m, 6H), 6.87 (bd, J=7.5 Hz, 1H), 4.80 (app. t, J=8.4 Hz, 1H), 3.66 (s, 3H), 2.05–1.94 (m, 2H), 1.37–1.31 (m, 1H), 1.09–1.02 (m, 1H).

4.3.8. (1*R*,2*R*)-Methyl 2-((*R*)-phenyl(pyrazine-2-carboxamido)methyl)cyclopropanecarboxylate (7{*1,10*}). According to the general protocol D, **7**{*1,2*} (15 mg, 0.062 mmol), PS-DMAP (50 mg, 0.074 mmol), triethylamine (20 μL, 0.12 mmol), 2-pyrazinecarbonyl chloride (11 mg, 0.074 mmol), MP-isocyanate (40 mg, 0.062 mmol) and MP-trisamine (21 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,10*} (15 mg, 76%) as an orange solid: ^{1}H NMR δ 9.42 (d, J=1.4 Hz, 1H), 8.77 (d, J=2.4 Hz, 1H), 8.54 (dd, J=2.4, 1.5 Hz, 1H), 8.23 (bd, J=4.9 Hz, 1H), 7.45–7.32 (m, 5H), 4.82 (app. t, J=8.8 Hz, 1H), 3.68 (s, 3H), 2.08–1.92 (m, 2H), 1.38–1.31 (m, 1H), 1.08–1.01 (m, 1H).

4.4. LC–MS analysis

LC–MS analysis was performed on a Thermo Finnigan octopole ion trap with APCI probe (positive ion detection mode), using a reversed-phase C_{18} column (acetonitrile/1% acetic acid in water 3/2, 1 mL/min). ELS detection was performed using split flow from the HPLC and a PL-ELS

2100 detector from Polymer Laboratories (nitrogen gas flow 1.25 SLM, evaporator 45 °C and nebulizer 45 °C).

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