Resin-to-Resin Acyl- and Aminoacyl-Transfer Reactions Using Oxime Supports

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Abstract: We describe a convergent approach to solid-phase synthesis in which two fragments of a molecule are synthesized on independent supports and then condensed in a key resin-to-resin transfer reaction. This approach has been utilized for the synthesis of amides and ureas by transferring acyl groups and aminoacyl groups from *p*-nitrophenyl(polystyrene)ketoxime resin to amino acid-functionalized Wang resins. Oxime resin-derived esters of peptides undergo transacylation to a solution-phase nucleophilic activator which then transfers the peptide to another resin bearing a nucleophilic amine terminus, resulting in amide bond formation. Likewise, oxime resin-derived carbamates, prepared from phosgenated *p*-nitrophenyl(polystyrene)ketoxime resin, undergo thermolytic isocyanate liberation in solution, which reacts with a second resin bearing a nucleophilic amino terminus resulting in urea bond formation.

Introduction

Merrifield's method of solid-phase peptide synthesis has had a revolutionary impact on organic chemistry,[1] allowing the rapid and convenient synthesis of a variety of biopolymers such as peptides,[2] oligonucleotides,[3] and oligosaccharides[4] as well as organic compounds.[5] In this method, a compound is synthesized on a solid support, thereby facilitating the isolation of intermediates and allowing the use of excess reagents in solution. A limitation of this method, however, is that it is linear in nature; thus, the functionality and protecting groups introduced early in the synthesis must be fully stable to all subsequent reaction conditions. An alternate convergent approach might involve synthesizing two fragments of a given molecule on separate supports and then condensing the fragments together in a key *resin-to-resin transfer reaction* (RRTR). Such an approach would have a number of distinct advantages over existing linear methods. This method should allow one to use conditions in the synthesis of one fragment of a target molecule that might not be tolerated during the elaboration of another fragment. Furthermore, in some cases, this approach may allow the purification of intermediates as in the solid-phase synthesis of peptides via segment condensation.[6,7] Finally, RRTRs might have attractive possibilities for the synthesis of combinatorial libraries; it should be possible to synthesize and store two focused libraries on supports and then combine them in appropriate combinations.

In the 1970s, triphasic reactions[8] between two solid supports were examined as a method to probe the mechanisms of acyl transfer,[9] phosphate transfer,[10] and other reactions.[11−13] For

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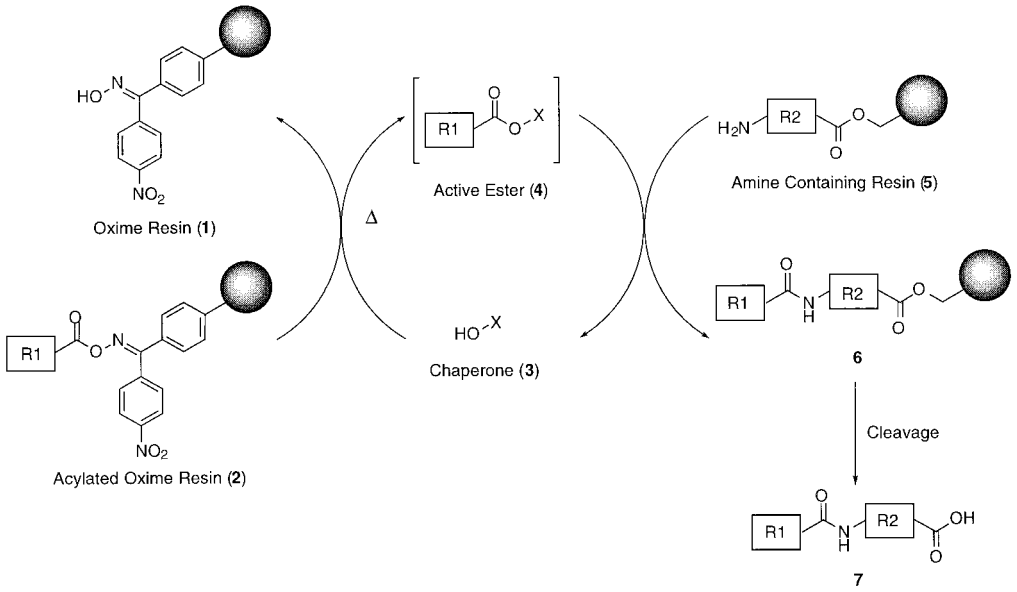
Scheme 1



instance, Rebek and Brown showed that the acyl group of a resin-bound active ester may be transferred to a second amine-containing polymer by addition of imidazole.[9b] Because of site isolation between the two supports, it could be inferred that the reaction occurred via nucleophilic catalysis, with imidazole acting as a catalyst to assist the transfer of the acyl group from the donor resin to the acceptor resin. In a similar manner it was possible to show that phosphate-transfer reactions may occur via a metaphosphate intermediate, which was sufficiently stable to diffuse between two supports.[10] Despite the elegance of these mechanistic investigations, to the best of our knowledge, RRTRs have not been fully utilized for synthetic purposes.[14−16]

In this paper, we explore the use of *p*-nitrophenyl(polystyrene)ketoxime polymer (**1**, Scheme 1)[6,17] for resin-to-resin acyl- and aminoacyl-transfer reactions. Oxime resin-derived esters **2** are designed to have a nucleophilic lability between that of benzyl ester resins such as Merrifield's[1] or Wang's[18] supports and other active ester polymers initially prepared by Patchornik and others.[19−25] These active esters contain acidic alcohol leaving groups and have been used to transfer acyl groups to amines in free solution. While one active ester resin has been employed for RRTR, in practice it was too reactive to allow many synthetic manipulations prior to the transfer reaction.[14] Thus while they are suitable for the mechanistic studies,[9,10] they may have less utility for construction of libraries. However, the oxime resin is stable enough to allow chemical transformations including the synthesis of peptides by standard solid-phase peptide methods[6,17] or the construction of β-carbolines by the Pictet−Spengler reaction.[26] Once fully elaborated, the desired compounds are removed under very mild condition by carboxylic acid-catalyzed nucleophilic attack. Indeed, oxime resin-derived peptide esters undergo transacylation by reaction with excess *N*-hydroxypiperidine, suggesting it may serve as a solution-phase nucleophilic activator[27] or *chaperone*.[14] However, the resulting esters are of insufficient reactivity to allow facile reaction with a variety of nucleophiles.[28] Here we examine a number of potential chaperones **3**, such as HOBt and HOSu for resin-to-resin acyl transfer reactions from oxime resin to nucleophilic amine-containing resins **5**. These derivatives are nucleophilic enough to liberate the acyl group from an oxime support to form active esters **4** in solution which then can react with amine containing resins **5** resulting in amide bond formation (Scheme 1).

In the second example of the use of the oxime resin in RRTRs, we describe the transfer of aminoacyl groups to a second amine-containing polymeric support via an isocyanate intermediate. In previous work, we described the use of phosgenated oxime resin, which reacts with amines to form oxime-derived carbamates **9**. Thermolysis of these carbamates **9** in the presence of amines in solution leads to the formation of ureas **11** via freely diffusible isocyanate intermediates (**10**; see Scheme 2).[29,30] However, secondary amine-derived carbamates of phosgenated oxime resin did not generate ureas,[31] supporting in situ formation of the isocyanate by the mechanism

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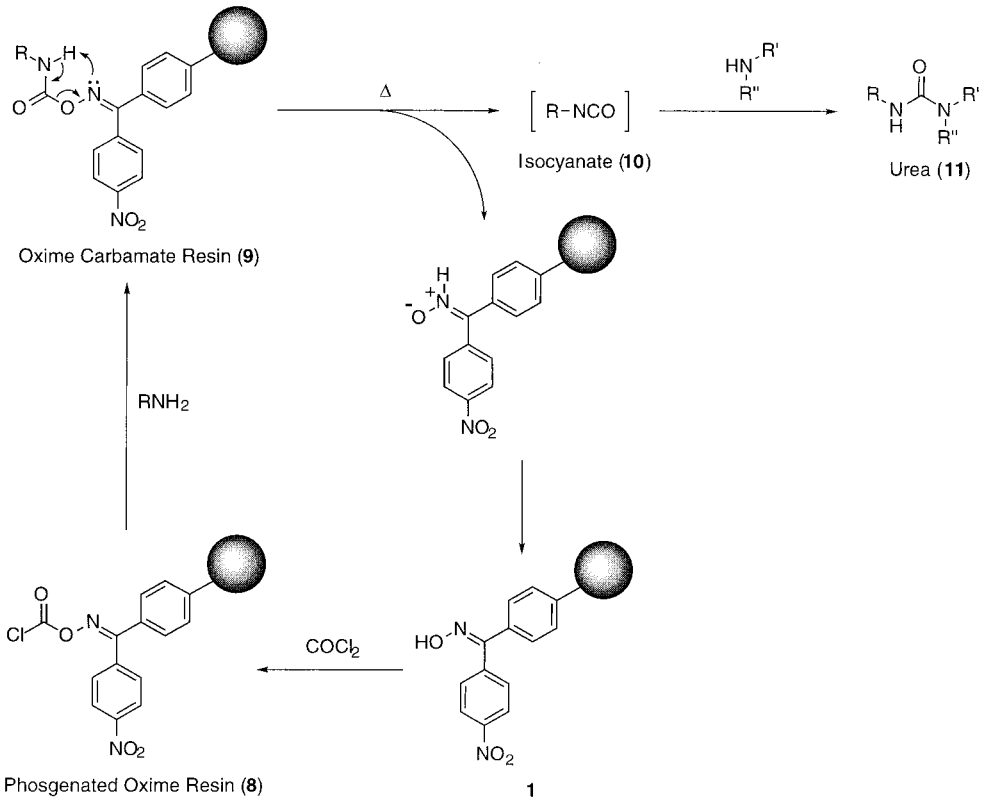
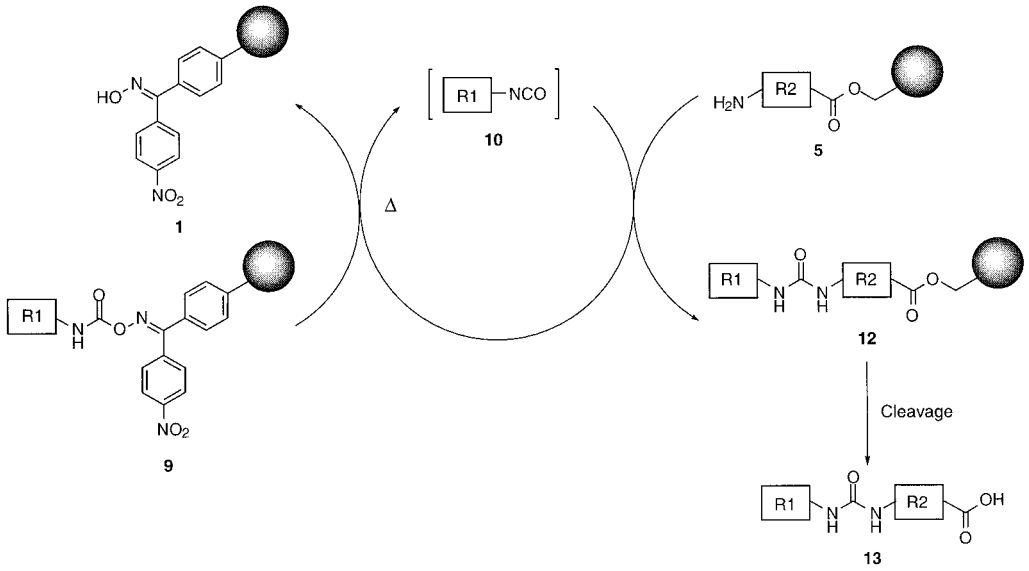
Scheme 2



Scheme 3



proposed by Levine and Frech.[32,33] Furthermore, TGA-MS and IR studies of carbamates derived from oxime resin also indicated thermolytic isocyanate generation.[34] These results led us to attempt the thermolysis of oxime carbamate resins **9** in the presence of polymer-supported amines (**5**; see Scheme 3).

Results and Discussion

Resin-to-Resin Acyl Transfer Reactions. (a) Evaluation of Chaperone Candidates for Resin-to-Resin Acyl Transfer. We initially examined a number of chaperone candidates for assisting the transfer of an acyl group from oxime resin to an amino group on Wang resin. A suspension of Z-Ala-oxime resin **2a**, H-Phe-Wang resin **5a** and a chaperone candidate **3** in CH_2Cl_2 was shaken overnight at room temperature. The resulting resin mixture (**1** and **6aa**) was treated with 50% TFA in CH_2Cl_2 for 1 h, and then the resin mixture was filtered and washed with CH_2Cl_2 (Scheme 4). The amount of Z-Ala-Phe-OH **7aa** in the combined filtrates was quantified using HPLC with nitrobenzene as an internal standard. Several chaperone candidates, thiophenol (PhSH), benzylthiol (BnSH), *N*,*N*-diethylhydroxyamine (Et_2NOH), *p*-nitrophenol (PnpOH), pentachlorophenol (PcpOH), pentafluorophenol (PfpOH), 1-hydroxy-7-azabenzotriazole (HOAt), hydroxybenzotriazole (HOBt), ethyl cyanoglycoxylate-2-oxime

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Scheme 4

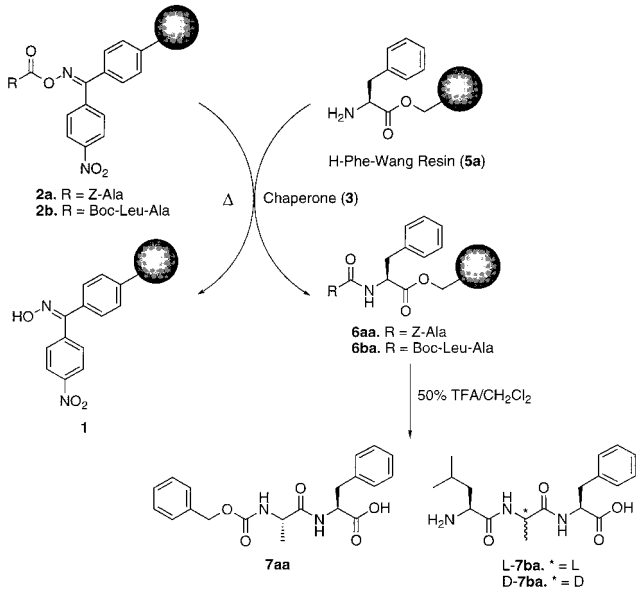

Table 1. Transfer of Z-Ala from Oxime Resin to H-Phe-Wang Resin with Various Chaperones[a]

chaperone	solvent	temp	yield,[b] %
(1) HOSu	CH_2Cl_2	rt	21
(2) HOBt	CH_2Cl_2	rt	21
(3) EACNOx	$CHCl_3$	rt	18
(4) PfpOH	CH_2Cl_2	rt	4.8
(5) HOAt[c]	$CHCl_3$	rt	3.0
(6) PnpOH	CH_2Cl_2	rt	2.1
(7) PcpOH	CH_2Cl_2	rt	2.1
(8) Et_{2NOH}	CH_2Cl_2	rt	1.7
(9) PhSH	CH_2Cl_2	rt	0
(10) BnSH	CH_2Cl_2	rt	0
(11) none	$ClCH_2CH_2Cl$	70 °C	0

[a] All resin-to-resin acyl-transfer reactions were carried out with 0.047 mmol of H-Phe-Wang resin, 1.6 equiv of Z-Ala-oxime resin and 6.4 equiv of chaperone in 5 mL of solvent. [b] The yield was obtained by HPLC with nitrobenzene as internal standard. [c] This chaperone was not completely soluble.

(EACNOx), and *N*-hydroxysuccinimide (HOSu), were tested (Table 1). HOSu, HOBt, and EACNOx provided yields of 27, 23, and 18%, respectively, while the other candidates gave rise to the dipeptide in less than 5% yield. Thus a further optimization was carried out using HOSu, HOBt, and EACNOx as chaperone candidates (Table 2).

(b) Optimization of Resin-to-Resin Acyl Transfer. Several additives (DBU,[35] DMAP, imidazole,[9b] AcOH) were tested with HOSu in CH_2Cl_2 at room temperature, and none of them were found to improve the yield (Table 2, entries 2−5). DMF was also evaluated as a solvent without success in the hope that increasing the polarity of the solvent might accelerate the reactions (entry 6). Also, increasing the molar excess of the chaperones beyond 6-fold failed to increase the yield, presumably because of their limited solubilities in the solvents required for these reactions (for example, compare entries 7 and 8 or entries 9 and 10). A larger equivalent of acylated oxime resin improved the yield slightly at 50 °C in chloroform (for example, compare entries 7 and 9 or entries 8 and 10). Most significantly, increasing the temperature greatly improved the yield (for example, compare entries 1 and 7 or entries 9 and 11).

The best yield obtained was 73% with 2.0 equiv of Z-Ala-oxime resin and 30 equiv of HOBt (saturated) in $CHCl_3$ at 50 °C for 16 h (entry 16). The major byproducts were a small amount of unreacted phenylalanine as well as dipeptide that was not cleaved from the Wang resin during the 1-h TFA cleavage step. The yields at 50 or 70 °C with HOSu or HOBt are over 60% and are practically useful (entries 9−12 and 14−18). IR spectra of the recovered resins showed peaks at 1780 (oxime ester) and 1727 cm^{-1}. This indicates that the excess Z-Ala remained on the oxime resin and that the acyl oxime group was not lost through side reactions.

(c) Epimerization during Resin-to-Resin Acyl Transfer. For the resin-to-resin acyl transfer to be a useful method for preparative purposes, the acyl transfer should proceed with very little epimerization. Epimerization should be suppressed in the case of urethane-protected amino acid transfer such as the aforementioned Z-Ala transfer; however, other acyl derivatives may present a problem. To clarify this issue, the transfer of Boc-Leu-Ala from oxime resin to H-Phe-Wang resin **5a** was carried out (Table 3). The authentic samples, H-Leu-Ala-Phe-OH (L-**7ba**) and H-Leu-D-Ala-Phe-OH (D-**7ba**) were prepared by standard Fmoc chemistry on Wang resin. These two diastereomers are fully resolved using a C_{18} column (acetonitrile 0−36% in water, linear gradient, 0.1% TFA buffered). Two equivalents of Boc-Leu-Ala-oxime resin **2b** and 6 equiv of a chaperone **3** and **5a** in 1,2-dichloroethane were stirred at 70 °C for 21 h, and the crude product was quantified by HPLC following removal from the Wang resin. When HOSu was used as a chaperone, only a single major peak was observed by HPLC and the L-**7ba** and D-**7ba** were obtained in 76 and 1.3% yield, respectively. The purity of the crude product was calculated as 88% by dividing the HPLC-quantified yield by the actual gravimetric yield. The reaction with HOBt also gave very little epimerization (1.8%), but a lower yield (59%), and the reaction with EACNOx gave a reasonable yield (67%), but epimerization was more than doubled (3.9%). Therefore, HOSu was chosen as the optimum chaperone for resin-to-resin acyl transfer reactions.

(d) Use of HOSu as the Chaperone under Optimized Conditions. The utility of acyl RRTR was exemplified through the synthesis of a series of tri- and tetrapeptides. Three different acylated oxime resins (Z-Ala-Oxime **2a**, Boc-Leu-Ala-Oxime **2b**, and Z-Leu-Ala-Oxime **2c**) and three different Wang resins (H-Phe-Wang **5a**, H-Ala-Phe-Wang **5b**, and H-Val-Phe-Wang **5c**) were reacted in different combinations at 70 °C with HOSu in 1,2-dichloroethane overnight. After TFA cleavage of the peptides from the Wang resin, the crude peptides were dissolved in $MeOH/CH_2Cl_2$ and then triturated with Et_2O/hexanes. The isolated products appeared pure by HPLC and NMR analysis and the yields were good to excellent (see Table 4 and Supporting Information).

The optimized acyl-transfer method was also applied to more practical targets, enkephalins.[36,37] Enkephalins are natural ligands for opiate receptors and known to consist of two subtypes, Leu-enkephalin (**7dd**, H-Tyr-Gly-Gly-Phe-Leu-OH) and Met-enkephalin (**7de**, H-Tyr-Gly-Gly-Phe-Met-OH). First, a tetrapeptide, Boc-Tyr(Bu^t)-Gly-Gly-Phe was grown on oxime resin using Boc-Phe-OH, Boc-Gly-Gly-OH and Boc-Tyr(Bu^t)-OH. Then, the oxime resin **2d** was split into two portions and the peptide was transferred onto H-Leu-Wang **5d** and H-Met-Wang **5e**. After TFA cleavage, **7dd** was obtained in reasonable purity

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Table 2. Optimization of Transfer of Z-Ala from Oxime Resin **2d** to H-Phe-Wang Resin **5a**[a]

	chaperone[b]		additive[b]					
oxime[b] equiv	equiv	type	equiv	type	solvent	temp, °C	time, h	yield,[c] %
(1) 1.6	6.4	HOSu		none	CH_2Cl_2	rt	26	27
(2) 1.6	6.4	HOSu	6.4	DBU	CH_2Cl_2	rt	23	26
(3) 1.6	6.4	HOSu	6.4	DMAP	CH_2Cl_2	rt	23	20
(4) 1.6	6.4	HOSu	6.4	Imidazole	CH_2Cl_2	rt	23	16
(5) 1.6	6.4	HOSu	9.9	AcOH	$CHCl_3$	rt	24	13
(6) 1.6	6.4	HOSu		none	DMF	50	24	10
(7) 1.6	6.4	HOSu		none	$CHCl_3$	50	24	58
(8) 1.5	30.0	HOSu[d]		none	$CHCl_3$	50	16	53
(9) 2.0	6.0	HOSu		none	$CHCl_3$	50	16	63
(10) 2.0	30.0	HOSu[d]		none	$CHCl_3$	50	16	65
(11) 2.0	6.0	HOSu		none	$ClCH_2CH_2Cl$	70	15	69
(12) 2.5	6.0	HOSu		none	$ClCH_2CH_2Cl$	70	15	69
(13) 1.6	6.4	HOBt		none	CH_2Cl_2	rt	26	21
(14) 1.5	30.0	HOBt[d]		none	$CHCl_3$	50	16	67
(15) 2.0	6.0	HOBt		none	$CHCl_3$	50	16	70
(16) 2.0	30.0	HOBt[d]		none	$CHCl_3$	50	16	73
(17) 2.0	6.0	HOBt		none	$ClCH_2CH_2Cl$	70	15	67
(18) 2.5	6.0	HOBt		none	$ClCH_2CH_2Cl$	70	15	67
(19) 1.6	6.4	EACNOx		none	$CHCl_3$	rt	16	18
(20) 1.6	6.4	EACNOx		none	$CHCl_3$	50	16	55
(21) 1.5	30.0	EACNOx		none	$CHCl_3$	50	16	55
(22) 2.0	6.0	EACNOx		none	$CHCl_3$	50	16	60
(23) 2.0	30.0	EACNOx		none	$CHCl_3$	50	16	59
(24) 2.0	6.0	EACNOx		none	$ClCH_2CH_2Cl$	70	15	55
(25) 2.5	6.0	EACNOx		none	$ClCH_2CH_2Cl$	70	15	54

[a] All resin-to-resin acyl-transfer reactions were carried out with 0.047 or 0.050 mmol of H-Phe-Wang resin in 5 mL of solvent. [b] All equivalents are relative to H-Phe-Wang resin. [c] The yield was obtained by HPLC with nitrobenzene as internal standard. [d] Chaperones were not completely soluble.

Table 3. Epimerization Associated with Resin-to-Resin Transfer of Boc-Leu-Ala **2b** to H-Phe-Wang **5a** by Three Chaperones[a]

chaperone	yield,[b] %	purity,[c] %	epimerization,[d] %
(1) HOSu	76	88	1.7
(2) HOBt	59	71	1.8
(3) EAcNOx	67	69	3.9

[a] Two equivalents of Boc-Leu-Ala-oxime resin **2b** and 6 equiv of chaperones were used for the reaction in $ClCH_2CH_2Cl$ at 70 °C for 21 h. [b] The yield was obtained by HPLC with phenol as an internal standard. [c] The purity was calculated by dividing the yields by gravimetric yields. [d] The degree of epimerization was calculated from the equation, epimerization = mol (L-**7ba**)/(mol (L-**7ba**) + mol (D-**7ba**)) after quantifying both isomers of L-**7ba** and D-**7ba** by HPLC with phenol as internal standard.

and good yield (see Table 4, entry 10). However, Met-enkephalin was obtained in very low purity with Met(S=O)-enkephalin and H-Tyr-Gly-Gly-Phe-OH as major impurities after TFA/thio-

anisole cleavage. The speculation was that methionine was oxidized during RRTR due to the high temperature. Further, thioanisole may catalyze the cleavage of excess peptide from the oxime resin during the TFA cleavage reaction (2 equiv of **2d** was used against **5e**). Thus, for the synthesis of **7de**, thioanisole was added to RRTR reaction to minimize the oxidation of methionine. Also, before TFA/thioanisole cleavage of the peptide from the resin, diethyamine acetate was reacted with the resin mixture to cleave excess peptide from the oxime resin. In this modified manner, **7de** was obtained in reasonable purity and yield (see Table 4, entry 11). The degree of epimerization in **7dd** and **7de** were found to be 4.0 and 3.9%, respectively, by integration of the areas in their HPLC chromatograms (see Table 4).[38]

(38) Part of the racemization might have occurred during the attachement of Boc-Phe onto oxime resin, as DMAP is known to cause racemization for the coupling between Boc-Phe anhydride and Wang resin. See: Atherton, E.; Benoiton, N. L.; Brown, E.; Sheppard, R. C.; Williams, B. J. *Chem. Commun.* **1981**, 336−337.

Resin-to-Resin Aminoacyl-Transfer Reactions. (a) Preparation of Oxime Carbamate Resins. Phosgenated oxime resin **8** can be reacted with either simple amines, amino acids, or diamines. The reaction conditions for the amine attachment depends on the solubilities of the amine. If the amine is soluble in dichloromethane, this is the preferred solvent. In cases where the amine is insoluble in dichloromethane, a solution of DMF/dichloromethane, DMF, or pyridine can be used with trimethylsilylating reagents (e.g., BSA,[39] TMS-Cl[40]) if necessary.

When the reaction is carried out with amino acids or diamines, the resulting resin-bound intermediates may be further elaborated by utilizing simple amide bond formation reactions for incorporation of additional functionalities[31] (Scheme 5). In this manner, many diverse functionalized oxime-derived carbamate resins **9** can be generated.

(b) Thermolytic Resin-to-Resin Aminoacyl-Transfer Reactions. The thermolytic resin-to-resin aminoacyl transfer was typically carried out using N-terminally deprotected peptide-Wang or amino acid-Wang resins **8** with 2 equiv of oxime carbamate resin **9** in toluene at 80 °C for 24−48 h (Scheme 3 and Table 5). Following the resin-to-resin aminoacyl transfer, the urea **13** was cleaved from the Wang resin by treatment with 50% TFA in CH_2Cl_2 for 1 h. When the aminoacyl group was transferred to amino acid-Wang resins, the TFA cleavage gave a mixture of hydantoic acid (**13**) and the corresponding hydantoin (**14**; Scheme 6). Therefore, following acid cleavage, the TFA solution was heated at 60 °C for 12 h to complete the cyclization (entries 1, 6, and 9−12). In general, aryl carbamates gave cleaner products in higher yield, presumably due to the better stabilities of aryl isocyanates compared with alkyl isocyanates.[32,33,41] In the case of dipeptidyl Wang resin, good

(39) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937−940.

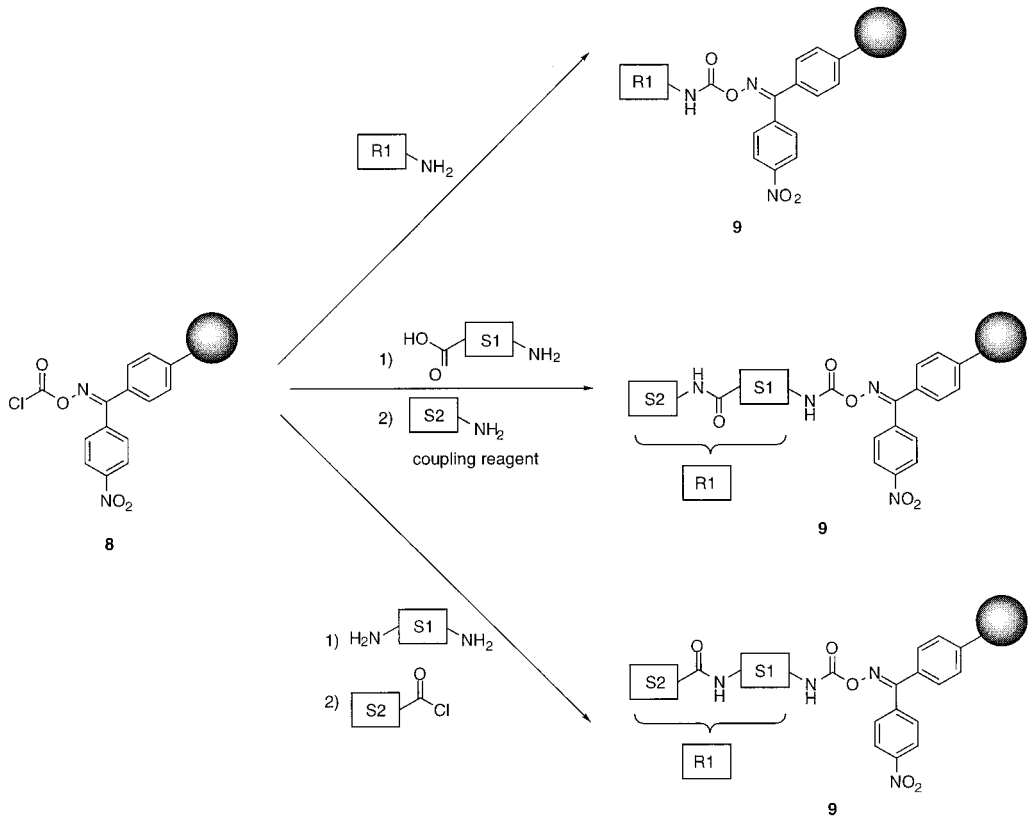
(40) Bolin, D. R.; Sytwu, I.-I.; Humiec, F.; Meinhofer, J. *Int. J. Pept. Protein Res.* **1989**, *33*, 353−359.

Table 4. Resin-to-Resin Acyl Transfer with HOSu as the Chaperone[a]

acyl group transferred	acceptor group on Wang resin	product	yield, %	purity (epimerization), %
(1) Z-Ala (**2a**)	H-Phe (**5a**)	Z-Ala-Phe-OH (**7aa**)	69[b]	77[c]
(2) Z-Ala (**2a**)	H-Ala-Phe (**5b**)	Z-Ala-Ala-Phe-OH (**7ab**)	90[d]	95[e]
(3) Z-Ala (**2a**)	H-Val-Phe (**5c**)	Z-Ala-Val-Phe-OH (**7ac**)	75[d]	87[e]
(4) Boc-Leu-Ala (**2b**)	H-Phe (**5a**)	H-Leu-Ala-Phe-OH (**7ba**)	76[b]	71[c] (1.7)[f]
(5) Boc-Leu-Ala (**2b**)	H-Ala-Phe (**5b**)	H-Leu-Ala-Ala-Phe-OH (**7bb**)	70[d]	96[e]
(6) Boc-Leu-Ala (**2b**)	H-Val-Phe (**5c**)	H-Leu-Ala-Val-Phe-OH (**7bc**)	80[d]	93[e]
(7) Z-Leu-Ala (**2c**)	H-Phe (**5a**)	Z-Leu-Ala-Phe-OH (**7ca**)	83[d]	93[e]
(8) Z-Leu-Ala (**2c**)	H-Ala-Phe (**5b**)	Z-Leu-Ala-Ala-Phe-OH (**7cb**)	67[d]	97[e]
(9) Z-Leu-Ala (**2c**)	H-Val-Phe (**5c**)	Z-Leu-Ala-Val-Phe-OH (**7cc**)	68[d]	91[e]
(10) Boc-Tyr(Bu^t)-Gly-Gly-Phe (**2d**)	H-Leu (**5d**)	Leu-Enkephalin (**7dd**)	87[b]	71[e] (4.0)[g]
(11) Boc-Tyr(Bu^t)-Gly-Gly-Phe (**2d**)	H-Met (**5e**)	Met-Enkephalin (**7de**)	53[b]	68[e] (3.9)[g]

[a] Two equivalents of acylated oxime resin and 6 equiv of HOSu were used for the resin-to-resin acyl-transfer reactions in $ClCH_2CH_2Cl$. [b] The yields were obtained by HPLC with phenol as internal standard. [c] The degree of purity of the crude product was estimated by HPLC, comparing the integrated intensity of the desired peak relative to the side products at 220 nm. [d] Isolated yields after triturating the crude product with MeOH/CH_2Cl_2/Et_2O/hexanes. [e] The purity was determined as in footnote *c* after triturating the crude product. [f] The degree of epimerization was calculated from the equation, epimerization = mol (D-**7ba**)/(mol (L-**7ba**) + mol (D-**7ba**)) after quantifying both isomers of L-**7ba** and D-**7ba** by HPLC with phenol as internal standard. [g] The degree of epimerization was calculated from the integrated intensities of the two epimers for enkephalins.

Scheme 5



yields and purities were obtained for the *p*-anisidine isocyanate transfer, although diketopiperazines were observed in the washings after the thermolytic aminoacyl-transfer reactions (entries 2 and 3). The aminoacyl-transfer reactions from oxime carbamate resin to H-Phe-2-chlorotrityl resin was also attempted (entries 13 and 14). Although small amounts of the desired products were observed in mass spectroscopic analysis, the reaction mixtures contained numerous impurities and were not optimized further.

Also, carbamates of Wang resin, derived from the commercially available *p*-nitrophenyl carbonate, have recently been employed for the preparation of hydantoins via thermolytic cyclitive cleavage of the carbamate amino acid amides with triethylamine in methanol.[39] To determine whether this reaction occurs via an isocyanate intermediate or via direct nucleophilic displacement of the Wang benzyloxy group, we attempted resin-to-resin aminoacyl transfer of these substrates under the same reaction conditions used for carbamates derived from phosgenated oxime resin (entries 15−18). Surprisingly, neither the carbamate of *p*-anisidine nor the carbamate of benzylamine showed any transfer to the acceptor resin, H-Phe-Wang. Both HPLC and mass spectroscopy showed phenylalanine as the major product, and no hydantoins or hydantoic acids were observed. This indicates that, unlike the carbamates derived from phosgenated oxime resin, carbamates derived from Wang resin do not undergo thermolytic isocyanate generation.

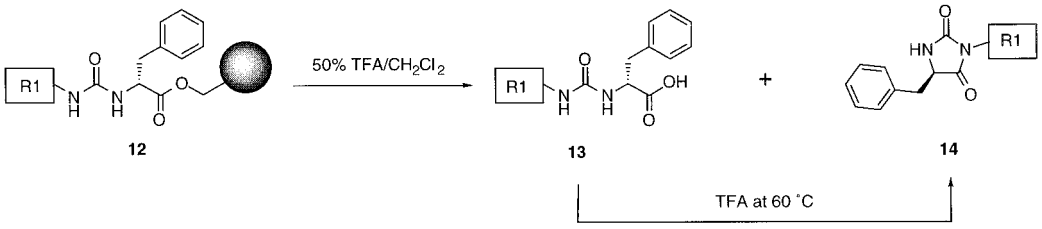
(41) Menger and co-worker studied the mechanism of aminolysis of *p*-nitrophenyl *N*-phenylcarbamate in toluene and found this compound reacts 10^4 times faster than the N-methylated compound and 200 faster than *N*-methylcarbamate; see: Menger, F. M.; Glass, L. E. *J. Org. Chem.* **1974**, *39*, 2469−2470.

Table 5. Resin-to-Resin Aminoacyl Transfer[a]

donor resin	first fragment	second fragment	acceptor resin	product	yield,[b] %	purity,[b] %
(1) **8**	*p*-anisidine		Phe-Wang (**5a**)	**14aa**	80[d]	93
(2) **8**	*p*-anisidine		Ala-Phe-Wang (**5b**)	**13ab**	68	89
(3) **8**	*p*-anisidine		Val-Phe-Wang (**5c**)	**13ac**	83	87
(4) **8**	*p*-anisidine		Val-Ala-Phe-Wang (**5f**)	**13af**	66	78
(5) **8**	*p*-anisidine		Leu-Ala-Phe-Wang (**5g**)	**13ag**	60	46
(6) **8**	benzylamine		Phe-Wang (**5a**)	**14ba**	46[d]	76
(7) **8**	benzylamine		Ala-Phe-Wang (**5b**)	**13bb**	37	61
(8) **8**	benzylamine		Val-Phe-Wang (**5c**)	**13bc**	33	80
(9) **8**	*p*-nitroaniline		Phe-Wang (**5a**)	**14ca**	79[d]	89
(10) **8**	2-aminopyridine		Phe-Wang (**5a**)	**14da**	77[d]	87
(11) **8**	*p*-Aba	*p*-anisidine	Phe-Wang (**5a**)	**14ea**	23	50
(12) **8**	*p*-Pda	*p*-Nbz-Cl	Phe-Wang (**5a**)	**14fa**	22[d]	49
(13) **8**	*p*-anisidine		Phe-ClTrt		0[e]	
(14) **8**	benzylamine		Phe-ClTrt		0[e]	
(15) WangCOPnp	*p*-anisidine		Phe-Wang (**5a**)		nr[f]	
(16) WangCOPnp	benzylamine		Phe-Wang (**5a**)		nr[f]	
(17) WangCOPnp[c]	*p*-anisidine		Phe-Wang (**5a**)		nr[f]	
(18) WangCOPnp[c]	benzylamine		Phe-Wang (**5a**)		nr[f]	

[a] *p*-Aba, *p*-aminobenzoic acid; *p*-Pda, *p*-phenylenediamine; *p*-Nbz-Cl, *p*-nitrobenzoyl chloride; ClTrt, 2-chlorotrityl resin; WangCOPnp, Wang *p*-nitrophenylcarbonate resin. [b] Purities are HPLC area percent of crude products at 220 nm. Yields are isolated yields after purification. [c] Amide transfer from *p*-nitrophenylcarbonate Wang resin with HOBt. [d] The isolated compounds were hydantoins, not hydantoic acids. [e] The desired products were observed in the crude products by MS, but HPLC spectra were too complicated to identify the product peaks and the compounds could not be isolated. [f] None of the desired products were observed.

Scheme 6



Conclusion

Although resin-to-resin transfer reactions were demonstrated as early as 1975, they have had very limited applications for preparative purposes. In this paper we demonstrate that, under optimized conditions, acyl- and aminoacyl-transfer reactions proceed in good yield and high chemical and stereochemical purity. This method should be broadly generalizable to a number of other transfer reactions and provides a convergent route for the solid-phase synthesis of libraries of small and large molecules.

Experimental Section

General Procedures. Oxime resin was prepared using Biobeads SX-1 (1% cross-linked polystyrene) from Biorad.[17] Leu-enkephalin and met-enkephalin were purchased from Sigma. Other protected amino acids and peptides were purchased from Bachem Bioscience Inc. and used without purification. HBTU was purchased from Advanced ChemTech, and amino acid-attached resins were purchased from Novabiochem. All other reagents were purchased from Aldrich. Thermolytic transfer reactions were carried out in 20-mL scintillation vials from Kimble Glass Inc. of Vineland, NJ. IR spectra of the functionalized resins were obtained with a Perkin-Elmer FT1600 infrared spectrometer using a KBr press. Low-resolution mass spectra were obtained with a VG Trio-2000 quadruple mass spectrometer using the atmospheric pressure chemical ionization (APCI) technique. High-resolution mass spectra were obtained with a VG-70-VSE high-resolution mass spectrometer. NMR experiments were carried out on Bruker DRX-500 and DRX-300 spectrometers. HPLC analyses were performed on a Hewlett-Packard 1090 liquid chromatography system using a photodiode array detector and a Vydac C_{18} column, 2.1 × 150 mm. HPLC area ratios in the text were determined by integrating the areas of the peaks at 220 nm.

General Procedure for Peptidyl-Oxime Resin 2.[42] **(a) First Amino Acid Attachment and Capping.** A mixture of oxime resin **1** (5.26 g, 0.76 mmol/g, 4.0 mmol), N-protected amino acid (8.0 mmol), DMAP (0.98 g, 8.0 mmol), and DIC (1.25 mL, 8.0 mmol) in CH_2Cl_2 (80 mL) was placed in a peptide synthesis apparatus, and the mixture was bubbled with N_2 at room temperature overnight. After the solution was drained, the resin was washed with DMF × 3, MeOH × 3, CH_2Cl_2 × 3, and DMF × 3. The unreacted oxime groups were capped by reaction with pivaloyl anhydride or acetic anhydride (20 mmol) and DIPEA (3.48 mL, 20 mmol) in DMF (30 mL) at room temperature for 2 h. After the solution was drained, the resin was washed with DMF × 3, MeOH × 3, and CH_2Cl_2 × 3.

(b) Second or after Amino Acid Attachment. The Boc group was deprotected with 25% TFA in CH_2Cl_2 (60 mL) for 40 min. After the solution was drained, the resin was washed with CH_2Cl_2 × 3, MeOH × 3, and DMF × 3. The resin was coupled to N-protected amino acid (8.0 mmol, only in the case of Boc-Tyr(Bu^t)-Gly-Gly-Phe-oxime resin **2d**, Boc-Gly-Gly-OH was used instead of Boc-Gly-OH twice) with HBTU (3.03 g, 8.0 mmol), HOBt·H_2O (1.22 g, 8.0 mmol), and DIPEA (4.18 mL, 24.0 mmol) in DMF (30 mL) for 2 h. After the solution was drained, the resin was washed with DMF × 3, MeOH × 3, and CH_2Cl_2 × 3 and then dried in vacuo.

General Procedure for Peptidyl Wang Resin 5.[43] Fmoc-Xxx-Wang resin (1.25 mmol) and 20% piperidine in DMF (20 mL) were placed in a benchtop peptide synthesis apparatus, and N_2 was bubbled at room temperature for 20 min. In the case of monoamino acid-attached Wang resin, after the solution was drained, the resin was washed with DMF × 3, MeOH × 3, and CH_2Cl_2 × 3 and dried in vacuo to obtain **5**. In the case of dipeptidyl Wang resin, the second amino acid attachment

(42) Jackson, S.; DeGrado, W.; Dwivedi, A.; Parthasarathy, A.; Higley, A.; Krywko, J.; Rockwell, A.; Markwalder, J.; Wells, G.; Wexler, R.; Mousa, S.; Harlow, R. *J. Am. Chem. Soc.* **1994**, *116*, 3220−3230.

(43) *Novabiochem Catalog & Peptide Synthesis Handbook*; 1997; pp S58−S59.

is as follows. The solution was drained and the resin was washed with DMF × 3, i-PrOH × 3, and DMF × 3. A solution of Fmoc-Xxx-OH (2.5 mmol, 2.0 equiv), HBTU (948 mg, 2.5 mmol, 2.0 equiv), and HOBt·H_2O (383 mg, 2.5 mmol, 2.0 equiv) in DMF (10 mL) was added to the resin. DIPEA (0.87 mL, 5.0 mmol, 4.0 equiv) was added to the mixture, which was then bubbled with N_2 at room temperature for 1 h. The solution was drained and washed with DMF × 3, 20% piperidine in DMF (20 mL) was added to the resin, and N_2 was bubbled at room temperature for 20 min. After the solution was drained, the resin was washed with DMF × 3, MeOH × 3, and CH_2Cl_2 × 3 and dried in vacuo to obtain **5**.

General Procedure for the Optimization of Resin-to-Resin Acyl Transfer. A suspension of Z-Ala-oxime resin **2a**, H-Phe-Wang resin **5a** (0.05 mmol), a chaperone candidate, and an additive in 5 mL of solvent was prepared in a vial, which was then shaken overnight at the designated temperature. The resin mixture was collected and washed with the reaction solvent × 3, MeOH × 3, and CH_2Cl_2 × 3. The collected resin mixture was treated with 50% TFA in CH_2Cl_2 for 1 h, and then the resin mixture was filtered and washed with CH_2Cl_2 × 3. The filtrates were combined and evaporated. The amount of Z-Ala-Phe-OH generated was quantified by HPLC with nitrobenzene as an internal standard.

General Procedure for the Epimerization Test of Resin-to-Resin Acyl Transfer. A suspension of Boc-Leu-Ala-oxime resin **2b** (302 mg, 0.66 mmol/g, 0.20 mmol), H-Phe-Wang resin **5a** (172 mg, 0.58 mmol/g, 0.10 mmol), and a chaperone candidate (0.60 mmol) in $ClCH_2CH_2Cl$ (10 mL) was prepared in a vial, which was then shaken at 70 °C for 21 h. The resin mixture was collected and washed with CH_2Cl_2 × 3, DMF × 3, MeOH × 3, and CH_2Cl_2 × 3. The collected resin mixture was treated with 50% TFA in CH_2Cl_2 (6 mL) for 70 min, and then the resin mixture was filtered off and washed with CH_2Cl_2 × 3. The filtrates were combined and evaporated. The amounts of L-**7ba** and D-**7ba** generated were quantified by HPLC with phenol as an internal standard.

General Procedure for Thermolytic Resin-to-Resin Acyl-Transfer Reaction from Oxime Resin to Wang Resin and Cleavage of Peptide 7. A suspension of acylated oxime resin (**2**, 0.50 mmol), peptidyl Wang resin (**5**, 0.25 mmol), and HOSu (173 mg, 1.50 mmol) in $ClCH_2CH_2Cl$ (15 mL) was prepared in a 20-mL vial, which was then shaken overnight at 70 °C. The resins were collected on a glass filter and washed with CH_2Cl_2 × 3, DMF × 3, MeOH × 3, and CH_2Cl_2 × 3. To the resin mixture was added 50% TFA in CH_2Cl_2 (15 mL), and the mixture was shaken at room temperature for 75 min. The resin was filtered and washed with CH_2Cl_2 × 3. The filtrate and washings were combined and evaporated in vacuo to give the crude cleavage product. The crude product was dissolved in MeOH/CH_2Cl_2 and filtered through a pipet with cotton. The solution was triturated with Et_2O and hexanes to obtain the product.

Procedure for Thermolytic Resin-to-Resin Acyl-Transfer Reaction from Oxime Resin to Wang Resin and Cleavage of Methionine-Containing Peptide. A suspension of acylated oxime resin (**2**, 0.40 mmol), peptidyl Wang resin (**5**, 0.20 mmol), HOSu (138 mg, 1.2 mmol), and thioanisole (0.47 mL, 4.0 mmol) in $ClCH_2CH_2Cl$ (15 mL) was prepared in a 20-mL vial, which was then shaken overnight at 70 °C. The resins were collected on a glass filter and washed with CH_2Cl_2 × 3, DMF × 3, MeOH × 3, and CH_2Cl_2 × 3. To the resin mixture was added diethylamine (103 μL, 1.0 mmol) and AcOH (57 μL, 1.0 mmol) in CH_2Cl_2 (15 mL), and the resultant mixture was stirred at room temperature overnight to cleave excess peptide from the oxime resin. To the resin mixture above was added 5% thioanisole in 50% TFA/50% CH_2Cl_2 (15 mL), and the mixture was shaken at room temperature for 90 min. The resin was filtered and washed with CH_2Cl_2 × 3 and MeOH × 3. The filtrate and washings were combined and evaporated in vacuo to give the crude cleavage product. The crude product was dissolved in MeOH/CH_2Cl_2 and filtered through a pipet with cotton. The solution was triturated with Et_2O and hexanes to obtain the product.

Preparation of Phosgenated *p*-Nitrophenyl(polystyrene)ketoxime (8, Phoxime Resin). The phosgenated oxime resin was prepared from oxime resin **1** by the procedure in ref 30. The loading of the resin was calculated as 0.711 mmol/g by the method described in the same reference: IR 3025, 2922, 1944, 1871, 1800, 1601, 1525, 1492, 1451, 1347 cm^{-1}. Anal. found Cl, 2.52%.

General Procedure for the Attachment of Amines to Phosgenated Oxime Resin 9. To a solution of amine (15 mmol) in CH_2Cl_2 (75 mL) was added phosgenated oxime resin (**8**, 0.711 mmol/g, 7.03 mg, 5.0 mmol), and the reaction mixture was stirred at room temperature for 2 h. The resin was collected on a glass filter, washed with CH_2Cl_2 × 2, DMF × 3, MeOH × 4, and CH_2Cl_2 × 4, and dried in vacuo. The reaction condition for the amine attachment depends on the solubility of the amine. If the amine is soluble in CH_2Cl_2, this is the preferred solvent. In case the amine is not soluble in CH_2Cl_2, DMF/CH_2Cl_2, DMF, or pyridine can be used with a trimethylsilylating reagent (e.g., BSA,[39] TMS−Cl[40]) if necessary.

General Procedure for Thermolytic Aminoacyl-Transfer Reaction 12. A mixture of the peptidyl Wang resin (**5**, 0.20 mmol) and oxime carbamate resin (**9**, 0.40 mmol) in toluene (16 mL) was shaken at 80 °C for 44 h. The resin mixture was collected on a glass filter, washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3, and dried in vacuo.

General Procedure for the Cleavage of Ureas from Wang Resin 13. To the above resin mixture **12** was added CH_2Cl_2 (5 mL) and TFA (5 mL), and the mixture was shaken at room temperature for 1 h. The resin was removed by filtration and washed with 25% TFA in CH_2Cl_2 × 2 and CH_2Cl_2 × 2. The filtrates were combined and evaporated in vacuo to give the crude cleavage product.

General Procedure for Hydantoin (14) Formation. The above-mentioned cleavage procedure gives a mixture of hydantoin (**14**) and hydantoic acid (**13**) when an amino acid Wang resin was used. To complete the cyclization reaction, 2 mL of TFA was added to the crude product and the mixture was shaken at 60 °C for 12 h. The TFA was evaporated in vacuo to give the crude hydantoin product.

3-[(4-Methoxy)phenyl]-5-[(*S*)-phenylmethyl]hydantoin (14aa). The HPLC purity of the crude product was 93%. The crude product was purified by column chromatography (SiO_2, 1/20 = MeOH/CH_2Cl_2) to obtain the titled compound as a pale yellow solid (47 mg, 80%): mp 121−122 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (s, 1H, Phe-N*H*), 7.4−7.2 (m, 5H, aromatics), 6.94 (d, J = 8.9 Hz, 2H, anisidine), 6.86 (d, J = 8.9 Hz, 2H, anisidine), 4.53 (t, J = 4.5 Hz, 1H, NHC*H*), 3.76 (s, 3H, CH_3O), 3.07 (m, 2H, PhCH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.7, 156.7, 136.1, 130.9, 129.1, 128.9, 127.9, 125.6, 115.0, 58.0, 56.4, 37.7; HRMS *m/e* calcd for $C_{17}H_{16}N_2O_3$ (M^+) 296.1161, found 296.1139.

***N*-((4-Methoxy)phenylaminocarbonyl)alanylphenylalanine (13ab).** The HPLC purity of the crude product was 89%. The crude product was purified by column chromatography (SiO_2, 1/6/60 = AcOH/MeOH/CH_2Cl_2) to obtain the titled compound as a pale yellow solid (52 mg, 68%): mp 194−197 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 (s, 1H, Ph-N*H*), 8.05 (d, J = 7.7 Hz, 1H, Phe-N*H*), 7.2−7.0 (m, 7H, aromatics), 6.73 (d, J = 8.9 Hz, 2H, anisidine), 6.22 (d, J = 7.7 Hz, 1H, Ala-N*H*), 4.31 (m, 1H, NHC*H*), 4.15 (m, 1H, NHC*H*), 3.61 (s, 3H, CH_3O), 3.02 (dd, J = 13.8, 4.9 Hz, 1H, Ph CH*H*), 2.84 (dd, J = 13.8, 8.8 Hz, 1H, Ph C*H*H), 1.11 (d, J = 6.9 Hz, 3H, Ala-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.0, 172.5, 154.5, 153.9, 137.8, 133.4, 129.1, 128.0, 126.2, 119.2, 113.8, 55.1, 53.7, 40.0, 36.7, 19.5; HRMS *m/e* calcd for $C_{20}H_{23}N_3O_5$ (M^+) 385.1638, found 385.1649.

***N*-((4-Methoxy)phenylaminocarbonyl)valylphenylalanine (13ac).** The HPLC purity of the crude product was 87%. The crude product was purified by column chromatography (SiO_2, 1/6/60 = AcOH/MeOH/CH_2Cl_2) to obtain the titled compound as a yellow solid (68 mg, 83%): mp 189−191 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 1H, Ph-N*H*), 8.22 (d, J = 7.7 Hz, 1H, Phe-N*H*), 7.3−7.1 (m, 7H, aromatics), 6.80 (d, J = 9.0 Hz, 2H, anisidine), 6.17 (d, J = 9.0 Hz, 1H, Val-N*H*), 4.42 (m, 1H, NHC*H*), 4.14 (m, 1H, NHC*H*), 3.69 (s, 3H, CH_3O), 3.07 (dd, J = 13.9, 5.1 Hz, 1H, Ph CH*H*), 2.91 (dd, J = 13.9, 9.0 Hz, 1H, Ph C*H*H), 1.97 (m, 1H, C*H*(CH_3)$_2$), 0.86 (d, J = 6.8 Hz, 3H, Val-CH_3), 0.78 (d, J = 6.8 Hz, 3H, Val-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 171.5, 155.0, 153.8, 137.7, 133.5, 129.0, 128.0, 126.2, 119.0, 113.8, 57.0, 55.0, 53.5, 36.6, 31.1, 19.1, 17.3; HRMS *m/e* calcd for $C_{22}H_{27}N_3O_5$ (M^+) 413.1951, found 413.1962.

***N*-((4-Methoxy)phenylaminocarbonyl)valylalanylphenylalanine (13af).** The HPLC purity of the crude product was 78%. The crude product was purified by repeated trituration with Et_2O to obtain the titled compound as an ivory solid (63 mg, 66%): mp 222−225 °C; ^{1}H

NMR (500 MHz, DMSO-d_6) δ 8.47 (s, 1H, Ph-N*H*), 8.08 (d, J = 7.6 Hz, 1H, Phe-N*H*), 7.97 (d, J = 7.8 Hz, 1H, Ala-N*H*), 7.3−7.1 (m, 7H, aromatics), 6.79 (d, J = 12.5 Hz, 2H, anisidine), 6.18 (d, J = 8.9 Hz, 1H, Val-N*H*), 4.41 (m, 1H, Phe-NHC*H*), 4.31 (quintet, J = 7.2 Hz, 1H, Ala-NHC*H*), 4.12 (dd, J = 5.3, 8.8 Hz, 1H, Val-NHC*H*), 3.67 (s, 3H, CH_3O), 3.03 (dd, J = 14.0, 5.4 Hz, 1H, Ph CH*H*), 2.90 (dd, J = 13.9, 8.3 Hz, 1H, Ph C*H*H), 1.93 (m, 1H, C*H*(CH$_3$)$_2$), 1.18 (d, J = 7.1 Hz, 3H, Ala-CH_3), 0.84 (d, J = 6.9 Hz, 3H, Val-CH_3), 0.76 (d, J = 6.8 Hz, 3H, Val-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6, 172.0, 171.3, 155.2, 153.9, 137.4, 133.6, 129.1, 128.1, 126.4, 119.1, 114.0, 57.2, 55.2, 53.3, 47.9, 36.7, 31.2, 19.3, 18.2, 17.5; HRMS *m*/*e* calcd for $C_{25}H_{33}N_4O_6$ (M + H$^+$) 485.2400, found 485.2394.

***N*-((4-Methoxy)phenylaminocarbonyl)leucylalanylphenylalanine (13ag).** The HPLC purity of the crude product was 46%. The crude product was purified by repeated trituration with Et$_2$O to obtain the titled compound as an ivory solid (60 mg, 60%): mp 217−220 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (s, 1H, Ph-N*H*), 8.11 (d, J = 7.6 Hz, 1H, Phe-N*H*), 7.93 (d, J = 7.7 Hz, 1H, Ala-N*H*), 7.3−7.1 (m, 7H, aromatics), 6.79 (d, J = 9.0 Hz, 2H, anisidine), 6.20 (d, J = 8.4 Hz, 1H, Leu-N*H*), 4.39 (m, 1H, Phe-NHC*H*), 4.3−4.2 (m, 2H, Ala-NHC*H* + Val-NHC*H*), 3.68 (s, 3H, CH_3O), 3.04 (dd, J = 13.9, 5.2 Hz, 1H, Ph CH*H*), 2.89 (m, 1H, Ph C*H*H), 1.62 (m, 1H, C*H*(CH$_3$)$_2$), 1.5−1.3 (m, 2H, CH_2CH(CH$_3$)$_2$), 1.19 (d, J = 7.1 Hz, 3H, Ala-CH_3), 0.87 (d, J = 6.0 Hz, 6H, Leu-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.0, 172.8, 172.3, 155.3, 154.3, 137.7, 133.8, 129.5, 128.4, 126.7, 119.5, 114.2, 55.5, 53.8, 51.4, 48.2, 37.0, 24.5, 23.5, 22.1, 18.4; HRMS *m*/*e* calcd for $C_{26}H_{35}N_4O_6$ (M + H$^+$) 499.2557, found 499.2585.

3-(Phenylmethyl)-5-[(*S*)-phenylmethyl]hydantoin (14ba). The HPLC purity of the crude product was 76%. The crude product was purified by column chromatography (SiO$_2$, 1/20 = MeOH/CH$_2$Cl$_2$) to obtain the titled compound as an ivory solid (26 mg, 46%): mp 131−133 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (s, 1H, Phe-N*H*), 7.2−7.1 (m, 10H, aromatics), 6.69 (m, 2H, aromatics),4.38 (t, J = 4.3 Hz, 1H, Phe-NHC*H*), 4.31 (d, J = 16.2 Hz, 1H, PhCH*H*N), 4.21 (d, J = 15.6 Hz, 1H, PhC*H*HN), 2.90 (d, J = 4.7 Hz, 1H, Ph CH_2CH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.9, 156.9, 137.0, 135.7, 130.6, 129.0, 128.8, 127.6, 127.5, 127.3, 57.9, 41.4, 36.8; HRMS *m*/*e* calcd for $C_{17}H_{16}N_2O_2$ (M$^+$) 280.1212, found 280.1211.

***N*-(Phenylmethylaminocarbonyl)alanylphenylalanine (13bb).** The HPLC purity of the crude product was 61%. The crude product was purified by column chromatography (SiO$_2$, 1/6/60 = AcOH/MeOH/CH$_2$Cl$_2$) to obtain the titled compound as an ivory solid (28 mg, 37%): mp 195−197 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, J = 7.5 Hz, 1H, Phe-N*H*), 7.3−7.0 (m, 10H, aromatics), 6.46 (t, J = 6.0 Hz, 1H, BnNH$_2$), 6.10 (d, J = 7.8 Hz, 1H, Ala-N*H*), 4.27 (m, 1H, NHC*H*), 4.10 (m, 3H, PhCH_2NH + NHC*H*), 3.01 (dd, J = 13.7, 5.1 Hz, 1H, Ph CH*H*), 2.84 (dd, J = 13.7, 8.1 Hz, 1H, Ph C*H*H), 1.07 (d, J = 7.0 Hz, 3H, Ala-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.0, 172.7, 157.2, 140.6, 137.9, 129.2, 128.2, 128.0, 126.9, 126.5, 126.2, 53.8, 48.6, 42.8, 36.8, 19.5; HRMS *m*/*e* calcd for $C_{20}H_{23}N_3O_4$ (M$^+$) 369.1689, found 369.1704.

***N*-(Phenylmethylaminocarbonyl)valylphenylalanine (13bc).** The HPLC purity of the crude product was 80%. The crude product was purified by column chromatography (SiO$_2$, 1/5/100 = AcOH/MeOH/CH$_2$Cl$_2$) to obtain the titled compound as an ivory solid (26 mg, 33%): mp 190−192 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (d, J = 7.1 Hz, 1H, Phe-N*H*), 7.4−7.1 (m, 10H, aromatics), 6.55 (t, J = 6.0 Hz, 1H, BnNH$_2$), 6.06 (d, J = 9.2 Hz, 1H, Ala-N*H*), 4.35 (m, 1H, NHC*H*), 4.20 (m, 2H, PhCH_2NH), 4.08 (m, 1H, NHC*H*), 3.06 (dd, J = 13.8, 5.3 Hz, 1H, Ph CH*H*), 2.84 (dd, J = 13.8, 8.3 Hz, 1H, Ph C*H*H), 1.94 (m, 1H, C*H*(CH$_3$)$_2$), 0.83 (d, J = 6.8 Hz, 3H, Val-CH_3), 0.75 (d, J = 6.8 Hz, 3H, Val-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.0, 171.7, 157.8, 140.7, 138.0, 129.2, 128.2, 128.0, 126.9, 126.5, 126.2, 57.6, 53.8, 48.6, 42.8, 36.8, 31.1, 19.3, 17.4; HRMS *m*/*e* calcd for $C_{22}H_{27}N_3O_4$ (M$^+$) 397.2002, found 397.1995.

3-(4-Nitrophenyl)-5-[(*S*)-phenylmethyl]hydantoin (14ca). The HPLC purity of the crude product was 89%. The crude product was purified by column chromatography (SiO$_2$, 1/20 = MeOH/CH$_2$Cl$_2$) to obtain the titled compound as an yellow solid (48 mg, 79%): mp 188−189 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (br, 1H, N*H*), 8.30 (d, J = 8.8 Hz, 2H, NO$_2$Ph-3H and 5H), 7.46 (d, J = 8.8 Hz, 2H, NO$_2$Ph-2H and 6H), 7.4−7.2 (m, 5H, Ph), 4.62 (m, 1H, NHC*H*), 3.11 (m, 2H, PhCH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.9, 154.2, 145.7, 137.5, 134.8, 129.5, 128.0, 126.8, 126.2, 123.9, 57.0, 36.5; HRMS *m*/*e* calcd for $C_{16}H_{13}N_3O_4$ (M$^+$) 311.0906, found 311.0905.

***N*-(2-Pyridylaminocarbonyl)phenylalanine (14da).** The HPLC purity of the crude product was 87%. The crude product was purified by column chromatography (SiO$_2$, 1/5/100 = AcOH/MeOH/CH$_2$Cl$_2$) to obtain the titled compound as a pale yellow oil (42 mg, 77%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.87 (br, 1H, COOH), 9.33 (br, 1H, N*H*-Py), 8.59 (br, 1H, N*H*-Ala), 8.11 (dd, J = 4.9, 1.2 Hz, 1H, Py-5H), 7.66 (td, J = 7.8, 1.9 Hz, Py-4H), 7.4−7.2 (m, 6H, Py-3H and Ph), 6.91 (td, J = 5.0, 0.7 Hz, 1H, Py-5H), 4.46 (m, 1H, NHC*H*), 3.13 (dd, 1H, J = 13.7, 5.0 Hz, PhC*H*H), 2.99 (dd, 1H, J = 13.6, 7.4 Hz, PhCH*H*); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.1, 154.2, 153.1, 146.3, 138.0, 137.0, 129.2, 128.0, 126.4, 116.7, 111.4. 53.8, 37.2; HRMS *m*/*e* calcd for $C_{15}H_{13}N_3O_2$ (M$^+$) 267.1008, found 267.1013.

3-(4-(4-Methoxy)phenylcarbamoyl)phenyl-5-[(*S*)-phenylmethyl]-hydantoin (14ea). The HPLC purity of the crude product was 50%. The crude product was purified by column chromatography (SiO$_2$, 1/50 = MeOH/CH$_2$Cl$_2$) to obtain the titled compound as a pale yellow solid (18 mg, 23%): mp 221−223 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.13 (s, 1H, anisidine-N*H*), 8.60 (s, 1H, Phe-N*H*), 7.94 (d, 9.7 Hz, 2H, p-Aba), 7.66 (d, 9.2 Hz, 2H, p-Aba), 7.4−7.2 (m, 5H, Phe), 7.17 (d, J = 8.6 Hz, 2H, anisidine), 6.92 (d, J = 9.1 Hz, 2H, anisidine), 4.58 (td, J = 4.9, 1.0 Hz, 1H, NHC*H*), 3.75 (s, 3H, CH_3O), 3.09 (m, 2H, Ph CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.3, 164.4, 155.6, 154.9, 135.0, 134.4, 134.1, 132.1, 129.8, 128.1, 127.9, 126.9, 125.8, 121.9, 113.7, 57.1, 55.1, 36.6; HRMS *m*/*e* calcd for $C_{24}H_{22}N_3O_4$ (M + H$^+$) 416.1611, found 416.1598.

3-[4-(4-Nitrophenyl)carbonylamino)phenyl]-5-[(*S*)-phenylmethyl]-hydantoin (14fa). The HPLC purity of the crude product was 49%. The crude product was purified by column chromatography (SiO$_2$, 1/50 = MeOH/CH$_2$Cl$_2$) to obtain the titled compound as a pale yellow solid (18 mg, 22%): mp 253−256 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.65 (s, 1H, p-Pda-N*H*), 8.50 (s, 1H, Phe-N*H*), 8.37 (d, 8.8 Hz, 2H, p-Nba), 8.19 (d, 8.8 Hz, 2H, p-Nba), 7.77 (d, 8.8 Hz, 2H, p-Pda), 7.4−7.2 (m, 5H, Phe), 6.99 (d, J = 8.8 Hz, 2H, p-Pda), 4.55 (t, J = 4.6 Hz, 1H, NHC*H*), 3.07 (m, 2H, Ph CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.7, 164.1, 155.5, 149.4, 140.5, 138.2, 135.2, 129.9, 129.4, 128.2, 127.8, 127.6, 126.9, 123.7, 120.7, 57.2, 36.8; HRMS *m*/*e* calcd for $C_{23}H_{19}N_4O_5$ (M + H$^+$) 431.1356, found 431.1377.

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Supporting Information Available: Preparation and characterization of resins (**2a**−**2d** and **5a**−**5e**) and peptides **7aa**−**7de** as well as HPLC chromatograms of peptides **7aa**−**7de** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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