ORGANIC
LETTERS

2005
Vol. 7, No. 4
581−584

Versatile Solid-Phase Synthesis of Peptide-Derived 2-Oxazolines. Application in the Synthesis of Ligands for Asymmetric Catalysis

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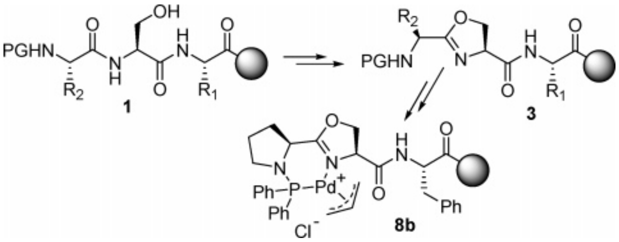
Received November 11, 2004

ABSTRACT



A mild and high-yielding procedure for the solid-phase synthesis of 2-oxazolines from amino acids is described. The two-step protocol is based on the iodination of serine containing peptides, followed by in situ nucleophilic attack of the carbonyl oxygen from the next amino acid. Phosphinylation of the terminal amino group cleanly furnishes a resin-bound phosphine–oxazoline ligand, which upon palladium complexation was applied as catalyst in asymmetric allylic substitution.

The oxazoline ring is a biologically relevant heterocycle widely spread in nature[1] and found in a variety of metal chelators,[1b] cytotoxic peptides,[1c] or antimitotic and neuroprotective agents.[1d] Furthermore, oxazolines have found applications in organic chemistry as synthetic intermediates,[2] protecting groups,[3] and more recently as chiral auxiliaries for homogeneous asymmetric synthesis.[4]

Diverse strategies toward the synthesis of 2-oxazolines have been reported, and the topic has been extensively reviewed.[5] Among them, those methodologies for the efficient conversion of peptides into 2-oxazolines are of particular interest in the research for useful ligands in asymmetric synthesis due to the availability and structural diversity of their building blocks. A variety of methods have been applied to directly convert serine/threonine-containing peptides into 2-oxazolines, including Mitsunobu conditions[6] and other phosphorus reagents,[7] Burgess reagent,[8] DAST, and Deoxo-

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10.1021/ol047675h CCC: $30.25

fluor.[9] But none of them seem to be applicable in a solid-phase combinatorial approach due to the concomitant formation of byproducts (i.e., elimination product, aziridine), reactivity depending on particular substrate, moisture sensitivity, or inconvenient reaction temperatures.

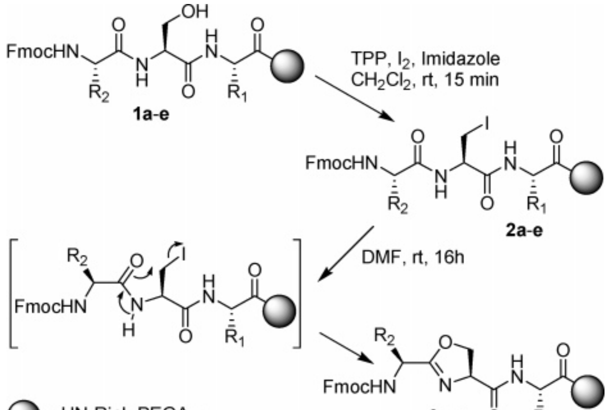
Although good 2-oxazoline-based ligands have been reported for different transition metal catalyzed processes,[10] these approaches suffer from the tedious solution-phase synthesis and characterization of individual putative ligands. To the best of our knowledge, a solid-phase strategy for the preparation of such ligands, also suitable for combinatorial synthesis of ligand libraries for latter high-throughput screening, has not yet been reported.[11]

In this paper, a simple procedure for the solid-phase synthesis of 2-oxazolines starting from the chiral pool of natural amino acids is reported. Attachment of a phosphine moiety in the last synthetic step furnishes a type of P−N ligand,[12] which has already been synthesized in solution and is known to achieve remarkable enantioselectivity in different reactions.[13]

The strategy is based on the introduction of a soft iodide leaving group, to be displaced by a properly located carbonyl group under mild conditions.

Although a variety of peptide-coupling reagents can be used for incorporation of β-iodo alanine building blocks[14] synthesized in solution, this approach was abandoned due to the low stability of the iodide moiety under conventional Fmoc-deprotection conditions.[15] For this reason, a high-yielding procedure for on-bead iodination of serine-containing peptides **1a**−**e** has been developed (Scheme 1). The tripeptides **1a**−**e** were synthesized using standard solid-phase peptide synthesis. The acid-labile Rink[16] linker was used in order to facilitate HPLC analysis of the iodinated peptides **2a**−**e**, since iodinated adducts undergo elimination under the basic conditions needed for cleavage of, e.g., the HMBA linker.

Scheme 1. Solid-Phase Synthesis of Peptide-Derived 2-Oxazolines[a]



[a] For R_1 and R_2 see Table 1.

After studying different reported iodination conditions, the best results were obtained using the reagent system triphenylphosphine−iodine−imidazole reported by Garegg and Samuelson for the iodination of carbohydrates.[17] The use of a 10-fold excess of reagents in dichloromethane turned out to be necessary in order to achieve complete iodination, as can be seen from the HPLC traces of cleaved model substrate **1a** and the iodinated equivalent **2a** (Figure 1A and B, respectively). This is probably due to the nature of the poly(ethylene glycol)-based support (PEGA resin),[18] having a considerable moisture retention capability. Surprisingly, even using these virtually neutral conditions and short reaction times (less than 15 min), a significant amount of the oxazoline **3a** was formed (Figure 1B), preventing isolation and characterization of the iodinated adduct **2a**. Furthermore, after washing out the excess reagents, treatment of the solid-sup-

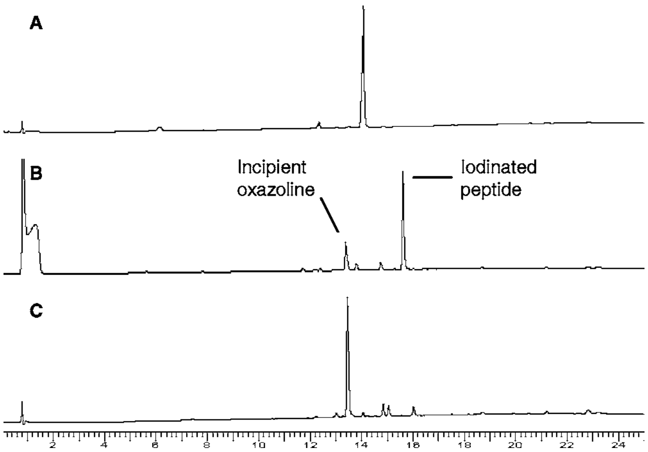


Figure 1. Analytical RP-HPLC of cleaved compounds: (A) serine-containing tripeptide **1a**, (B) iodinated intermediate **2a**, and (C) peptido-oxazoline **3a**.

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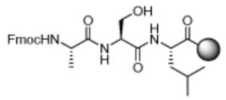
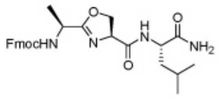
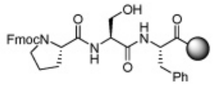
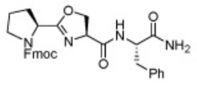
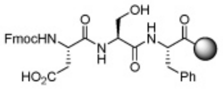
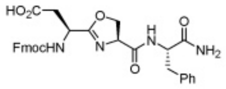
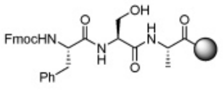
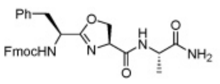
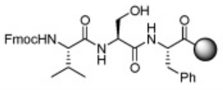
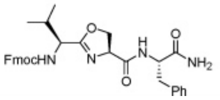
ported iodide **2a** with DMF overnight completed the cyclization to afford the corresponding 2-oxazoline **3a** in excellent yield and purity (Figure 1C).

On the other hand, using this procedure for solution-phase synthesis of a **3a** analogue (see the Supporting Information) resulted in a disappointingly low overall yield due to the tedious purification of its corresponding iodinated intermediate, pointing to the suitability of the solid-phase approach for the synthesis of such compounds. The solution-phase assay also showed the pure iodinated adduct to be relatively stable in DMF solution and the need of at least 1 equiv of weak base to promote the intramolecular nucleophilic attack. On PEGA resin the resin itself may buffer the hydroiodic acid generated upon cyclization, thus driving the reaction to completion.

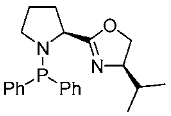
Submitting substrates **1a**−**e** possessing different side chains to these conditions furnished the desired products **3a**−**e** in good yields after purification by preparative RP-HPLC (Table 1). Only minor amounts of side products were observed, and although not identified, they were probably elimination adducts already detected in substantial amounts during solution-phase synthesis. It is noteworthy that the addition of bases (i.e., NEM or DIPEA) to **2a**−**e**, although accelerating the reaction, also significantly increases the formation of side products, probably due to less selective proton abstraction.

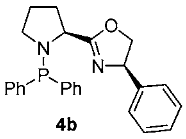
Table 1. Solid-Phase Synthesis of Peptido-2-oxazolines

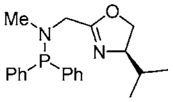
	substrate **1**	cleaved product **3**[a]	yield (%)[b]
a			60
b			70
c			56
d			64
e			72

[a] Cleaved from the Rink linker. [b] Overall yield calculated from the initial resin loading after preparative RP-HPLC.

The isolated Fmoc-protected peptido-2-oxazolines cleaved **3a**−**e** were characterized by NMR and HR-MS. The ^{1}H NMR studies confirmed the oxazoline structure by the absence of the resonances for the serine hydroxyl group and the adjacent amide proton, and by the downfield shifting of the serine β-protons upon oxazoline formation.

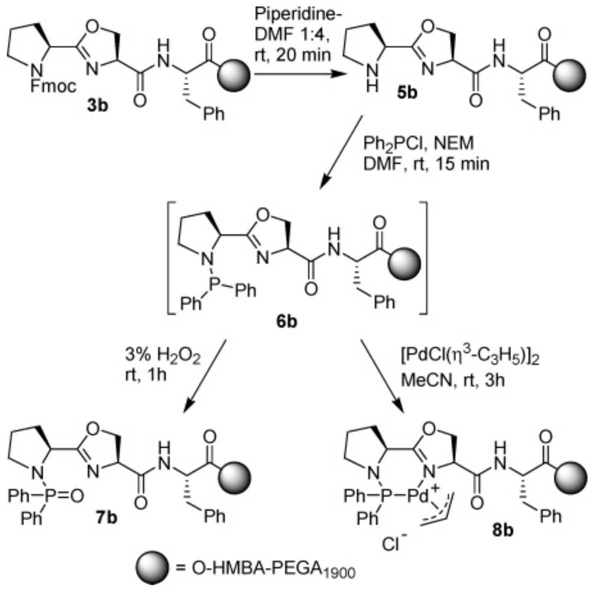

4a


4b


4c

Gilbertson and co-workers[13a,b] have carried out the solution-phase synthesis of a range of phosphine-oxazoline ligands, including **4a**−**c**, and achieved excellent selectivity in palladium catalyzed asymmetric allylic substitution reactions. Enantioselectivity in the range of 41−94% ee was obtained. However, the solution-phase synthesis of the ligands reported by Gilbertson and later in an almost similar manner by Blanc et al.[13c] is very laborious. Thus using compound **3b** as easily synthesized starting material, resin bound ligand **6b**, similar in structure to **4a**,**b**, was prepared for comparison (Scheme 2). This new methodology not only reduces the number of synthetic steps needed for the synthesis of such ligands but also immobilizes the ligand and the derived catalyst on solid support, thereby gaining the possibility to generate ligand libraries using standard solid-phase combinatorial techniques.[11]

Scheme 2. Synthesis of a Phosphine-2-oxazoline Ligand



Whereas the Rink linker was well suited for the cleavage of the iodinated intermediates **2a**−**e**, it was not compatible with the synthesis and characterization of ligand **6b**, since the P−N bond is cleaved under acidic conditions.[19] Therefore, the base-labile HMBA linker was selected for the synthesis of a batch of peptido-2-oxazoline **3b**.[20]

Standard Fmoc-deprotection of HMBA-linked **3b** and subsequent treatment of the terminal secondary amine with

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[19] Although more stable, the P−N bond of **7b** is also cleaved under the acidic conditions needed to cleave the Rink linker.

diphenylphosphine chloride furnished the desired ligand **6b** (Scheme 2). However, ligand **6b** could not be cleaved and characterized without concomitant oxidation of the phosphine moiety. Thus a sample of **6b** was treated with a dilute aqueous solution of hydrogen peroxide to furnish clean and complete oxidation to the corresponding phosphine oxide **7b** prior to cleavage and characterization.

Analytical RP-HPLC chromatograms of cleaved crude samples of the Fmoc-deprotected proline-oxazoline intermediate **5b** and the oxidized ligand **7b**, respectively, show the clean solid-phase phosphinylation of **5b** (Figure 2).

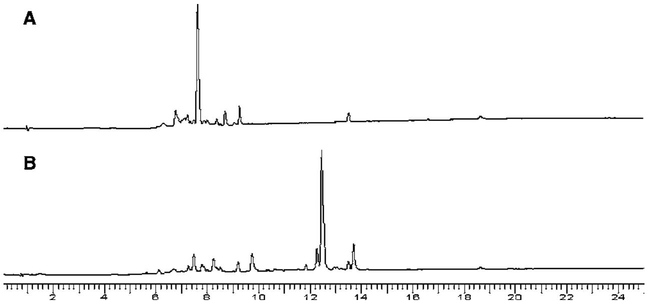


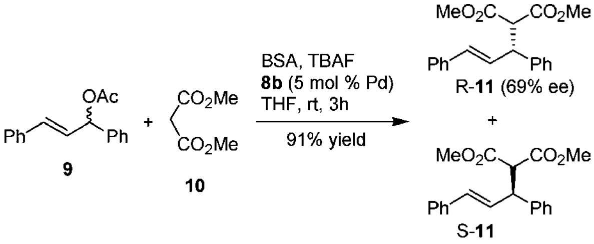
Figure 2. Analytical RP-HPLC of cleaved compounds: (A) deprotected peptido-oxazoline **5b** and (B) oxidized phosphine−oxazoline ligand **7b**.

Cleaved **7b** was also purified by preparative RP-HPLC and characterized by NMR and HR-MS.

As a preliminary screening of the potential of solid-supported peptido-phosphine-oxazolines as chiral ligands for asymmetric catalysis, we decided to prepare complex **8b**, for the palladium catalyzed asymmetric allylic substitution reaction. Freshly prepared ligand **6b** was treated with allyl palladium chloride dimer to give resin bound complex **8b**.

Using the conditions described by Gilbertson and co-workers,[13b] solid-supported catalyst **8b** was used for the reaction of 1,3-diphenylpropenyl acetate **9** with dimethyl malonate **10** under basic conditions (Scheme 3). After 3 h, the reaction was worked up and **11** was isolated as a mixture of enantiomers in 91% yield. The enantiomeric excess was determined by ^{1}H NMR, using a chiral shift reagent,[21] to be 69% in favor of *R*-**11**. This is a promising result for the synthesis and screening of solid-supported peptido-phosphine−oxazoline libraries and comparable with the ee values obtained using ligands **4a**−**c** in solution.[13b]

Scheme 3. Palladium-Catalyzed Asymmetric Allylic Substitution



In conclusion, an efficient strategy for the modular synthesis of solid-supported enantiopure peptido-2-oxazolines has been reported, using the readily available chiral pool of amino acids as starting materials. The utility of this methodology is demonstrated, by the efficient solid-phase synthesis of a phosphine-oxazoline ligand. The ligand was used for palladium catalyzed asymmetric allylic substitution, showing good selectivity. This approach constitutes an interesting entry into the high-throughput combinatorial screening of ligands for metal catalyzed asymmetric synthesis. Current investigations are being directed toward the optimization of the catalytic activity by the design of focused libraries of solid-supported phosphine−oxazoline ligands for on-bead screening.

Acknowledgment. We are grateful to the Danish National Research Foundation for financial support and to the European Community for a Marie Curie Individual Fellowship under the program IHP awarded to J.M.B. (Contract No. HPMF-CT-2002-01858).

Supporting Information Available: Synthesis and characterization data of cleaved compounds **1a**−**e**, **3a**−**e**, and **7b**. Synthesis of complex **8b** and experimental details for the palladium catalyzed asymmetric allylic substitution reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] Peptido-2-oxazolines **3a**−**e** were all resynthesised in small amounts using the HMBA linker (see the Supporting Information for HR-MS data), and the HMBA linker proved to be fully compatible with the developed synthetic methodology.

[21] By the means of the chiral shift reagent [Eu(hfc)$_3$], see: Brenchley, G.; Fedouloff, M.; Mahon, M. F.; Molloy, K. C.; Wills, M. *Tetrahedron* **1995**, *51*, 10581−10592.