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Iodine-Mediated Oxidative Coupling of Hydroxamic Acids with Amines towards a New Peptide-Bond Formation

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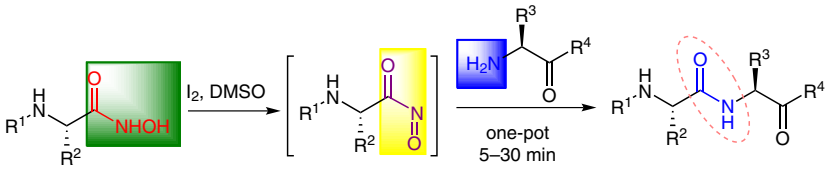

R^1 = protecting group
R^2, R^3 = amino acid side chain
R^4 = amino acid ester

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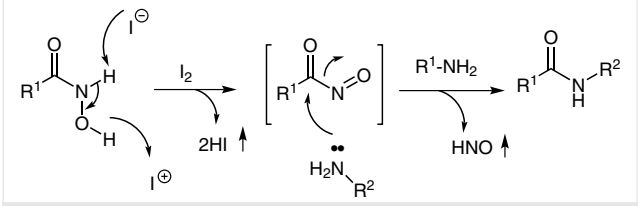
Abstract An efficient and straightforward approach for the coupling of N^{α}-protected hydroxamic acids with an amino component in the presence of iodine is delineated. The reaction is mediated by the formation of unstable but reactive acyl nitroso intermediates. The peptide hydroxamic acids were found to be useful substrates in coupling reactions.

Key words N^{α}-protected amino hydroxamic acids, amino acid esters, oxidative acylation, acyl nitroso intermediate, iodine

The amide bond[1] is a key backbone of many organic and biological molecules including pharmaceuticals,[2] natural products,[3] peptides,[4] and proteins.[5] Development of a new amide-bond-forming reaction is one of the most important synthetic transformations for which improved methods are sought.[6] A protocol for the coupling of peptide fragments constitutes an important step in the total chemical synthesis of proteins.[7] In this context, there has been an impressive growth in the past two decades in native chemical ligation (NCL)[8] and an alternative to NCL[9,10] such as Staudinger ligation,[11] oxo-ester ligation,[12] peptide hydrazide ligation,[13] various oxidative activation ligation methods using peptide thioacids,[14] and ligation of C-terminal α-keto acid with N-terminal hydroxyl amine.[15] Although the application of each of these methods is fully demonstrated in unprotected peptide-fragment coupling, the difficulty in the preparation of desired starting substrates has necessitated the search for alternative and easily synthesizable peptide substrates.

Thus our attention was caught by a little known reaction involving oxidative coupling of hydroxamic acids with amines,[16] which results in the formation of amides. The proposed mechanism confirms the formation of a reactive acyl nitroso intermediate followed by trapping with an amine with loss of volatile HNO (Scheme 1).[17] The reaction between hydroxamic acid and amine has also been applied to the synthesis of di- and tripeptide esters. However, without the presence of an oxidant in this reported case, poor yields and prolonged reaction times were obtained.[18] We now report promising results of an oxidative coupling of N-protected α-amino hydroxamic acids with amines, with loss of nitrous oxide leading to the formation of peptides in short duration. The central feature of this reaction represents a novel traceless and fast synthesis of peptides. Additionally, we hope that peptide hydroxamic acids can be used for oxidative coupling reactions of polypeptides and protein synthesis. Research interest in hydroxamic acids derived from amino and peptide acids has experienced a renaissance since their initial utility in Lossen rearrangement for the identification of the parent structure.[19]



Scheme 1 General reaction mechanism for the amide bond formation

Our group has described the synthesis of ureidopeptides through in situ generation of isocyanate from amino and peptide hydroxamic acids followed by trapping with an amine under mild conditions.[20] Recently, there is a wide range of methods developed for the synthesis of ureas and carbamates from Lossen rearrangement of hydroxamic acids.[21] Meanwhile, oxidative activation of hydroxamic acids for the production of an acyl nitroso intermediate has been studied and confirmed since the 1960's.[22] For example, the

acyl nitroso intermediate has been used as a reactive dienophile in Diels–Alder-type reactions[23] and it is a current topic of interest in natural product synthesis.[24]

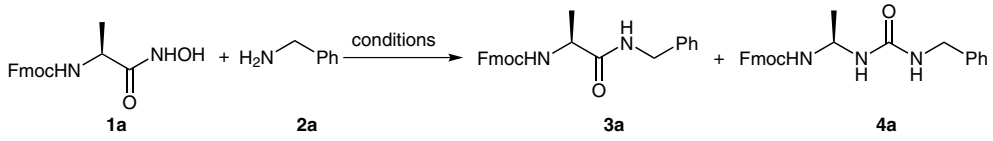
In the course of our investigation on the epimerization-free synthesis of amides and peptides by novel reagents and substrates,[25] we envisioned that hydroxamic acid could be used to couple with amines for the production of peptides. The reaction conditions were optimized using optically pure Fmoc-Ala-NHOH (**1a**) with benzyl amine (**2a**) as our model reaction, and the results are summarized in Table 1.[26] When the direct reaction of **1a** with **2a** was conducted in toluene by following the reported protocol[18] only 15% of the desired product **3a** was obtained (Table 1, entry 1). However, when the reaction was studied at 70 °C for eight hours, the formation of the two products was observed. One of these products was the expected amide **3a**, and the other product was identified as urea derivative **4a** which was obtained by the thermal Lossen rearrangement of hydroxamic acid (Table 1, entry 2).[27]

The Danishefsky group reported that DMSO could act as an oxidant for the direct ligation of peptide thioacids with amines without additives.[28] Thus, the reaction of **1a** and **2a** was carried out in DMSO at room temperature and yielded 51% of **3a** (Table 1, entry 3). Interestingly, ureido compound **4a** was not present. These observations highlight the requirement of room temperature for the selective formation of an amide.

In an attempt to improve the yield of **3a**, various oxidants and solvents were screened at room temperature (Table 1, entries 4–13). The oxidants H_2O_2 and $NaIO_4$ were found to be inefficient for this transformation (Table 1, entries 4–7). Solvent also played an important role, and the reaction in toluene, DMF, THF, MeOH, H_2O, and MeOH–H_2O led to lower yield and requires long reaction duration. When I_2 was used in the presence of DMSO, the desired product **3a** was formed in 95% yield (Table 1, entry 8). Thus, the optimized protocol was selected to be hydroxamic acid (1.0 equiv), amine (1.2 equiv), I_2 (0.3 equiv) in DMSO, at room temperature for 5–30 minutes.

With the optimized conditions in hand, various amino acid esters **6** were employed to couple with N$^{\alpha}$-protected hydroxamic acids **5**, and the results are furnished in Table 2. Both simple and sterically hindered amino acids performed well to produce the dipeptide esters **7** in good to excellent yields. The question of epimerization during the course of coupling is also addressed using chiral HPLC. The diastereomeric products Fmoc-(L)-Phg-Phe-OMe (**7l**), Fmoc-(D)-Phg-Phe-OMe (**7l***) obtained from the Fmoc-protected L-Phg-NHOH (**5l**) and D-Phg-NHOH (**5l***) were analyzed. Both **7l** and **7l*** showed peaks at t_R = 14.82 min and t_R = 18.47 min, respectively. Also, an intentionally prepared equimolar mixture of **7l** and **7l*** showed distinct peaks at t_R = 15.69 min and t_R = 18.45 min. From these observations, it was proved that the present protocol is free from racemization.

Table 1 Synthesis of N$^{\alpha}$-Protected Aryl Amide **3a**: Optimization of Reaction Conditions

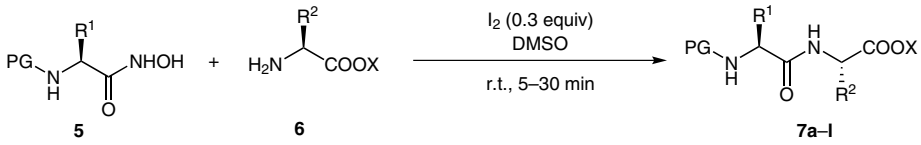


1a **2a** **3a** **4a**

Entry	Solvent	Oxidant (equiv)	Temp (°C)	Time	Yield of **3a** (%)[a]	Yield of **4a** (%)[a]
1	toluene	–	r.t.	16 h	15	–
2	toluene	–	70	8 h	35	21
3	DMSO	–	r.t.	6 h	51	–
4	DMF	H_2O_2 (1.0)	r.t.	3h	54	–
5	DMSO	H_2O_2 (1.0)	r.t.	3 h	61	–
6	DMSO	$NaIO_4$ (0.5)	r.t.	40 min	80	–
7	THF	$NaIO_4$ (0.5)	r.t.	1 h	62	–
8	DMSO	I_2 (0.3)	r.t.	30 min	95	–
9	THF	I_2 (0.3)	r.t.	1 h	60	–
10	MeOH	I_2 (0.3)	r.t.	1 h	75	–
11	DMF	I_2 (0.3)	r.t.	1 h	68	–
12	H_2O	I_2 (0.3)	r.t.	1 h	–	–
13	MeOH–H_2O	I_2 (0.3)	r.t.	1 h	45	–

[a] Yields corresponding to the isolated pure product **3a**.

Table 2 Synthesis of Dipeptide Esters **7**[28–32]



Entry	Product **7**	Yield (%)[a]
1	Fmoc-Ala-Phe-Ome **7a**	93
2	Fmoc-Val-Ala-Ome **7b**	91
3	Fmoc-Leu-Phe-Obn **7c**	85
4	Fmoc-Phe-Gly-Ome **7d**	96
5	Cbz-Leu-Phe-Ome **7e**	90
6	Cbz- Phe-Aib-Ome **7f**	71
7	Cbz-Ile-Gly-Ome **7g**	89
8	Boc-Aib-Aib-Ome **7h**	65
9	Boc-Phe-Val-Ome **7i**	90
10	Boc-Leu-Phe-Ome **7j**	92
11	Boc-Pro-Phe-Ome **7k**	94
12	Fmoc-(L)-Phg-Phe-Ome **7l**	88
13	Fmoc-(D)-Phg-Phe-Ome **7l***	85

[a] Yields corresponding to the isolated pure dipeptide esters **7**.

Much work remains to be done to develop hydoxamic acid mediated peptide ligation. In particular, the reaction in aqueous buffer is currently under investigation. We have (nevertheless) presented here a peptide-bond strategy from simple N^{α}-protected hydroxamic acid and amines. This process was mediated by the formation of known acyl nitroso intermediate. The optimized reaction for coupling of hydroxamic acids and amines took place under mild conditions and in short duration of time. The chemistry can be easily operated, and the isolation of the product is simple. The reaction showed tolerance towards Fmoc, Boc, and Cbz protecting groups.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560266.

References and Notes

(1) Pattabiraman, V. R.; Bode, J. W. *Nature (London, U.K.)* **2011**, *480*, 471.
(2) (a) Allen, C. L.; Chhatwal, R.; Williams, J. M. J. *Chem. Commun.* **2012**, 666. (b) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron* **2012**, *68*, 9867. (c) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L. Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411. (d) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.
(3) (a) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, *33*, 7453. (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606. (c) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405. (d) Basavaprabhu; Vishwanatha, T. M.; Nageswarao, P.;

Sureshbabu, V. V. *Synthesis* **2013**, *45*, 1569. (e) Joullie, M. M.; Lassen, K. M. *ARKIVOC* **2010**, *(viii)*, 189. (f) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386.

(4) (a) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557. (b) Lippert, J. W. III. *ARKIVOC* **2005**, *(xiv)*, 87. (c) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. (d) Han, S. Y.; Kim, Y. A. *Tetrahedron* **2004**, *60*, 2447. (e) Wilson, R. M.; Stockdill, J. L.; Wu, X.; Li, X.; Vadola, P. A.; Park, P. K.; Wang, P.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 2834. (f) Bode, J. W. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765.

(5) (a) Kent, S. B. H. *Chem. Soc. Rev.* **2009**, *38*, 338. (b) Spasser, L.; Brik, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6840. (c) Chalker, J. M. *Chem. Biol. Drug. Des.* **2013**, *81*, 122.

(6) (a) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature (London, U.K.)* **2010**, *465*, 1027. (b) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790. (c) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667. (d) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064. (e) Cadoni, R.; Porcheddu, A.; Giomelli, G.; Luca, L. D. *Org. Lett.* **2012**, *14*, 5014. (f) Orliac, A.; Pardo, D. G.; Bombrun, A.; Cossy, J. *Org. Lett.* **2013**, *15*, 902. (g) Tian, J.; Gao, W. C.; Zhou, D. M.; Zhang, C. *Org. Lett.* **2012**, *14*, 3020.

(7) (a) Pellois, J. P.; Muir, T. W. *Curr. Opin. Chem. Biol.* **2006**, *10*, 487. (b) Aimoto, S. *Biopolymers* **1999**, *51*, 247. (c) Rademann, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4554. (d) Hemantha, H. P.; Narendra, N.; Sureshbabu, V. V. *Tetrahedron* **2012**, *68*, 9491. (e) Payne, R. J.; Wong, C. H. *Chem. Commun.* **2010**, *46*, 21. (f) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974.

(8) (a) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H. *Science* **1994**, *266*, 776. (b) Sohma, Y.; Hua, Q. X.; Whittaker, J.; Weiss, M. A.; Kent, S. B. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5489.

(9) (a) Dirksen, A.; Dawson, P. E. *Curr. Opin. Chem. Biol.* **2008**, *12*, 760. (b) Hackenberger, C. P. R.; Schwarzer, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 10030. (c) Dawson, P. E.; Kent, S. B. H. *Annu. Rev. Biochem.* **2000**, *69*, 923. (d) Kent, S. B. H. *J. Pept. Sci.* **2003**, *9*, 574. For a review on ligation of noncysteine amino acids, see: (e) Wong, C. T. T.; Tung, C. L.; Li, X. *Mol. BioSyst.* **2013**, *9*, 826.

(10) Mende, F.; Beisswenger, M.; Seitz, O. *J. Am. Chem. Soc.* **2010**, *132*, 11110.

(11) (a) Nilsson, B. L.; Kiessling, L. L.; Raines, R. *T. Org. Lett.* **2000**, *13*, 1939. (b) Van Berkel, S. S.; Van Eldijk, M. B.; van Hest, J. C. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8806.

(12) (a) Wan, Q.; Chen, J.; Yuan, Y.; Danifshesky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 15814. (b) Strehin, I.; Gourevitch, D.; Zhang, Y.; Heber Katz, E.; Messersmith, P. B. *Biomater. Sci.* **2013**, *1*, 603. (c) Warren, J. D.; Miller, J. S.; Keding, S. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6576.

(13) (a) Fang, G. M.; Li, Y. M.; Shen, F.; Huang, Y. C.; Li, J.-B.; Lin, Y.; Cui, H.-K.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 7645. (b) Zheng, J. S.; Tang, S.; Huang, Y. C.; Liu, L. *Acc. Chem. Res.* **2013**, *46*, 2475.

(14) (a) McKervey, M. A.; O'Sullivan, M. B.; Myers, P. L.; Green, R. H. *J. Chem. Soc., Chem. Commun.* **1993**, 94. (b) Merkx, R.; Brouwer, A.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125. (c) Merkx, R.; Van Haren, M. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *J. Org. Chem.* **2007**, *72*, 4574. (d) Raz, R.; Rademann, J. *Org. Lett.* **2012**, *14*, 5038. (e) Mhidia, R.; Beziere, N.; Blanpain, A.; Pommery, N.; Melnyk, O. *Org. Lett.* **2010**, *12*, 3982. (f) Crich, D.; Sana, K.; Guo, S. *Org. Lett.* **2007**, *9*, 4423. (g) Crich, D.; Sharma, I. *Angew. Chem. Int. Ed.* **2009**, *48*, 2355. (h) Sasaki, K.; Crich, D. *Org. Lett.* **2010**, *12*, 3254. (i) Talan, R. S.; Sanki, A. K.; Sucheck, S. J. *Carbohydr. Res.* **2009**, *344*, 2048. (j) Mhidia, R.; Boll, E.; Fecourt, F.; Ermolenko, M.; Ollivier, N.; Sasaki, K.; Crich, D.; Delpech, B.; Melnyk, O. *Bioorg. Med. Chem.* **2013**, *21*, 3479. (k) Crich, D.; Sasaki, K. *Org. Lett.* **2009**, *11*, 3514. (l) Chen, W.; Shao, J.; Hu, M.; Yu, W.; Giulianotti, M. A.; Houghten, R. A.; Yu, Y. *Chem. Sci.* **2013**, *4*, 970. (m) Wu, X.; Stockdill, J. L.; Wang, P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 4098. (n) Yamashiro, D.; Blake, J. F. *Int. J. Pept. Prot. Chem.* **1981**, *18*, 383. (o) Dyer, F. B.; Park, C. M.; Joseph, R.; Garner, P. *J. Am. Chem. Soc.* **2011**, *133*, 20033. (p) Joseph, R.; Dyer, F. B.; Garner, P. *Org. Lett.* **2013**, *15*, 732. (q) Pan, J.; Devarie-Baez, N. O.; Xian, M. *Org. Lett.* **2011**, *11*, 1092. (r) Wu, W.; Zhang, Z.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 14256. (s) Mali, S. M.; Jadhav, S. V.; Gopi, H. N. *Chem. Commun.* **2012**, *48*, 7085. (t) Wang, P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 17045. (u) Wang, P.; Li, X.; Zhu, J.; Chen, J.; Yuan, Y.; Wu, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2011**, *133*, 1597.

(15) (a) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248. (b) Wu, J.; Ruiz-Rudriguez, J.; Comstock, J. M.; Dong, J. Z.; Bode, J. W. *Chem. Sci.* **2011**, *2*, 1976. (c) Carrillo, N.; Davalos, E. A.; Russak, J. A.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 1452. (d) Ju, L.; Lippert, A. R.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 4253. (e) Ju, L.; Bode, J. W. *Org. Biomol. Chem.* **2009**, *7*, 2259. (f) Pattabiraman, V. R.; Ogunkoya, A. O.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 5114.

(16) (a) Sklarz, B.; Al-Sayab, A. F. *J. Chem. Soc.* **1964**, 1318. (b) Ozaki, S.; Masui, M. *Chem. Pharm. Bull.* **1977**, *25*, 1179.

(17) Atkinson, R. N.; Storey, B. M.; King, S. B. *Tetrahedron Lett.* **1996**, *37*, 9287.

(18) Hoffmann, E.; Faiferman, I. *J. Org. Chem.* **1964**, *29*, 748.

(19) (a) Seifter, S.; Gallop, P. M.; Michaels, S.; Meilman, E. *J. Biol. Chem.* **1960**, *235*, 2613. (b) Gallop, P. M.; Seifter, S.; Lukin, M.; Meilman, E. *J. Biol. Chem.* **1960**, *235*, 2619. (c) Wieland, T.; Fritz, H. *Chem. Ber.* **1953**, *86*, 1186.

(20) (a) Narendra, N.; Chennakrishnareddy, G.; Sureshbabu, V. V. *Org. Biomol. Chem.* **2009**, *7*, 3520. (b) Vasantha, B.; Hemantha, H. P.; Sureshbabu, V. V. *Synthesis* **2010**, 2990.

(21) (a) Yoganathan, S.; Miller, S. J. *Org. Lett.* **2013**, *15*, 602; and references cited therein. (b) Dube, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622.

(22) (a) Boyland, E.; Nery, R. *J. Chem. Soc.* **1966**, 354. (b) Kobashi, K.; Sakaguchi, K.; Takebe, S.; Hosaka, K. *Anal. Biochem.* **1985**, *146*, 7.

(23) (a) Miller, T. W.; Isenberg, J. S.; Roberts, D. D. *Chem. Rev.* **2009**, *109*, 3099. (b) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007. (c) Kirby, G. W. *Chem. Soc. Rev.* **1978**, *6*, 1. (d) Corrie, J. E. T.; Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 883. (e) Kirby, G. W.; Mcguigan, H.; Mackinnon, J. W. M. McLean D.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1437. (f) Iwasa, S.; Tajima, K.; Tsushima, S.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 5897.

(24) (a) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107. (b) Keck, G. E.; Webb, R. R. II. *J. Org. Chem.* **1982**, *47*, 1302. (c) Chaiyaveij, D.; Cleary, L.; Batsanov, A. S.; Marder, T. B.; Shea, K. J.; Whiting, A. *Org. Lett.* **2011**, *13*, 3442.

(25) (a) Tantry, S. J.; Venkataramanarao, R.; Chennakrishnareddy, G.; Sureshbabu, V. V. *J. Org. Chem.* **2007**, *73*, 9360. (b) Madhu, C.; Vishwanatha, T. M.; Sureshbabu, V. V. *Synthesis* **2013**, *45*, 2727. (c) Gopi, H. N.; Sureshbabu, V. V. *Tetrahedron Lett.* **1998**, *39*, 9769.

(26) Enantiopurehydroximate of α-amino acids and peptides were synthesized through reported protocol, see: Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett.* **2003**, *5*, 2715.

(27) (a) Anilkumar, R.; Chandrasekhar, S.; Sridhar, M. *Tetrahedron Lett.* **2000**, *41*, 5291. (b) Dube, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622.

(28) Wang, P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 17045.

(29) **General Procedure for the Preparation of Dipeptide Esters 7a–l***

To a solution of N^{α}-protected amino hydroxamic acid **5** (1.0 equiv) in DMSO (5 mL), I_2 (0.3 equiv), and amino acid ester **6** (1.2 equiv) were added at r.t. and stirred. After completion of the reaction, as monitored by TLC analysis (5–30 min), the solvent was removed under reduced pressure, and the crude residue was diluted with EtOAc (20 mL). The organic layer was washed with 10% Na_2CO_3 (15 mL), 10% citric acid (15 mL), H_2O (10 mL) and brine solution (10 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude residue was purified through silica gel column chromatography (100–200 mesh), EtOAc–hexane (40:60) as eluent to obtain dipeptide esters.

(30) **Methyl 2-[2-({[(4a*H*-Fluoren-9-yl)methoxy]carbonyl}-amino)propanamido]-3-phenylpropanoate [Fmoc-Ala-Phe-OMe, 7a].**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 3 Hz, 3H , CH_3), 3.12–3.17 (m, 2 H, CH_2Ph), 3.70 (s, 3 H, OCH_3), 4.05–4.09 (m, 1 H, δCH, NHC*H*CH_3, Ala), 4.17–4.20 (m, 1 H, αCH,-NHC*H*CH_2, Phe), 4.31 (t, *J* = 9 Hz, 1 H, CH_2C*H*, Fmoc), 4.34 (d, *J* = 9 Hz, 2 H, C*H*$_2$CH, Fmoc), 5.32 (br d, *J* = 6 Hz, 1 H, NH, Fmoc), 6.46 (br d, *J* = 6 Hz, 1 H, NH, amide), 7.06–7.76 (m, 13 H, 5 CH, Ph, 8 CH, Fmoc). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (CβAla), 37.9 (CβPhe), 47.2 (CαFmoc), 50.2 (CαAla), 52.5 (Me), 53.3 (CαPhe), 67.2 (CβFmoc), 120.1, 125.1, 127.3, 127.8, 128.6, 128.7, 129.3 (CH, Ar), 135.7 (C, Ar), 141.4 and 143.9 (C, Fmoc), 156.4 (C=O, Fmoc), 171.7 and 171.8 (C=O). HRMS: *m/z* [M + H]$^+$ calcd for $C_{28}H_{29}N_2O_5$: 473.2076; found: 473.2062.

(31) **Methyl 2-[2-({[(4a*H*-Fluoren-9-yl)methoxy]carbonyl}-amino)methylbutanamido]propanoate [Fmoc-Val-Ala-OMe (7b)]**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 [d, *J* = 5 Hz, 6 H, CHCH(C*H*$_3$)$_2$], 1.26 (d, *J* = 5 Hz, 3 H, CHC*H*$_3$), 2.04–2.10 [m, 1 H, CHC*H*(CH$_3$)$_2$], 3.69 (s, 3 H, OCH_3), 4.18–4.25 (m, 2 H, δCH, NHC*H*CH, Val, αCH, NHC*H*CH_3, Ala), 4.35 (t, *J* = 3 Hz, 1 H, CH_2C*H*, Fmoc), 4.42 (d, *J* = 5 Hz, 2 H, C*H*$_2$CH, Fmoc), 5.28 (br d, *J* = 6 Hz, 1 H, NH, Fmoc), 6.42 (br d, *J* = 5 Hz, 1 H, NH, amide), 7.26–7.77 (m, 8 H, 8 CH, Fmoc). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5 (CβAla), 19.1 (CγVal), 31.1 (CβVal), 47.3 (CαFmoc), 50.1 (CαAla), 52.3 (Me), 59.0 (CαVal), 67.2 (CβFmoc), 120.1, 125.1, 127.2, 127.8 (CH, Fmoc), 141.4 and 143.8 (C, Fmoc), 156.4 (C=O, Fmoc), 172.2 and 172.3 (C=O). HRMS: *m/z* [M + H]$^+$ calcd for $C_{24}H_{29}N_2O_5$: 425.2076; found: 425.2082.

(32) Optical purity of products **7b**,**c** was determined by HPLC. See Supporting Information for the HPLC chromatograms.