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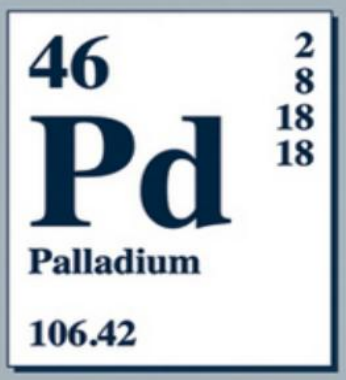
Solid-Phase Organic Syntheses

Solid-Phase Palladium Chemistry

Volume 2



EDITED BY
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VOLUME 2
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Preface

When I had the privilege of taking over as the Editor-in-Chief of *Solid-phase Organic Syntheses* from Anthony Czarnik in 2009, I chose to introduce themed volumes into the series to showcase the elegant solid-phase organic synthesis (SPOS) that has been developed in the last few decades. After completing doctoral studies in solid-phase palladium chemistry with Dr. Patrick Steel at the University of Durham, this area seemed like the natural starting point for continuation of the series. Every organic chemist is aware of, and thankful for, the development of the palladium-mediated cross-coupling reactions. Since their introduction in the late seventies and early eighties, it is fair to say that they have revolutionized the science of carbon–carbon bond formation and become a workhorse in the modern synthetic organic chemistry laboratory. Thus it seems fitting that the release of this volume coincides with the recognition of palladium chemistry and Professors Heck, Negishi, and Suzuki by the Nobel Foundation (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/).

Solid-Phase Organic Syntheses, Volume 2: Solid-Phase Palladium Chemistry initially provides an overview of solid-phase palladium chemistry by Carmen Gil (Instituto de Química Médica, Spain), showcasing the synergistic effect of combining Nobel Prize winning SPOS with Nobel Prize winning palladium chemistry. The remainder of the volume is then divided into three sections offering highlights from the field through a series of monographs covering palladium reactions on solid phase (Part 2), supported ligands and catalysts for palladium chemistry (Part 3), and the use of palladium chemistry as a multifunctional cleavage strategy (Part 4).

I am deeply indebted to the authors and editorial board that have made Volume 2 a reality. These experts in both SPOS and palladium chemistry have responded to this volume with endless enthusiasm, whether by preparing the monographs found herein, or through their careful reviewing of the reported synthetic procedures. Thanks are also due to Tony for entrusting me with the series, and Jonathan Rose at Wiley who has enthusiastically backed this project from the start and patiently seen it through to publication. I also appreciate the support and encouragement of all my family, and particularly my wife Nicole, who tolerates all the early mornings, late nights, and weekends spent in my office, which are essential for bringing such projects to fruition. I would like to dedicate this book to my grandmother, Ena, who passed away in 2011 before publication was complete.

Finally, *SPOS Volume 3* will focus on microwave-enhanced solid-phase synthesis and will be published in due course. Potential authors, as well as guest volume editors, are encouraged to submit proposals for monographs and/or future volumes to the Editor (pjhscott@umich.edu).

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October 2011

Abbreviations

AAEMA	2-(Acetoacetoxy)ethylmethacrylate
acac	Acetylacetonate
ACN	Acetonitrile
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Ar	Aryl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
BuLi	Butyl lithium
dba	Dibenzylideneacetone
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIC	*N,N*′-Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
E+	Electrophile
equiv.	Equivalents
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
GC	Gas chromatography
GC-MS	Gas chromatography–mass spectrometry
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
*i*Pr	*iso*-Propyl
LC-MS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide
*m*CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MeOH	Methanol
MW	Microwave
NMR	Nuclear magnetic resonance
OAc	Acetate

PA-Pd	Polyaniline-palladium
PANI	Polyaniline
PEG	Polyethylene glycol
Ph	Phenyl
PS	Polystyrene
PTSA	*p*-Toluenesulfonic acid
R	Alkyl
rt	Room temperature
SPOS	Solid-phase organic synthesis
*t*Bu	*tert*-Butyl
TC	Thiophene-2-carboxylate
TEA	Triethylamine
TES	Triethyl silane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMOF	Trimethyl orthoformate
TMS	Tetramethyl silyl
TMSOK	Potassium trimethylsilanolate

Part I

Introduction

Chapter 1

An Introduction to Solid-Phase Palladium Chemistry

Carmen Gil

1 Introduction

Palladium chemistry has a central position in organic chemistry because of its ability to selectively form carbon–carbon and carbon–heteroatom bonds between organic fragments [1].

Palladium-catalyzed reactions represent one of the most powerful and versatile tools in organic synthesis for the preparation of fine chemicals, pharmaceutical intermediates, active pharmaceutical ingredients, and also bioactive drugs [2].

In recent years, the synthesis of combinatorial libraries has emerged as a valuable tool in the search for novel lead structures. The success of combinatorial chemistry in drug discovery is dependent, in part, on further advances in solid-phase organic synthesis (SPOS). The generation of molecular diversity to create libraries for drug discovery was originally focused on the synthesis of peptide and nucleotide libraries. However, the limitation of such libraries is the pharmacokinetic properties of large polymeric and often hydrophilic structures that make these molecules less suitable as leads in drug discovery [3]. It is therefore desirable to develop methods to prepare small,

nonpolymeric molecules with sufficient diversity [4]. The rapid generation of such small-molecule libraries can be executed effectively by employing combinatorial or simultaneous parallel synthesis on solid supports [5–7]. Considerable work has been carried out to optimize many of the useful reactions from the organic chemists' arsenal for solid-phase conditions and to design versatile linkers [8, 9]. In this respect, palladium chemistry is a powerful synthetic methodology for the preparation of libraries of small organic compounds by multiparallel synthesis schemes on solid supports [10]. In particular, the development of reliable procedures with a wide scope for the formation of carbon–carbon bonds is of great importance together with the new solid-supported reagents, ligands, and catalysts [11, 12].

Some of the commonly employed palladium-catalyzed organic couplings that lead to the formation of carbon–carbon or carbon–heteroatom bonds have been named by prominent researchers in this field, such as Stille, Heck, Suzuki, Sonogashira, Kumada, Negishi, Nozaki–Hiyama, Buchwald–Hartwig, and Tsuji–Trost [13]. These reactions are usually very efficient, although the main drawback is that palladium is often retained by the isolated product. This is, however, a serious drawback because pharmaceutical ingredients official guidelines place exacting limits on the permissible levels of heavy-metal contaminants. In this sense, the use of resin-bound catalyst systems is particularly beneficial in reducing metallic contamination of the final products [14].

Numerous research groups have developed new metal complexes and ligands, expanding the scope of these transformations to give access to more complex molecules [15, 16]. The development of solid-phase palladium chemistry is also another approach to access such molecules, offering straightforward syntheses, without tedious and time-consuming purifications.

2 Palladium-Catalyzed Reactions

Palladium-catalyzed coupling reactions are very efficient for the introduction of new carbon–carbon bonds onto molecules attached to solid supports. The mild reaction conditions, the compatibility with a broad range of functionalities, and high reaction yields have made this kind of transformation a very common tool for the combinatorial synthesis of small organic molecules.

2.1 Heck Reactions

This reaction has become one of the most powerful tools to bring up complex structural changes, in particular when conducted intramolecularly. Owing to the mild conditions employed and the toleration of many functional groups, the Heck reaction has been successfully adapted in a broad scope to organic synthesis in the solid phase [11, 17]. This reaction between terminal olefins and alkyl/aryl halides has been widely employed in various intra- and intermolecular versions in solid phase, taking advantage of the ready accessibility of starting materials. The Heck reaction involves immobilized aryl or alkenyl halides with soluble alkenes as well as vice versa (Scheme 1.1) [18, 19].

Figure 1.1 Heck reactions in solid-phase synthesis [18].