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Facile and purification free synthesis of peptides utilizing ROMPgel- and ROMPsphere-supported coupling reagents

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Abstract—5-Norbornene-2-carboxaldehyde and norbornadiene were respectively converted into norbornene derivatives functionalized with fluoroformamidinium hexafluorophosphate and 2-bromo-*N*-methylpyridinium tetrafluoroborate residues. Both these norbornene monomers were ring opening metathesis polymerized or graft copolymerized onto polystyrene cores to produce ROMPgel and ROMPsphere peptide-coupling reagents. These were used to prepare hindered amides, dipeptides and tripeptides with minimal purification in parallel arrays.

1. Introduction

The synthesis of structurally diverse combinatorial oligopeptide libraries using purification free processes originated from the pioneering work of Merrifield and Letsinger.[1] Since the advent of this methodology, an array of techniques including parallel synthesis,[2] tagging,[3] split and mix,[4] and indexing[5] has been developed for the generation of peptide and non-peptide libraries on solid supports. The need to synthesize chemically diverse libraries of small drug-like entities through automation has resulted in a shift from the traditional solid support approach to the use of solid supported reagents.[6] This approach significantly facilitates the process of library synthesis for high throughput assay[7] since the undesired by-products are bound to the support facilitating purification through simple filtration. The use of polymer-supported reagents was conceived as a practical solution for simplifying tedious workup procedures associated with the removal of undesired by-products[8] such as phosphine oxides, sulfonamides and urea type reagents. Over the past three decades this approach has been further extended to include transformations such as oxidations,[9] reductions,[10] halogenations,[11] carbon–carbon bond formation[12] and also the use of polymer bound catalysts.[13] These supported reagents are normally synthesized on cross-linked polystyrene beads, macroporous ion exchange resins, or inorganic supports. The major focus of combinatorial chemistry and parallel synthesis has been the generalization of synthetic protocols to maximize functional group diversity through automation. We have sought to address this need by the introduction of new classes of high-loading polymer-supported reagents for purification-free (mix, filter and evaporate) parallel synthesis.

Recently, we have reported the use of ring opening metathesis (ROM) polymerization for the synthesis of high-loading, insoluble, polymer-gel supported reagents (ROMPgels). These reagents have several major advantages. Firstly, alkene metathesis catalysts are noted for tolerance of diverse functionalities thereby permitting the production of fully functionalized (reagent) monomers prior to the polymerization process. Secondly, such monomers are readily available from inexpensive precursors. Thirdly, ROMPgels are high-loading reagents, which have been employed for Horner–Emmons reactions,[14] in TOSMIC condensation reactions,[15] in acylation reactions including the preparation of Mosher amides,[16] and in reactions using triphenylphosphine,[17] *N*-hydroxysuccinimide,[18] naphthalene and biphenyl,[19] Wilkinson's catalyst,[20] allylboronate reagents,[21] and diazoketophosphonates,[22] in catalyzing the Stetter reaction[23] and as scavengers for amines and hydrazines.[24] Hanson and Flynn,[25] Roberts[26] and Janda[27] have described related ROMPolymer-supported reagents and supports and the area of ROMPolymer-supported reagents has been reviewed.[28] To further expand on our current methodologies, we now wish to provide details for the synthesis and application of immobilized fluoroformamidinium and immobilized 2-bromopyridinium ROMPgel and ROMPsphere reagents for peptide-coupling reactions and the synthesis of hindered amides.[28]

Keywords: Acylations; Combinatorial chemistry; Peptides; Parallel synthesis; Supported reagents.
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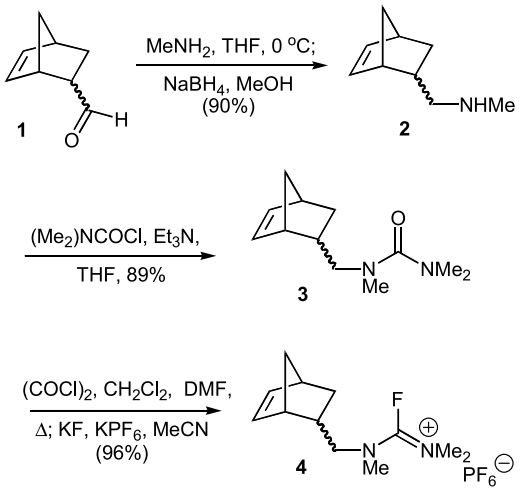
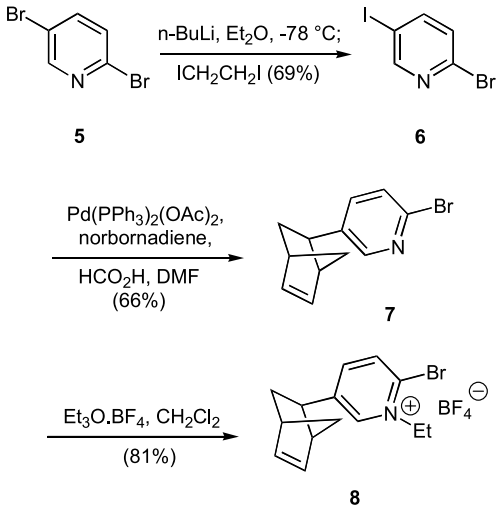
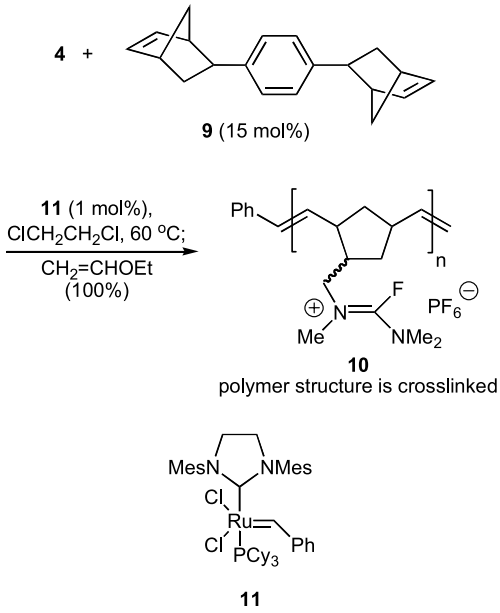
Gramicidin,[29] an antibiotic first isolated in 1941, was found to contain a $C^{\alpha\alpha}$ di-substituted amino acid residue. Since then such amino acid residues have been identified in a number of natural products[30] and their occurrence has led to significant interest in the development of efficient methods for their synthesis.[31] Traditional peptide-coupling protocols, using activated esters and anhydrides,[32] and carbodimides with *N*-hydroxybenzotriazole,[33] have been found to be inadequate for coupling such hindered moieties. The next real advancement in coupling activity came with the development of phosphonium salt based reagents such as (1-benzotriazolyoxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP)[34] and (1-benzotriazolyoxy)tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP).[35] Due to toxicity of their side products, they soon were replaced by uronium reagents such as *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)[36] and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).[37] Recently an immobilized version of as *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) based on a polystyrene bound benzotriazole was published.[38] These uronium reagents show a remarkable activity and low racemization in standard peptide-couplings but are still of limited use for the coupling of $C^{\alpha\alpha}$ di-substituted amino acid residues, due to the steric demand of the activating group. Other very active onium type coupling reagents for hindered amide bonds include thiazolium (2-bromo-3-ethyl-4-methylthiazolium tetrafluoroborate, BEMT)[39] and iminium (benzotriazol-1-yloxy-*N*,*N*-dimethylmethan-iminium hexachloroantimonate, BOMI)[40] type reagents. Recently, onium type coupling reagents, that generate acid fluorides or bromides, have been reported to be effective in the synthesis of amides derived from mono- and di-substituted amino acids in acceptable yields, with good reaction rates and with minimal racemization. The most promising and synthetically accessible candidates are fluoroformamidinium salts (tetramethylfluoro-formamidinium hexafluorophosphate, TFFH and bis(tetramethylenefluoroformam-idinium) hexafluorophosphate, BTFFH)[41] and 2-halopyridinium salts (2-bromo-1-ethylpyridinium tetrafluoroborate, BEP and 2-fluoro-1-ethylpyridinium tetrafluoroborate, FEP).[42] The inherent problem of all reagents mentioned, including the immobilized TBTU, is the formation of undesired by-product, which may be toxic[43] and that necessitate extensive work-up after peptide-couplings in solution. Consequently, we sought to prepare related polymer-supported reagents to simplify work-up and to minimize the need for chromatographic purification. Herein we report the synthesis of monomers **4** and **8** (Schemes 1 and 2), their polymerization and graft ROM-polymerization using starter divinylbenzene cross-linked polystyrene cores (Scheme 3) and their use in the elaboration of hindered peptides and amides in the solution phase with minimal purification (Scheme 4).



Scheme 1. Synthesis of the fluoroformamidinium monomer **4**.



Scheme 2. Synthesis of the 2-bromopyridinium monomer **8**.

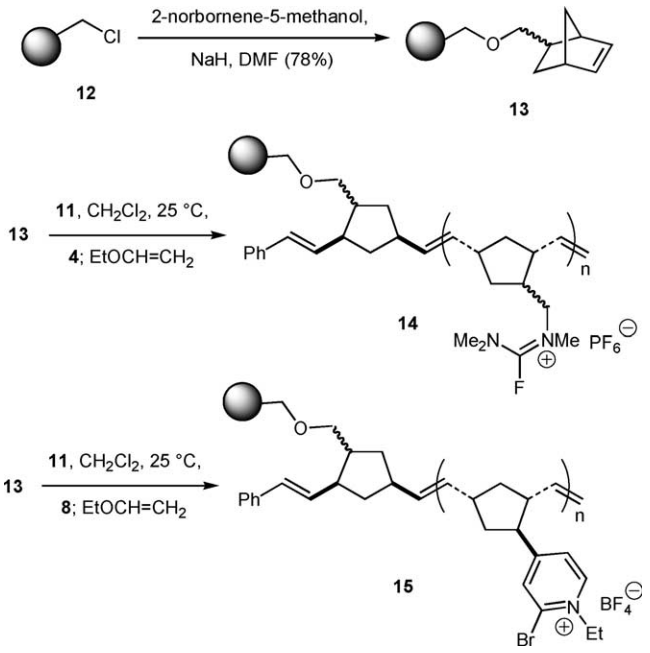


Scheme 3. Synthesis of the ROMPgel reagent **10**.

2. Results and discussion

2.1. Synthesis of monomers

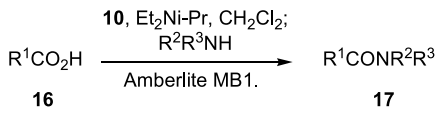
The fluoroformamidinium monomer **4** was synthesized in four steps from commercially available 5-norbornene-2-carboxaldehyde (**1**) (Scheme 1). Reductive amination of



Scheme 4. Synthesis of the ROMPsphere reagents **14** and **15**.

aldehyde **1** gave amine **2**[44] which was allowed to react with dimethylcarbamoyl chloride to afford the urea derivative **3** in 89% yield. Formation of the formamidinium salt **4** was achieved using a one-pot phosgene-free procedure described by Nájera et al.[45] Thus, reaction of the amide **3** with oxalyl chloride and DMF in dichloromethane afforded the formamidinium chloride salt. Subsequent treatment with potassium hexafluorophosphate and potassium fluoride in acetonitrile gave the formamidinium hexafluorophosphate **4** as a crystalline solid.

The second coupling reagent prepared was an immobilized variant of the 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) coupling reagent (Scheme 2). Monomer **8** was synthesized in 3 steps from the commercially available



Scheme 5. Parallel synthesis of hindered amides using the ROMPgel **10**.

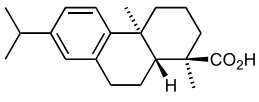
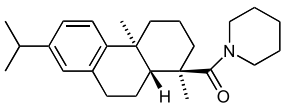
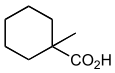
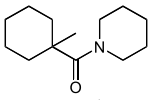
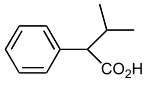
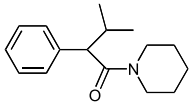
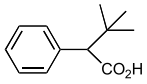
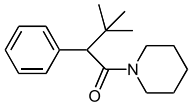
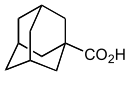
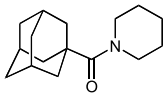
2,5-dibromopyridine. Selective bromine–lithium exchange,[46] upon treatment of the dibromide **5** with *n*-butyllithium at −78 °C and iodination using 1,2-diiodoethane gave 2-bromo-5-iodopyridine **6** (69%). Palladium catalyzed *exo*-hydroarylation[47] of iodide **6** gave the bromide **7** (66%). Subsequent ethylation using triethyloxonium tetrafluoroborate[48] gave the norbornene pyridinium salt **8** (81%).

2.2. Ring opening metathesis polymerization: synthesis of ROMPgel and ROMPsphere coupling reagents

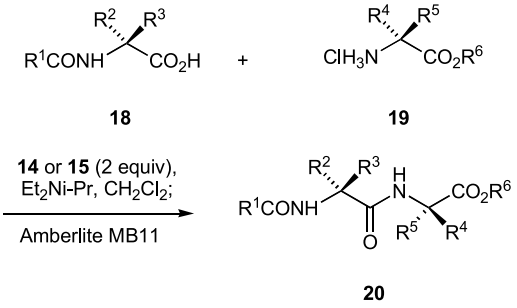
With monomers **4** and **8** in hand, the stage was set for both ROM-polymerization in the presence of a crosslink to provide the ROMPgel reagent **10** and graft ROM-polymerization reactions onto polystyrene beads to provide the corresponding ROMPsphere[49] reagents **14** and **15**. ROMPsphere reagents are analogous to functionalized Hodges Rasta resins[50] due to the fact that both types of polymers are derived from living polymerization reactions to increase the mass and loading of core divinylbenzene cross-linked polystyrene beads. ROM polymerization of monomer **4** in the presence of catalyst **11**[51] (1 mol%) and cross-linker **9**[22] gave the fluoroformamidinium ROMPgel **10** (Scheme 3). This was isolated in excellent yield (98%) after quenching with ethyl vinyl ether and extensive washing with dichloromethane and diethyl ether.

Secondly, Merrifield resin **12** (0.9 mmol/g^{-1}) was allowed to react with excess 2-norbornene-5-methanol in DMF under basic conditions for 24 h at reflux (Scheme 4). The polymer was sequentially washed with dichloromethane and methanol and dried. The loading of the norbornene **13** was

Table 1. Parallel synthesis of hindered amides using the ROMPgel **10**

Entry	R^1CO_2H (**16**)		$R^1CONR^2R^3$ (**17**)		Yield % (purity %)[a]
1	**16a**		**17a**		87 (88)
2	**16b**		**17b**		98 (97)
3	**16c**		**17c**		73 (88)
4	**16d**		**17d**		95 (90)
5	**16e**		**17e**		81 (88)

[a] Yields refer to isolated products; the purities were estimated by ^1H and ^{13}C NMR spectra and, for volatile acids and amides, also by GC–S analysis.



Scheme 6. Peptide—coupling reactions using ROMPsphere reagents **14** and **15**.

estimated by an increase in mass and by elemental analysis. The supported norbornene **13** (0.65 mmol/g^{-1}) was allowed to react with carbene **11** (3 mol%) in dichloromethane to afford a red colored polymer, which was subsequently washed with dichloromethane and 2-propanol. The resin was immediately treated separately with the monomers **4** or **8** for 2 h and the polymerization reactions terminated with ethyl vinyl ether, and the beads were washed with dichloromethane and diethyl ether. Both ROMPsphere reagents **14** and **15** were obtained with loadings of 1.45 and 1.80 mmol/g^{-1} respectively as determined by an increase in mass and by elemental analysis. We investigated the swelling properties of the ROMPsphere salts **14** and **15** in a range of solvents and observed significant swelling for both ROMPspheres in dichloromethane, THF and DMF. Dichloromethane, as the most volatile, was selected for amide and peptide synthesis.

2.3. Parallel synthesis of hindered amides and peptides

As previously discussed, both fluoroformamidinium and 2-bromopyridinium salts have proven to be effective coupling reagents for formation of peptides from α,α-dialkylated amino acids with minimal racemization. Thus we evaluated the effectiveness of the ROMPgel **10** (Scheme 5, Table 1) and the ROMPsphere reagents **14** and **15** (Scheme 6, Table 2) in the purification-minimized parallel synthesis of hindered amides and di-peptides containing the sterically hindered Aib (α-aminoisobutyric acid). In several examples of dipeptide synthesis, the degree of racemization was determined using both the Anteunis test[52] and Young's test.[53] ROMPgel reagent **10** was suspended in dichloromethane at room temperature and allowed to react with ethyldiisopropylamine and the acid component. After ten minutes, a secondary amine was added and the resulting mixture stirred at room temperature for 12 h. Pre-washed Amberlite MB1 ion exchange resin was added and the mixture shaken for a further 2 h. The suspension was filtered, and the ROMPgel washed alternatively with CH_2Cl_2 and MeOH. Evaporation of the solvent afforded the desired amides in reasonable yields and high purities (Table 1, entries 1–5).

The ROMPsphere reagents **14** and **15** were suspended in dichloromethane at −10 °C, and allowed to react with ethyldiisopropylamine (3 equiv), an *N*-protected amino acid **18** (0.5 equiv) and an amino ester hydrochloride **19** (0.5 equiv) at 25 °C for 12 h. Pre-washed Amberlite MB11 ion exchange resin was added and the mixture shaken for a further 2 h. The suspension was simply filtered, washed with dichloromethane and methanol to afford the corresponding di- and tri-peptides **20** (Scheme 6, Table 2). The reactions could also be very effectively performed in Bohdan Miniblocks: the peptide-coupling was performed in one block and afterwards the liquid reaction components were transferred in parallel into a second block containing the ion exchange resin. After agitating the resin for further 1 h, the solution was free of salt by-products and the pure dipeptides **20** were released into a deep well Miniblock and evaporated. The preparation of $C^{\alpha\alpha}$-disubstituted peptides was shown to be extremely effective in terms of reaction time, yields and purities, as exemplified in by **20b**, **20c**, **20d**, **20g** and **20h**. The results in Table 2 indicate that there is little difference in term of yield and purity when using the ROMPsphere reagents **14** or **15**. In several cases the Anteunis test was conducted at −78 °C using ethyldiisopropylamine as the base and samples were taken after 10 min, 1 h and finally 12 h and the DL values were determined by HPLC using a protocol described by Li and Xu.[42] Unfortunately, complete epimerization was observed after only 10 min reaction using the ROMPsphere reagents **14** and **15** (Table 2, entries 9 and 10). Changing the base for the peptide-coupling from ethyldiisopropylamine to a weaker base such as 2,6-lutidine or *N*-methylmorpholine failed to suppress complete epimerization. Our optical rotation values for the coupling of *Z*-Gly and PheOEt were shown to be zero (Table 2, entries 1 and 2). These unexpected results were possibly due to slow

Table 2. Yields and purities of dipeptides **20** synthesized using ROMPspheres **14** or **15**

Entry	Dipeptide	**18**	**19**	ROMPsphere	% Yield[a]	% Purity[b]
1	**20a**	Z-Gly	(L)-Phe-OEt ·HCl	**14**	96	95[c]
2	**20a**	Z-Gly	(L)-Phe-OEt ·HCl	**15**	86	87[c]
3	**20b**	Boc-Aib	Gly-OEt ·HCl	**14**	97	98
4	**20c**	Z-Gly	Aib-OMe·HCl	**14**	97	98
5	**20c**	Z-Gly	Aib-OMe·HCl	**15**	84	96
6	**20d**	Boc-Aib	Aib-OMe·HCl	**14**	90	98
7	**20e**	Z-(L)-Leu	Gly-OEt·HCl	**14**	89	92[d]
8	**20e**	Z-(L)-Leu	Gly-OEt·HCl	**15**	92	94[d]
9	**20f**	Z-Gly-(L)-Phe	(L)-Val-OMe·HCl	**14**	95	90[c]
10	**20f**	Z-Gly-(L)-Phe	(L)-Val-OMe·HCl	**15**	87	87[c]
11	**20g**	*N*-Fmoc-Aib	Gly-OEt·HCl	**15**	85	88
12	**20h**	*N*-Fmoc-Aib	(L)-Ala-OEt·HCl	**15**	80	89[d]

[a] Isolated yields.
[b] Purity as determined by ^{1}H NMR.[54]
[c] Product completely racemized (epimerized).
[d] Extent of racemization not determined.

diffusion of the amine to the ROMPsphere immobilized activated acid thereby facilitating racemization. In spite of this limitation, the ROMPsphere coupling reagents **14** and **15** are valuable in the parallel synthesis of hindered peptides containing α,α-disubstituted amino acid residues (Table 2, entries 3–6 and 11).

3. Conclusions

We have demonstrated the utility of a ROMPgel-supported fluoroformamidinium hexafluorophosphate, a ROMPsphere-supported fluoroformamidinium hexafluoro-phosphate and a ROMPsphere-supported *N*-ethylpyridinium tetrafluoroborate for the parallel synthesis of hindered amides with minimal purification. The approach, whilst useful for hindered peptides containing α,α-disubstituted amino acid residues, it is unsatisfactory for standard peptide-coupling reactions on account of racemization.

4. Experimental

4.1. General

All reactions were carried out in an atmosphere of dry nitrogen or argon at room temperature unless otherwise stated. Reaction temperatures other than room temperature were recorded as bath temperatures unless otherwise stated. Flash chromatography was carried out on BDH silica 60, 230–400 mesh ASTM (eluants are quoted in parenthesis). Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica 60 F_{254} plates. Hexanes refers to redistilled alkanes with bp 40–60 °C. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were purified by distillation under N_2 respectively from CaH_2 and Ph_2CO/K, All other organic solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were concentrated using a rotary evaporator at <40 °C bath temperature. Non volatile oils and solids were vacuum dried at <2 mm Hg. Bohdan miniblocks with 8 mL glass reactors with bottom filtration and the option for transfer from one block to the other were used for parallel reactions.

4.1.1. 5-(Methylaminomethyl)bicyclo[2.2.1]hept-2-ene (2).[55] $MeNH_2$ in THF (2.0 M; 65 mL, 132 mmol) was added to aldehyde **1** (8.0 g, 66 mmol), Et_2–O (50 mL) and 4 Å molecular sieves (8.0 g) at 0 °C. The mixture was stirred for 2 h, filtered and rotary evaporated to afford the imine as an oil, which was dissolved in MeOH (100 mL) and $NaBH_4$ (3.7 g, 99 mmol) was added in portions at 0 °C. After stirring at 25 °C for 4 h, the mixture was rotary evaporated to afford a residue, which was portioned between CH_2Cl_2 and hydrochloric acid (2 M; 66 mL). The aqueous solution was basified to a pH 8–9 and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and rotary evaporated to afford **2** (8.1 g, 90%) as a pale yellow oil; IR (thin film) 3291, 1623, 1468, 1447, 1341, 1150, 718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.08–5.88 (m, 2H), 2.80–2.74 (m, 2H), 2.57–2.54 (m, 1H), 2.41–2.36 (m, 3H), 2.34–2.14 (m, 2H), 1.85–1.77 (m, 1H), 1.28–1.10 (m, 3H), 0.50–0.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 132.1, 56.7, 49.5, 44.3, 42.3, 39.1, 36.8, 30.6; MS (CI, NH_3) *m/z* 138 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_9H_{16}N$ $(M+H)^+$, 138.1283; found: $(M+H)^+$, 138.1280.

4.1.2. *N*-(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-*N*,*N*′,*N*′-trimethylurea (3). Dimethyl-carbamoyl chloride (4.7 g 44 mmol) was added slowly with stirring to amine **2** (6.0 g, 44 mmol) in THF (250 mL) and Et_3N (12.2 mL, 88 mmol) at 25 °C. After 3 h, the reaction mixture was filtered through Celite and silica gel and rotary evaporated to afford a residue. Chromatography (hexane/Et_2O 2:1) gave urea **3** (8.2 g, 89%) as a yellow oil: R_f 0.14 (EtOAc/hexanes 2:3); IR (thin film) 1644, 1495, 1461, 1382, 1343, 1260, 1123, 1112, 1063, 782, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (dd, $J=5.3$, 2.8 Hz, 1H), 5.84 (dd, $J=5.3$, 2.8 Hz, 1H), 3.20 (m, 1H), 2.85 (dd, $J=2.6$, 7.7 Hz, 2H), 2.75 (br s, 3H), 2.74 (br s, 6H), 2.36 (m, 1H), 1.76 (m, 1H), 1.36 (m, 1H), 1.29–1.18 (m, 2H), 0.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 137.3, 132.3, 54.1, 49.5, 44.4, 42.2, 38.6, 37.4, 37.3, 30.0; MS (CI, NH_3) *m/z* 209 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{12}H_{21}N_2O$ $(M+H)^+$209.1654; found: $(M+H)^+$, 209.1645. Anal. calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.39; H, 9.84; N, 13.12.

4.1.3. *N*-(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-*N*,*N*′,*N*′-trimethylfluoroform-amidinium hexafluorophosphate (4). Oxalyl chloride (1.0 mL, 11.5 mmol) was added dropwise to the urea **3** (2.1 g, 10 mmol) and DMF (75 μL) in CH_2Cl_2 (10 mL) at 25 °C. After 1 h, the solution was heated to reflux for 4 h when rotary evaporation gave the crude chloroformamidinium salt. KPF_6 (2.2 g, 12.0 mmol) and KF (0.56 g, 10.0 mmol) in MeCN (10 mL) were added and the mixture was stirred for 48 h. The suspension was filtered and the filtrate was concentrated in vacuo to afford a residue. Recrystallization from CH_3CN and Et_2O gave the salt **4** (2.3 g, 64%) as a white solid: mp 91–93 °C; IR (solid) 1647, 1473, 1457, 1412, 1398, 1245, 1058, 833, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (m, 1H), 5.92 (m, 1H), 3.80–3.60 (m, 1H), 3.42 (br s, 3H), 3.41 (br s, 6H), 2.91 (br s, 1H), 2.84 (br s, 1H), 2.54 (m, 1H), 2.00–1.98 (m, 1H), 1.59–1.55 (m, 1H), 1.38–1.36 (m, 1H), 1.24–1.16 (m, 1H), 0.60–0.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 139.5, 131.0, 61.1, 49.9, 44.6, 44.5, 43.2, 42.4, 37.4, 30.1; MS (FAB +) *m/z* 211 (M^+); HRMS (FAB +) *m/z* calcd for $C_{12}H_{20}FN_2$ (M^+), 211.1611; found: (M^+), 211.1614.

4.1.4. 2-Bromo-5-iodopyridine (6). *n*-BuLi in hexanes (2.5 M; 7.00 mL, 17.5 mmol) was added dropwise to 2,5-dibromopyridine **5** (3.76 g, 15.9 mmol) in THF (190 mL) at −78 °C and the mixture stirred for 40 min. ICH_2CH_2I (5.78 g, 20.5 mmol) in THF (25 mL) was added and the mixture was allowed to warm up to 25 °C over 12 h. The solution was diluted with H_2O and Et_2O (1:1, 300 mL) and the aqueous phase was extracted with additional $Et_{-2}O$ (4× 50 mL). The combined organic phases were washed with $Na_2S_2O_4$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and rotary evaporated to afford a yellow solid. Chromatography (hexanes/CH_2Cl_2 4:1) gave iodide **6** (3.2 g, 69%) as a white solid: mp 119 °C (EtOH); IR (film) 1544, 1439, 1354, 1278, 1141, 1086, 994, 911, 828, 716, 666, 624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, $J=2.0$ Hz, 1H), 7.82 (dd, $J=$ 2.0, 8.3 Hz, 1H), 7.28 (d, $J=8.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 146.6, 145.5, 130.0, 91.8; MS

(EI, *m/z*) 283 ($M^{\cdot+}$), 237, 204, 156, 127; calcd for C_5H_3BrIN: ($M^{+\cdot}$), 282.8494; found: ($M^{+\cdot}$), 282.8497. Anal. calcd for C_5H_3BrIN: C, 21.15; H, 1.06; N, 4.93. Found: C, 21.14; H, 0.95; N, 4.87.

4.1.5. 2-Bromo-5-(*exo*-bicyclo[2.2.1]hept-2-en-5-yl)pyridine (7). Norbornadiene (3.0 mL, 28 mmol), $(Ph_3P)_2$-$Pd(OAc)_2$ (266 mg, 0.35 mmol), piperidine (2.1 mL, 21 mmol) and HCO_2H (0.6 g, 0.5 mL, 14 mmol) were added to 2-bromo-5-iodopyridine **6** (2.0 g, 7.0 mmol) in DMF (5 mL) and the suspension was slowly heated to 55 °C and maintained at that temperature for 12 h. The solution was diluted with H_2O (100 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (200 mL), dried (Na_2SO_4), rotary evaporated and chromatographed (hexane/EtOAc 97:3) to afford **7** (1.84 g, 66%) as a clear oil; IR (film) 1573, 1555, 1451, 1384, 1331, 1316, 1285, 1251, 1200, 1133, 1088, 1020, 1003, 947, 904, 827, 776, 733, 714, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.44 (m, 2H), 6.23 (m, 2H), 3.02 (s, 1H), 2.89 (s, 1H), 2.67 (t, $J=6.7$ Hz, 1H), 1.68 (dd, $J=1.8$. 6.7 Hz, 2H), 1.48 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 140.8, 139.0, 137.6, 136.8, 127.5, 47.9, 45.6, 42.4, 40.9, 33.6; MS (EI) *m/z* 250 ($M^{\cdot+}$), 184, 104. Anal. calcd for $C_{12}H_{12}BrN$: C, 57.63; H, 4.83, N, 5.60. Found: C, 57.71, H, 4.71, N, 5.58.

4.1.6. 2-Bromo-5-(*exo*-bicyclo[2.2.1]hept-2-en-5-yl)-1-ethylpyridinium tetrafluoroborate (8). Et_3OBF_4 (874 mg, 4.60 mmol) in CH_2Cl_2 (3 mL) was added dropwise to pyridine **7** (1.1 g, 4.4 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 3 h at 25 °C, the solution was heated to reflux for 30 min. The salt was precipitated upon the addition of Et_2O (12 mL) at 0 °C, filtered and dried to afford salt **8** (1,36 g, 81%) as a white solid: mp 174–176 °C (Et_2O); IR (film) 1617, 1571, 1507, 1468, 1391, 1332, 1287, 1213, 1163, 1053, 903, 836, 797, 734, 713, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.22 (m, 2H), 6.22 (m, 2H), 4.87 (q, $J=7.2$ Hz, 2H), 3.04 (s, 2H), 2.89 (t, $J=6.7$ Hz, 1H), 1.77 (m, 2H), 1.64 (t, $J=7.2$ Hz, 3H), 1.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 147.1, 145.4, 138.1, 136.7, 133.7, 133.3, 59.4, 47.9, 45.6, 42.7, 41.5, 33.7, 15.5; MS (FAB$^+$) *m/z* 278 (M^+), 212, 89, 77; calcd for $C_{14}H_{17}BrN$: (M^+), 278.0554; found: (M^+), 278.0544. Anal. calcd for $C_{14}H_{17}BBrF_4N$: C, 45.94; H, 4.68; N, 3.83. Found: C, 45.87, H, 4.68; N, 3.78.

4.1.7. *N,N′,N′*-Trimethylfluoroformamidinium hexafluorophosphate functionalized ROMPgel (10). Catalyst **11** (2.7 mg, 3.17 μmol) in $ClCH_2CH_2Cl$ (0.25 mL) was added to monomer **4** (225.8 mg, 0.63 mmol) and cross-linker **9** (24.9 mg, 0.09 mmol) in $ClCH_2CH_2Cl$ (1 mL). The mixture was heated at 50 °C for 0.5 h and allowed to cool to 25 °C. After 16 h, CH_2Cl_2 (1 mL), CH_3CN (0.5 mL) and ethyl vinyl ether (0.5 mL) were added and the mixture heated to 50 °C for 1.5 h. After cooling, the mixture was cooled to 25 °C, filtered and the ROMPgel extracted with CH_2Cl_2 (3×20 mL), THF (2×20 mL) and Et_2O (3×20 mL) followed by concentration in vacuo to give ROMPgel **10** (252.4 mg, 100%) as a white solid; IR (solid) 1640, 1457, 1407, 1250, 1099, 834 cm^{-1}. Anal. calcd for $C_{13.04}H_{20.26}P_{0.87}F_{6.09}N_{1.74}$: C, 45.53; H, 5.94; N, 7.08. Found: C, 45.43; H, 5.80; N, 6.95.

4.1.8. Polystyrene-supported norbornene (13). *endo*/*exo*-Bicyclo[2.2.1]hept-5-en-2-ylmethanol (**12**) (2.5 g, 20 mmol) and KH (0.8 g, 20 mmol) were added to Merrifield resin (Polymer Labs, 75–150 μm, 0.9 mmol/g^{-1}; 10 g) in DMF (100 mL). The mixture was heated at 60 °C for 16 h, quenched with MeOH and filtered, washed with DMF (3× 30 mL), CH_2Cl_2 (3×30 mL) and MeOH (3×30 mL) and dried to afford resin beads **13** (10.6 g, 76%, 0.65 mmol/g^{-1}); IR (film) 1094, 1017, 857, 819 cm^{-1}. Anal. calcd: C, 89.96, H; 7.82. Found C, 89.99; H, 7.98.

4.1.9. ROMPsphere-supported fluoroformamidium hexafluorophosphate (14). Resin **13** (1.00 g) was suspended in CH_2Cl_2 (9 mL) and agitated for 15 min, the solvent was removed by decantation and catalyst **11** (255 mg, 3 mmol) in CH_2Cl_2 (1.5 mL) was added and agitation continued for 45 min. The resin was thoroughly washed with CH_2Cl_2 and 2-PrOH, suspended in CH_2Cl_2 (10 mL) and monomer **4** (3.00 g, 14 mmol) in CH_2Cl_2 (15 mL) was added. After agitating for 3 h, the resin was washed with CH_2Cl_2 and Et_2O (3×3 mL) and dried to yield the ROMPsphere supported reagent **14** (2.0 g, 1.45 mmol). Anal. calcd C, 62.36; H, 6.70, N, 3.93. Found C, 62.7; H, 6.86; N, 3.52.

4.1.10. ROMPsphere-supported 2-Bromo-1-ethylpyridinium tetrafluoroborate (15). The resin 13 (200 mg) was suspended in CH_2Cl_2 (6 mL) and agitated for 15 min, the solvent was removed by decantation and catalyst **11** (60 mg, 0.6 mmol) in CH_2Cl_2 (1.5 mL) was added and agitation continued. After 15 min, the resin was further diluted with CH_2Cl_2 (6 mL) and agitated for an additional 1 h, and thoroughly washed with CH_2Cl_2. Monomer **8** (600 mg, 1.6 mmol) in CH_2Cl_2 (3 mL) was added to the resin and agitation continued for 12 h. The resin was washed with CH_2Cl_2 and Et_2O (3×3 mL) and dried to yield the ROMPsphere reagent 15 (636 mg, 1.8 mmol/g^{-1}); IR (film) 1733, 1499, 1288, 1052, 864 cm^{-1}. Anal. calcd C, 57.95; H, 5.54; N, 2.75. Found C, 58.37; H, 5.93; N, 2.31.

4.2. General procedure for amide synthesis using ROMPgel reagent 10

i-Pr_2NEt (3 equiv) was added to acid 16 (0.07–0.11 mmol) and ROMPgel 10 (2 equiv) in CH_2Cl_2 (0.5 mL). After 0.5 h, piperidine (6.9–11.0 μL; 1 equiv) was added and the mixture shaken for 12 h. Amberlite MB1 ion exchange resin was added and the mixture shaken for a further 3.5 h. Filtration and rotary evaporation gave amide **17e**[56] (22.2 mg, 81% yield, 88% purity): mp 85.5–87.5.0 °C; lit[56] 86–87 °C.

4.2.1. 12-Isopropyl-2,6-dimethyltricyclo[8.4.0.0]tetradeca-1(14),10,12-trien-6-yl-piperidinomethanone (17a). (24.0 mg, 87% yield, 88% purity) as a clear yellow oil: R_f 0.60 (EtOAc/hexanes 1:1); IR ($CHCl_3$) 1625, 1457, 1409, 1247, 1120, 1012, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, $J=8.0$ Hz, 1H), 7.00 (d, $J=7.6$ Hz, 1H), 6.91 (s, 1H), 3.66–3.52 (m, 4H), 3.03–2.94 (m, 1H), 2.91–2.79 (m, 2H), 2.35–2.26 (m, 2H), 1.84–1.30 (m, 13H), 1.33 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 147.1, 145.5, 135.2, 127.0, 124.1, 123.6, 47.0, 46.7, 45.2, 44.7, 37.6, 37.5, 35.2, 33.4, 30.7, 26.2, 25.5, 24.7, 23.9, 22.1, 18.9, 15.7; MS (CI, NH_3) *m/z* 368

$(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{25}H_{38}NO$ $(M+H)^+$, 368.2953; found: $(M+H)^+$, 368.2952.

4.2.2. 1-[(1-Methylcyclohexyl)carbonyl]piperidine (17b). (14.9 mg, 98% yield, 97% purity) as a clear colorless oil: R_f 0.50 (EtOAc/hexanes 1:1); IR ($CHCl_3$) 1696, 1629, 1592, 1448, 1127, 1104, 1014 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (m, 4H), 2.04–2.01 (m, 2H), 1.64–1.16 (m, 14H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 46.4, 44.6, 37.1, 35.1, 26.3, 26.0, 25.6, 24.8, 24.2, 23.1, 22.9, 15.7; MS (CI, NH_3) *m/z* 210 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{13}H_{24}NO$ $(M+H)^+$210.1858; found: $(M+H)^+$, 210.1859.

4.2.3. 1-(3-Methyl-2-phenylbutanoyl)piperidine (17c). (12.5 mg, 73% yield, 88% purity) as a clear yellow oil; R_f 0.50 (EtOAc/hexanes 1:1); IR ($CHCl_3$) 1639, 1442, 1247, 1221, 1138, 1108, 1016, 772, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (m, 5H), 3.53–3.37 (m, 4H), 3.31 (d, $J=10.0$ Hz, 1H), 2.51–2.41 (m, 1H), 1.58–1.35 (m, 5H), 1.10–1.07 (m, 1H), 1.01 (d, $J=6.4$ Hz, 3H), 0.66 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 139.5, 128.5, 128.4, 126.7, 56.2, 46.8, 43.2, 31.9, 26.3, 25.5, 24.6, 22.3, 20.4; MS (CI, NH_3) *m/z* 263 $(M+NH_4)^+$246 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{16}H_{24}NO$ $(M+H)^+$246.1858; found: $(M+H)^+$, 246.1850.

4.2.4. 1-(3,3-Dimethyl-2-phenylbutanoyl)piperidine (17d). (17.5 mg, 95% yield, 90% purity) as a white solid: R_f 0.80 (EtOAc/hexanes, 1:1); mp 73.0–75.0 °C; IR ($CHCl_3$) 1620, 1456, 1437, 1264, 1136, 1016, 850, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.21 (m, 5H), 3.64–3.58 (m, 1H), 3.56 (s, 1H), 3.43–3.32 (m, 3H), 1.58–1.35 (m, 6H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 137.4, 130.2, 127.8, 126.6, 57.1, 47.3, 42.8, 34.8, 28.3, 26.1, 25.6, 24.6; MS (CI, NH_3) *m/z* 260 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{17}H_{26}NO$ $(M+H)^+$260.2014; found: $(M+H)^+$, 260.2014.

4.3. General procedure for dipeptide synthesis using ROMPsphere reagents 14 and 15

ROMPspheres **14** or **15** (0.4 mmol) and $^{iso}Pr_2NEt$ (104 μL, 0.6 mmol) were added to the *N*-protected α-aminoacid **18** (0.2 mmol) and the hydrochloric salt of the α-aminoester **19** (0.2 mmol) in CH_2Cl_2 (1 mL) and the mixture was shaken for 12 h at 25 °C. Amberlite MB11 (ion exchange resin, 0.5 g) was added and shaking continued for 1 h. The suspension was filtered and the remaining solid was subsequently washed with CH_2Cl_2 (2×2 mL) and MeOH (2×2 mL) and rotary evaporated to afford the desired peptide **20**: *N*-Cbz-Gly-L-Phe-OEt (**20a**)[57] (71 mg, 96%); Boc-Aib-Gly-OEt (**20b**)[58] (56 mg, 97%); Boc-Aib-Aib-OMe (**20d**)[59] (54 mg, 90%); *N*-Cbz-L-Leu-Gly-OEt (**20e**)[60] (15 mg, 89%); *N*-Cbz-Gly-L-Phe-L-Val-OMe (**20f**)[42] (89 mg, 95%).

4.3.1. Z-Gly-Aib-OMe (20c). (60 mg, 97%); IR (film) 3331, 1731, 1670, 1533, 1457, 1387, 1274, 1153, 1051, 978, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (br s, 5H), 6.71 (br s, 1H), 5.55 (br s, 1H), 5.11 (s, 2H), 3.84 (d, $J=5.2$ Hz, 2H), 3.71 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 168.2, 156.6, 136.1, 128.6, 128.2, 128.0, 67.3, 56.6, 52.7, 44.6, 24.7; HRMS (CI^+, NH_4) calcd for $C_{15}H_{21}N_2O_5$: $(M+H)^+$, 309.1458; found: $(M+H)^+$, 309.1451.

4.3.2. *N*-Fmoc-Aib-Gly-OEt (20g). (67 mg, 85%); IR (film) 3343, 1715, 1669, 1524, 1449, 1254, 1191, 1091, 909, 824, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br d, $J=7.2$ Hz, 2H), 7.62 (d, $J=7.2$ Hz, 2H), 7.41 (t, $J=7.2$ Hz, 2H), 7.32 (t, $J=7.2$ Hz, 2H), 6.10 (br s, 1H), 5.31 (br s, 1H), 4.23 (m, 3H), 4.13 (q, $J=7.1$ Hz, 2H), 3.89 (m, 2H), 1.54 (s, 6H), 1.29 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 170.2, 156.2, 143.7, 140.5, 128.1, 127.4, 123.2, 120.1, 66.9, 61.9, 56.8, 47.6, 42.9, 25.8, 25.5, 14.5; HRMS (CI^+, NH_4) calcd for $C_{23}H_{26}N_2O_5$: $(M^{\cdot+})$, 410.1842; found: $(M^{\cdot+})$, 410.1844.

4.3.3. *N*-Fmoc-Aib-L-Ala-OEt (20h). (65 mg, 80%); IR (film) 3343, 1731, 1655, 1522, 1449, 1254, 1153, 1090, 910, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br d, $J=7.2$ Hz, 2H), 7.62 (d, $J=7.2$ Hz, 2H), 7.41 (t, $J=7.2$ Hz, 2H), 7.32 (t, $J=7.2$ Hz, 2H), 6.72 (br s, 1H), 5.34 (br s, 1H), 4.55 (m, 1H), 4.43 (m, 2H), 4.23 (m, 3H), 1.55 (s, 6H), 1.41 (d, $J=6.57$ Hz, 3H), 1.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 173.3, 155.4, 144.3, 141.7, 128.1, 127.4, 125.4, 120.1, 66.9, 61.9, 57.2, 47.6, 42.9, 25.5, 18.7, 14.5; MS (CI^+, NH_4) 58 (32), 118 (86), 179 (78), 198 (89), 203 (40), 229 (15), 299 (14), 340 (340), 357 (94), 425 (6) HRMS (CI^+, NH_4) calcd for $C_{24}H_{28}N_2O_5$: $(M^{\cdot*******+})$, 424.1998; found: $(M^{\cdot+})$, 424.2001.

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