SOLID-PHASE ORGANIC SYNTHESIS

Concepts, Strategies, and Applications

EDITED BY
PATRICK H. TOY
YULIN LAM

WILEY

SOLID-PHASE ORGANIC SYNTHESIS

SOLID-PHASE ORGANIC SYNTHESIS

Concepts, Strategies, and Applications

Edited by

Patrick H. Toy

Yulin Lam

WILEY

A JOHN WILEY & SONS, INC., PUBLICATION

Copyright © 2012 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at http://www.wiley.com/go/permission.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Solid-phase organic synthesis : concepts, strategies, and applications / edited by Patrick H. Toy, Yulin Lam. – 1st ed.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-470-59914-3 (hardback)
1. Solid-phase synthesis. I. Toy, Patrick H. II. Lam, Yulin.
QD262S584 2012
547'.2–dc23

2011019936

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

CONTENTS

Part II Applications 205

PREFACE

Merrifield first introduced the concept of solid-phase peptide synthesis nearly half a century ago, and since then the use of heterogeneous materials to facilitate synthesis has evolved and become widespread in many contexts. For example, the automated solid-phase synthesis of oligomeric biomolecules, such as polypeptides and polynucleotides, has become the standard methodology for the production of such compounds.

The aim of this book is to highlight the state of the art regarding the use of a solid material to support and thereby facilitate organic synthesis. The book is divided into two parts: Part I introduces some general concepts and strategies, while Part II presents specific examples of the solid-phase synthesis of various classes of organic molecules. Since the field regarding solid-phase synthesis of polypeptides and polynucleotides is very mature and well understood, these topics are not included in this book. However, since the solid-phase synthesis of oligosaccharides is not yet routine and straightforward, a chapter on this subject is presented.

Part I includes chapters focusing on the linker groups used to attach the synthesis substrate to the solid support, colorimetric tests that identify the presence of functional groups, combinatorial synthesis (especially interesting due to its historical perspective), and diversity-oriented synthesis. These contributions showcase solid-phase synthesis that is currently used to facilitate the discovery of new molecular functionality. Finally, a chapter highlighting how using a support can change or increase reaction selectivity closes this part. Part II includes chapters on general asymmetric synthesis on a support, various strategies for heterocycle synthesis (including one focusing on the use of microwave heating), synthesis of radioactive organic molecules, dyes, dendrimers, and, last but not least, oligosaccharides.

It is hoped that this book will serve as an introduction and a starting point for those new to this field and interested in using concepts and techniques of solid-phase synthesis. As already mentioned, the application of this technology in the synthesis of small, nonoligomeric organic molecules is relatively underdeveloped compared to other applications, and thus new minds and different perspectives can help to advance this field.

Patrick H. Toy
Yulin Lam

ACKNOWLEDGMENTS

We would like to thank all the contributors to this book. Their time is very valuable, and thus their generosity in working on this book is priceless. We also wish to thank Tracy Yuen-Sze But, Julia Hermeke, and Jinni Lu for their editorial assistance.

CONTRIBUTORS

Prasad Appukkuttan, Laboratory for Organic & Microwave-Assisted Chemistry, Department of Chemistry, Katholieke Universiteit Leuven, Leuven, Belgium

Baburaj Baskar, Department of Chemical Biology, Max Planck Institute of Molecular Physiology, Dortmund, Germany

Young-Tae Chang, Department of Chemistry, National University of Singapore, Singapore

Wenteng Chen, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, P. R. China

Alexander Deiters, Department of Chemistry, North Carolina State University, Raleigh, NC, USA

Koichi Fukase, Department of Chemistry, Osaka University, Osaka, Japan

Warren R. J. D. Galloway, Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Marc Giulianotti, Torrey Pines Institute for Molecular Studies, San Diego, CA, USA

Young-Dae Gong, Department of Chemistry, Dongguk University, Seoul, South Korea

Kerem Goren, School of Chemistry, Tel Aviv University, Tel Aviv, Israel

Hyung-Ho Ha, Department of Chemistry, National University of Singapore, Singapore

Kirsi Harju, Division of Pharmaceutical Chemistry, University of Helsinki, Helsinki, Finland

Jan Hlaváč, Department of Organic Chemistry, Palacky University, Olomouc, Czech Republic

Raphaël Hoareau, Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Richard A. Houghten, Torrey Pines Institute for Molecular Studies, San Diego, CA, USA

Brett M. Ibbeson, Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Albert Isidro-Llobet, Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Jonghoon Kim, Department of Chemistry, Seoul National University, Seoul, South Korea

Viktor Krchňák, Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, USA

Kamal Kumar, Department of Chemical Biology, Max Planck Institute of Molecular Physiology, Dortmund, Germany

Yulin Lam, Department of Chemistry, National University of Singapore, Singapore

Sung Chan Lee, Department of Chemistry, National University of Singapore, Singapore

Taeho Lee, Center for High Throughput Synthesis Platform Technology, Korea Research Institute of Chemical Technology, Daejeon, South Korea

Zhi Li, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, P. R. China

Vaibhav P. Mehta, Laboratory for Organic & Microwave-Assisted Chemistry, Department of Chemistry, Katholieke Universiteit Leuven, Leuven, Belgium

Kieron M. G. O'Connell, Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Cornelius J. O'Connor, Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Seung Bum Park, Department of Chemistry, Seoul National University, Seoul, South Korea

Moshe Portnoy, School of Chemistry, Tel Aviv University, Tel Aviv, Israel

Peter J. H. Scott, Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Chai Hoon Soh, Department of Chemistry, National University of Singapore, Singapore

Miroslav Soural, Department of Organic Chemistry, Palacky University, Olomouc, Czech Republic

David R. Spring, Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Katsunori Tanaka, Department of Chemistry, Osaka University, Osaka, Japan

Yan Teng, Department of Chemistry, University of Hong Kong, Hong Kong, P. R. China

Patrick H. Toy, Department of Chemistry, University of Hong Kong, Hong Kong, P. R. China

Erik Van der Eycken, Laboratory for Organic & Microwave-Assisted Chemistry, Department of Chemistry, Katholieke Universiteit Leuven, Leuven, Belgium

Marc Vendrell, Department of Chemistry, National University of Singapore, Singapore

Jari Yli-Kauhaluoma, Division of Pharmaceutical Chemistry, University of Helsinki, Helsinki, Finland

Douglas D. Young, Department of Chemistry, North Carolina State University, Raleigh, NC, USA

Yongping Yu, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, P. R. China

Part I

CONCEPTS AND STRATEGIES

1

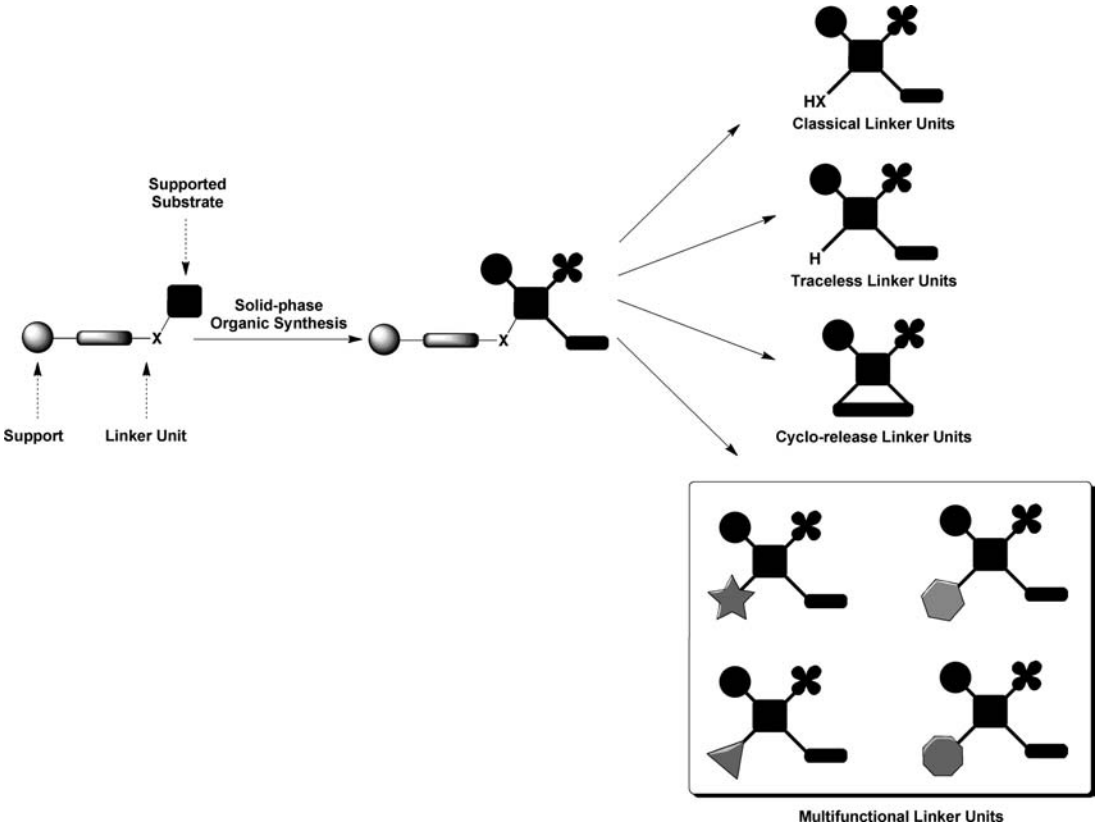
LINKER STRATEGIES IN MODERN SOLID-PHASE ORGANIC SYNTHESIS

Peter J. H. Scott

1.1 INTRODUCTION

The vast array of linker units available to the modern solid-phase organic chemist is impressive and allows a lot of exciting chemistry to be carried out using solid-phase techniques.[1–11] Linker units are molecules that possess a functional group that is used to attach substrates to a solid support and can release them at a later date upon treatment with the appropriate "cleavage cocktail." With this in mind, linker units have long been regarded as solid-supported protecting groups. Moreover, linker units are frequently lengthy molecules, which improve reactivity by holding substrates away from the polymer matrix to create a pseudo-solution-phase environment. Typically, linker units are conveniently categorized by the functionality left at the "cleavage site" in the target molecule (Scheme 1.1). Initially, following the late Prof. Merrifield's original investigations into preparing peptides on solid supports, solid-phase organic synthesis (SPOS) focused on strategies for preparing peptides and oligonucleotides. This focus was, in part, due to the relative simplicity of peptide chemistry that meant it could easily be adapted for use with solid-phase techniques. Moreover, the ease of automating peptide chemistry allowed straightforward preparation of multiple target peptides in parallel and signaled the beginning of combinatorial chemistry. Many of the classical linker units developed during this period (1960s–1990s) still represent some of the most widely used linker units in use today and an overview of these linker strategies is presented in Section 1.2. When employing a classical linker unit, a common (typically polar) functionality, that was the site of

Solid-Phase Organic Synthesis: Concepts, Strategies, and Applications, First Edition.
Edited by Patrick H. Toy and Yulin Lam.
© 2012 John Wiley & Sons, Inc. Published 2012 by John Wiley & Sons, Inc.



Scheme 1.1. Classification of modern linker units.

attachment of the molecule to the solid support, remains following cleavage of the target molecule.

In the 1990s, the use of solid-phase organic synthesis experienced an explosion in popularity. This was driven by the advent of combinatorial chemistry, as well as strategies such as split-and-mix, which exploited techniques for automating thousands of reactions in a parallel fashion. A combination of the ability to (i) run many solid-phase reactions in parallel using fritted tubes and commercial shakers, (ii) drive reactions to completion using excess reagents, and (iii) easily purify reactions by simple washing and filtration made SPOS particularly attractive to the combinatorial chemists.

Out of the combinatorial chemistry boom came the framework for modern solid-phase organic synthesis. While a lot of the early work with SPOS focused on reliable and relatively straightforward peptide coupling reactions, the ambitious library syntheses of the 1990s required access to a much more extensive array of solid-phase reactions. That decade saw initial strides made in adapting many well-known solution-phase reactions for use in the solid-phase arena, development that continues to the present day,[12–27] and a move beyond peptide and nucleotide chemistry toward preparation of small molecule libraries on solid phase.

In time, the vast libraries of combinatorial chemistry have given way to the smaller designed libraries of diversity-oriented synthesis (DOS). Rather than preparing multimillion compound libraries in the hope of finding new lead scaffolds, DOS concentrates on

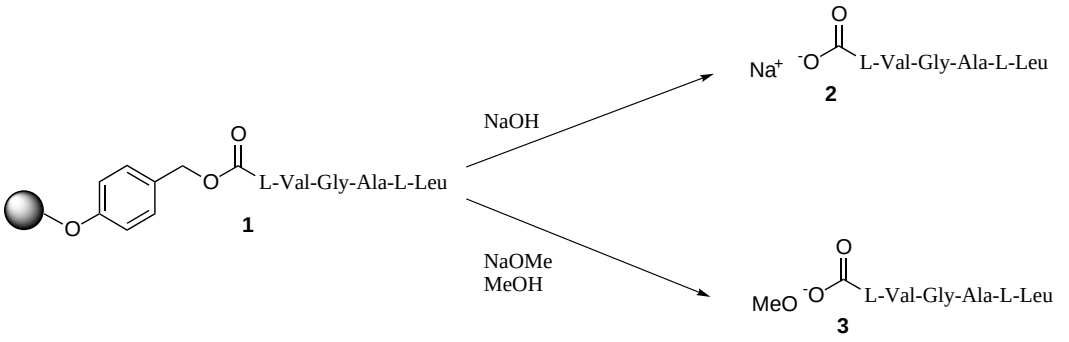
preparing smaller "focused" libraries for lead development.[28] Moreover, with the advent of chemical genetics, the interest in generating diverse compound libraries to explore chemical space has become a significant synthetic objective in its own right. These fields of research, in combination with related computational methods, are receiving much attention in the continuing quest to discover new biologically active compounds in chemical space. Reflecting these new challenges, the science of linker design in the last two decades has predominantly focused on the design and synthesis of new multifunctional linker units. Unlike the classical linker units described above that use a common cleavage cocktail for all members of a library, multifunctional linker units maximize diversity by using the cleavage step to incorporate additional structural variation into compound libraries. This final class of linker unit is discussed in Section 1.3.

1.2 CLASSICAL LINKER STRATEGIES

1.2.1 Acid and Base Cleavable Linker Units

In 1963, Merrifield reported the first example of a synthesis carried out using substrates immobilized on an insoluble polymer support.[29] In this work, the polymer Merrifield used was a chloromethylated copolymer of styrene and divinylbenzene, a polymer support that now bears his name. This polymer was functionalized with a benzyloxy group and then Merrifield was able to construct the L-Leu-L-Ala-Gly-Val tetrapeptide **1** by exploiting the Cbz protecting group strategy (Scheme 1.2). Cleavage from the ester linker unit was achieved using sodium hydroxide or a methanolic solution of sodium methoxide to generate the salt of the carboxylic acid **2** or methyl ester **3**, respectively. This work in itself represents a simple and straightforward example of multifunctional cleavage that will be discussed further later.

Reflecting this genesis in solid-phase peptide and oligonucleotide synthesis, many early linker units typically possessed a polar functional group (e.g., OH, CO_2H, NH_2, SH) that was used to attach substrates to a solid support. These linker units can be classified according to whether acidic or basic conditions are required for cleavage of target molecules, and many of them are still employed routinely in twenty-first century solid-phase organic synthesis. The main advantage is that cleavage of substrates from acid and base labile linker units can be readily achieved using mild conditions. Moreover, target molecules can frequently be isolated in sufficient purity by simple evaporation of volatile cleavage reagents.



Scheme 1.2. Merrifield's original solid-phase synthesis of a tetrapeptide.

Two of the most used acid labile linker units, illustrated in Table 1.1, are the hydroxymethylphenyl linker unit reported by Wang (Table 1.1, Entry 1)[30] and the aminomethylphenyl linker (Table 1.1, Entries 2 and 3), stabilized by an additional anisole unit, developed by Rink.[31] The *para*-oxygen atom in the Wang linker has a stabilizing effect on the cation generated upon treatment with acid, allowing cleavage to be achieved using 50% trifluoroacetic acid (TFA) in dichloromethane(DCM). As a comparison, greater stabilization of the intermediate carbocation occurs in the presence of the *ortho*- and *para*-methoxy groups of the Rink linker. This enhanced stability allows cleavage to be realized under comparatively milder conditions (e.g., 0.1–50% TFA/DCM). For example, trichloroacetylurea was cleaved from the Rink linker using 5% TFA in DCM (Table 1.1, Entry 2).[32] The use of methoxy groups to afford greater stability to the intermediate carbocation has also been exploited in development of the hyperlabile SASRIN (or HMPB) linker (Table 1.1, Entry 4).[33–36] Similar to the Rink linker, cleavage of substrates from the SASRIN linker can be achieved using mild conditions such as 0.1–1% TFA.[36]

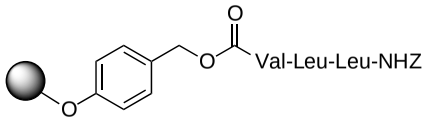
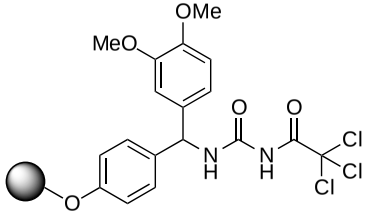
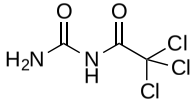
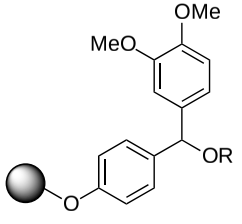
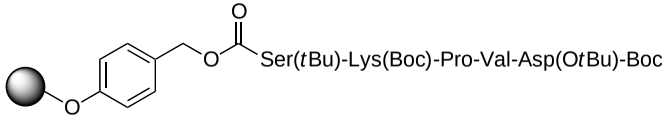
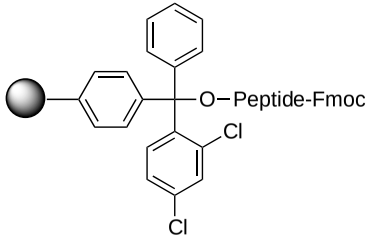
Other acid labile linker units from which substrates can be cleaved by treatment with TFA include the trityl linker units. Typically, the chlorotrityl linker unit is employed (Table 1.1, Entries 5 and 6) because it is more stable than the parent trityl linker unit, although cleavage can still be achieved using 1% TFA or acetic acid.[38,55] One advantage of using trityl linker units over, for example, the benzyl linker units discussed above is that the steric bulkiness of the trityl group makes the linkage more stable against nucleophilic bases. On the other hand, however, this steric bulkiness can cause problems if the substrate to be attached is itself a large molecule. In such situations, steric interference can reduce loading efficiency and should be taken into account before employing the trityl linker unit.

All these TFA labile linker units are well suited to SPOS using the Fmoc protective group strategy. Thus, Fmoc protecting group manipulations can be achieved using piperidine without risk of cleaving the acid labile substrate. However, if a SPOS design plans to use the Boc peptide strategy (i.e., TFA deprotection of Boc groups throughout the synthesis), then a linker unit from which substrates are cleavable with TFA is clearly not suitable. Apart from the TFA labile linkers previously discussed, a number of other acid labile linker units have been reported, allowing the ability to tailor the choice of linker unit to a given synthetic application. If it is necessary to employ the Boc protective group strategy throughout SPOS, one might select the phenylacetamide (PAM) linker (Table 1.1, Entry 7). Substrates are attached to the PAM linker through an ester linkage that is reasonably stable toward TFA. After completion of SPOS, the target molecule can then be cleaved using a stronger acid such as HF or HBr.[40]

Note that many of the linker units described above are available in multiple forms, allowing a range of substrates to be attached and cleaved. A discussion of all these related linker units is outside the scope of this chapter, but Kurosu has written a comprehensive review.[56] By way of example, multiple versions of the Rink (Table 1.1, Entries 2 and 3) and trityl linker units (Table 1.1, Entries 5 and 6)[39] are commercially available and can be selected according to the desired substrate. However, beyond these general linker units, there are also examples of substrate-specific linker units. For example, the benzhydrylamine (BHA, Table 1.1, Entry 8)[57] and Sieber (Table 1.1, Entry 9)[42–44] linkers find widespread use as acid labile carboxamide linker units, while the DHP (Table 1.1, Entry 10)[45–48] and silyl linker units (e.g., Table 1.1, Entry 11) can be used to attach alcohols to polymer supports.[58]

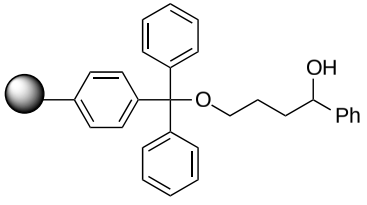
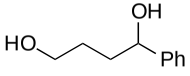
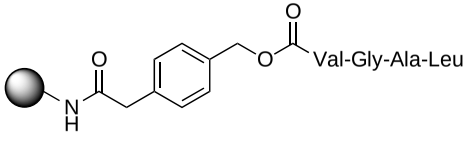
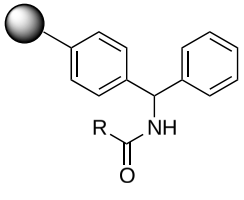
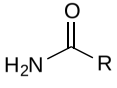
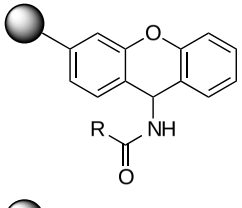
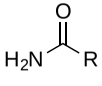
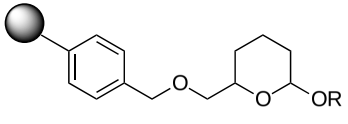
A number of linker units designed specifically for immobilization of amines have also been developed. One noticeable example exploits the versatility of the 9-phenylfluorenyl-9-yl group (PHFI). The PHFI group has previously been used as a protecting group for amines and was adapted into a linker unit by Bleicher (Table 1.1, Entry 12).[51] Cleavage from this

TABLE 1.1. Common Acid Cleavable Linker Units

	Linker	Cleavage Conditions	Product	References
1		50% TFA/ DCM	HO_2C-Val-Leu-Leu-NHZ (yield: 69%)	30
2		5% TFA/ DCM	 (yield: 72%)	32
3		5% TFA	ROH	37
4		1% TFA/ DCM	Boc-Asp(O*t*Bu)-Val-Pro-Lys (Boc)-Ser(*t*Bu)-OH (crude yield: 90%, purity: 78%)	36
5		2:2:6 AcOH: TFE:DCM	Peptide (seven examples, 86–100% yield, 69–89% purity)	38

(*Continued*)

TABLE 1.1. (*Continued*)

	Linker	Cleavage Conditions	Product	References
6		1 M HCl	 (yield: 32%)	39
7		(a) 16% HBR in 1:1 AcOH: TFA; (b) 9:1 HF:anisole	Leu-Ala-Gly-Val (a: 35% yield, b: 87% yield)	40
8		HF, 0°C		41
9		2% TFA		42–44
10		TFA–water (95:5)	ROH	45–48