

Laboratory of Organic Chemistry
Department of Chemistry
Faculty of Science
University of Helsinki
Finland

PALLADIUM- AND COPPER-CATALYSED REACTIONS OF UNSATURATED AMINES ON SOLID SUPPORT

Tuomo Leikoski

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Science of
the University of Helsinki, for public examination in lecture room A129,
Department of Chemistry, on 6th June 2014, at 12 noon.

Helsinki 2014

Supervisors

Docent Jussi Sipilä

Laboratory of Organic Chemistry, Department of Chemistry, Faculty of Science
University of Helsinki
Finland

Professor Jari Yli-Kauhaluoma

Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy
University of Helsinki
Finland

Reviewers

Professor Ari Koskinen

Department of Chemistry, School of Chemical Technology
Aalto University
Finland

Professor Robert Franzén

Department of Chemistry and Bioengineering
Tampere University of Technology
Finland

Opponent

Professor Tõnis Kanger

Chair of Organic Chemistry, Department of Chemistry, Faculty of Science
Tallinn University of Technology
Estonia

ISBN 978-952-10-9862-8 (pbk.)

ISBN 978-952-10-9863-5 (PDF)

Unigrafia Oy
Helsinki 2014

Abstract

Formation of carbon–carbon bonds constitutes the basis of synthetic organic chemistry. The growing demand of safer and environmentally friendlier processes, combined with continuing need for more efficient and selective reactions, has given challenges to industrial and fundamental academic research. The objective of this thesis was to develop novel ways to perform important carbon–carbon bond-forming reactions on solid support. Of special focus were palladium- and copper-catalysed reactions of unsaturated amines.

Polymer-bound propargylamine and allylamine were arylated successfully by the palladium-catalysed Sonogashira and Heck reaction, respectively. Additionally, allenes were produced in the Crabbé homologation of polymer-bound propargylamine, where copper acetylide is acting as an intermediate. All of these reactions would give rise to biologically interesting molecules: 1,3-arylamino propanes after hydrogenation of the Sonogashira and Heck products and nitrogen-containing allenes by the Crabbé reaction. By varying the aryl iodide in solution, a series of arylated propargylamines and allylamines were synthesised and isolated as their acetamides. From the polymer-bound propargylamine, various allene amides were obtained after *N*-acylation followed by the Crabbé reaction. It was also briefly explored if the arylation of propargylamine on solid-phase could be possible without expensive palladium *via* the Castro-Stephens reaction, using a polymer-bound copper acetylide and the aryl iodide in solution. However, attempts to perform the first Castro-Stephens reaction on solid-phase failed.

Free amines are problematic in the Sonogashira and Heck reactions, due to coordination with the palladium catalyst and nucleophilicity toward the allene in the Crabbé reaction. These incompatibilities were solved by using the resin linkers simultaneously as protecting groups for the amines: as carbamates in the Sonogashira and Heck reaction, and as *N*-acyltriazines in the Crabbé reaction. For the Heck reaction, finding the right reaction conditions turned out to be particularly difficult, the additional challenges being the narrow temperature window and the need to avoid polyarylation. Nevertheless, a regioselective β -arylation could be performed giving similar yields as in the Sonogashira studies. In summary, alternative methods to perform important carbon–carbon bond-forming reactions on solid support were developed.

*“Wenn ein Chemiker kein Mystiker wird,
ist er auch kein Chemiker”*

Albert Hofmann

Acknowledgements

This work was carried out in the University of Helsinki, at the Division of Pharmaceutical Chemistry, Faculty of Pharmacy, and at the Laboratory of Organic Chemistry, Department of Chemistry, Faculty of Science. There are several people, for whom it is impossible to mention all names here, who have contributed to the success of this work.

I am grateful to my supervisor at the Division of Pharmaceutical Chemistry, Professor Jari Yli-Kauhaluoma, for introducing me into the field of solid-phase synthesis and into the scientific way of thinking. Without Jari's contribution this project would never have started. I would like to express my gratitude to my supervisor at the Laboratory of Organic Chemistry, Docent Jussi Sipilä, for adopting me into his research group to complete this thesis. Numerous discussions with Jussi, within and outside of science, have been particularly important for me. Moreover, his long-term experience in the scientific community has been of great value in avoiding academic pitfalls.

I thank Professor Risto Kostiainen, former head of the Division of Pharmaceutical Chemistry, and Professor Ilkka Kilpeläinen, head of the Laboratory of Organic Chemistry, for providing the excellent research facilities, at my disposal. I am grateful to Professor Mikko Oivanen for his never-ending interest and help to bring my work to completion. I also thank Professors Ari Koskinen and Robert Franzén for reviewing this thesis.

I greatly acknowledge and appreciate the financial support for this project from TEKES, Juvantia Pharma Ltd., Orion Corporation, Hormos Medical, Academy of Finland, Drug Discovery and Development Technology Center (DDTC) research programme of the University of Helsinki, The Finnish Work Environment Fund, Faculty of Science, the Chancellor of the University of Helsinki and Alfred Kordelin Foundation.

I thank my co-authors Dr. Jorma Matikainen, Sirkku Jäntti, Pauli Wrigstedt and Jussi Helminen for their help in the analytical methods and fruitful discussions. I am also grateful to Dr. Alistair King for his efforts in language checking. Although this work has mainly been a one-man project, I have never felt alone when working on it. I thank my colleagues in Viikki, especially Dr. Taina Sten, Dr. Päivi Uutela, Dr. Kirsi Harju, Irene Kylänlahti and Ismo Väisänen. Positions change but contacts do not disappear. I express my gratitude to my colleagues in Kumpula, who have created a pleasant working atmosphere. I highly appreciate the friendly discussions with Dr. Pirkko Karhunen, Dr. Maarit Lahtinen, Paula Nousiainen, Harri Kiljunen and Katja Sievänen, as well the unselfish support I have received from all in the last few months of this process.

My deepest thanks and respect belong to my wife Mervi, whose patience has been endless. Thank you for being by my side on both hard and delightful moments.

Contents

Abstract	3
Acknowledgements	4
List of original publications	7
Abbreviations	8
1 Introduction	9
1.1 The need for alternative carbon–carbon bond-forming methods	9
1.2 Solid-phase synthesis	10
1.2.1 General benefits and drawbacks of solid-phase methods	11
1.2.2 Solvents and swelling properties of resins	13
1.3 Aryl- and heteroarylaminopropane derivatives	15
1.3.1 Use and significance	15
1.3.2 Access to 1,3-arylaminopropanes by solid-phase methods	16
1.4 The Sonogashira coupling	17
1.4.1 Sonogashira couplings on solid-phase	19
1.4.2 The Castro–Stephens reaction	20
1.5 The Heck reaction	21
1.5.1 Regio- and stereoselectivity – use of additives	24
1.5.2 Heck reactions on solid-phase	27
1.6 Free and protected amines as reactants	28
1.7 The allene amines and amides	29
1.7.1 The Crabbé reaction	30
2 Aims of the study	32
3 Results and discussion	33
3.1 The Sonogashira coupling of polymer-supported propargylamine	33

3.1.1 Preliminary experiments with the Castro–Stephens reaction	36
3.2 The Heck reaction of polymer-supported allylamine	38
3.3 The Heck or Sonogashira reaction for construction of the arylpropane unit?	41
3.4 Solid-phase synthesis of allene amides	42
3.4.1 The triazene linker in solid-phase synthesis	42
3.4.2 The Crabbé homologation of polymer-supported propargylamine	43
4 Conclusions	46
5 Experimental	48
5.1 General	48
5.2 The Castro–Stephens reaction with a stoichiometric amount of preformed copper acetylide on solid-phase	48
5.2.1 Copper acetylide from polymer-bound propargylamine	48
5.2.2 Reaction of the polymer-bound copper-acetylide with 4-iodonitrobenzene, cleavage and acetylation	48
5.3 The Castro–Stephens reaction, with a catalytic amount of copper acetylide formed <i>in situ</i> , on solid-phase	49
5.3.1 Reaction of polymer-bound propargylamine with 4-iodonitrobenzene and a catalytic amount of copper(I) iodide, cleavage and acetylation	49
References	50

List of original publications

This thesis is based on the following original publications:

- I Leikoski, T., Kallonen, S., and Yli-Kauhaluoma, J. The Sonogashira Coupling of Polymer-Supported Propargylamine with Aryl Iodides *Helv. Chim. Acta* **2010**, *93*, 39–47.
- II Leikoski, T., Wrigstedt, P., Helminen, J., Matikainen, J., Sipilä, J., and Yli-Kauhaluoma, J. The Heck Reaction of Polymer-Supported Allylamine with Aryl Iodides *Tetrahedron* **2013**, *69*, 839–843.
- III Leikoski, T., Wrigstedt, P., Matikainen, J., Sipilä, J., and Yli-Kauhaluoma, J. Solid-Phase Synthesis of *N*-(buta-2,3-dien-1-yl)amides by the Crabbé Reaction *Can. J. Chem.* **2013**, *91*, 38–42.

The publications are referred to in the text by their Roman numerals. This thesis contains also data and results not presented in these publications.

Abbreviations

Ac	acetyl
Bu	butyl
<i>c</i> -hex	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
Et	ethyl
FTIR	Fourier transform infrared spectroscopy
GC-MS	gas chromatography-mass spectrometry
<i>i</i> -Pent	isopentyl
Me	methyl
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
<i>o</i> -Tol	<i>o</i> -tolyl
Ph	phenyl
ppb	parts per billion
ppm	parts per million
rt	room temperature
S RAM	Standard Rink Amide resin
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	4-toluenesulfonyl

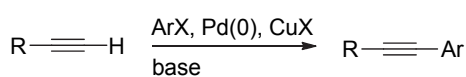
1 Introduction

1.1 The need for alternative carbon–carbon bond-forming methods

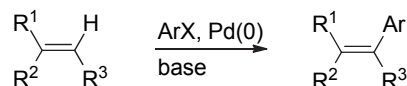
Carbon–carbon bond-forming reactions constitute the basis for the construction of complex organic molecules and are the most important connections in organic synthesis. Despite the existing knowledge and methodology, development of a new synthesis route is always a time-consuming process. Therefore, the more comprehensive the selection of methods is, the more effective are the tools available to face the synthetic challenges. On the other hand, during the past few decades the impetus for safer and environmentally friendlier processes has grown. The research, development and actions made in the chemical industry represent the most immediate answers to these demands, but the fundamental research of synthetic organic chemistry has nonetheless its own important contribution to the entity of ‘green chemistry’.

The possibility to utilise solid-phase synthetic methods was the starting point for this research. These methods have their own advantages and offer their own partial answers to the gradually increasing standards of green chemistry. It is possible to bind highly reactive, explosive, malodorous or toxic chemicals covalently on an insoluble polymer, prior to subjecting them to further chemical modification. However, even if the reaction would be convertible to solid-phase, the total gain is not always straightforward as the possible lower yields, more complex procedures or increased consumption of solvents, upon isolation and purification, may surpass the desired advantages.

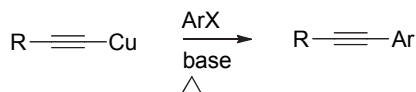
The objective of this study was not the targeted synthesis of specific molecules, but instead to develop new environmentally friendlier and safer methods to be available for analogous reactions. From the extremely broad area of carbon–carbon bond-forming reactions, the efforts were focused on the Sonogashira, Castro-Stephens, Heck and Crabbé reactions (**Figure 1**) on solid support. These four reactions are all well-known methods in constructing basic units and substructures in synthetic products. However, the number of published solid-phase versions of the Sonogashira and Heck reactions is relatively limited. Moreover, before these studies there were no examples in the literature about the Crabbé and Castro-Stephens reaction on solid support.



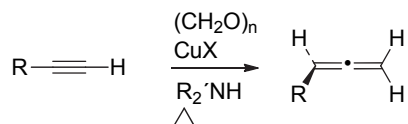
Sonogashira



Heck



Castro-Stephens



Crabbé

Figure 1 The carbon–carbon bond-forming reactions studied in this thesis.

One important objective in the solid-phase studies was the comparison of the effectiveness of the Sonogashira and the Heck reaction on polymer-bound propargylamine and allylamine, respectively. Reaction with aryl iodides allows for construction of the biologically and pharmacologically important 1,3-arylamino propane moiety. The one-carbon atom homologation of polymer-bound propargylamine, using the Crabbé reaction, was chosen for synthesis of allene amine derivatives, which are highly versatile synthetic intermediates. In all of these solid-phase reactions, the synthetic linker to the polymer offers the advantageous possibility to simultaneously protect the amino functionalities. Nucleophilic amines strongly complex to the palladium catalysts, in the Sonogashira and Heck reactions, but can also react with allenes under the Crabbé reaction conditions. On the other hand, the Castro-Stephens reaction would enable the same transformation as in the Sonogashira coupling, but without expensive palladium, and therefore, also in presence of amines.

1.2 Solid-phase synthesis

Since the preliminary studies in the 1960's by Merrifield in the field of peptide synthesis,¹ the research and applications of solid-phase synthesis have expanded into all fields of synthetic organic chemistry. This includes the synthesis of low molecular weight fine chemicals, such as pharmaceuticals.^{2, 3} The basic idea of solid-phase synthesis is to bind one of the reactants covalently on an insoluble solid support, most commonly on divinylbenzene-crosslinked polystyrene resin, while keeping all other reactants in solution. In a multistep synthesis the polymer-bound product is not cleaved until the final synthetic operation is performed. After each reaction step the resin is simply washed to remove soluble byproducts and excess reagents.

Numerous organic reactions have been converted to solid-phase and very sophisticated automated parallel methods have been developed for the efficient production of vast compound libraries, in the field of combinatorial chemistry. There are hundreds of specifically functionalised resins commercially available, with various loadings of the functionality, particle size, swelling properties etc. Although hydrophobic polystyrene resins are the most common support, there are also polystyrenes derivatised with hydrophilic chains of variable size available (the most well-known are the TentaGel, HypoGel and ArgoGel resins, named by their manufacturer), making them compatible with water. There are functionalised inorganic materials, such as glass or silica, available as well. However, their use and significance are limited compared to the polystyrene-based resins.

1.2.1 General benefits and drawbacks of solid-phase methods

Compared to conventional syntheses in solution, solid-phase syntheses possess several advantages – but not straightforward – most of which are summarised briefly as follows:

- Work-up of the reactions is easy. The solid resins are separated from the reagents and soluble byproducts by filtering and washing.
- The crude products are obtained often with high purity.
- Only final purification is necessary in multi-step syntheses.
- The reaction conditions are simple. Typically the resins are shaken or stirred with the solvents and reagents.
- There are highly developed automated techniques available.
- There are possibilities and methods for combinatorial synthesis of large product libraries.
- Safety can be improved by immobilising toxic, volatile, flammable, explosive or malodorous compounds on resins.
- Polymer-bound reagents are nonvolatile and odourless.
- Labile or reactive precursors can be stabilised by immobilising them on resins.
- Cleaning the reactors and other equipment to quality standards is not as laborious as with solution-phase batch reactions.
- High-boiling solvents are easily removed by filtering and washing.

- Low-boiling reagents can be immobilised and treated at high temperatures under atmospheric pressure.
- Resins can serve also as protecting groups for sensitive functionalities.
- Intermolecular reactions between polymer-bound reagents are normally avoided if the loading of the resin is low enough
- Reactions are often highly regioselective.

However, there are also many drawbacks, many of which are very case-specific and unpredictable:

- Reactions are much slower compared to unsupported solution-phase batch reactions, due to the bulkiness and limited mobility of the polymer.
- Not all reactions are applicable on solid-phase, e.g. due to steric or stereoelectronic factors. The origin of the failure is often difficult to find.
- The attachment to and cleavage from the polymer normally results in two extra steps.
- The cleavage step can be difficult despite an otherwise successful modification.
- In order to enable the reaction the polymer must be swollen. Unfortunately, many common organic solvents are not capable for this. (See **Table 1**).
- Yields in solid-phase synthesis can be variable.
- In a multi-step synthesis, determination of the yield of an individual synthesis reaction is tricky.
- Reactions at high temperatures are limited due to degradation or decomposition of the resins.
- High consumption of solvents in the washing steps may surpass the ‘green’ benefits.
- Vigorous stirring of the reaction mixtures can easily lead to mechanical degradation of the polymer beads.

- Dry polymers are often difficult to handle, especially in bulk, as they are dusty, adherent and flowing powders.
- Monitoring reaction progress is inconvenient (e.g. by FTIR, solid-state NMR or by analysis of the cleavage mixture).

1.2.2 Solvents and swelling properties of resins

An unhindered contact between the reagents on solid support and in solution is necessary for a successful reaction. The divinylbenzene-crosslinked polystyrene resins are insoluble, but in certain solvents they swell strongly. They can form a thick polymer gel, where the polymer-bound reagent can under favourable conditions act as in a solvent-like environment. This behaviour is highly dependent on the solvent, but also on the resin type, particle size, linkers, functional groups and on the attached reagents themselves. In an appropriate solvent, with excellent swelling properties, the volume of the resin can be several times larger than in an unsuitable solvent (polymer-shrinking). Representative examples of the swelling properties of hydrophobic Wang resin and hydrophilic TentaGel Standard Rink Amide resin (S RAM), in common solvents, have been collected in **Table 1**.⁴

Polar aprotic solvents, such as DMF or NMP, generally swell polystyrene resins effectively. Other common solvents in solid-phase synthesis are THF, 1,4-dioxane, dichloromethane, chloroform, pyridine and toluene. On the other hand, water, aliphatic alcohols and hydrocarbons as well diethyl ether are incompatible with hydrophobic resins due to their strong non-solvating properties. The swelling properties of hydrophilic polystyrene resins are somewhat different and strongly dependent on the resin type and the attached functionalities. Although it is not possible to use polymer shrinking solvents in reactions, they are very beneficial in washing sequences with swelling solvents. Their use allows for the polymer network to be closed and reopened from various sites, thus aiding the removal of impurities.

A particular, but very simple, so called low-solvent volume method has been developed in order to maximise the reaction rate and, on the other hand, minimise consumption of the reaction solvent.⁵ The principle is to use just the minimum amount of solvent needed for complete swelling of the resin. Because the reaction takes place solely on the surface of the swollen polymer, excess solvent phase causes unnecessary dilution of the soluble reactants. This method is applicable in most solid-phase reactions, unless evaporation of the solvent is too fast, and it should be applied whenever possible to enhance the reaction rate and economy.

Table 1 The swelling properties of Wang resin and TentaGel Standard Rink Amide resin in common solvents^{4, a}

Solvent	Wang resin, low loading (ml / g resin)	TentaGel S RAM (ml / g resin)
<i>N</i> -methyl-2-pyrrolidone	6.4	4.4
Pyridine	6.0	4.6
Tetrahydrofuran	6.0	4.0
<i>N,N</i> -Dimethylacetamide	5.8	4.0
Chloroform	5.6	5.6
1,4-Dioxane	5.6	4.2
Dichloromethane	5.4	5.6
<i>N,N</i> ,-dimethylformamide	5.2	4.4
1,2-Dichlorobenzene	4.8	5.2
Ethylene glycol	4.8	2.0
1,2-Dimethoxyethane	4.8	2.0
Butanone	4.4	2.0
Benzene	4.4	4.4
1,2-Dichloroethane	4.4	5.4
Dimethyl sulfoxide	4.2	3.8
Ethyl acetate	4.2	2.0
Toluene	4.0	3.6
Acetone	3.6	2.8
Xylene	3.0	2.0
Tetrahydrofuran-Water 1:1	2.8	5.2
Acetic acid	2.8	5.2
Diethyl ether	2.8	2.0
Carbon tetrachloride	2.4	2.8
Acetonitrile-Water 1:1	2.0	4.0
<i>N,N</i> -dimethylformamide-water 1:1	2.0	4.0
2-Propanol	2.0	2.0
Acetonitrile	2.0	4.0
Ethanol	2.0	1.8
Trifluoroacetic acid	2.0	6.4
Heptane	1.6	1.6
Methanol	1.6	3.6
Water	1.6	3.6

^aReprinted from Tetrahedron Letters, Vol 39, Santini, R.; Griffith, M. C.; Qi, M., A Measure of Solvent Effects on Swelling of Resins for Solid Phase Organic Synthesis, 8951–8954, Copyright (1998), with permission from Elsevier.

1.3 Aryl- and heteroarylaminopropane derivatives

1.3.1 Use and significance

Aromatic rings with a three-carbon atom substituent are widespread in nature. For example, they form the structural backbone of lignin sub-units⁶ and lignans.⁷ Additionally, 1,3-aryl- and 1,3-heteroarylaminopropane (and also the homologous ethane and butane) moieties are found in numerous natural and synthetic, biologically important and pharmacologically active molecules. These are often associated, for example, with central nervous system stimulating,⁸ antimalarial,⁹ positive inotropic¹⁰ and antifungal¹¹ properties.

Well known examples of arylaminopropane derivatives are selegiline, which is applied together with L-dopa in the treatment of Parkinson's disease,¹² and enalapril, which is used in the treatment of hypertension.¹³ Novel antidepressants based on serotonin reuptake inhibition, such as fluoxetine and duloxetine, are also modified arylaminopropanes (**Figure 2**).¹⁴

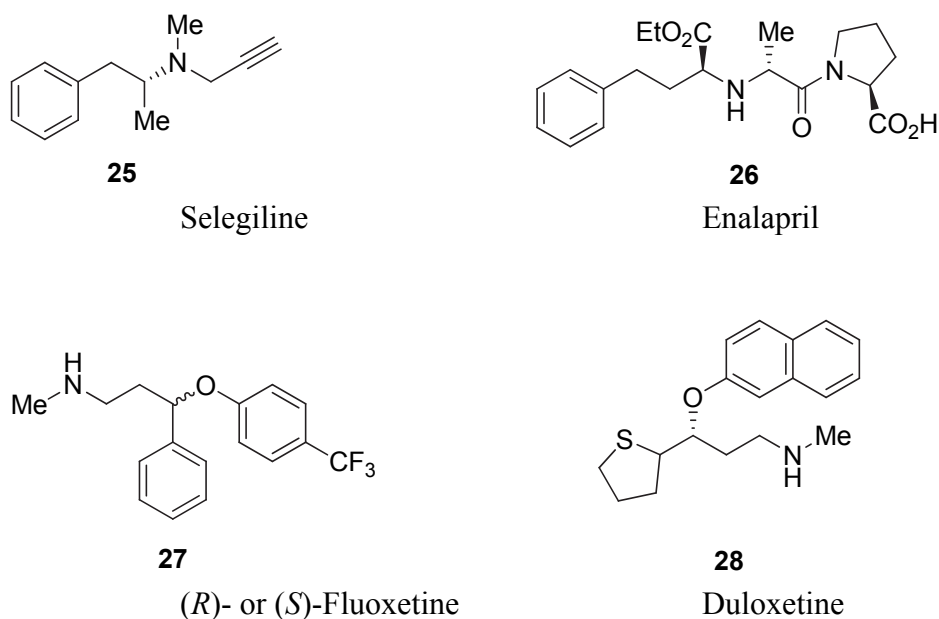
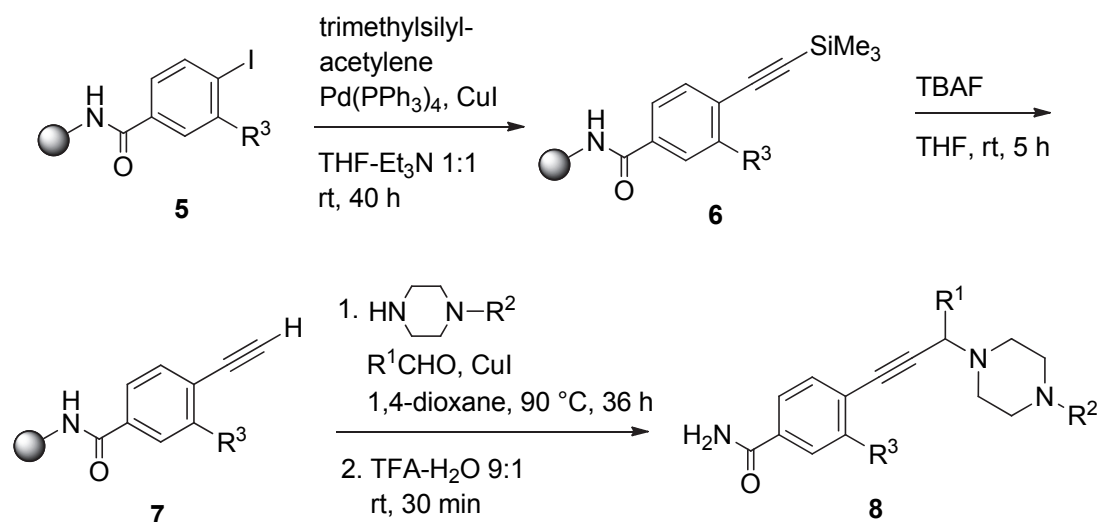


Figure 2 Examples of arylaminopropane derivatives as pharmaceuticals¹²⁻¹⁴

The general importance and versatility of the 1,3-arylamino propane unit was one starting point of this study. The objective was to develop new solid-phase synthetic methods for low molecular weight model compounds containing this substructure. The efforts were focused on palladium- and copper-catalysed coupling reactions, among which special focus was on the Sonogashira and Heck reactions. The expected products in these Sonogashira and Heck studies would be 1,3-arylamino-1-propynes (3-arylpropargylamines) and (*E*)-1,3-arylamino-1-propenes (cinnamylamines), respectively. These kinds of products can be converted to the corresponding propanes by reduction but the unsaturated derivatives may also be interesting. Some propargylamines, or their metabolites, selectively inhibit physiologically crucial enzymes, such as aldehyde dehydrogenase¹⁵ and monoamine oxidase B.¹⁶ On the other hand, modified cinnamylamines have been studied as inhibitors of bovine plasma semicarbazide-sensitive amine oxidase.¹⁷ Generally they are also important synthetic intermediates, for example, as precursors in 4-*endo-trig* cyclisations to form azetidines.¹⁸

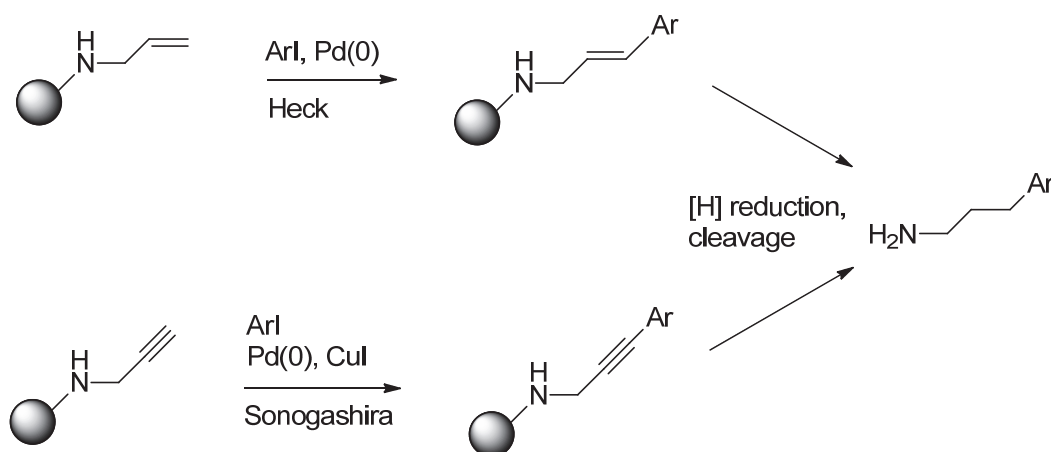
1.3.2 Access to 1,3-arylamino propanes by solid-phase methods

Due to the relative simplicity of the 1,3-arylamino propane moiety, the number of methods available for its construction on solid-phase, are voluminous. On the other hand, neither the solid-phase synthesis of the aromatic ring with a three-carbon atom unit, nor the solid-phase synthesis of 1,3-arylamino propanes themselves, has been studied systematically. As an interesting example, the solid-phase synthesis as presented by Dyatkin and Rivero can be mentioned, where a set of tertiary 3-arylpropargylamines were prepared using a combination of the Sonogashira and Mannich reactions (**Scheme 1**).¹⁹ This method offers the freedom to vary the secondary amine as a substrate. However, the aromatic precursor is limited to iodobenzoic acids.



Scheme 1 Solid-phase synthesis of tertiary 3-arylpropargylamines using a combination of the Sonogashira and Mannich reactions¹⁹

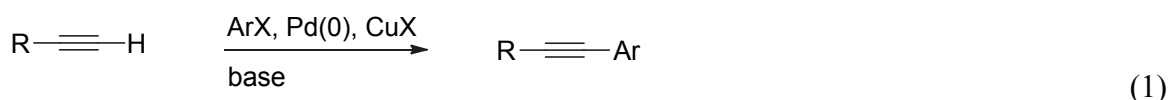
The research was focused on arylation of polymer-bound propargylamine and allylamine by the Sonogashira and Heck reactions, respectively (**Scheme 2**). The number of publications concerning these reactions on solid-phase is relatively limited. On the other hand, the palladium-catalysed coupling reactions, as modern and efficient chemistry, have been widely studied and hence, the methodology available is comprehensive. Furthermore, the palladium couplings have a wide functional group tolerance and, for the reactant in solution, a vast number of substituted aryl iodides are commercially available. Amines are generally incompatible with palladium catalysts (see section 1.6), but the point of attachment on the polymer can be simultaneously used as a protecting group for the amine.



Scheme 2 Solid-phase methods for the syntheses of 1,3-arylaminopropanes using the Sonogashira and Heck reactions prior to reduction

1.4 The Sonogashira coupling

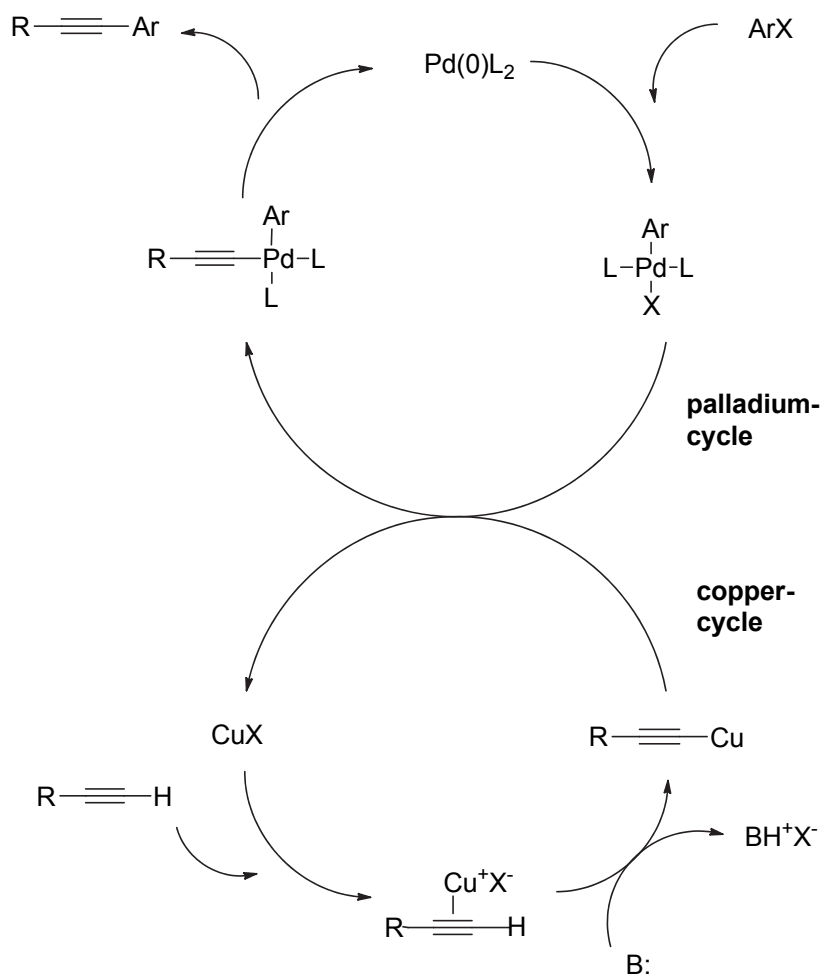
The Sonogashira coupling was introduced by Kenkichi Sonogashira in 1975.²⁰ Since then it has developed into one of the most important and reliable carbon–carbon bond-forming methods.²¹ The coupling reaction gives an internal acetylene from a terminal acetylene, combined with an aryl (and heteroaryl or vinyl) iodide or bromide (sometimes tosylate, mesylate and other pseudohalides), with a base, with a palladium(0) catalyst and with a copper(I) co-catalyst (eq. 1). It is often considered a palladium-catalysed version of the reaction between a copper acetylide and aryl halide, the Castro–Stephens reaction,²² and has largely displaced the latter due to much milder reaction conditions and better yields. The aryl halide can often be substituted in any position with very diverse groups, although electron donating groups at *ortho* or *para* positions can sometimes be problematic. Additionally, functionalities that coordinate strongly to the palladium atom, such as free amines, often retard the reaction regardless if they are attached to the acetylene or aryl halide. Otherwise, the Sonogashira coupling has a very wide functional group tolerance.



Many modifications of the Sonogashira coupling have been developed. Common catalysts are complexes of zero-valent palladium, such as Pd(PPh₃)₄ or Pd₂(dba)₃. Alternatively, Pd(II) precatalysts, mostly Pd(PPh₃)₂Cl₂, that are easily reduced to the catalytically active zero-valent form in the reaction medium, can be used. Copper(I) iodide is the most common co-catalyst and the use of a wide variety of organic and inorganic bases is possible. Soluble organic bases are often beneficial, because they efficiently neutralise the acid HX formed in the reaction. Among the most common solvents used are THF, DMF, dichloromethane and 1,4-dioxane. Excellent results have been obtained when pyrrolidine or piperidine has been used simultaneously as a base and solvent.²³ The reaction is very often completed within a few hours at room temperature.

Like for all palladium-catalysed coupling reactions, it is not possible to present an unequivocal mechanism for the Sonogashira coupling. In **Scheme 3** the mechanism shown with a palladium cycle and a copper cycle is a very common version.^{20, 24, 25} Formation of the aryl palladium halide ArPdXL₂, where the assisting ligand L is very often PPh₃, and of the copper acetylide intermediate is undoubtedly necessary for the progress of the coupling. Moreover, it is considered that the palladium and copper cycles join simultaneously to give the transmetallation product.

Some of the proposed mechanistic steps are very controversial. For instance, amines or carbonates, typical bases used in Sonogashira reactions, are not basic enough for quantitative deprotonation of acetylenes. It has been postulated that coordination of Cu(I), as a Lewis acid, to the acetylene triple bond could increase the acidity of the terminal proton, thus leading to the copper acetylide with the help of the base.²⁴ On the other hand, there are a lot of procedures without added copper(I) cocatalyst with successful coupling. However, the observation that some commercially available palladium(II) salts actually contain traces of copper as a contaminant has doubted the existence of copper-free Sonogashira reactions.²⁶



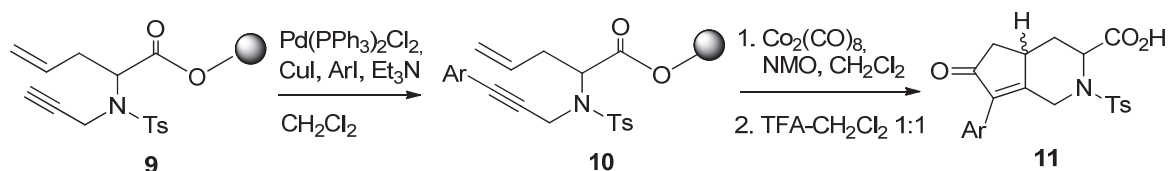
Scheme 3 The proposed mechanism for the Sonogashira coupling^{20, 24, 25}

1.4.1 Sonogashira couplings on solid-phase

There are various approaches presented in the literature where the high performance of the Sonogashira reaction has been combined with the advantages of solid-phase methods (page 11).^{19, 27-53} It is possible to immobilise the acetylene as well as the aryl halide (mainly iodide), or even the palladium catalyst complex or amine base on solid support. Performing the Sonogashira coupling on solid-phase is in some respect particularly beneficial. For example, formation of the diyne byproduct is avoided if the acetylene component is covalently bound on polymer. Additionally, the typically mild reaction conditions and excellent yields allow for particularly convenient preparation of large combinatorial libraries by automation.

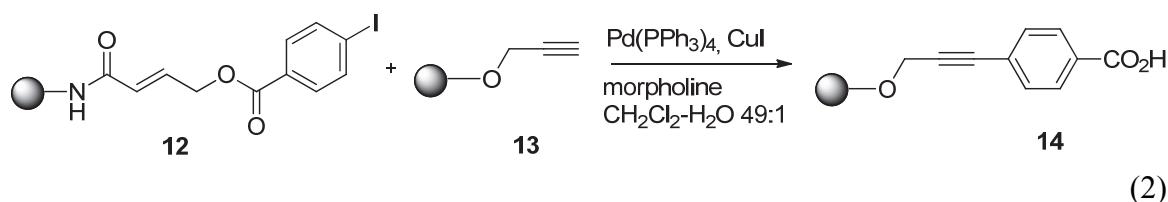
Some reports in the literature are exemplary. Nelson *et al.* generated a resin-bound terminal acetylene by deprotecting the trimethylsilyl group with *n*-Bu₄NF and subjected it

to Sonogashira conditions, with (trimethylsilyl)acetylene-functionalized aryl iodides. After repeating the reaction cycles, oligomeric arylacetylenes were obtained as final products.²⁷ Huang and Tour applied a related sequence-specific methodology in solid-phase synthesis of linear, oligomeric arylacetylenes by subsequently introducing aryl diiodides and monoprotected phenylenebis[acetylenes].³⁵ Bolton *et al.* used the Sonogashira coupling in the arylation of a Wang resin-bound olefinic acetylene, prior to its Pauson–Khand cyclisation (Scheme 4).²⁸



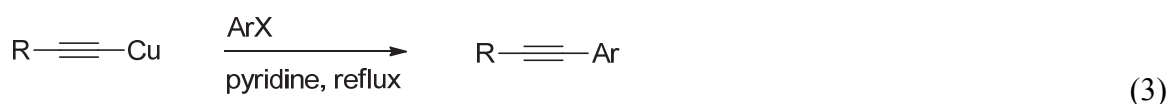
Scheme 4 The Sonogashira coupling followed by the Pauson–Khand cyclisation on solid-phase²⁸

Tulla-Puche and Barany applied an interesting strategy where both reactants were attached on different resins, with Wang and allyl linkages. Treatment with Pd(0) cleaves the allyl-linked component, which subsequently undergoes a resin-to-resin transfer Sonogashira reaction (eq. 2).⁵²



1.4.2 The Castro–Stephens reaction

Before the development of the Sonogashira coupling the same transformation had been accomplished by the reaction of a copper acetylide with aryl halides, referred to as the Castro–Stephens reaction (eq. 3). This reaction was introduced in 1963 by C. E. Castro and R. D. Stephens. In its typical form a preformed copper acetylide reacts with an aryl iodide in refluxing pyridine.^{22, 54}



In a variation of this method a catalytic amount of copper(I) iodide is used, with triphenylphosphine as an additive and K_2CO_3 as a base, in DMF or DMSO at 120 °C.⁵⁵ This catalytic version has not formally been referred to as the Castro–Stephens reaction, although analogous involvement of the copper acetylide in the key reaction step is very plausible.

Although it is possible to use acetylenes and aryl halides with a diverse substitution and the yields can be good to excellent, the importance of this reaction is low today. The Sonogashira coupling gives the same products under much milder conditions, with even better yields and wider functional group tolerance. Despite this fact new interest in the Castro–Stephens reaction, with mechanistic considerations, has appeared recently.

Zuidema and Bolm studied the coupling of aryl acetylenes with aryl iodides using the preformed catalyst from copper(II) chloride and *N,N'*-dimethylethylenediamine. The ligand-accelerated catalysis, enhanced by the excess of the diamine, significantly increased the reaction rate and yield.⁵⁶ Wang *et al.* managed to couple phenylacetylene with an isolated, highly reactive organocopper(III) complex, prepared from an iodo-substituted azacalix[1]arene[3]pyridine derivative and copper(I) trifluoromethanesulfonate. Because the same product was obtained by the Castro–Stephens reaction of the free precursors, an arylcopper(III) intermediate was suggested for the reaction.⁵⁷

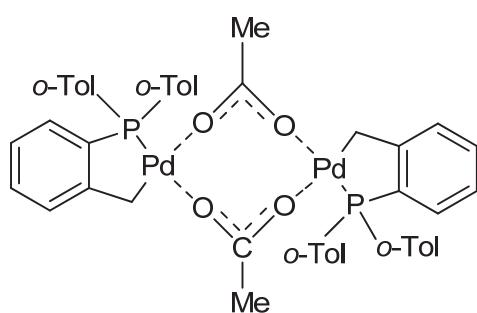
However, there are no literature examples of the Castro–Stephens reactions on solid-phase. Development of one would give an alternative method to synthesise aryl acetylenes, without the use of expensive palladium catalysts. This would be especially beneficial for large-scale preparation. Moreover, considering the objective of this study was to synthesise arylaminopropane derivatives, on solid support, a palladium-free medium would be very attractive in order to avoid the problem of reaction retarding palladium-nitrogen coordination.

1.5 The Heck reaction

The Heck reaction has been extensively studied, developed and utilised in the arylation and vinylation of olefins (eq. 4), since Richard Heck and Tsutomu Mizoroki independently introduced it in the early 1970's.^{58, 59} Like the Sonogashira coupling, the Heck reaction is an efficient method for formation carbon–carbon bonds with wide functional group tolerance.^{60–62} However, despite the vast number of various procedures there are no general reaction conditions available. Instead, the success of the reaction is often substrate-dependent. Finding satisfactory reaction conditions can be challenging.



Very often the same palladium catalysts, aryl (or vinyl) halides, bases and solvents that are used in the Sonogashira reaction are commonly used in the Heck reaction. Moreover, palladium(II) acetate combined with ligands, such as triphenylphosphine or particularly tri-*o*-tolylphosphine, is a very common Pd(0)-forming precatalyst. In addition to stabilising the zero-valent palladium catalyst, presence of the phosphine ligand can aid *in situ* reduction to Pd(0).⁶³ A preformed complex from Pd(OAc)₂ and P(*o*-Tol)₃, known as Herrmann's palladacycle catalyst (**Figure 3**), is an extremely efficient catalyst, with turnover numbers of millions and stability up to 250 °C.^{64, 65} Aryl and vinyl bromides, tosylates, mesylates and sometimes even chlorides, can be used as substrates. The reaction temperature is usually relatively high. A typical range is 80–130 °C, which is a notable difference between the Sonogashira and Heck reactions.



15

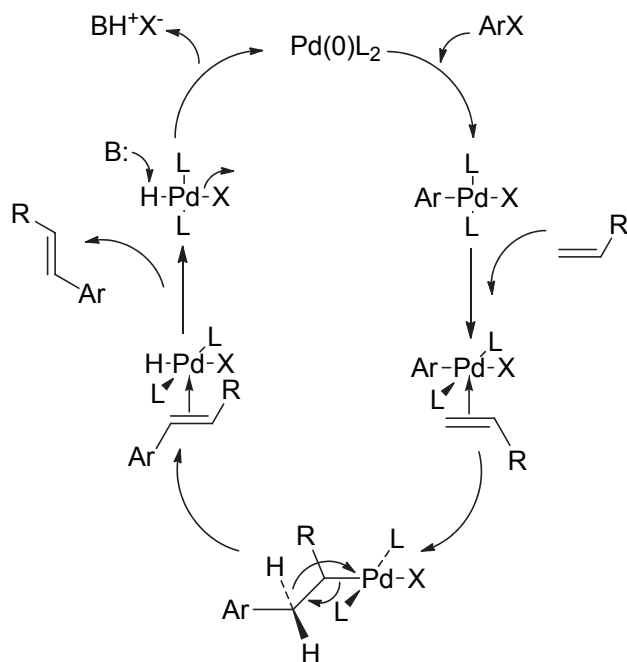
Figure 3. Herrmann's palladacycle catalyst^{64, 65}

At first glance the Heck reaction could be hypothesised to be an olefin analogous version of the Sonogashira coupling. However, it is mechanistically somewhat different, not only due to the absence of copper. The catalytic cycle presented in **Scheme 5**^{58, 66} contains some simplifications. Formation of the arylpalladium(II) halide species, ArPdXL₂, where L is an assisting ligand like P(*o*-Tol)₃, proceeds through oxidative addition, as in the Sonogashira coupling. After this the cycle continues by the migratory insertion of ArPdXL₂ to the olefin, followed by release of the coupling product through β-hydride elimination of HPdXL₂. The latter is neutralised by the base and the zero-valent palladium species is fed back into the cycle.

Torsional strain relieving rotation leading to the eclipsed conformation with least possible steric hindrance, prior to β-hydride elimination, proceeding in a *syn* manner renders the reaction stereoselective, favouring the *E*-olefin (**Figure 4**). This is very often found as the exclusive product. On the other hand, formation of substantial amounts of the *Z*-isomer has been observed when there is additional steric hindrance in the reaction entity.⁶⁷ Comparing the Newman projections in **Figure 4** it is understandable that formation of

Z-isomer requires somehow forcing conditions to lead to the more strained eclipsed conformation prior to the β -hydride elimination proceeding similarly *syn* manner.

Although Pd(0)/Pd(II) cycle presented above is the most commonly accepted form, it is often considered that instead of one uniform mechanism, depending on the reagents and conditions, various reaction pathways may operate. In the reactions with cyclic Pd(II) complexes, the existence of a Pd(II)/Pd(IV) cycle has been suggested.^{64, 68}



Scheme 5 The proposed mechanism of the Heck reaction^{58, 66}



Figure 4 The eclipsed conformations prior to the β -hydride elimination leading to E or Z olefin

1.5.1 Regio- and stereoselectivity – use of additives

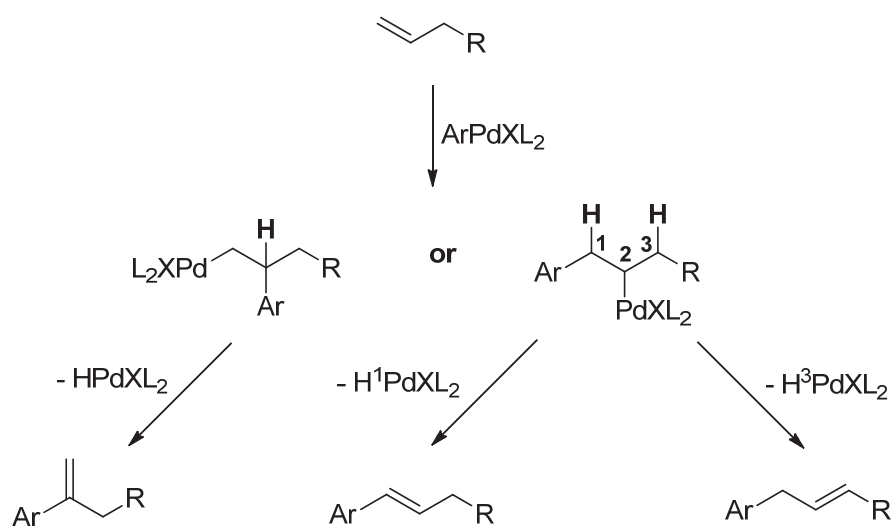
To improve the yield, rate, selectivity and the stability of the catalyst, several combinations of catalysts with various ligands and additives have been explored. The mechanistic requirement for each substance in the success of the reaction is not always easy to interpret. Finding satisfactory conditions often requires time-consuming optimisation and screening.

Quaternary ammonium salts, typical in phase-transfer catalysis reactions, are important additives. In Heck reactions, their real function is not to act as a phase-transfer catalyst, because all the stages of the coupling occur in the organic phase. Instead, the quaternary ammonium cation improves the solubility of the salt, the active species of which is rather the halide or acetate counterion. Moreover, the positive charge of the nitrogen atom in the quaternary ammonium ion is very sterically shielded rendering the acetate ion in *n*-Bu₄NOAc more ‘naked’, thus increasing its basicity.⁶⁹

Carlström and Frejd noticed a clear increase in yields when *n*-Bu₄NCl, *n*-Bu₄NBr, or even lithium chloride was used as an additive.⁷⁰ Calo *et al.* used *n*-Bu₄NBr as an ionic liquid solvent with palladium nanoparticles, in the presence of *n*-Bu₄NOAc. They explained the excellent *E*-stereoselectivity through intramolecular neutralisation of the palladium hydride intermediate, still ligated to the olefin, by the acetate ion.⁷¹ Detailed discussions on the role of acetate and halide ions in the Heck reactions have been provided by Knowles and Whiting⁷² and by Amatore and Jutand.⁷³

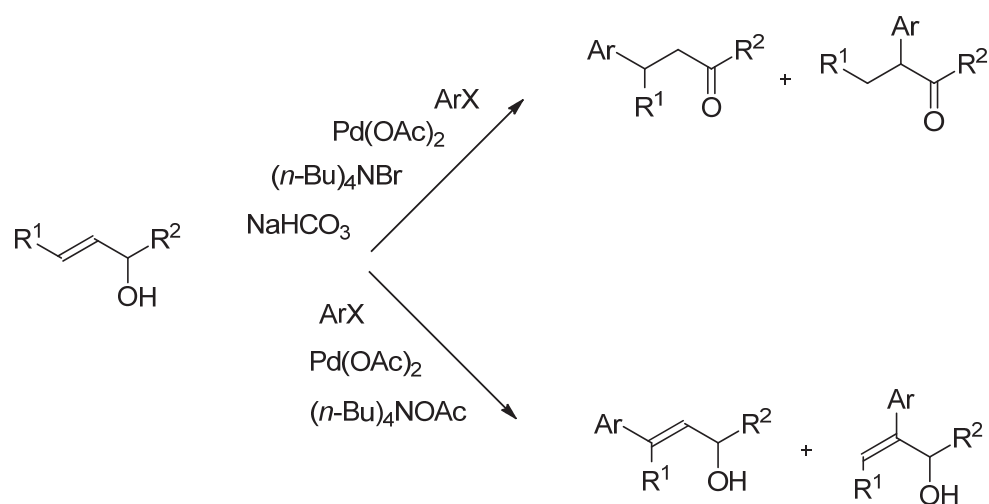
In olefins with three carbon units the regiochemistry causes additional concern. It is possible to obtain β- as well as γ-arylated products, depending on the direction of migratory insertion of the arylpalladium halide into the C=C bond. In addition, two allylic isomers are possible from the γ-arylation, due to the potential for two different eliminating hydrogens in the β-hydride elimination step (**Scheme 6**).¹¹

Calo *et al.* controlled the β-hydride elimination, in the arylation of allyl alcohols, with the help of the base and the quaternary ammonium salt that was used as an ionic liquid solvent. With *n*-Bu₄NBr and NaHCO₃ mainly carbonyl compounds were obtained, after tautomerisation of the enol products. The simultaneous use of *n*-Bu₄NOAc, as a solvent and base, preferred formation of arylated allyl alcohols (**Scheme 7**). The latter phenomenon was explained by formation of a cationic Pd complex (**Figure 5**), with the acetate ion as counterion and chelation of palladium with the hydroxyl group. This favours the necessary *syn* relationship for the benzylic hydrogen atom with palladium, prior to the β-hydride elimination. With *n*-Bu₄NBr and NaHCO₃ the Pd–H readdition-elimination mechanism can operate, leading to the thermodynamically more stable carbonyl compounds. On the other hand, steric factors affect the position of the arylation, favoring the terminal carbons of olefins.⁶⁹



Scheme 6 Regiochemistry in the Heck reaction of three carbon units^{II, a}

^aReprinted from Tetrahedron, Vol 69, Leikoski, T., Wrigstedt, P., Helminen, J., Matikainen, J., Sipilä, J., and Yli-Kauhaluoma, J., The Heck Reaction of Polymer-Supported Allylamine with Aryl Iodides, 839–843, Copyright (2013), with permission from Elsevier.



Scheme 7 Control of the β -hydride elimination in the arylation of allyl alcohols⁶⁹

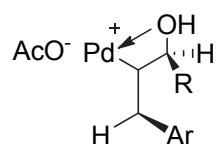


Figure 5 The cationic Pd complex with an acetate ion prior to the β -hydride elimination⁶⁹

Pan *et al.* performed selective γ -arylations of allylic esters with aryl iodides using Pd(OAc)₂ together with silver(I) carbonate as a halide scavenger and base. Arylated allylic esters were obtained without rearrangement of the double bond. This was explained by chelation of the palladium atom with the carbonyl oxygen atom (**Figure 6**). This leads to impeded rotation across the C₁-C₂ bond but the favourable *syn* position between the benzylic hydrogen and Pd atom.⁶⁷

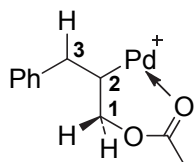


Figure 6 Chelation of palladium with the carbonyl oxygen prior to the β -hydride elimination⁶⁷

Recently, Jiang *et al.* prepared arylated allylamine derivatives, which are structurally very similar to the target structures in this study.⁷⁴ This was through the Heck reaction, with aryl bromides but without phosphine ligands. The reactions exhibited excellent stereo- and regioselectivity, leading to exclusive formation of γ -arylated (*E*)-allylamine products. This transformation was achieved with Pd(OAc)₂ as a catalyst, K₂CO₃ as a base and the (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO), or hydroquinone, as an additive. Use of *N,N*-(*t*-BOC)₂-allylamine, a diprotected primary amine with a carbamate moiety, was crucial for success of this reaction. Chelation between the carbamate carbonyl group and the palladium atom (**Figure 7**) was again expected to control the regiochemistry of the double bond but also formation of the *E* isomer, due to the ideal position of the γ -carbon for migration of the aryl group. Moreover, the double protection was believed to prevent β -arylation due to steric hindrance.

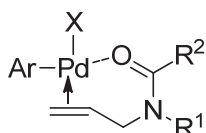


Figure 7 Chelation of palladium with the carbamate carbonyl group⁷⁴

In a recent study by Deng *et al.* arylation of allylamine was controlled by the choice of the solvent, protecting group, ligand and additive.⁷⁵ The combination of Pd(OAc)₂, 1,3-bis(diphenylphosphino)propane and triethylamine, in ethylene glycol at 145 °C, favored β -arylation of *N*-*t*-BOC-allylamine with aryl bromides. In contrast, with Pd(OAc)₂, *n*-Bu₄NBr, TEMPO and K₂CO₃, in water at 90 °C, *N*-(*t*-BOC)₂-allylamine gave almost exclusively the *E* isomer of the γ -arylated product.

There are also other examples in the literature where allylamine derivatives have been arylated selectively at the β -position. Olofsson *et al.* performed the Heck reaction of *N,N*-dimethylallylamine and aryl triflates, using both thermal and microwave conditions.⁷⁶ Use of the bidentate ligand, 1,1'-bis(diphenylphosphino)ferrocene (dppf) was essential for the success of the reaction. Formation of a cationic, five-membered *N*-complexed Pd cyclic intermediate (**Figure 8**) as a result of palladium–nitrogen controlled migratory insertion, was believed to generate the observed regioselectivity. Pd(OAc)₂ was used as a catalyst with K₂CO₃ in DMF, under thermal reactions and with Et₃N in acetonitrile, under microwave conditions.

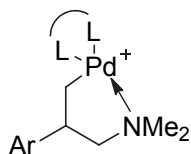


Figure 8 The cationic intermediate Pd complex with a five-membered ring⁷⁶

Subsequently, a modified version of the above-mentioned procedure, where *N-t*-BOC- or *N*-phthalimido-protected allylamines were used as substrates, was introduced. The regiochemical outcome was again attributed to the five-membered ring intermediate, this time with an anionic nitrogen. The Pd–N coordination was assumed to facilitate the deprotonation of the nitrogen atom.⁷⁷

Wu *et al.* achieved a regioselective β -arylation of *N,N*-dibenzylallylamine, with a variety of aryl triflates.⁷⁸ This procedure resembled the conditions of Olofsson *et al.* with Pd(OAc)₂ and dppf,⁷⁶ using DABCO as the ligand and DMSO as the solvent. Baxter *et al.* also utilised a modified version of Olofsson's method in the Heck reaction of *N-t*-BOC-allylamine, with a series of *o*-chlorotriflates, followed by cyclisation and isomerisation in a route to 3-methylindoles.⁷⁹

1.5.2 Heck reactions on solid-phase

Similar to research on Sonogashira couplings, compared to the vast number of studies conducted on conventional solution-phase reactions, the number of published studies on Heck reactions on solid-phase is relatively limited. There are examples in the literature where either the aryl halide or olefin component has been covalently bound on the polymeric support.^{33, 37, 80–88} In addition, intramolecular Heck reactions have been performed on solid-phase.^{89–95} Even the palladium catalyst complexes have been bound covalently to polystyrene, while keeping all the other reactants in solution.^{96, 97} A few very unique studies have been reported. As an example, Frei and Blackwell attached the olefinic component covalently to cellulose, with the help of a Rink amide linker, to produce stilbenes.⁹⁸ These were cleaved from cellulose with trifluoroacetic acid vapour.

Likewise, Kopylovich *et al.* absorbed reaction components onto silica gel and performed microwave-assisted Heck reactions, in the absence of solvent.⁹⁹

1.6 Free and protected amines as reactants

The wide functional group tolerance is one of the most significant advantages of palladium-catalysed coupling reactions. However, due to strong coordination of the nitrogen lone-pair to palladium, free amines are incompatible with palladium catalysis, as a rule. A general strategy to overcome this problem is protection of amines, as neutral or much less basic and coordinating derivatives. The most common compounds are carbamates, phthalimides and trifluoroacetamides. When applied to allylamine derivatives, the focus of interest for this study, these functional groups also render the olefin less electron-rich and hence more reactive. With primary amines, Heck reactions have been performed quite successfully using double-carbamate protection. As an example, Jiang *et al.* utilised *N,N*-(*t*-BOC)₂-allylamine, as an efficient substrate in a regioselective and stereoselective reaction with various aryl bromides.⁷⁴

Some exceptions to this general rule of amine incompatibility exist. In many of these instances, sterically hindered and mainly tertiary amines have been used. For example, Nakamura *et al.* performed straightforward Sonogashira couplings with heteroaryl bromides and *N,N*-diisopropylpropargylamine.¹⁰⁰ In addition, Lemhadri *et al.* obtained their best results using Sonogashira couplings with bulky, tertiary propargylamines.¹⁰¹ However, there are also a few examples in the literature where secondary propargylamines,^{17, 102} primary propargylamines,^{17, 40, 103} and even unsubstituted propargylamine,^{17, 104} have been used as substrates. In the study of Soberats *et al.* primary free, and also *t*-BOC-protected propargylamines were subjected to “on water” conditions with aryl iodides. The success of the reaction was explained mainly by increase in the effective local concentration of water-insoluble substrates and catalysts, within the organic droplets surrounded by water.¹⁰³

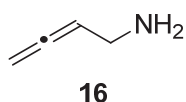
In Heck reactions, the use of free amines as substrates is also generally unfavourable. For example, attempts to arylate free allylamine have failed yielding only unidentified mixtures.^{77, 105–107} Very typically, free amines have been employed in the intramolecular reactions of *N*-allyl-*o*-haloaniline derivatives for the syntheses of indoles.^{108, 109} Conjugation of the lone pair on the nitrogen with the aromatic π -electron system clearly enhances the reactivity of anilines. The successful reactions of some free tertiary amines^{76, 78, 110} might be explained by steric hindrance on the nitrogen atom. On the other hand, in all the three examples cited, tertiary phosphines were used as ligands, which might have had a positive effect as well. Moreover, Jiang and Li obtained even better results when they used *n*-Bu₄NBr as an additive.¹¹⁰ Carlström and Frejd discussed the ability of the halide ions to break the Pd–N coordination and to give a more reactive Pd complex.⁷⁰

Recently, Kore and Shanmugasundaram managed to couple free allylamine with 5-iodouridine-5'-triphosphates in water at room temperature, using K_2PdCl_4 as the catalyst. Allylamine reacted at the γ -position giving almost exclusively the *E* isomers of the 5-aminoallyl nucleotides of interest.¹¹¹

It should be remembered that free amines are problematic mainly in the proximity of the reaction centers. This is evident as amines, such as diethylamine or triethylamine, are frequently used as bases, or even as solvents, in many types of palladium couplings. Therefore, the observed phenomenon with amines may not be considered as catalyst poisoning, e.g. as commonly observed with sulphur, because the effect of the amine on the catalyst is not permanent, thus not incapacitating it.

1.7 The allene amines and amides

Allenes are dienes with cumulated double bonds that possess partially comparable properties those of alkenes or dienes. However, their reactivity is considerably higher. In addition, by specific position of substituents allenes give rise to axial chirality. Consequently, allenes have been found to be extremely versatile synthetic intermediates in numerous applications.^{112, 113} Descriptive examples are the gold-catalysed intramolecular hydroamination reactions¹¹⁴ and the photoinduced [2 + 2] cycloadditions with olefins.¹¹⁵ Recently, Boutier *et al.* reported a palladium-catalysed asymmetric synthesis of *N*-allenyl amides from *N*-allenyl acetates, in a route to enantioenriched pyrrolidones by gold-catalysed intramolecular hydroalkylation.¹¹⁶ In general, nitrogen-containing allenes, such as amines, amides, amino esters, phthalimides, sulfonamides or hydrazines, are useful precursors in organic synthesis.^{114, 117-123} Certain allene amines, including the simple *N*-(buta-2,3-dien-1-yl)amine **16**, have been associated with monoamine oxidase B inhibition.¹²⁴

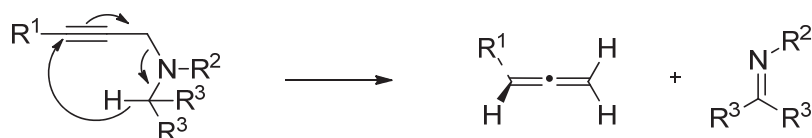
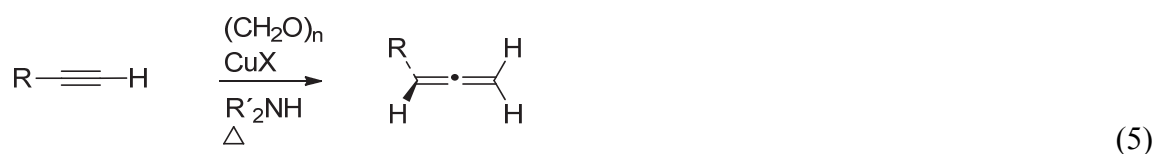


The objective in this study was to synthesise stable derivatives of *N*-(buta-2,3-dien-1-yl)amine **16** from polymer-bound propargylamine by the Crabbé reaction, where copper acetylide is involved as an intermediate as in the Sonogashira coupling. This is to be achieved through concurrent immobilisation of reactive allenes and to use the point of attachment as a protecting group for the nucleophilic nitrogen atom. Free amines are problematic for allenes. For instance, primary amines easily attack as nucleophiles at the central carbon atom of allenes, to give enamines.¹²⁵ Consequently, the linker for the nitrogen atom has to be chosen carefully. This should also especially allow for rapid cleavage of the product as a stable derivative and under as mild conditions as possible.

Solid-phase synthesis of allenes has not previously been reported in the literature. There are a few examples for the syntheses of *N*-(buta-2,3-dien-1-yl)amines and their derivatives in solution.^{114, 120, 121, 124, 126} Interestingly, a solution-phase synthesis of some *N*-(buta-2,3-dien-1-yl)amides, where propargylamides were subjected to the Crabbé reaction, was presented recently.¹²⁷

1.7.1 The Crabbé reaction

Among the several alternatives available for construction of the allenic backbone,¹²⁸ the Crabbé reaction, introduced by Piere Crabbé in 1979,¹²⁹ has turned into one of the most important methods for the synthesis of terminal allenes. In principle, it is a one-carbon atom homologation of terminal alkynes. In a typical procedure the alkyne is heated several hours with paraformaldehyde, copper(I) iodide (or bromide), a secondary amine and very often in 1,4-dioxane at 100 °C (eq. 5). Since the reaction involves a Mannich base derived from an alkyne, formaldehyde, and amine as an intermediate, which turns into the allene *via* the copper-mediated 1,5-hydride transfer, the use of a secondary amine is necessary. Moreover, there must be a hydrogen atom available for the hydride transfer at the α -position of the amine (**Scheme 8**).¹³⁰



Scheme 8 Formation of an allene from Mannich base via the 1,5-hydride transfer¹³⁰

Anhydrous conditions are also essential. For comparison, in a study by Bieber and da Silva, a series of terminal alkynes was subjected to otherwise very similar Mannich conditions in aqueous dimethyl sulfoxide at 30 °C. This gave tertiary propargylamines as products instead of allenes.¹³¹

Recently, modifications of the Crabbé reaction that produce internal allenes from terminal alkynes and aliphatic or aromatic aldehydes have been reported. Kuang and Ma treated an alkyne and aldehyde with morpholine and ZnI_2 , in toluene at 130 °C,¹³² whereas Kitagaki *et al.* exposed the precursors to microwave conditions, at 200 °C with CuI and dicyclohexylamine in toluene.¹³⁰ Hence, the Crabbé reaction is not limited to the synthesis of terminal allenes any longer. However, the methodology of the internal version still requires further development, lacking generality and satisfactory yields.

2 Aims of the study

The objective of this thesis was to develop new synthetic methods to create carbon–carbon bonds using palladium- and copper-catalysed reactions on solid-phase. More specifically:

- To investigate the Sonogashira and Heck reaction on polymer-bound propargylamine and allylamine, respectively, in the synthesis of 1,3-arylamino propane derivatives and to compare the feasibilities of these methods
- To develop a solid-phase synthesis of stable allene amine derivatives from polymer-bound propargylamine, using the Crabbé reaction
- To find suitable functionalised polystyrene resins to immobilise volatile, unsaturated amines to enable their reactions also above their boiling points
- To explore the linkers of the solid supports as protecting groups for amines in the above-mentioned reactions
- To investigate possibilities to utilise the Castro-Stephens reaction instead of the Sonogashira reaction on polymer-bound propargylamine, thus avoiding the necessity of palladium, and therefore, also protection of amines

3 Results and discussion

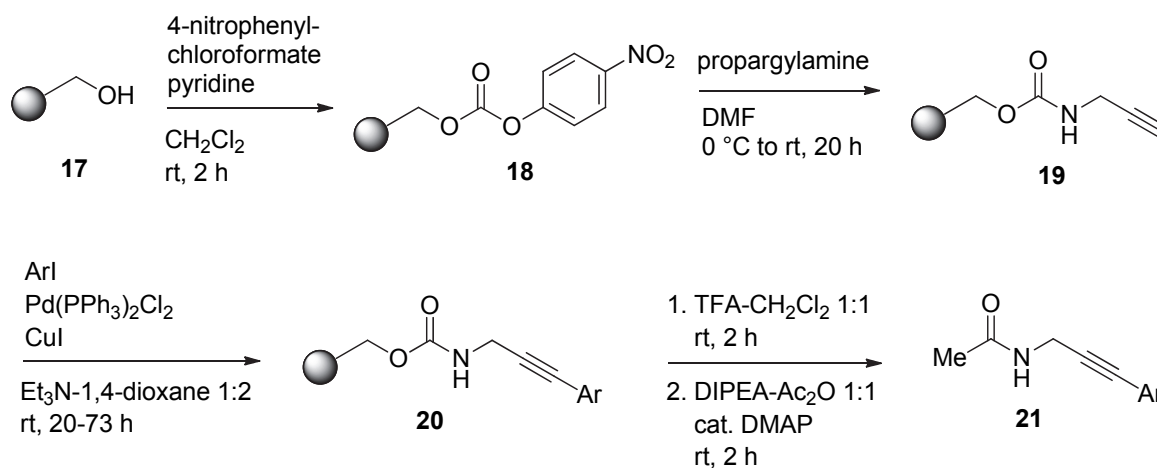
3.1 The Sonogashira coupling of polymer-supported propargylamine

The first objective in the Sonogashira studies was to find a reliable and reproducible method to attach propargylamine on polymeric support. For example, propargylamine was coupled successfully to trityl chloride resin using the corresponding method, developed for 2-chlorotrityl chloride resin.¹³³ However, typical Sonogashira conditions, with Pd(PPh₃)₄ or Pd(PPh₃)₂Cl₂ as catalyst and CuI as co-catalyst^{42, 134} for this polymer-bound acetylene did not give even a trace of the desired arylacetylene.¹ Keeping in mind the general incompatibility of free amines as reactants with palladium catalysts (Section 1.6), the reason for this failure is obvious.

Despite the appearance a few examples of the successful solution-phase Sonogashira couplings of tertiary, secondary and even unsubstituted primary propargylamine (Section 1.6, and references therein), it is possible that the coupling is too slow on the solid-phase to compete with the strong Pd–N coordination.

At this stage it was clear that propargylamine needs simultaneous protection at the attachment stage. In the Sonogashira couplings amines have typically been protected as carbamates or amides. As an example, Khan and Greenstaff used *N*-trifluoroacetyl- and *N*-(*t*-BOC)-propargylamine in solution, with polymer-bound 5-iodouridines.³⁶ On the other hand, Berteina *et al.* studied the coupling of propargylamine with aryl iodides in solution and observed formation of the desired arylacetylene in an excellent yield. However, this was only when the propargylamine was *t*-BOC-protected.³³

After having compared these reports with the preliminary results, propargylamine was attached on Wang resin with a carbamate linker.¹ This polymer-supported amine can be prepared by the known¹³⁵ two-step procedure using Wang-resin, 4-nitrophenyl chloroformate and pyridine in dichloromethane. This was followed by reaction of the isolated 4-nitrophenyl carbonate resin with propargylamine in DMF (**Scheme 9**). This light-yellow carbamate-linked Wang resin is air-stable at room temperature. The progress of the attachment can be monitored by FTIR, where the terminal alkyne gives the characteristic signals at 3290 cm⁻¹ and 2100 cm⁻¹ and the carbamate a strong carbonyl peak at 1710 cm⁻¹.¹



Scheme 9 Coupling of propargylamine on Wang resin, the Sonogashira coupling, cleavage and acetylation^{1, a}

^aReprinted with permission from John Wiley and Sons. Leikoski, T., Kallonen, S., and Yli-Kauhaluoma, J. The Sonogashira Coupling of Polymer-Supported Propargylamine with Aryl Iodides *Helv. Chim. Acta* **2010**, *93*, 39–47, © 2010 Verlag Helvetica Chimica Acta AG, Zürich.

Formation of the Sonogashira products was observed using this carbamate-Wang resin and aryl iodides when a literature procedure for polymer-bound aryl iodide with phenylacetylene in solution was applied.¹ In this procedure, Pd(PPh₃)₂Cl₂ and CuI constitute the catalyst system and dry 1,4-dioxane–Et₃N 2:1 (v:v) the solvent.³⁷ A three- to five-fold excess of aryl iodides over polymer-bound propargylamine was used and the reactions proceeded at room temperature within 20–73 hours.

The above successful Sonogashira-conditions were also tested for propargylamine bound on Merrifield resin with the triazene linker that was used in the solid-phase synthesis of nitrogen-containing allenes (see section 3.4.1).^{III} Interestingly, not a trace of the coupling products was observed after the cleavage with 5% TFA in CH₂Cl₂. It is, therefore, evident that the NH group of the triazene moiety similarly retards the palladium-catalysis as free amines.

To enable the coupling reaction use of the amine base as the co-solvent was crucial. The initial experiments using the same carbamate-Wang resin with iodobenzene and Pd(PPh₃)₂Cl₂ in THF or with Pd(PPh₃)₄ in DMF, wherein only ca. 1.5 equiv. of Et₃N with respect to the polymer-bound propargylamine were used, did not give even a trace of the desired Sonogashira product.¹

The coupling products were cleaved from the resin using TFA–CH₂Cl₂ 1:1 (v:v) at room temperature over two hours. As the amine products were obtained as TFA salts, they were liberated with *N,N*-diisopropylethylamine and subsequently acetylated with acetic anhydride, and a catalytic amount of DMAP. The products were acetylated due to the

sluggish separation of free amines using SiO₂ column chromatography. After purification by flash chromatography, the coupling products were obtained in 15–60% yields (**Table 2**).¹

Table 2 Yields of isolated *N*-(3-arylpropargyl)acetamides obtained with various aryl iodides^{1, a}

Entry	Aryl group	Yield (%)
1	Ph	41
2	4-NO ₂ -C ₆ H ₄	52
3	4-CN-C ₆ H ₄	60
4	2-Cl-C ₆ H ₄	55
5	3-Br-C ₆ H ₄	55
6	3-CHO-C ₆ H ₄	44
7	4-F-C ₆ H ₄	15
8	pyridin-3-yl	47
9	3-Cl-C ₆ H ₄	51
10	4-Cl-C ₆ H ₄	36
11	3-MeO-C ₆ H ₄	24

^a Reprinted with permission from John Wiley and Sons. Leikoski, T., Kallonen, S., and Yli-Kauhaluoma, J. The Sonogashira Coupling of Polymer-Supported Propargylamine with Aryl Iodides *Helv. Chim. Acta* **2010**, 93, 39–47, © 2010 Verlag Helvetica Chimica Acta AG, Zürich.

In general, the best results were obtained with aryl iodides containing electron-withdrawing substituents. The highest yield (60%) was with 4-iodobenzonitrile. When 1-chloro-2-iodobenzene and 1-bromo-3-iodobenzene were used as aryl iodides they both gave a 55% yield of the coupling product. The latter reactant showed total selectivity of iodine over bromine as a leaving group. Considering the results, the position of the substituent in the aromatic ring does not play an important role in the success of the coupling. With the high electronegativity of the fluorine atom, a higher yield than 15% was expected using 1-fluoro-4-iodobenzene. Of course, it is possible that the high electron-withdrawal induces unexpected side reactions.¹

The reaction of 4-iodoanisole did not give the desired coupling product at all, either at room temperature overnight or even after 92 h at 70 °C. However, 3-iodoanisole, where the electron density is donated only by the inductive effect through σ -bonds, gave

a 24% yield. According to this observation, the coupling reaction is retarded much more strongly when electron density is donated by conjugation.¹

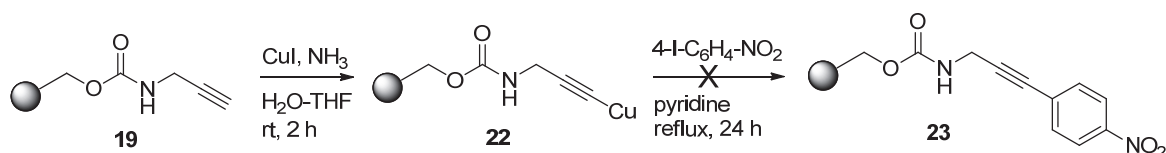
In addition, the coupling reaction of 3-iodobenzaldehyde proceeded successfully. After cleavage from the polymer, the product was released from its TFA salt and acetylated immediately at -100 °C. This exceptional acetylation procedure was applied to avoid the polymerization of the aminoaldehyde at room temperature. The corresponding acetylated derivative could be routinely purified by silica-gel column chromatography. Generally, all the acetylenic acetamides that were prepared were sufficiently stable when stored under dry conditions at room temperature.¹

After publishing these results, some interesting variations of the Sonogashira reaction of propargylamines have appeared in the literature. Kore *et al.* coupled propargylamine without protection, in the Sonogashira reaction of 5-iodouridine-5'-triphosphates. However, they suggested that the pre-requisite for a successful reaction is the presence of a hydrophobic counterion, e.g. triethylammonium cation.¹³⁶ Lin *et al.* presented a very peculiar one-pot synthesis, where the Mannich-type formation of the propargylamine derivative, from calcium carbide, secondary amine and aromatic aldehyde, was followed by the Sonogashira coupling with iodobenzene.¹³⁷

3.1.1 Preliminary experiments with the Castro–Stephens reaction

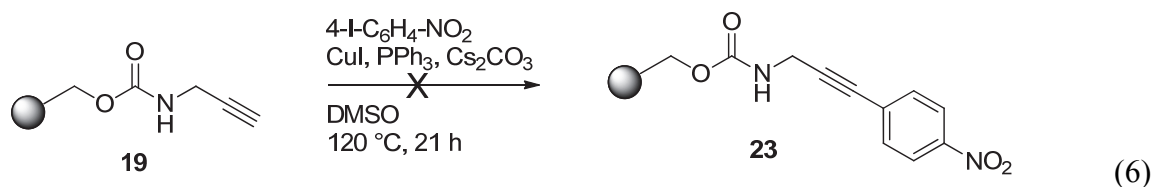
It would be highly desirable if the arylation of polymer-supported propargylamine and polymer-supported alkynes, in general, were possible without the use of a palladium catalyst. Therefore, the Castro–Stephens reaction was attempted with the same propargylamine carbamate-Wang resin, as was successful in the Sonogashira studies (See Chapter 5, Experimental). The reaction was tested with either a stoichiometric amount of the preformed copper acetylide^{22, 54} or a catalytic amount formed *in situ*.⁵⁵

To create the polymer-supported copper acetylide, propargylamine carbamate-Wang resin was treated with CuI in aqueous ammonia and THF at room temperature, for two hours (**Scheme 10**). After washing and drying, the resin was subjected to the Castro–Stephens conditions using 4-iodonitrobenzene in refluxing dry pyridine, under argon for 24 hours. However, after cleavage with TFA–CH₂Cl₂ and acetylation with DIPEA and Ac₂O, formation of the arylated product **23** was not observed according to GC–MS and TLC.



Scheme 10 The Castro–Stephens reaction with preformed copper acetylide on solid-phase

In the catalytic version, the mixture of propargylamine carbamate-Wang resin, 4-iodonitrobenzene, CuI, PPh₃ and Cs₂CO₃ was heated in dry DMSO, at 120 °C under argon for 21 hours (eq. 6). After the same cleavage and acetylation procedure, not a trace of the desired product could be found.



Although too wide generalisations about these preliminary experiments should be avoided, there are some factors that can lie behind the failure of both these test reactions. The acetylenic moieties, on the propargylamine carbamate-Wang resin, may simply be too far away from each other to adopt the four-centered transition state with neutral ligands L if the ligand L is the acetylene itself as proposed in the literature (**Figure 9**).^{22, 55} Use of very long flexible linkers for propargylamine, e.g. alkyl or poly(ethylene glycol) chains of 10 atoms or even more could enable the possibly necessary vicinity of terminal acetylenes.

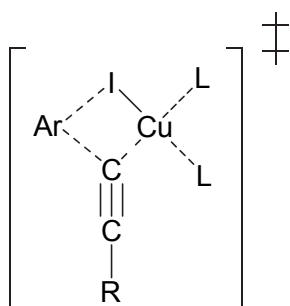


Figure 9 The proposed four-centered transition state for the Castro–Stephens reaction^{22, 55}

On the other hand, in a recent study, Gonda *et al.* presented that the copper-catalysed couplings of acetylenes with aryl halides actually need palladium to occur and that even ppb-levels can be enough.¹³⁸ If this result is carefully expanded further the Castro–Stephens reaction could actually be catalysed by palladium contamination. Therefore, it would essentially be the Sonogashira reaction at elevated temperature. Hence, it might be possible that in the experiments mentioned above, the trace levels of palladium were simply not high enough to catalyse the slow solid-phase reactions.

In general, insufficient knowledge about the mechanism of the Castro–Stephens reaction restricts its development and general utility. Furthermore, it would be highly beneficial if the necessity of trace levels of palladium in the reaction medium could be confirmed or excluded unquestionably.

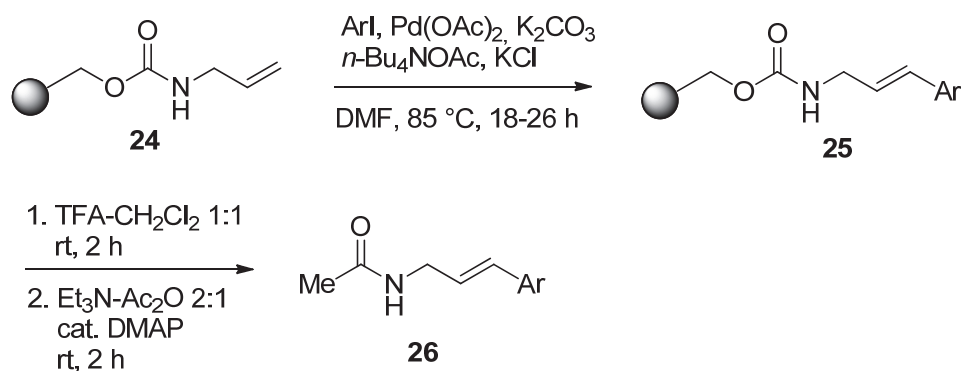
3.2 The Heck reaction of polymer-supported allylamine

Encouraged from the results for the Sonogashira coupling of resin-bound propargylamine, allylamine was similarly attached to Wang resin, using the same carbamate linker, which would serve again as a protecting group for the primary amine, thus avoiding reaction inhibiting Pd–N coordination. Loading of allylamine to Wang resin was performed routinely, and the success of the attachment can be verified conveniently by the strong carbamate carbonyl peak at 1722 cm^{-1} in FTIR.^{II}

However, optimisation of the Heck reaction itself was a much more demanding task than originally anticipated. More variation in reaction conditions, for the test reaction system with Wang resin-bound allylamine and iodobenzene, was applied. Only trace levels, or none at all, of the desired cinnamylamine product were obtained.^{II} Pd(OAc)₂, Pd₂(dba)₃ and Herrmann's palladacycle^{64, 65} were applied as catalysts with triethylamine, sodium acetate, caesium acetate, potassium carbonate, sodium hydrogen carbonate, caesium carbonate, pyrrolidine and 1,1,3,3-tetramethylguanidine, as bases. Experiments in the presence and absence of tri(*o*-tolyl)phosphine, additives, e.g., potassium chloride and caesium chloride and ionic mediators, such as *n*-Bu₄NCl, *n*-Bu₄NBr and *n*-Bu₄NOAc, were performed. The solvents *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide, *N*-methylpyrrolidone and even oxygen-free water as co-solvent were studied. The temperature range of the reactions was 50–130 °C.^{II}

Finally, a regioselective γ -arylation was achieved when the solution-phase method of Battistuzzi *et al.*,¹³⁹ with Pd(OAc)₂ (5 mol %), potassium carbonate, *n*-Bu₄NOAc and potassium chloride in DMF, was applied. The reaction with iodobenzene at 85 °C for 22 hours gave a 44% yield of *N*-cinnamylacetamide, *E* isomer, after cleavage with 50% TFA–CH₂Cl₂. This was followed by liberation of the amine product from its TFA salt with triethylamine, acetylation with acetic anhydride, triethylamine and DMAP (**Scheme 11**) and followed by purification by flash chromatography.^{II} This procedure was originally developed to control the selectivity of the β -hydride elimination (see **Scheme 6**, page 25) in the synthesis of cinnamaldehydes from acrolein diethyl acetal and aryl halides, a related electron-rich system with the aromatic ring and three carbon unit.¹³⁹

Almost as good a result was achieved when Pd(OAc)₂ was replaced with Herrmann's palladacycle catalyst (**Figure 3**, page 22), using the same Heck procedure. After the test reaction of iodobenzene with 1 mol % of the catalyst, a 40% yield of *N*-cinnamylacetamide was obtained.^{II} Keeping in mind the high performance of this catalyst, even at ppm levels,^{64, 65} its use in solid-phase Heck reactions might be worth more detailed studies.



Scheme 11 The Heck reaction of Wang resin-bound allylamine, cleavage and acetylation^{II, a}

^aReprinted from Tetrahedron, Vol 69, Leikoski, T., Wrigstedt, P., Helminen, J., Matikainen, J., Sipilä, J., and Yli-Kauhaluoma, J., The Heck Reaction of Polymer-Supported Allylamine with Aryl Iodides, 839–843, Copyright (2013), with permission from Elsevier.

The yields of these experiments, using the procedure mentioned above with Pd(OAc)₂, varied between 23–61% (**Table 3**). Only products arising from a regioselective γ -arylation were observed.^{II} Jiang *et al.* explained this kind of regioselectivity and also the excellent *E*-stereoselectivity, by chelation between the carbamate carbonyl group and the palladium atom.⁷⁴ However, in the reactions with 2-chloriodobenzene, 1-iodonaphthalene and 3-iodoanisole, an inseparable mixture of *E* and *Z* isomers with an approximate ratio of 4:1, according to ¹H NMR spectroscopy, was obtained.^{II} The unusually high yield of the *Z* isomer, with respect to the *E* isomer, commonly obtained in the Heck reaction has been associated with the additional steric hindrance.⁶⁷ (See pages 22–23 and **Figure 4**). In fact, reactions on solid-phase themselves can be considered to be sterically more demanding.

The time and temperature window of the Heck reaction system studied is narrow. When the duration of the reaction at 85 °C was increased from 22 to 74 hours the yield decreased from 44 to 29%. The yield dropped below 5% when the three-day reaction was performed at 100 °C. The stoichiometry is also essential. A mixture of diarylated isomers dominated if iodobenzene was applied in excess. Therefore, only one molar equivalent of the aryl iodide, with respect to polymer-bound allylamine, was introduced throughout the whole series of reactions.^{II}

No clear relationship between the yields (**Table 3**) and the structures of the aryl iodides can be stated. According to these results, the position of the substituent in the aromatic ring is not important either. On the other hand, with 4'-iodoacetophenone and 4-iodobenzonitrile, significantly higher yields would have been expected. Interestingly, 2-iodothiophene and 4-iodonitrobenzene did not give even a trace of the Heck products.^{II} These unexpected features may be due to the slow reaction rates on solid-phase. The arylpalladium iodide species is undoubtedly easily formed from each of these substrates, by oxidative addition of Pd(0). However, these highly reactive intermediates may be consumed by fast and unwanted side reactions in solution, without reaching the polymer-bound allylamine.

Table 3 Yields of isolated *N*-cinnamylacetamides obtained with various aryl iodides^{II, a}

Entry	Aryl group	Yield (%)
1	Ph	44
2	4-Cl-C ₆ H ₄	54
3	3-Cl-C ₆ H ₄	49
4	2-Cl-C ₆ H ₄	61 ^b
5	4-CH ₃ CO-C ₆ H ₄	35
6	Naphthalen-1-yl	39 ^b
7	4-CN-C ₆ H ₄	25
8	3-MeO-C ₆ H ₄	23 ^b
9	4-NO ₂ -C ₆ H ₄	n.r.
10	Thiophen-2-yl	n.r.

^aReprinted from Tetrahedron, Vol 69, Leikoski, T., Wrigstedt, P., Helminen, J., Matikainen, J., Sipilä, J., and Yli-Kauhaluoma, J., The Heck Reaction of Polymer-Supported Allylamine with Aryl Iodides, 839–843, Copyright (2013), with permission from Elsevier.

^bAs an inseparable mixture of *E* and *Z* isomers with an approximate ratio of 4:1, as determined by ¹H NMR spectroscopy

These reaction conditions possess characteristics which enhance their usability in solid-phase synthesis. DMF, as a polar aprotic solvent, swells the resin efficiently and simultaneously assists in the separation of various ionic species, thus increasing their solubilities. Suitable concentrations of halide (KCl) and acetate (*n*-Bu₄NOAc) ligands in the reaction medium are likely to increase the stability, reactivity and selectivity of the catalyst.^{69, 72, 73} Moreover, it is possible that Pd(OAc)₂ and KCl in the reaction medium form potassium tetrachloropalladate, K₂PdCl₄, which has been used successfully in the Heck reaction of free allylamine.¹¹¹ Nevertheless, the stabilisation effect of the additive ligands is very evident as black metallic palladium precipitates, typical for Heck reactions with Pd(OAc)₂, were not observed at all in most of the trials.^{II}

3.3 The Heck or Sonogashira reaction for construction of the arylpropane unit?

If the final objective is to synthesise 1,3-arylamino propanes by solid-phase methods both the Sonogashira and the Heck reaction can be used for the attachment of the aromatic ring with a three-carbon atom unit, as the double and triple bond are both easily reducible. There are no significant differences in the results of these reactions on solid-phase. The yields are similar and the carbamate linker can be utilised in both cases. Additionally, in both reactions the position of the substituent in the aromatic ring does not generally affect the yield.^{1,11}

However, there are some factors that generally support the choice of the Sonogashira coupling. First, in most instances the Sonogashira reaction can be performed at room temperature, whereas the Heck reaction requires heating and according to the results, its feasible temperature window can be very narrow. Secondly, finding satisfactory Heck reaction conditions may require tedious optimisation and screening, due to the variable reaction conditions available. In addition, electron-rich allylamine derivatives are not particularly reactive precursors and as a three-carbon unit they may give rise to several possible regioisomers. Moreover, it is not advisable to use excess aryl halides to push the reaction forward. As observed, polyarylation may become the dominating process. Furthermore, it is very likely that some aryl halides, such as 4-iodonitrobenzene and 2-iodothiophene, form too reactive intermediates for slow solid-phase Heck reactions.¹¹ It should also be pointed out that a single crystalline product is typically more easily produced in the Sonogashira reaction, whereas the possible mixture of stereo- or regioisomers may hamper isolation and purification of the Heck product.

In some circumstances, such as in large-scale preparations, use of the Heck reaction should be considered. In exothermic Sonogashira reactions the hazards associated with copper acetylides would require special precautions.¹⁴⁰ Additionally, in some special occasions, where a stereospecific reduction of a *E* isomer of a substituted allylamine derivative is required, the Heck reaction should be chosen for the arylation step.

As these studies have been performed with simple model substrates, unnecessary generalisations should be avoided. In the syntheses of specifically substituted and more complex 1,3-arylamino propanes, it cannot be stated in advance which one of these two reactions, or if neither of them, is feasible. Nevertheless, according to these preliminary results both the Sonogashira and the Heck reactions are potential arylation methods.

3.4 Solid-phase synthesis of allene amides

3.4.1 The triazene linker in solid-phase synthesis

In the solid-phase route to nitrogen-containing allenes, the linker should tolerate the reaction conditions and stabilise the allene product, by acting as the protecting group for the amino functionality. Additionally, the product should be easily cleavable under as mild conditions as possible and as some stable derivative of allene amine.

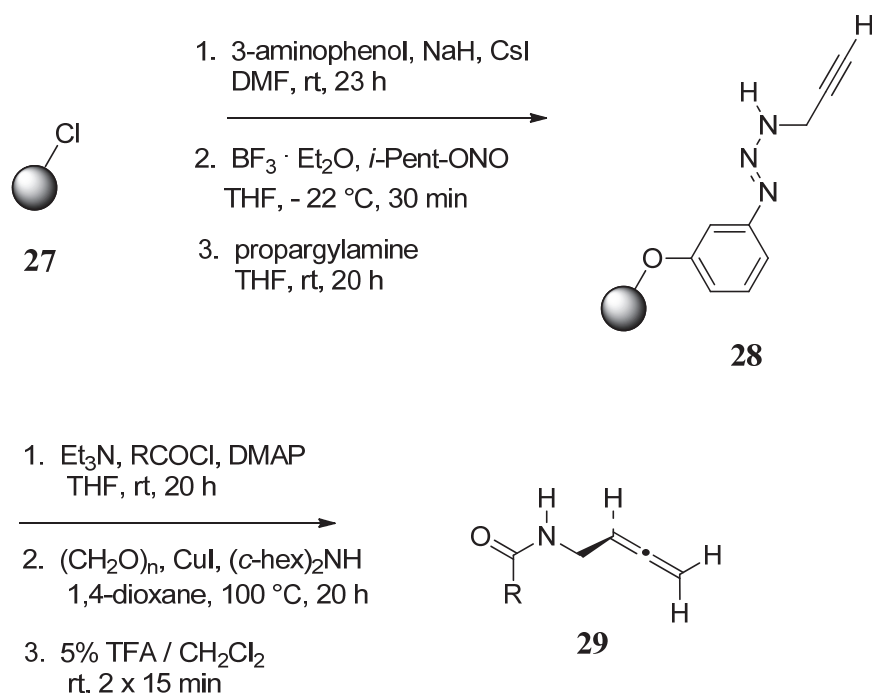
To fit these requirements, a triazene linkage was studied for immobilisation of propargylamine. This extremely acid-labile linker is prepared from Merrifield resin-bound 3-aminophenol, by diazotisation and addition of a primary amine to the polymer-bound diazonium salt. The triazene moiety, that is stable under neutral or basic conditions, can be acylated with acyl chlorides and is cleavable as an amide, with dilute (5%) TFA in CH₂Cl₂, at room temperature within a few minutes.¹⁴¹ These immobilised triazenes are remarkably stable at room temperature under dry conditions and they are safe to handle when compared with triazenes in solution, which are potent carcinogens.¹⁴²

Propargylamine was immobilised on Merrifield resin (**Scheme 12**) according to the known literature procedure for primary amines,¹⁴¹ with minor modifications. In the attachment of 3-aminophenol to the Merrifield resin, 5 mol % of caesium iodide was added to increase the rate of the substitution reaction. For the formation of the diazonium salt, from polymer-bound 3-aminophenol, isopentyl nitrite was used instead of *t*-butyl nitrite. The intermediate polymer-bound diazonium salt is relatively stable in air and safe to handle. The air-stable propargyltriazene resin is formed by addition of propargylamine to the polymer-bound diazonium salt, in dry tetrahydrofuran (THF) at room temperature.^{III}

To broaden the product applicability and to ensure the stability of the allenes, the NH group of the triazene linker was acylated with various acyl chlorides,¹⁴¹ prior to the Crabbé reaction and cleavage (**Scheme 12**).^{III} Actually, in the acylation sequence the properties of the triazene and *N*-acyltriazene moieties resemble those of amines and amides, respectively. Otherwise the literature occurrence of the *N*-acyltriazene functionality is very scarce, even in solution-phase chemistry.^{143, 144}

At the acylation stage, the order of introduction of the reagents into the reaction medium is particularly important. Triethylamine must be added before the acyl chloride to maintain a basic solution phase throughout the reaction. Acyl chlorides alone cleave the extremely acid-labile triazene,¹⁴⁵ liberating propargylamine as an amide into the solution. In fact, it was observed that the triazene linker was cleaved using far more dilute TFA

concentrations, than 5% in CH₂Cl₂, so acidic contamination must be excluded in all operations.^{III}



Scheme 12 Loading of propargylamine to polystyrene through a triazene linker, *N*-acylation, the Crabbé reaction and subsequent cleavage^{III, a}

^aReprinted with permission from NRC Research Press, Leikoski, T., Wrigstedt, P., Matikainen, J., Sipilä, J., and Yli-Kauhaluoma, J. Solid-Phase Synthesis of *N*-(buta-2,3-dien-1-yl)amides by the Crabbé Reaction *Canadian Journal of Chemistry* **2013**, 91 (1), 38–42.

3.4.2 The Crabbé homologation of polymer-supported propargylamine

For the allene formation, an updated modification¹⁴⁶ of the original procedure by Crabbé *et al.*¹²⁹ was used. In this method the alkyne is heated with paraformaldehyde, dicyclohexylamine and CuI in 1,4-dioxane at 100 °C (**Scheme 12**). In the studies with seven polymer-bound *N*-acyltriazenes, the yield of allene from propargyltriazenes resin varied between 10% and 63%, depending strongly on the R group in the *N*-acyl substituent (**Table 4**). Shortly after submitted these results for publication,^{III} an interesting and related solution-phase study, where *N*-(buta-2,3-dienyl)amides were prepared from *N*-propargylamides using a method comparable to the updated Crabbé procedure,¹⁴⁶ was published.¹⁴⁷

Table 4 Yields of isolated *N*-(buta-2,3-dien-1-yl)amides obtained with various acyl chlorides.^{III, a}

Entry	R in RCOCl	Yield (%)
1	CH ₃	63
2	CMe ₃	53
3	PhCH ₂	10
4	4-NO ₂ -C ₆ H ₄	13
5	(<i>E</i>)-Ph-CH=CH	20
6	CH ₂ =CH	18
7	CH ₃ (CH ₂) ₆	11

^aReprinted with permission from NRC Research Press, Leikoski, T., Wrigstedt, P., Matikainen, J., Sipilä, J., and Yli-Kauhaluoma, J. Solid-Phase Synthesis of *N*-(buta-2,3-dien-1-yl)amides by the Crabbé Reaction *Canadian Journal of Chemistry* **2013**, *91* (1), 38–42.

It is very likely that the allene formation is controlled by steric factors, as the best yields were obtained using simple small-sized acyl *N*-substituents, i.e. acetyl and pivaloyl groups. On the other hand, a significantly higher yield than 11% for the electronically very similar *N*-octanoyl-substituted product should have been expected. However, it can be speculated that, although the pivaloyl group is sterically crowded, its reach may be too short to reach the vicinity of the terminal acetylene unit, to interfere with the reaction. On the other hand, the reactivity of the acryloyl group apparently suppresses the yield, despite its small size.^{III}

The low to moderate yields can be considered satisfactory, only due to the very preliminary nature of these studies. On the other hand, it must be remembered that the yields of the Crabbé reaction in general are far from quantitative. Yet, some new ideas have arisen after publication of these results. If steric factors play an important role in the formation or in the further reaction of the Mannich base one option would be to use a less bulky secondary amine, such as di-*n*-butylamine or piperidine, instead of dicyclohexylamine. Furthermore, NOE experiments with soluble derivatives of the acetylenes or Mannich bases may give useful information about the possible steric hindrance of the reactants.

In the solid-phase study by Youngman and Dax, propargylamine was bound on 2-chlorotriethyl resin and treated with a secondary amine, copper(I)chloride and paraformaldehyde, in 1,4-dioxane at 70–75 °C for three hours.¹³³ Despite these anhydrous conditions, which are very similar in the Crabbé reaction with the exception of the lower temperature, this reaction produces Mannich bases, but not allenes. It is therefore worth studying whether the Crabbé reaction on solid-phase is actually so slow that it requires even a higher temperature than 100 °C, or a very long reaction time to furnish allenes from Mannich bases. An increase in the amount of CuI would also be worth testing.

In general, the solid-phase method studied^{III} opens new possibilities in the syntheses of biologically interesting nitrogen-containing allenes. All reagents required in this reaction sequence are inexpensive and isolable allene amide products are obtained, by the cleavage reaction under very mild conditions. However, owing to the versatility of allenes, as synthetic intermediates, the possibility of immobilising potentially labile cumulated carbon–carbon double bonds, on solid support for further reactions, is even more interesting.

4 Conclusions

In this study, new and encouraging results for methods to perform carbon–carbon bond-forming reactions on solid support have been obtained. In the Sonogashira and Heck reactions of polymer-bound propargylamine and allylamine, respectively, the general benefits of solid-phase synthesis were combined with the efficiency of palladium catalysis. These amines were attached on Wang resin *via* an acid-labile carbamate linker, which serves simultaneously as a protecting group for the palladium-incompatible amines. Both of these reactions give arylated propargylamines and allylamines, which are isolated and purified as acetamides, giving similar yields. The Heck reaction of polymer-supported allylamine proceeds with a regioselective γ -arylation. Formation of the *E* isomer is dominant. Unfortunately the Castro–Stephens experiments, with the copper acetylide generated from polymer-bound propargylamine, were unsuccessful. More detailed knowledge about the mechanism of this reaction would be of great value. Moreover, the possible role of trace palladium contamination should be clarified.

If the objective is to ultimately reduce the Sonogashira or Heck products to biologically interesting 1,3-arylamino propane derivatives both of these reactions are applicable. However, optimisation of the Heck reaction can be rather tedious and according to the results of this study, the Sonogashira reaction would be preferable when possible, in part due to milder reaction conditions. However, with more complex molecules the situation can be very case specific.

Due to the electrophilic nature of the allene product, from the Crabbé homologation of solid-supported propargylamine, protection of the amino group was similarly necessary as in the Sonogashira coupling. This time propargylamine was attached to Merrifield resin *via* an *N*-acyltriazene linker, which is cleavable under very mild acidic conditions. The Crabbé reaction of polymer-bound propargylamine with paraformaldehyde, copper(I) iodide and dicyclohexylamine gives allene amides after cleavage. Some derivatives of these are biologically interesting molecules and important synthetic intermediates. There are no reports of the solid-phase synthesis of allenes in the literature prior to this study. The results are very preliminary with at most moderate yields. Therefore, the reaction conditions still require optimisation.

There are several advantages in solid-phase synthesis but for individual instances it should always be assessed if there is some extra benefit, compared to the synthesis in solution. For example, it is possible that the reagents used in excess, or the high consumption of solvents, increase the total costs and render the process actually less environmentally friendly. Moreover, some substrates turned out to be too reactive for the slow polymeric reactions.

The results of this thesis gave additional information about the reactivity of various substrates on alternative media. The first examples of the formation of allenes on solid-phase were presented. Moreover, a better understanding, in addition to the relatively few existing reports, concerning palladium-catalysed reactions of solid-supported propargylamine and allylamine was obtained. In general and despite the observed limitations, these results offer a wider variety of alternatives to perform synthetically important carbon–carbon bond-forming reactions.

5 Experimental

A description of the Castro–Stephens experiments on solid-phase is included in this thesis but not in the original publications I–III.

5.1 General

Propargylamine carbamate-Wang resin was prepared, as described in the original publication II. Known literature methods with minor modifications were applied, for the procedures described in sections 5.2^{22, 54} and 5.3.⁵⁵ The reagents were obtained from Acros, Aldrich and Riedel-de Haën. The commercially available anhydrous solvents were used in all reactions. Merck aluminium sheets, coated with silica gel 60 F254, were used for thin-layer chromatography and were visualised using UV light at 254 nm. GC–MS analyses were performed with a Hewlett-Packard-HP-5890A gas chromatograph, equipped with an HP-5970 mass-selective detector.

5.2 The Castro–Stephens reaction with a stoichiometric amount of preformed copper acetylide on solid-phase

5.2.1 Copper acetylide from polymer-bound propargylamine

Copper(I) iodide (936 mg, 4.91 mmol) was dissolved in 12% aqueous ammonia (4.0 ml). The blue solution was added dropwise to the propargylamine carbamate-Wang resin (1.0 g, 0.93 mmol/g, 0.93 mmol) in 20 ml of THF. The resulting dark green mixture was stirred at room temperature for two hours, filtered and washed (4×10 ml) with each of 25% aq. NH₃–ethanol 1:1 (v:v), THF, 25% aq. NH₃–ethanol 1:1 (v:v) and CH₂Cl₂. The resin was subsequently subjected to the procedure 5.2.2.

5.2.2 Reaction of the polymer-bound copper-acetylide with 4-iodonitrobenzene, cleavage and acetylation

The resin obtained from procedure 5.2.1 (approx. 1.0 g, 0.93 mmol/g, 0.93 mmol) was dried azeotropically with 2-propanol and benzene. The resin and 4-iodonitrobenzene (497 mg, 2.00 mmol) were stirred in dry pyridine, under argon at 120 °C for 24 hours. The resin was filtered and washed (2×10 ml) with each of DMF, methanol, THF, diethyl ether and CH₂Cl₂. For the cleavage step, the resin was stirred with 5.0 ml of TFA–CH₂Cl₂ 1:1 (v:v), at room temperature for one hour. The resin was filtered and washed (10 ml) with each of CH₂Cl₂, methanol and CH₂Cl₂. The filtrate was azeotroped with toluene (10 ml).

For the acetylation step, the residue was stirred with DIPEA (1.0 ml), acetic anhydride (1.0 ml) and a catalytic amount of DMAP, at room temperature for 90 minutes. The solvents were azeotroped with ethanol (2×25 ml). TLC (acetone–EtOAc 1:2) and GC–MS did not show any trace of the previously prepared coupling product, *N*-[3-(4-nitrophenyl)prop-2-yn-1-yl]acetamide.¹

5.3 The Castro–Stephens reaction, with a catalytic amount of copper acetylide formed *in situ*, on solid-phase

5.3.1 Reaction of polymer-bound propargylamine with 4-iodonitrobenzene and a catalytic amount of copper(I) iodide, cleavage and acetylation

Propargylamine carbamate-Wang resin (0.86 g, 0.93 mmol/g; 0.80 mmol), 4-iodonitrobenzene (651 mg, 2.61 mmol), copper(I) iodide (17.5 mg; 0.0919 mmol), triphenylphosphine (47.4 mg, 0.181 mmol) and caesium carbonate (495 mg, 1.52 mmol) were stirred in dry DMSO (10 ml), under argon at 120 °C for 21 hours. The resin was filtered and washed (2×10 ml) with each of DMF, methanol, THF, diethyl ether and CH₂Cl₂. For the cleavage step, the resin was stirred with 5.0 ml of TFA–CH₂Cl₂ 1:1 (v:v), at room temperature for one hour. The resin was filtered and washed (10 ml) with each of CH₂Cl₂, methanol and CH₂Cl₂. The filtrate was azeotroped with toluene (10 ml). For the acetylation step, the residue was stirred with DIPEA (1.0 ml), acetic anhydride (1.0 ml) and a catalytic amount of DMAP, at room temperature for 90 minutes. The solvents were azeotroped with ethanol (25 ml). TLC (acetone–EtOAc 1:2) and GC–MS did not show any trace of the previously prepared coupling product, *N*-[3-(4-nitrophenyl)prop-2-yn-1-yl]acetamide.¹

References

1. Merrifield, R. B. Solid-Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.
2. Guillier, F.; Orain, D.; Bradley, M. Linkers and Cleavage Strategies in Solid-Phase Organic Synthesis and Combinatorial Chemistry *Chem. Rev.* **2000**, *100*, 2091–2157.
3. Blaney, P.; Grigg, R.; Sridharan, V. Traceless Solid-Phase Organic Synthesis *Chem. Rev.* **2002**, *102*, 2607–2624.
4. Santini, R.; Griffith, M. C.; Qi, M. A Measure of Solvent Effects on Swelling of Resins for Solid Phase Organic Synthesis *Tetrahedron Lett.* **1998**, *39*, 8951–8954.
5. Morphy, J. R.; Rancovic, Z.; York, M. Low Dilution Procedures in Solid-Phase Organic Synthesis: Diels-Alder and Heck Reactions *Tetrahedron Lett.* **2002**, *43*, 5973–5975.
6. Lewis, N. G.; Davin, L. B.; Sarkanen, S. The Nature and Function of Lignins *Compr. Nat. Prod. Chem.* **1999**, *3*, 617–745.
7. Lee, K.-H.; Xiao, Z. Lignans in Treatment of Cancer and Other Diseases *Phytochem. Rev.* **2003**, *2*, 341–362.
8. Moffett, R. B.; Pickering, T. L. Central Nervous System Agents. 2. Synthesis of Diphenyl Primary and Secondary Aminopropanols *J. Med. Chem.* **1971**, *14*, 1100–1106.
9. Colwell, W. T.; Brown, V.; Christie, P.; Lange, J.; Reece, C.; Yamamoto, K.; Henry, D. W. Antimalarial Arylaminoopropanols *J. Med. Chem.* **1972**, *15*, 771–775.
10. Buschauer, A. Synthesis and in Vitro Pharmacology of Arpromidine and Related Phenyl(pyridylalkyl)guanidines, a Potential New Class of Positive Inotropic Drugs *J. Med. Chem.* **1989**, *32*, 1963–1970.
11. Roje, M.; Vinkovic, V.; Sunjic, V.; Solladié-Cavallo, A.; Diep-Vohuule, A.; Isarno, T. Stereoselective Cyclopropanation and Ring-Opening: Application to the Synthesis of Pure (*S*)-2-Methyl-3-arylpropylamines *Tetrahedron* **1998**, *54*, 9123–9128.
12. Birkmayer, W.; Knoll, J.; Riederer, P.; Youdim, M. B. H.; Hars, V.; Marton, J. Increased Life Expectancy Resulting from Addition of l-Deprenyl to Madopar[®] Treatment in Parkinson's Disease: A Longterm Study *J. Neural Transm.* **1985**, *64*, 113–127.

13. Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. A New Class of Angiotensin-Converting Enzyme Inhibitors *Nature (London)* **1980**, *288*, 280–283.
14. Wang, G.; Liu, X.; Zhao, G. Polymer-Supported Chiral Sulfonamide Catalyzed One-Pot Reduction of β -Keto Nitriles: a Practical Synthesis of (*R*)-fluoxetine and (*R*)-duloxetine *Tetrahedron: Asymmetry* **2005**, *16*, 1873–1879.
15. Shirota, F. N.; DeMaster, E. G.; Nagasawa, H. T. Propiolaldehyde, a Pargyline Metabolite That Irreversibly Inhibits Aldehyde Dehydrogenase. Isolation from a Hepatic Microsomal System *J. Med. Chem.* **1979**, *22*, 463–464.
16. Yu, P. H.; Davis, B. A.; Boulton, A. A. Aliphatic Propargylamines: Potent, Selective, Irreversible Monoamine Oxidase B Inhibitors *J. Med. Chem.* **1992**, *35*, 3705–3713.
17. Conn, C.; Shimmon, R.; Cordaro, F.; Hargraves, T.-L.; Ibrahim, P. Combinatorial Synthesis of SSAO Inhibitors Using Sonogashira Coupling: SAR of Aryl Propargylic Amines *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2565–2568.
18. Robin, S.; Rousseau, G. Preparation of Azetidines by 4-*endo trig* Cyclizations of *N*-Cinnamyl Tosylamides *Eur. J. Org. Chem.* **2000**, 3007–3011.
19. Dyatkin, A. B.; Rivero, R. A. The Solid Phase Synthesis of Complex Propargylamines Using the Combination of Sonogashira and Mannich Reactions *Tetrahedron Lett.* **1998**, *39*, 3647–3650.
20. Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes, and Bromopyridines *Tetrahedron Lett.* **1975**, 4467–4470.
21. Chinchilla, R.; Nájera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry *Chem. Rev.* **2007**, *107*, 874–922.
22. Stephens, R. D.; Castro, C. E. The Substitution of Aryl Iodides with Cuprous Acetylides. A Synthesis of Tolanes and Heterocyclics *J. Org. Chem.* **1963**, *28*, 3313–3315.
23. Alami, M.; Ferri, F.; Linstrumelle, G. An Efficient Palladium-Catalysed Reaction of Vinyl and Aryl Halides or Triflates with Terminal Alkynes *Tetrahedron Lett.* **1993**, *34*, 6403–6406.
24. Bertus, P.; Fécourt, F.; Bauder, C.; Pale, P. Evidence for the *in situ* Formation of Copper Acetylides during Pd/Cu Catalyzed Synthesis of Enynes: a New Synthesis of Allenynols *New. J. Chem.* **2004**, *28*, 12–14.

25. Amatore, C.; Jutand, A.; Suarez, A. Intimate Mechanism of Oxidative Addition to Zerovalent Palladium Complexes in the Presence of Halide Ions and Its Relevance to the Mechanism of Palladium-Catalyzed Nucleophilic Substitutions *J. Am. Chem. Soc.* **1993**, *115*, 9531–9541.
26. Gil-Moltó, J.; Nájera, C. Direct Coupling Reactions of Alkynylsilanes Catalyzed by Palladium (II) Chloride and a Di(2-pyridyl)methylamine-Derived Palladium(II) Chloride Complex in Water and in NMP *Adv. Synth. Catal.* **2006**, *348*, 1874–1882.
27. Nelson, J. C.; Young, J. K.; Moore, J. S. Solid-Phase Synthesis of Phenylacetylene Oligomers Utilizing a Novel 3-Propyl-3-(benzyl-supported) Triazene Linkage *J. Org. Chem.* **1996**, *61*, 8160–8168.
28. Bolton, G. L.; Hodges, J. C.; Rubin, J. R. Solid Phase Synthesis of Fused Bicyclic Amino Acid Derivatives via Intramolecular Pauson-Khand Cyclization: Versatile Scaffolds for Combinatorial Chemistry *Tetrahedron* **1997**, *53*, 6611–6634.
29. Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. Solid-Phase Synthesis of Indoles Using the Palladium-Catalysed Coupling of Alkynes with Iodoaniline Derivatives *Tetrahedron Lett.* **1997**, *38*, 2307–2310.
30. Collini, M. D.; Ellingboe, J. W. The Solid Phase Synthesis of Tri-Substituted Indoles *Tetrahedron Lett.* **1997**, *38*, 7963–7966.
31. Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. Solid Phase Synthesis of 2-Substituted Benzofurans via the Palladium-catalysed Heteroannulation of Acetylenes *Tetrahedron Lett.* **1997**, *38*, 2311–2314.
32. Jones, L.; Schumm, J. S.; Tour, J. M. Rapid Solution and Solid Phase Syntheses of Oligo(1,4-phenylene ethynylene)s with Thioester Termini: Molecular Scale Wires with Alligator Clips. Derivation of Iterative Reaction Efficiencies on a Polymer Support *J. Org. Chem.* **1997**, *62*, 1388–1410.
33. Berteina, S.; Wendeborn, S.; Brill, W. K.-D.; De Mesmaeker, A. Pd-Mediated C-C Bond Formation with Olefins and Acetylenes on Solid Support: A Scope and Limitations Study *Synlett* **1998**, 676–678.
34. Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. Stereoselective Synthesis of over Two Million Compounds Having Structural Features Both Reminiscent of Natural Products and Compatible with Miniaturized Cell-Based Assays *J. Am. Chem. Soc.* **1998**, *120*, 8565–8566.
35. Huang, S.; Tour, J. M. Rapid Solid-Phase Synthesis of Oligo(1,4-phenylene ethynylene)s by a Divergent/Convergent Tripling Strategy *J. Am. Chem. Soc.* **1999**, *121*, 4908–4909.
36. Khan, S. I.; Grinstaff, M. W. Palladium(0)-Catalyzed Modification of Oligonucleotides during Automated Solid-Phase Synthesis *J. Am. Chem. Soc.* **1999**, *121*, 4704–4705.

37. Stieber, F.; Grether, U.; Waldmann, H. An Oxidation-Labile Traceless Linker for Solid-Phase Synthesis *Angew. Chem. Int. Ed.* **1999**, *38*, 1073–1077.
38. Tan, D. S.; Foley, M. A.; Stockwell, B. R.; Shair, M. D.; Schreiber, S. L. Synthesis and Preliminary Evaluation of a Library of Polycyclic Small Molecules for Use in Chemical Genetic Assays *J. Am. Chem. Soc.* **1999**, *121*, 9073–9087.
39. Beilstein, A. E.; Grinstaff, M. W. On-Column Derivatization of Oligodeoxynucleotides with Ferrocene *Chem. Commun.* **2000**, 509–510.
40. Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. Optimization Study of Sonogashira Cross-Coupling Reaction on High-Loading Macrobeads Using a Silyl Linker *Tetrahedron Lett.* **2001**, *42*, 1815–1818.
41. Cassel, J. A.; Leue, S.; Gachkova, N. I.; Kann, N. C. Solid-Phase Synthesis of Substituted Alkynes Using the Nicholas Reaction *J. Org. Chem.* **2002**, *67*, 9460–9463.
42. Hudson, R. H. E.; Li, G.; Tse, J. The Use of Sonogashira Coupling for the Synthesis of Modified Uracil Peptide Nucleic Acid *Tetrahedron Lett.* **2002**, *43*, 1381–1386.
43. Erdélyi, M.; Gogoll, A. Rapid Microwave Promoted Sonogashira Coupling Reactions on Solid Phase *J. Org. Chem.* **2003**, *68*, 6431–6434.
44. Louërat, F.; Gros, P.; Fort, Y. Solid Phase Palladium-Catalysed C–C Bond Formation in the Pyridine Series: Access to Aryl and Alkynyl Pyridylpiperazines *Tetrahedron Lett.* **2003**, *44*, 5613–5616.
45. Rist, M.; Amann, N.; Wagenknecht, H.-A. Preparation of 1-Ethynylpyrene-Modified DNA via Sonogashira-Type Solid-Phase Couplings and Characterization of the Fluorescence Properties for Electron-Transfer Studies *Eur. J. Org. Chem.* **2003**, 2498–2504.
46. Spivey, A. C.; McKendrick, J.; Srikanan, R.; Helm, B. A. Solid-Phase Synthesis of an A–B Loop Mimetic of the Cε3 Domain of Human IgE: Macrocyclization by Sonogashira Coupling *J. Org. Chem.* **2003**, *68*, 1843–1851.
47. Cironi, P.; Tulla-Puche, J.; Barany, G.; Albericio, F.; Álvarez, M. Solid-Phase Syntheses of Furopyridine and Furoquinoline Systems *Org. Lett.* **2004**, *6*, 1405–1408.
48. Meyer, E.; Valis, L.; Wagner, C.; Rist, M.; Amann, N.; Wagenknecht, H.-A. 1-Ethynylpyrene as a Tunable and Versatile Molecular Beacon for DNA *ChemBioChem* **2004**, *5*, 865–868.
49. Filichev, V. V.; Pedersen, E. B. Stable and Selective Formation of Hoogsteen-Type Triplexes and Duplexes Using Twisted Intercalating Nucleic Acids (TINA) Prepared via Postsynthetic Sonogashira Solid-Phase Coupling Reactions *J. Am. Chem. Soc.* **2005**, *127*, 14849–14858.

50. Garg, N. K.; Woodroffe, C. C.; Lacanere, C. J.; Quake, S. R.; Stoltz, B. M. A Ligand-Free Solid-Supported System for Sonogashira Couplings: Applications in Nucleoside Chemistry *Chem. Commun.* **2005**, 4551–4553.
51. Kaval, N.; Dehaen, W.; Van der Eycken, E. Solid-Phase Synthesis of the 2(1*H*)-Pyrazinone Scaffold: A New Approach toward Diversely Substituted Heterocycles *J. Comb. Chem.* **2005**, *7*, 90–95.
52. Tulla-Puche, J.; Barany, G. Development of Resin-to-Resin Transfer Reactions (RRTR) Using Sonogashira Chemistry *Tetrahedron* **2005**, *61*, 2195–2201.
53. Yao, T.; Yue, D.; Larock, R. C. Solid-Phase Synthesis of 1,2,3-Trisubstituted Indoles and 2,3-Disubstituted Benzofurans via Iodocyclization *J. Comb. Chem.* **2005**, *7*, 809–812.
54. Castro, C. E.; Stephens, R. D. Substitution by Ligands of Low Valent Transition Metals. A Preparation of Tolanes and Heterocyclics from Aryl Iodides and Cuprous Acetylides *J. Org. Chem.* **1963**, *28*, 2163.
55. Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. Synthesis of Aryl- and Vinylacetylene Derivatives by Copper-Catalyzed Reaction of Aryl and Vinyl Iodides with Terminal Alkynes *J. Org. Chem.* **1993**, *58*, 4716–4721.
56. Zuidema, E.; Bolm, C. Sub-Mol% Catalyst Loading and Ligand-Acceleration in the Copper-Catalyzed Coupling of Aryl Iodides and Terminal Alkynes *Chem.–Eur. J.* **2010**, *16*, 4181–4185.
57. Wang, Z.-L.; Zhao, L.; Wang, M.-X. Construction of C_{aryl}–C_{alkynyl} Bond from Copper-Mediated Arene–Alkyne and Aryl Iodide–Alkyne Cross-Coupling Reactions: A Common Aryl-Cu^{III} Intermediate in Arene C–H Activation and Castro–Stephens Reaction *Org. Lett.* **2012**, *14*, 1472–1475.
58. Heck, R. F.; Nolley, Jr., J. P. Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides *J. Org. Chem.* **1972**, *37*, 2320–2322.
59. Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
60. Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. Application of Palladacycles in Heck Type Reactions *J. Organomet. Chem.* **1999**, *576*, 23–41.
61. Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis *Chem. Rev.* **2000**, *100*, 3009–3066.
62. Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. Advances in the Heck Chemistry of Aryl Bromides and Chlorides *Tetrahedron* **2001**, *57*, 7449–7476.

63. Amatore, C.; Jutand, A.; M'Barki, M. A. Evidence of the Formation of Zerovalent Palladium from Pd(OAc)₂ and Triphenylphosphine *Organometallics* **1992**, *11*, 3009–3013.
64. Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. Palladacycles as Structurally Defined Catalysts for the Heck Olefination of Chloro- and Bromoarenes *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844–1848.
65. Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. Palladacycles: Efficient New Catalysts for the Heck Vinylation of Aryl Halides *Chem.–Eur. J.* **1997**, *3*, 1357–1364.
66. Heck, R. F. Palladium-Catalyzed Reactions of Organic Halides with Olefins *Acc. Chem. Res.* **1979**, *12*, 146–151.
67. Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. Ligand-Free Pd-Catalyzed Highly Selective Arylation of Allylic Esters with Retention of the Traditional Leaving Group *Angew. Chem., Int. Ed.* **2008**, *47*, 4729–4732.
68. Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. Highly Active Pd(II) PCP-Type Catalysts for the Heck Reaction *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688.
69. Calò, V.; Nacci, A.; Monopoli, A.; Ferola, V. Palladium-Catalyzed Heck Arylations of Allyl Alcohols in Ionic Liquids: Remarkable Base Effect on the Selectivity *J. Org. Chem.* **2007**, *72*, 2596–2601.
70. Carlström, A.-S.; Frejd, T. Aspects of the Palladium-Catalyzed Coupling between Aryl Halides and 2-Amidoacrylates *Acta Chem. Scand.* **1992**, *46*, 163–171.
71. Calò, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. Pd Nanoparticles Catalyzed Stereospecific Synthesis of β -Aryl Cinnamic Esters in Ionic Liquids *J. Org. Chem.* **2003**, *68*, 2929–2933.
72. Knowles, J. P.; Whiting, A. The Heck-Mizoroki Cross-Coupling Reaction: A Mechanistic Perspective *Org. Biomol. Chem.* **2007**, *5*, 31–44.
73. Amatore, C.; Jutand, A. Anionic Pd(0) and Pd(II) Intermediates in Palladium-Catalyzed Heck and Cross-Coupling Reactions *Acc. Chem. Res.* **2000**, *33*, 314–321.
74. Jiang, Z.; Zhang, L.; Dong, C.; Ma, B.; Tang, W.; Xu, L.; Fan, Q.; Xiao, J. Palladium-Catalyzed Highly Regioselective and Stereoselective Arylation of Electron-Rich Allylamines with Aryl Bromides *Tetrahedron* **2012**, *68*, 4919–4926.
75. Deng, Y.; Jiang, Z.; Yao, M.; Xu, D.; Zhang, L.; Li, H.; Tang, W.; Xu, L. Palladium-Catalyzed, Highly Efficient, Regiocontrolled Arylation of Electron-Rich Allylamines with Aryl Halides *Adv. Synth. Catal.* **2012**, *354*, 899–907.

76. Olofsson, K.; Larhed, M.; Hallberg, A. Highly Regioselective Palladium-Catalyzed β -Arylation of *N,N*-Dialkylallylamines *J. Org. Chem.* **2000**, *65*, 7235–7239.
77. Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. Regioselective Palladium-Catalyzed Synthesis of β -Arylated Primary Allylamine Equivalents by an Efficient Pd-N Coordination *J. Org. Chem.* **2001**, *66*, 544–549.
78. Wu, J.; Marcoux, J.-F.; Davies, I. W.; Reider, P. J. β -Regioselective Intermolecular Heck Arylation of *N,N*-Disubstituted Allylamines *Tetrahedron Lett.* **2001**, *42*, 159–162.
79. Baxter, C. A.; Cleator, E.; Alam, M.; Davies, A. J.; Goodyear, A.; O'Hagan, M. A Novel Approach to 3-Methylindoles by a Heck/Cyclization/Isomerization Process *Org. Lett.* **2010**, *12*, 668–671.
80. Yu, K.-L.; Deshpande, M. S.; Vyas, D. M. Heck Reactions in Solid Phase Synthesis *Tetrahedron Lett.* **1994**, *35*, 8919–8922.
81. Hiroshige, M.; Hauske, J. R.; Zhou, P. Formation of C-C Bond in Solid Phase Synthesis Using the Heck Reaction *Tetrahedron Lett.* **1995**, *36*, 4567–4570.
82. Koh, J. S.; Ellman, J. A. Palladium-Mediated Three-Component Coupling Strategy for the Solid-Phase Synthesis of Tropane Derivatives *J. Org. Chem.* **1996**, *61*, 4494–4495.
83. Ruhland, B.; Bombrun, A.; Gallop, M. A. Solid-Phase Synthesis of 4-Arylazetidines via Suzuki and Heck Cross-Coupling Reactions *J. Org. Chem.* **1997**, *62*, 7820–7826.
84. Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. A Surprising Solid-Phase Effect: Development of a Recyclable “Traceless” Linker System for Reactions on Solid Support *Angew. Chem., Int. Ed.* **1998**, *37*, 3413–3415.
85. Bräse, S.; Schroen, M. Efficient Cleavage – Cross-Coupling Strategy for Solid-Phase Synthesis—A Modular Building System for Combinatorial Chemistry *Angew. Chem., Int. Ed.* **1999**, *38*, 1071–1073.
86. Kulkarni, B. A.; Ganesan, A. Solid-Phase Synthesis of β -Keto Esters via Sequential Baylis-Hillman and Heck Reactions *J. Comb. Chem.* **1999**, *1*, 373–378.
87. Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. A Fluorescence-Based Assay for High-Throughput Screening of Coupling Reactions. Application to Heck Chemistry *J. Am. Chem. Soc.* **1999**, *121*, 2123–2132.
88. Wiehn, M. S.; Lindell, S. D.; Bräse, S. Solid-Phase Organic Synthesis of Difluoroalkyl Entities Using a Novel Fluorinating Cleavage Strategy: Part 1. Linker Development: Scope and Limitations *J. Comb. Chem.* **2009**, *11*, 960–981.

89. Goff, D. A.; Zuckermann, R. N. Solid-Phase Synthesis of Highly Substituted Peptoid 1(2*H*)-Isoquinolinones *J. Org. Chem.* **1995**, *60*, 5748–5749.
90. Hiroshige, M.; Hauske, J. R.; Zhou, P. Palladium-Mediated Macrocyclization on Solid Support and Its Applications to Combinatorial Synthesis *J. Am. Chem. Soc.* **1995**, *117*, 11590–11591.
91. Yun, W.; Mohan, R. Heck Reaction on Solid Support: Synthesis of Indole Analogs *Tetrahedron Lett.* **1996**, *37*, 7189–7192.
92. Arumugam, V.; Routledge, A.; Abell, C.; Balasubramanian, S. Synthesis of 2-Oxindole Derivatives via the Intramolecular Heck Reaction on Solid Support *Tetrahedron Lett.* **1997**, *38*, 6473–6476.
93. Zhang, H.-C.; Maryanoff, B. E. Construction of Indole and Benzofuran Systems on the Solid Phase via Palladium-Mediated Cyclizations *J. Org. Chem.* **1997**, *62*, 1804–1809.
94. Berteina, S.; De Mesmaeker, A. Radical and Palladium-Mediated Cyclizations of *Ortho*-Iodo Benzyl Enamines: A Scope and Limitation Study *Synlett* **1998**, 1227–1230.
95. Berteina, S.; Wendeborn, S.; De Mesmaeker, A. Radical and Palladium-Mediated Cyclizations of *Ortho*-Iodo Benzyl Enamines: Application to Solid Phase Synthesis *Synlett* **1998**, 1231–1233.
96. Schwarz, J.; Böhm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringer, W.; Raudaschl-Sieber, G. Polymer-Supported Carbene Complexes of Palladium: Well-Defined, Air-Stable, Recyclable Catalysts for the Heck Reaction *Chem.–Eur. J.* **2000**, *6*, 1773–1780.
97. Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. Concise Construction of Novel Bridged Bicyclic Lactams by Sequenced Ugi/RCM/Heck Reactions *Org. Lett.* **2007**, *9*, 5119–5122.
98. Frei, R.; Blackwell, H. E. Small Molecule Macroarray Construction via Palladium-Mediated Carbon–Carbon Bond-Forming Reactions: Highly Efficient Synthesis and Screening of Stilbene Arrays *Chem.–Eur. J.* **2010**, *16*, 2692–2695.
99. Kopylovich, M. N.; Lasri, J.; Guedes da Silva, M. F. C.; Pombeiro, A. J. L. Single-Pot Template Transformations of Cyanopyridines on a Pd^{II} Centre: Synthesis of Ketoimine and 2,4-Dipyridyl-1,3,5-triazapentadiene Palladium(II) Complexes and Their Catalytic Activity for Microwave-Assisted Suzuki-Miyaura and Heck Reactions *J. Chem. Soc., Dalton Trans.* **2009**, 3074–3084.
100. Nakamura, H.; Onagi, S.; Kamakura, T. Synthesis of Heterocyclic Allenes via Palladium-Catalyzed Hydride-Transfer Reaction of Propargylic Amines *J. Org. Chem.* **2005**, *70*, 2357–2360.

101. Lemhadri, M.; Doucet, H.; Santelli, M. Alkynylation of Aryl Bromides with Propargylamines Catalyzed by a Palladium-Tetraphosphine Complex *Synthesis* **2005**, 1359–1367.
102. Nomak, R.; Snyder, J. K. Inverse Electron-Demand Diels-Alder Chemistry in the Synthesis of a Regioselectively Protected Analogue of the Staurosporine Aglycone *Tetrahedron Lett.* **2001**, *42*, 7929–7933.
103. Soberats, B.; Martínez, L.; Vega, M.; Rotger, C.; Costa, A. Conventional Tetrakis(triphenylphosphine)palladium-Copper(I) Iodide-Catalyzed Sonogashira Coupling of Free and BOC-Protected Propargylic Amines “On Water” *Adv. Synth. Catal.* **2009**, *351*, 1727–1731.
104. Hashmi, A. S. K.; Haufe, P.; Rivas Nass, A.; Bats, J. W. The Absolute Configuration of the Products of the Enantioselective Rhodium(I)/BINAP-Catalyzed Enyne Cyclization *Adv. Synth. Catal.* **2004**, *346*, 421–424.
105. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. Heck Reaction of Arenediazonium Salts with *N,N*-Diprotected Allylamines. Synthesis of Cinnamylamines and Indoles *Org. Biomol. Chem.* **2011**, *9*, 1727–1730.
106. Busacca, C. A.; Dong, Y. A Facile Synthesis of 4-Aryl-2,3-Dihydropyrroles *Tetrahedron Lett.* **1996**, *37*, 3947–3950.
107. Malek, N. J.; Moormann, A. E. Palladium-Catalyzed Synthesis of Cinnamylamines *J. Org. Chem.* **1982**, *47*, 5395–5397.
108. Larock, R. C.; Babu, S. Synthesis of Nitrogen Heterocycles via Palladium-Catalyzed Intramolecular Cyclization *Tetrahedron Lett.* **1987**, *28*, 5291–5294.
109. Weinrich, M. L.; Beck, H. P. One-Pot *N*-Alkylation/Heck Approach to Substituted Indoles *Tetrahedron Lett.* **2009**, *50*, 6968–6972.
110. Jiang, T.-S.; Li, J.-H. Palladium-Catalyzed Oxidative Tandem Reaction of Allylamines with Aryl Halides Leading to α,β -Unsaturated Aldehydes *Chem. Commun.* **2009**, 7236–7238.
111. Kore, A. R.; Shanmugasundaram, M. Highly Stereoselective Palladium-Catalyzed Heck Coupling of 5-Iodouridine-5'-triphosphates with Allylamine: A New Efficient Method for the Synthesis of (*E*)-5-Aminoallyl-uridine-5'-triphosphates *Tetrahedron Lett.* **2012**, *53*, 2530–2532.
112. Ma, S. Some Typical Advances in the Synthetic Applications of Allenes *Chem. Rev.* **2005**, *105*, 2829–2871.
113. Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses *Angew. Chem., Int. Ed.* **2012**, *51*, 3074–3112.

114. Morita, N.; Krause, N. Gold Catalysis in Organic Synthesis: Efficient Cycloisomerization of α -Aminoallenes to 3-Pyrrolines *Org. Lett.* **2004**, *6*, 4121–4123.
115. Lutteke, G.; AlHussainy, R.; Wrigstedt, P. J.; Hue, B. T. B.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. Formation of Bicyclic Pyrroles and Furans Through an Enone Allene Photocycloaddition and Fragmentation Sequence *Eur. J. Org. Chem.* **2008**, 925–933.
116. Boutier, A.; Kammerer-Pentier, C.; Krause, N.; Prestat, G.; Poli, G. Pd-Catalyzed Asymmetric Synthesis of *N*-Allenyl Amides and Their Au-Catalyzed Cycloisomerizative Hydroalkylation: A New Route Toward Enantioenriched Pyrrolidones *Chem.–Eur. J.* **2012**, *18*, 3840–3844.
117. Zbieg, J. R.; McInturff, E. L.; Leung, J. C.; Krische, M. J. Amplification of Anti-Diastereoselectivity via Curtin-Hammett Effects in Ruthenium-Catalyzed Hydroxyalkylation of 1,1-Disubstituted Allenes: Diastereoselective Formation of All-Carbon Quaternary Centers *J. Am. Chem. Soc.* **2011**, *133*, 1141–1144.
118. Kinsman, R.; Lathbury, D.; Vernon, P.; Gallegher, T. Stereoselectivity in the Synthesis of 2,5-Disubstituted Pyrrolidines *J. Chem. Soc., Chem. Commun.* **1987**, 243–244.
119. Mitasev, B.; Brummond, K. M. Synthesis of Functionalized Δ^3 -Pyrrolines via a Ag(I)-Catalyzed Cyclization of Amino Acid Derived Allenes *Synlett* **2006**, 3100–3104.
120. Dieter, R. K.; Nice, L. E. Synthesis of Amino Allenes via Reaction of α -Aminoalkylcuprates with Propargyl Substrates *Tetrahedron Lett.* **1999**, *40*, 4293–4296.
121. Dieter, R. K.; Yu, H. Synthesis of 3-Pyrrolines, Annulated 3-Pyrrolines, and Pyrroles from α -Amino Allenes *Org. Lett.* **2001**, *3*, 3855–3858.
122. Breuil-Desvergnès, V.; Compain, P. Vatière, J.-M.; Goré, J. Reaction of the Lithio-Derivative of Methoxy Allene with SAMP-Hydrazones: Access to Enantiopure 3-Pyrrolines *Tetrahedron Lett.* **1999**, *40*, 5009–5012.
123. Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. Stereoselective Synthesis of Chiral Aminoallenes by Organocopper-Mediated *anti*- S_N2^0 -Substitution Reaction of Chiral Ethynylaziridines *Tetrahedron* **2000**, *56*, 2811–2820.
124. Qiao, C.; Jeon, H.-B.; Sayre, L. M. Selective Inhibition of Bovine Plasma Amine Oxidase by Homopropargylamine, a New Inactivator Motif *J. Am. Chem. Soc.* **2004**, *126*, 8038–8045.
125. Eglinton, G.; Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. Researches on Acetylenic Compounds. Part XLV. The Alkaline Isomerisation of But-3-ynoic Acid *J. Chem. Soc.* **1954**, 3197–3200.

126. Casara, P.; Jund, K.; Bey, P. General Synthetic Access to α -Allenyl Amines and α -Allenyl- α -Aminoacids as Potential Enzyme Activated Irreversible Inhibitors of PLP Dependent Enzymes *Tetrahedron Lett.* **1984**, *25*, 1891–1894.
127. Hashmi, A. S. K.; Schuster, A. M.; Litters, S.; Rominger, F.; Pernpointner, M. Gold Catalysis: 1,3-Oxazines by Cyclisation of Allene Amides *Chem.–Eur. J.* **2011**, *17*, 5661–5667.
128. Yu, S.; Ma, S. How Easy Are the Syntheses of Allenes? *Chem. Commun.* **2011**, *47*, 5384–5418.
129. Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. Efficient Homologation of Acetylenes to Allenes *J. Chem. Soc., Chem. Commun.* **1979**, 859–860.
130. Kitagaki, S.; Komizu, M.; Mukai, C. Can the Crabbé Homologation Be Successfully Applied to the Synthesis of 1,3-Disubstituted Allenes? *Synlett* **2011**, 1129–1132.
131. Bieber, L. W.; da Silva, M. F. Mild and Efficient Synthesis of Propargylamines by Copper-Catalyzed Mannich Reaction *Tetrahedron Lett.* **2004**, *45*, 8281–8283.
132. Kuang, J.; Ma, S. One-Pot Synthesis of 1,3-Disubstituted Allenes from 1-Alkynes, Aldehydes, and Morpholine *J. Am. Chem. Soc.* **2010**, *132*, 1786–1787.
133. Youngman, M. A.; Dax, S. L. Mannich Reactions of a Resin-Bound Terminal Alkyne *Tetrahedron Lett.* **1997**, *38*, 6347–6350.
134. Thorand, S.; Krause, N. Improved Procedures for the Palladium-Catalyzed Coupling of Terminal Alkynes with Aryl Bromides (Sonogashira Coupling) *J. Org. Chem.* **1998**, *63*, 8551–8553.
135. Zaragoza, F.; Vejle Petersen, S. Solid-Phase Synthesis of Substituted 1,2,3-Triazoles *Tetrahedron* **1996**, *52*, 10823–10826.
136. Kore, A. R.; Senthilvelan, A.; Shanmugasundaram, M. Highly Chemoselective Palladium-Catalyzed Sonogashira Coupling of 5-Iodouridine-5'-Triphosphates with Propargylamine: A New Efficient Method for the Synthesis of 5-Aminopropargyl-Uridine-5'-Triphosphates *Tetrahedron Lett.* **2012**, *53*, 3070–3072.
137. Lin, Z.; Yu, D.; Sum, Y. N.; Zhang, Y. Synthesis of Functional Acetylene Derivatives from Calcium Carbide *ChemSusChem* **2012**, *5*, 625–628.
138. Gonda, Z.; Tolnai, G. L.; Novák, Z. Dramatic Impact of ppb Levels of Palladium on the “Copper-Catalyzed” Sonogashira Coupling *Chem.–Eur. J.* **2010**, *16*, 11822–11826.
139. Battistuzzi, G.; Cacchi, S.; Fabrizi, G. An Efficient Palladium-Catalyzed Synthesis of Cinnamaldehydes from Acrolein Diethyl Acetal and Aryl Iodides and Bromides *Org. Lett.* **2003**, *5*, 777–780.

140. Brown Ripin, D. H.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M., III; Vetelino, M. G.; Wei, L. Evaluation of Kilogram-Scale Sonogashira, Suzuki, and Heck Coupling Routes to Oncology Candidate CP-724,714 *Org. Process Res. Dev.* **2005**, *9*, 440–450.
141. Bräse, S.; Dahmen, S.; Pfefferkorn, M. Solid-Phase Synthesis of Urea and Amide Libraries Using the T2 Triazene Linker *J. Comb. Chem.* **2000**, *2*, 710–715.
142. Dahmen, S.; Bräse, S. The First Stable Diazonium Ion on Solid Support—Investigations on Stability and Usage as Linker and Scavenger in Solid-Phase Organic Synthesis *Angew. Chem.–Int. Ed.* **2000**, *39*, 3681–3683.
143. Chung, Y.; Lee, H.; Ahn, K. H. *N*-Acyl Triazenes as Tunable and Selective Chemodosimeters Toward Cyanide Ion *J. Org. Chem.* **2006**, *71*, 9470–9474.
144. Štefane, B.; Černigoj, U.; Kočevar, M.; Polanc, S. 3-Acyl-1,3-Diaryltriazenes as Neutral and Selective Acylating Agents *Tetrahedron Lett.* **2001**, *42*, 6659–6662.
145. Bräse, S.; Köbberling, J.; Enders, D.; Lazny, R.; Wang, M.; Brandtner, S. Triazenes as Robust and Simple Linkers for Amines in Solid-Phase Organic Synthesis *Tetrahedron Lett.* **1999**, *40*, 2105–2108.
146. Kuang, J.; Ma, S. An Efficient Synthesis of Terminal Allenes from Terminal 1-Alkynes *J. Org. Chem.* **2009**, *74*, 1763–1765.
147. Chen, B.; Wang, N.; Fan, W.; Ma, S. Efficient Synthesis of *N*-(Buta-2,3-dienyl) Amides from Terminal *N*-Propargyl Amides and Their Synthetic Potential Towards Oxazoline Derivatives *Org. Biomol. Chem.* **2012**, *10*, 8465–8470.