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Microwave-Assisted Synthesis of C₂-Symmetric HIV-1 Protease Inhibitors

*Development and Applications of In Situ
Carbonylations and other Palladium(0)-Catalyzed
Reactions*

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Abstract

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The HIV protease is an essential enzyme for HIV replication and constitutes an important target in the treatment of HIV/AIDS. Efficient combination therapies using inhibitors of the reverse transcriptase and protease enzymes have led many to reevaluate HIV infections from a terminal condition to a chronic-but-manageable disease in the developed world. Unfortunately, the emergence of drug resistant viral strains and severe treatment-related adverse effects limit the benefits of current anti-HIV/AIDS drugs for many patients. Furthermore, less than one in ten patients infected with HIV in low- and middle-income countries have access to proper treatment. These important shortcomings highlight the need for new, cost effective anti-HIV/AIDS drugs with unique properties.

Microwave heating has recently emerged as a productivity-enhancing tool for the medicinal chemist. Reaction times can often be reduced from hours to minutes or seconds and chemistry previously considered impractical or unattainable can now be accessed.

In this thesis, the search for unique HIV-1 protease inhibitors and the development and application of new microwave-promoted synthetic methods useful in small-scale medicinal chemistry applications are presented. Protocols for rapid amino- and hydrazidocarbonylations were developed. $Mo(CO)_6$ was used as a solid source of carbon monoxide, enabling a safe, efficient and simple way to exploit carbonylation chemistry without the direct use of toxic carbon monoxide gas. The aminocarbonylation methodology was applied in the synthesis of two series of new HIV-1 protease inhibitors. A biological evaluation suggested that *ortho*-substitution of P1 and/or P1' benzyl side chains might provide a new approach to HIV-1 protease inhibitors with novel properties. To assess the scope and limitations of the *ortho*-substitution concept, a new series of compounds exhibiting fair potency was prepared by various microwave-heated, palladium-catalyzed coupling reactions. Finally, computer modeling was applied to rationalize the binding-modes and structure-activity relationships of these HIV-1 protease inhibitors.

Keywords: HIV, protease inhibitors, palladium, carbonylations, molybdenum hexacarbonyl, dihydropyrimidone, DHPM, microwave, cross-coupling, diazylhydrazines, carbon monoxide, synthesis, C_2 -symmetric, HIV-1 protease inhibitors, aminocarbonylation, fluorous

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Tack för kaffet!

PAPERS INCLUDED IN THE THESIS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

- I Wannberg, J.; Larhed, M. Increasing Rates and Scope of Reactions: Sluggish Amines in Microwave-Heated Aminocarbonylation Reactions under Air. *J. Org. Chem.* **2003**, *68*, 5750-5753.
- II Herrero, M. A.; Wannberg, J.; Larhed, M. Direct Microwave Synthesis of *N,N'*-diacylhydrazines and Boc-protected Hydrazides by *in situ* Carbonylations under Air. *Synlett* **2004**, *13*, 2335-2338.
- III Wannberg, J.; Dallinger, D.; Kappe, C. O.; Larhed, M. Microwave-Enhanced and Metal-Catalyzed Functionalizations of the 4-Aryl-Dihydropyrimidone Template. *J. Comb. Chem. In Press*
- IV Wannberg, J.; Kaiser, N.-F. K.; Vrang, L.; Samuelsson, B.; Larhed, M.; Hallberg, A. High-Speed Synthesis of Potent C₂-Symmetric HIV-1 Protease Inhibitors by *in Situ* Aminocarbonylations. *J. Comb. Chem. Accepted*
- V Wannberg, J.; Sabnis, Y. A.; Vrang, L.; Samuelsson, B.; Karlén, A.; Larhed, M.; Hallberg, A. A New Structural Theme in C₂-Symmetric HIV-1 Protease Inhibitors: *ortho*-Substituted P1/P1' Side Chains. *Manuscript*.

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Abbreviations and Definitions

Ac	acetyl
AIDS	acquired immunodeficiency syndrome
Aq.	aqueous
Ar	aryl
Asp	aspartic acid
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
CD4	receptor found on surface of certain immune cells Cluster of Differentiation antigen 4
CD4 ⁺ cell	cell bearing the CD4 surface receptor
CO	carbon monoxide
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DHPM	dihydropyrimidone
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
e ⁻	electron
equiv	equivalent(s)
Et	ethyl
FC-84	liquid perfluorocarbon, average Mw 388 (C ₇ F ₁₆)
FDA	US Food and Drug Administration
Gag	precursor polyprotein for structural viral proteins
GC	gas chromatography
gp	glycoprotein
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
Ile	isoleucine
IN	integrase
K _i	inhibition constant/dissociation constant for inhibitor-enzyme binding, $K_i = [E][I]/[EI]$
L	ligand

LC	liquid chromatography
M	metal
Me	methyl
Mo	molybdenum
MS	mass spectrometry
NMR	nuclear magnetic resonance
Pd	palladium
PDB	Protein Data Bank
Ph	phenyl
Pol	precursor polyprotein for viral enzymes
Pr	propyl
PR	protease
ref.	reference
RP	reversed phase
RT	reverse transcriptase
SAR	structure-activity relationship
scissile bond	the amide bond hydrolysed by a protease
SPE	solid-phase extraction
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tol	tolyl
UV	ultraviolet
Val	valine

1 Introduction

1.1 HIV/AIDS

1.1.1 Introduction to HIV/AIDS

Two and a half decades after the first cases of acquired immunodeficiency syndrome (AIDS) emerged in the US, and more than twenty years after the etiological agent was isolated and identified as the Human Immunodeficiency Virus (HIV), we are still far from finding a cure for this scourge on humanity. Since 1981, more than 20 million people have died of AIDS and the latest update from the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 39.4 million people were living with an HIV infection at the end of 2004.¹ Despite recent progress, less than one in ten patients infected with HIV in low- and middle-income countries have access to proper treatment.²

The Chronology of Early HIV/AIDS Research

In 1981, several cases of unusual opportunistic infections (e.g. *Pneumocystis carinii* pneumonia) and a rare cancer (Kaposi's sarcoma) in previously healthy homosexual males were reported.^{3,4} Evidently a decline in the number of circulating CD4⁺ T cells (T-helper lymphocytes) was causing a degeneration of cell-mediated immunity leading to severe immunodeficiency.^{5,6} As the number of cases grew, the condition was given the name AIDS.⁷ Clinical and epidemiological studies soon gathered convincing evidence that the syndrome was caused by an infectious agent,⁸ most likely a virus. Intense research efforts were devoted to trying to identify and isolate the etiological agent behind AIDS and remarkable progress was made between 1982 and 1985. Prominent participants in this quest were the team of Robert C. Gallo at the National Institutes of Health in the US and the team of Luc Montagnier at the Institut Pasteur in France. The two groups had experience working with retroviruses and they recognized signs consistent with a CD4⁺ T-lymphotropic retrovirus.⁹ Although both groups were able to detect the presence of retroviral activity in samples from AIDS patients,¹⁰⁻¹² the French group was first with a clear-cut isolate of a new retrovirus from the abnormally enlarged lymph nodes of a patient showing signs of pre-AIDS (lymphadenopathy) in 1983.¹⁰ The new virus was called lymphadenopathy-

associated virus (LAV)¹³ by Montagnier and human T cell leukemia (or T-lymphotropic) virus III (HTLV-III)¹⁴ by Gallo. Virological and epidemiological evidence soon proved the virus to be the cause of AIDS.¹⁵ The virus, now known as human immunodeficiency virus 1 (HIV-1)¹⁶ was cloned in 1984^{17,18} and its genomic sequence published in 1985.¹⁹⁻²² This definitely established that the virus belonged to the retrovirus subfamily of *lentiviridae*. In 1986 another related retrovirus, now designated as HIV-2, was isolated from Senegalese patients.²³

The Human Immunodeficiency Virus

Viruses in general are supramolecular complexes 20-300 nm in size that are able to infect bacterial, plant or animal cells. Outside of host cells, viruses consist of the genetic material, DNA or RNA, surrounded by a protective capsid shell and sometimes also a membranous envelope. In this extracellular transmission phase the virus particle or virion is metabolically inert and can be considered non-living. Once it has infected a host cell, it becomes an intracellular parasite that diverts the cellular machinery (e.g. enzymes and ribosomes) to the production of new infectious virions. In some cases the new virions escape through the cell membrane without causing much damage but in other cases the release of virions kills the host cell by causing cell lysis.

The discovery that some RNA viruses contain an RNA dependent DNA polymerase in 1970 was the first proof that genetic information could flow ‘backwards’, from RNA to DNA (reverse transcription).^{24,25} A consequence of the discovery of this enzyme class, the reverse transcriptases (RT), was that the central dogma for the flow of genetic information had to be extended (Figure 1). The RNA viruses using RT are called retroviruses (from the Latin word *retro*, backwards). When retroviruses infect a cell, RT catalyses the synthesis of a DNA strand complementary to the viral RNA. RT then degrades the RNA part of the RNA-DNA hybrid and replaces it with DNA. The double stranded DNA sequence is subsequently integrated into the host cell genome (see also Section 1.1.2).²⁶

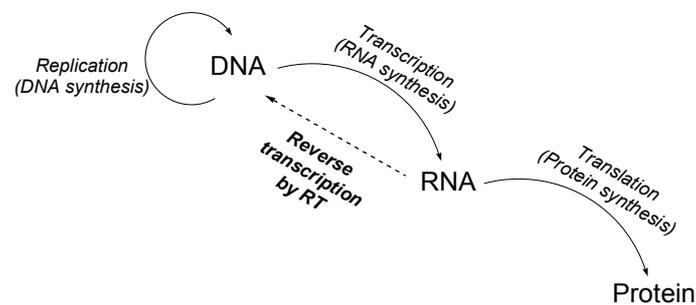


Figure 1. Extended central dogma of molecular biology

Members of the retrovirus family, *retroviridae*, are known to infect cells of many types of animals, from flies to humans. Depending on the type of retrovirus and animal species, retroviral infections can cause different types of diseases such as cancers, neurological diseases, anemias and immunodeficiencies but in other cases an infection can be totally asymptomatic. The retroviridae family is divided into seven genera. The two retroviruses that are known to cause human immunodeficiencies, HIV-1 and HIV-2 belong to the genus of *lentiviridae*. Lentivirus infections are characterized by a slow disease progression (Lat. *Lentus*, slow).^{26,27}

The human immunodeficiency virus particle is practically spherical with a diameter of about 100 nm (Figure 2). It consists of a central conical capsid made from about 2000 copies of the capsid protein (CA, p24) that encapsulates two copies of the 10 kb, positive-sense, single-stranded RNA genome stabilized with about 2000 copies of the nucleocapsid protein (NC, p7). Also enclosed within the capsid are the functional enzymes reverse transcriptase (RT), protease (PR) and integrase (IN) and the accessory proteins Nef, Vif and Vpr. A matrix shell comprising approximately 2000 matrix protein units (MA, p17) surround the capsid and in similarity to all other lentiviruses the HIV virion is enveloped by a lipid bilayer. The envelope membrane is derived from the host cell and in addition to cellular membrane proteins it features the viral surface glycoprotein (SU, gp120) anchored to the transmembrane protein (TM, gp41) (Figure 2).²⁸

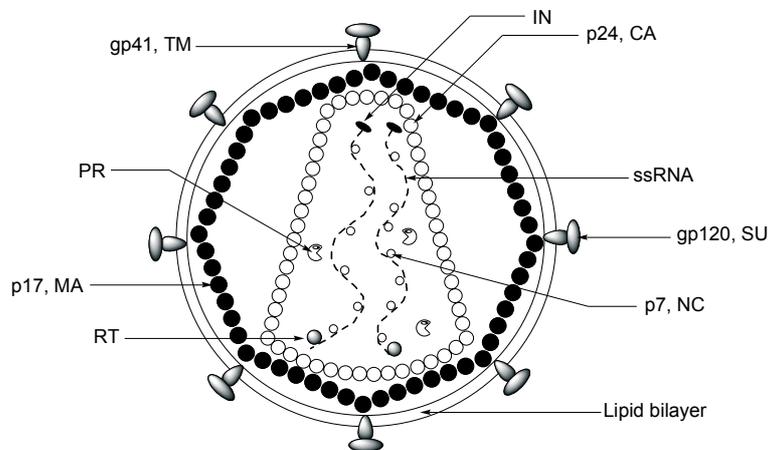


Figure 2. Schematic representation of the morphology of an HIV virion

The HIV virus only infect cells expressing the CD4 glycoprotein (Cluster of Differentiation antigen 4) on the cell surface.^{29,30} CD4 is primarily found on helper T lymphocytes (a.k.a. T_H or $CD4^+$ T cells) and functions as a receptor that recognizes fragments of antigens displayed by antigen-presenting cells (APCs). Once bound to an antigen, the T_H cell is activated and starts to release cytokines (eg. interleukin-2, a T cell growth factor) in order to acti-

vate cytotoxic T cells (a.k.a. T_C , T_K or $CD8^+$ T cells) or B cells. Alternatively, it turns into an antigen specific memory T_H cell. Other cells that express CD4 to a lesser extent are macrophages and dendritic cells.

1.1.2 HIV Replication and Antiretroviral Drug Targets

Once the retrovirus HIV was identified as the causative agent of AIDS, an intense search for effective anti-AIDS drugs began. The first logical move was to target the synthesis of proviral DNA by reverse transcriptase. A screening of compounds intended for other purposes identified the first effective antiretroviral drug, zidovudine (AZT). The nucleoside analog zidovudine was originally intended as an anti-cancer drug but the screening also identified it as an effective inhibitor of reverse transcription. Zidovudine was the first anti-AIDS drug to be approved by the US Food and Drug Administration (FDA) in 1987.^{31,32}

As the research into the mechanisms of retroviral replication progressed, an increasing number of potential drug targets were identified. Some of the targets that have been pursued are listed below in the order of their relation to the different stages of the virus replication cycle shown in Figure 3.

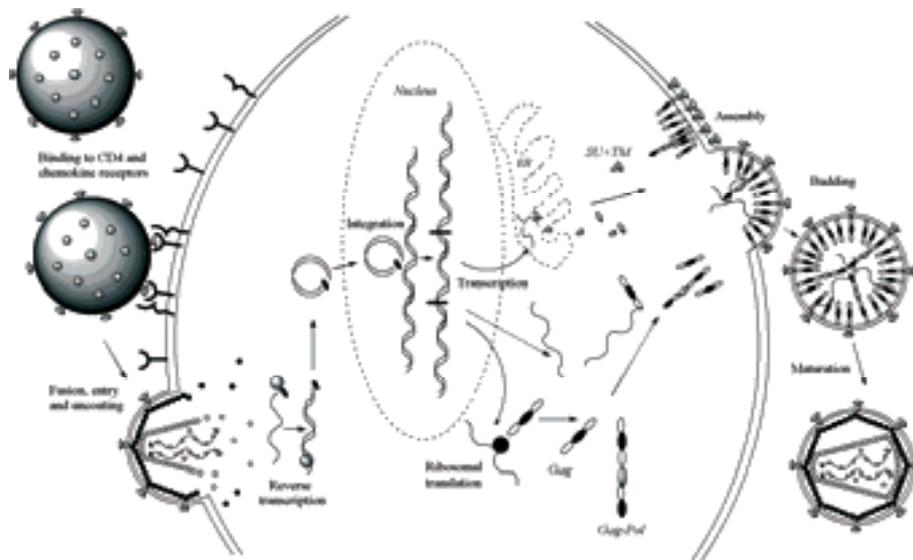


Figure 3. Replication of HIV

Viral entry

The infection of a $CD4^+$ cell starts with the high affinity binding of the viral gp120 (SU) protein to the cellular CD4 protein.^{29,30} The gp120 then has to bind one of two chemokine receptors (CXCR4 for T cell-trophic X4 strains or CCR5 for macrophage-trophic R5 strains).^{33,34} This triggers a conforma-

tional change in the transmembrane gp41 that initiates fusion of the virus with the cell membrane.

Several different strategies for the prevention of viral entry have been developed. Agents that bind either to the cellular CD4 receptor or to the viral gp120 can block this crucial CD4-gp120 interaction.³⁵⁻³⁸ Compounds that down-regulate the expression of CD4 have also been identified.³⁹ Several low-molecular-weight inhibitors of CXCR4 and CCR5 have shown promising results in early clinical trials, providing proof-of-principle for this strategy.⁴⁰⁻⁴³ Furthermore, compounds that bind to gp41 can prevent the conformational change that precedes the virion-cell fusion. This last strategy has yielded the first approved inhibitor of viral entry, the 36 amino acid synthetic peptide enfuvirtide (T-20).⁴⁴

Reverse transcription

The virion is uncoated in the cytosol to reveal the viral RNA genome. The reverse transcriptase converts the single stranded RNA into complementary double stranded DNA. As mentioned, the first anti-AIDS drug, zidovudine (Figure 4), is an inhibitor of reverse transcription. Zidovudine and the other nucleoside analogs (nucleoside reverse transcriptase inhibitors, NRTI) need to be phosphorylated in the body and these substrate analogs then compete with the natural nucleotide bases in the DNA synthesis. When inserted into the DNA they cause chain termination, thereby preventing further reverse transcription.

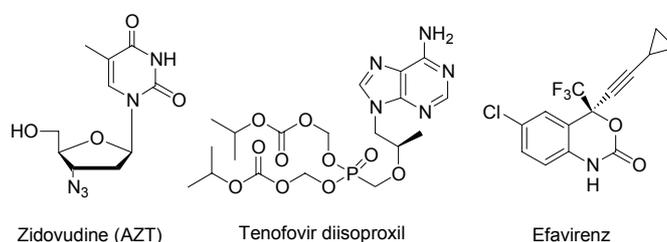


Figure 4. Examples of reverse transcriptase inhibitors

There are currently seven NRTIs and one closely related nucleotide reverse transcriptase inhibitor (tenofovir, Figure 4) approved for use against HIV/AIDS. There are also three non-nucleoside reverse transcriptase inhibitors (NNRTI) approved by FDA. The NNRTIs are a structurally diverse group of compounds that share the ability to bind to a non-substrate (allosteric) binding site of the reverse transcriptase. This allosteric binding causes a conformational change of the enzyme that inhibits its normal function.⁴⁵ The structure of the most frequently used NNRTI, efavirenz, is shown in Figure 4.

proteins (MA, CA and NC) and with subsequent rearrangement to the mature morphology. This process is initiated by the autocatalytic cleavage of the protease from the Gag-Pol protein. The dimeric protease then divides the polyproteins into the individual parts. The structural MA and CA proteins rearrange to form the matrix and capsid of the now mature, infectious HIV virion.

A highly successful strategy to prevent virion maturation has been the inhibition of HIV protease⁵¹⁻⁵⁶ (see Section 1.1.3). Inhibition of maturation can also be accomplished without the direct interference with the protease enzyme. One interesting compound, PA-457 (Figure 6), has recently entered phase IIa clinical trials. This betulinic acid derivative inhibits the conversion of the CA precursor (p25) to mature CA (p24) at a late stage in the Gag-processing cascade by a so far unknown mechanism. The lack of mature CA prevents the formation of the capsid and renders an immature, non-infectious virion.⁵⁷

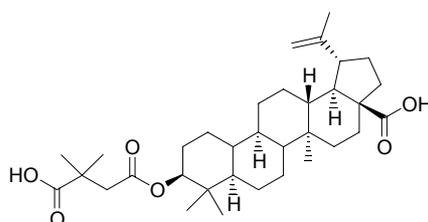


Figure 6. The chemical structure of PA-457, an inhibitor of viral maturation

1.1.3 The HIV Protease and Protease Inhibitors

There are four major classes of proteolytic enzymes: aspartic, serine, cysteine and metallo proteases. The HIV protease is a member of the aspartic proteases. Aspartic proteases are characterized by their ability to hydrolyse peptide bonds with the aid of two catalytic aspartic acids in the active site. Each aspartic acid is generally situated in a highly conserved catalytic triad (Asp-Thr-Gly or Asp-Ser-Gly), which makes it relatively simple to identify genes that encode these types of enzymes in large DNA sequences.

The cleavage mechanism most likely involves a nucleophilic attack by an activated water molecule on the scissile (hydrolysable) peptide bond carbonyl. One of the aspartic acids activate the water molecule while the other donates a proton to the amide nitrogen, creating a hydrogen-bond stabilized tetrahedral intermediate which subsequently collapses into the carboxylic acid and amine cleavage products.⁵²

According to the convention of Schechter and Berger,⁵⁸ the amino acids on the N-terminal side of the scissile bond of the substrate are designated P1, P2, P3 etc. with the side chains binding into the enzyme subsites S1, S2, S3,

respectively. On the C-terminal side the amino acids P1', P2', P3' and so on, bind into the corresponding S1', S2', S3' subsites (Figure 7).

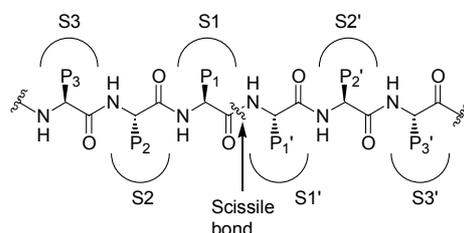


Figure 7. Designation of peptide residues and protease subsites according to Schechter and Berger⁵⁸

The first aspartic protease used as a target in drug discovery was renin. Efforts were made in the 1970s and 1980s to develop renin inhibitors as a new class of anti-hypertensive drugs.^{59,60} During the development of renin inhibitors, substrate sequences where non-hydrolysable surrogates replaced the scissile bonds of the natural substrate were found to be effective blockers of enzyme function, especially when using replacements that can be considered to be analogs or mimics of the tetrahedral intermediate of the peptide cleavage mechanism. This strategy of using a central 'transition-state' isoster (most commonly $-\text{CH}(\text{OH})\text{CH}_2\text{N}-$) at the position where cleavage normally occur was proven so effective that it has become the basis for virtually all aspartic protease inhibitors.^{59,61,62}

Other aspartic proteases of interest in drug discovery beside renin and the HIV protease are the plasmepsins (malaria), the SAPs (*candida* infections) and β -secretase (Alzheimer's disease).

Identification and validation of the HIV-1 protease as a drug target

In conjunction with the determination of the genetic sequence of HIV,¹⁹⁻²² it was postulated that the second open reading frame of the HIV-1 genome was encoding a protease in analogy with other retroviruses.¹⁹ Analysis of the sequence revealed the Asp-Thr-Gly triad typical of aspartic proteases,⁶³ and the question was raised if inhibitors of this protease would prevent viral replication.⁶⁴ However, the suggested protease sequence was unusually short, coding for about half the amino acids of known fungal and mammalian aspartic proteases and only one catalytic triad was found within the protease gene. This led to the proposition that the catalytically active form of the enzyme was a homodimer.⁶⁵

Mutagenesis experiments where the proposed catalytic Asp was substituted for other amino acids produced virus without proteolytic ability and rendered non-infectious viral particles.⁶⁶ These experiments supported the aspartic protease theory and equally important, it demonstrated that the virally encoded protease was essential for viral replication and hence a valid

target for drug intervention. Early experiments where prototypical aspartic protease inhibitors (eg. acetylpepstatin) were shown to inhibit enzyme activity also supported the designation of the enzyme as an aspartic protease.^{67,68} With the publication of the first crystal structures of the protease⁶⁹⁻⁷¹ and protease-inhibitor complexes,⁷²⁻⁷⁴ definitive proof of the homodimeric nature of the HIV-1 protease was established. The crystal structures also paved the way for effective drug discovery with structure-based design and synthesis of potent HIV-1 protease inhibitors.⁷⁵

Structure of HIV-1 Protease

The active form of the HIV-1 protease is composed of two identical 99 amino acid polypeptide chains forming a C₂-symmetric homodimer with a single active site (Figure 8).

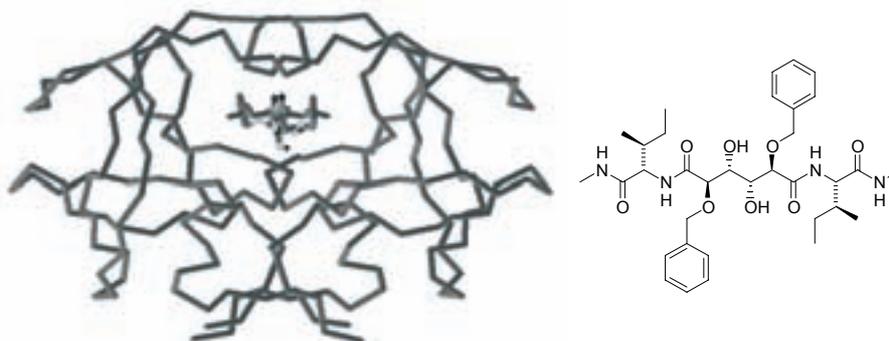


Figure 8. The HIV-1 protease co-crystallized with the inhibitor to the left⁷⁶ (PDB ID: 1ebw)

The formation of active protease dimers is a reversible process that requires high concentrations of monomers. These high concentrations are present in a virus particle after budding but not in the host cell, explaining why the protease does not cause degradation of cellular proteins or premature cleavage of viral polypeptides. Each monomer contributes one catalytic aspartic acid (Asp 25/25') situated at the bottom of the active site. A glycine-rich loop called the flap (residues 47-52 in each monomer) closes down on the substrate upon binding to form the top of the active site. A water molecule forms a bridge between the flap and the substrate by hydrogen bonding to the nitrogens of the Ile50/50' flap residues and to two carbonyls in the substrate. This is also believed to stretch the scissile peptide bond, making it more susceptible to catalytic hydrolysis. When the flaps close, a cylindrical active site is formed with mainly hydrophobic subsites for the binding of a maximum of eight amino acid residues (S1/S1'-S4/S4' and P1/P1'-P4/P4').

HIV-1 Protease Inhibitors

Once the three dimensional structure of the HIV-1 protease was known, development of inhibitors progressed rapidly. The extensive knowledge gained from the development of renin inhibitors (e.g. knowledge about transition-state mimics) and the identification of the HIV protease cleavage sites (Tyr | Pro, Phe | Pro, Leu | Ala, Met | Met, Phe | Tyr, Phe | Leu, and Leu | Phe) contributed to the first generation of highly potent inhibitors designed towards the HIV-1 protease. Rational, iterative drug design and development processes supported by structural studies (X-ray crystallography) and molecular modeling resulted in the first three HIV-1 protease inhibitors being approved by the FDA in short succession between December 1995 and March 1996. So far (April 2005) seven HIV protease inhibitors have been approved for clinical use (eight counting the prodrug fosamprenavir), all with a central hydroxyl-containing transition-state isoster unit (Figure 9).

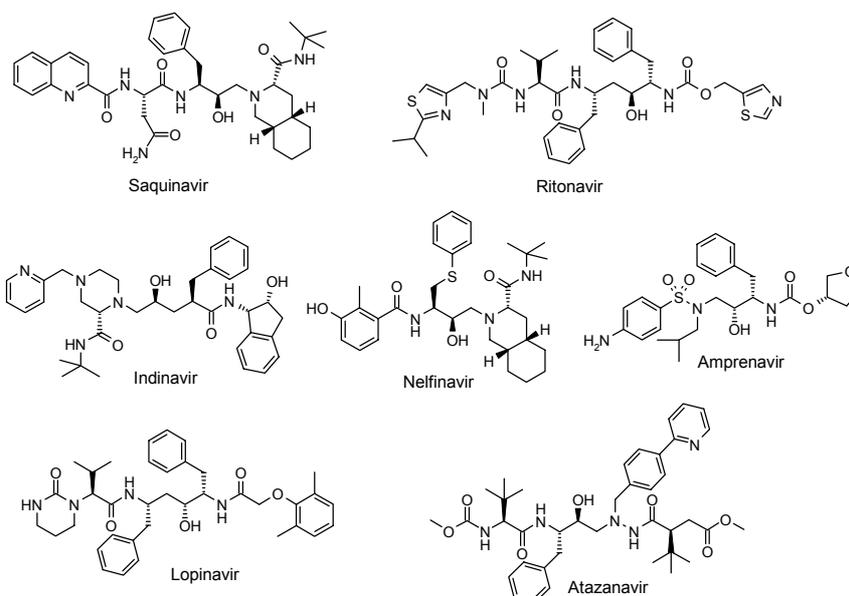


Figure 9. HIV protease inhibitors approved for clinical use

1.1.4 Potent Combination Antiretroviral Therapy

The treatment of HIV infections has evolved continuously since the introduction of zidovudine monotherapy in the late 1980s. An important breakthrough came with the approval of the first protease inhibitors and consequently the beginning of the era of potent combination antiretroviral therapy (also known as highly active antiretroviral therapy, HAART).

The introduction of HAART in 1996 (initially a triple combination of one protease inhibitor and two nucleoside reverse transcriptase inhibitors) resulted in a sharp decline in HIV/AIDS related morbidity and mortality across North America⁷⁷ and Europe⁷⁸ with many AIDS patients literary rising from their deathbeds. Plasma viral loads could now routinely and continuously be suppressed below the detectable limit in individual patients. This has led many to reevaluate HIV infections from a terminal to a chronic-but-manageable condition.

The antiretroviral arsenal currently (April 2005) consists of 20 approved drugs (Table 1) divided into four classes: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and fusion inhibitors (FI).

Table 1. Antiretroviral agents approved for clinical use as of April 2005

Class/Generic Name	FDA Approval Date	Manufacturer
<i>NRTIs</i>		
Zidovudine	March 19, 1987	GlaxoSmithKline
Didanosine	Oct. 9, 1991	Bristol-Myers Squibb
Zalcitabine	June 19, 1992	Hoffmann-La Roche
Stavudine	June 24, 1994	Bristol-Myers Squibb
Lamivudine	Nov. 17, 1995	GlaxoSmithKline
Abacavir	Dec. 17, 1998	GlaxoSmithKline
Tenofovir DF*	Oct. 26, 2001	Gilead Sciences
Emtricitabine	July 2, 2003	Gilead Sciences
<i>NNRTs</i>		
Nevirapine	June 21, 1996	Boehringer Ingelheim
Delaviridine	April 4, 1997	Pfizer
Efavirenz	Sept. 17, 1998	Bristol-Myers Squibb
<i>Protease Inhibitors</i>		
Saquinavir	Dec. 6, 1995	Hoffmann-La Roche
Ritonavir	March 1, 1996	Abbott Laboratories
Indinavir	March 13, 1996	Merck
Nelfinavir	March 14, 1997	Agouron Pharmaceuticals
Amprenavir/Fosamprenavir	April 15, 1999/Oct. 20, 2003	GlaxoSmithKline/Vertex Ph.
Lopinavir	Sept. 14, 2000	Abbott Laboratories
Atazanavir	June 20, 2003	Bristol-Myers Squibb
<i>Fusion Inhibitors</i>		
Enfuvirtide	March 13, 2003	Hoffmann-La Roche/Trimeris

*Tenofovir DF is a nucleotide reverse transcriptase inhibitor (NtRTI)

Current guidelines recommend the use of either a PI-based regimen (1 or 2 PIs + 2 NRTIs) or an NNRTI-based regimen (1 NNRTI + 2 NRTIs) for the initial treatment of HIV-infected patients.⁷⁹ The treatment does not cure a patient from the infection because of the persistence of long-lived latently

infected CD4⁺ cells even after many years of effective treatment with complete viral suppression. The treatment is instead aimed at maximal and durable suppression of viral loads thereby restoring or preserving immunologic functions and consequently reducing HIV-related morbidity and mortality and improving quality of life.

Unfortunately, there are a number of sometimes inter-related factors that can contribute to a sub-optimal response to the treatment regimen (treatment failure), for example poor adherence to the prescribed regimen, drug side effects and toxicity,⁸⁰ sub-optimal potency of the regimen, pharmacokinetic problems (e.g. poor bioavailability and/or fast metabolism) and the emergence of drug resistant viral strains.⁸¹ Treatment failure generally initially involves an increase in viral load (virologic failure) followed by a decrease in circulating CD4⁺ T cells (immunologic failure) and finally a clinical progression to AIDS and ultimately death.

Despite the success of HAART, the limitations listed above indicate a continuous need for new, inexpensive antiretroviral drugs with fewer and less severe side effects and with unique resistance profiles.

1.2 Palladium(0)-Catalyzed Reactions

Palladium is a silvery-white precious metal of the Platinum group (Group 10) of the periodic table with the atomic number 46. Palladium was discovered in 1803 by the British scientist William Hyde Wollaston (1766-1828) and was named after the recently discovered (1802) asteroid Pallas. The name is derived from the Greek goddess Pallas Athena, the protector of cities and goddess of battle, wisdom and certain crafts.

The present world market price of palladium is about 200 \$/troy oz (~50,000 SEK/kg) (April 2005). About 60% of the world production of 200 metric tons in 2003 was used in car exhaust catalysts. Approximately 15% was used in electrical components like integrated circuits and about the same amount in dental alloys. About 5% was used in jewelry (e.g. in 'white gold') and the remaining 5% found use in chemical research and industry.

1.2.1 Catalytic Properties of Palladium

Palladium is the most frequently used transition metal catalyst in organometallic chemistry. It has the ability to catalyze a wide variety of carbon-carbon and carbon-heteroatom bond forming reactions.^{82,83} An impressive range of functional groups is tolerated and the reactions usually proceed with high chemo- and regioselectivity. Palladium primarily adopts the 0 or +2 oxidation states and the low energy barrier between the two is an important factor for its usefulness in catalytic processes. To be useful as a catalyst, a transition metal complex must be 'bench-stable' but should quickly become

activated in solution by loss of ligands to become a coordinatively unsaturated species that can interact with a substrate. For a transition metal complex to be coordinatively saturated, the central metal atom should adopt the 18 valence electron configuration of the nearest noble gas. Palladium(0) has 10 electrons in the outer shells ($4d^{10}5s^0$ or $4d^85s^2$) so four ligands must coordinate and contribute with $2 e^-$ each to Pd in order to form a stable $18 e^-$ complex. The Pd^0 in these complexes can be considered electron rich and the ligands are arranged around the metal in a tetrahedral configuration. The catalytically active species in Pd^0 -catalyzed coupling chemistry is generally considered to be a coordinatively unsaturated $14 e^-$ species of the Pd^0L_2 type, formed by the reversible dissociation of two ligands in solution (Figure 10). Palladium(II) salts or stable $16 e^- Pd^{II}$ complexes are often used as precatalysts in Pd^0 chemistry. The reduction of Pd^{II} by the simultaneous oxidation of phosphine ligands, amines, solvent or other reagents provides *in situ* formation of catalytically active Pd^0 .^{84,85}

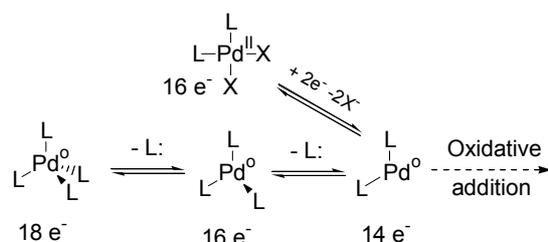


Figure 10. Formation of a catalytically active 14 electron palladium(0) complex

1.2.2 Fundamental Reactions in Palladium(0) Catalysis

Listed here are some fundamental processes involved in the catalytic cycles of the Pd^0 -catalyzed reactions discussed in this thesis.⁸⁴⁻⁸⁶

Oxidative Addition

The first step in the catalytic cycle of Pd^0 catalyzed reactions involves the oxidative addition of a molecule to a $14 e^-$ palladium(0) species with the cleavage of one covalent bond and the formation of two new bonds. From another perspective one might also view it as an insertion of Pd into a bond of a substrate. The ‘oxidative’ part of the name comes from the fact that two previously non-bonding electrons of Pd becomes involved in bonding and the formal oxidation state of Pd increases from 0 to +2, hence an ‘oxidation’ of palladium occurs. Common substrates for oxidative addition are $C_{sp^2}-X$ bonds, where X is usually a halogen or a pseudohalogen (e.g. triflate or diazonium salt). The product of the oxidative addition is a square planar $16 e^- Pd^{II}$ complex logically named an oxidative addition complex.

Transmetallation

Transmetallation is the reaction of (commonly main group) organometallic compounds with an oxidized palladium species (e.g. an oxidative addition complex) whereby the organic group is transferred from the metal to the palladium by substitution of the halide or pseudohalide. This reaction is the second step of the catalytic cycle of cross-coupling reactions (see Section 1.2.3). Generally the metal has to be more electropositive than Pd for this reaction to occur and well-known examples are organometallics of Mg, Zn, B, Al, Sn, Si and Hg.

Insertion

A ligand substitution and an insertion process follow the oxidative addition in Heck and carbonylation chemistry (see Section 1.2.3). The insertion can be described as a migration of a ligand from the palladium to the Pd-bound unsaturated ligand. There are two general types, α,α - and α,β -insertion. In the Heck reaction a ligand dissociates from the oxidative addition complex and the available coordination site is occupied by an alkene, forming a π -complex to Pd. The alkene is then 'inserted' (α,β) between the palladium and aryl or alkenyl group, forming a new C-C bond and an alkyl-Pd σ -complex. The insertion can also be viewed as the migration of the aryl group from Pd to the β carbon of the alkene with the α carbon forming a σ -complex to Pd. This reaction is also known as carbopalladation. In carbonylations of Ar-X substrates the carbon monoxide carbon coordinates to the available site on Pd. The aryl group then migrates to the CO carbon forming an acylpalladium complex, or viewed in another way, the CO inserts (α,α) into the Pd-aryl bond.

β -Hydride Elimination

In the Heck reaction, the carbopalladation (α,β -insertion) can be followed by a *syn* β -hydride elimination. The arylated alkene is released providing there is a free coordination site on Pd and a β -hydrogen that can align *cis* to the Pd-alkyl bond. This *syn* elimination yields an unstable H-Pd^{II}-X species, delivering Pd⁰ complexes in the presence of base.

Reductive Elimination

In cross-coupling reactions, the reductive elimination involves two ligands in *cis* configuration on Pd. The two groups leave Pd and combine to form a new C-C or C-heteroatom bond, affording the coupling product and regenerated Pd⁰.

1.2.3 Palladium(0)-Catalyzed Coupling Reactions

In the following section, a brief summary of the different types of Pd⁰ catalyzed coupling reactions performed and discussed in this thesis is presented.

Cross-Coupling Reactions

In general, cross-couplings are reactions catalyzed by palladium(0) between a main group organometallic compound and an organic halide (or pseudohalide) with the formation of a new carbon-carbon bond. The mechanism of these reactions follows the general cycle (Figure 11):

1. Oxidative addition of the organic halide to Pd⁰.
2. Transmetalation of the organic part of the organometallic reagent to Pd^{II}.
3. Reductive elimination to couple the two different organic moieties with the simultaneous regeneration of Pd⁰, which is then available to undergo a new oxidative addition.

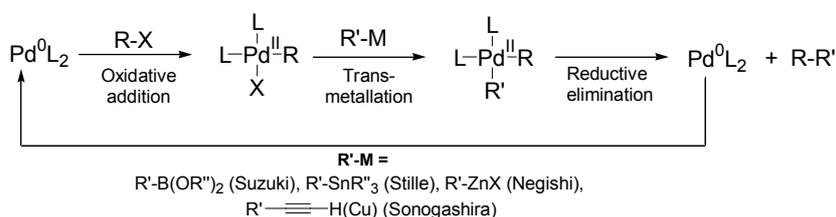


Figure 11. General catalytic cycle for cross-coupling reactions

The most commonly used cross-coupling reactions are the Suzuki, Stille and Negishi reactions. The frequently used Sonogashira reaction is a closely related coupling of terminal alkynes with R-X. Here, copper present in catalytic amounts probably forms the active transmetalating agent *in situ* by coordinating to a deprotonated terminal alkyne.⁸²

The Heck Reaction

The Heck reaction is the Pd⁰ catalyzed carbon-carbon coupling reaction of an aryl, benzyl, or vinyl halide (or pseudohalide) with an alkene in a basic solution. The mechanism starts with an oxidative addition followed by ligand substitution and formation of a π -complex between the alkene and palladium. The alkene then undergoes carbopalladation (insertion) to produce an alkyl-palladium σ -complex. A *syn* β -hydride elimination then release the substituted olefin and a base mediated elimination of H-Pd^{II}-X regenerates catalytically active palladium(0) (Figure 12).⁸⁷

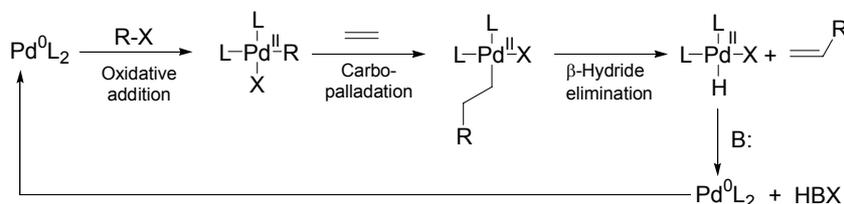


Figure 12. Simplified catalytic cycle for the Heck reaction

Carbon-Heteroatom Couplings

In recent years substantial progress has been made in the area of palladium(0) catalyzed C-N, C-O and C-S bond forming reactions. These are related to the cross-couplings and generally require the assistance of strong alkoxide or carbonate bases. The proposed mechanisms involve the formation of amido- or alkoxo-palladium complexes by direct ligand displacement. The R-Pd^{II}-heteroatom complexes then undergo reductive elimination with formation of a new carbon-heteroatom bond. Examples of reactions that have generated significant interest recently are the N-arylation (or vinylation) of amines (Buchwald-Hartwig chemistry) and the N-arylation of amides.⁸⁸⁻⁹⁰

Carbonylation Reactions

Palladium(0) catalyzed carbonylation reactions use carbon monoxide in the synthesis of ketones, aldehydes, carboxylic acids and their derivatives.⁹¹⁻⁹³ Fundamental in the carbonylations discussed here is the formation of an acylpalladium complex (see *Insertion* Section 1.2.2) from Ar-X, carbon monoxide and Pd⁰. The acylpalladium species can be viewed as an activated carboxylic acid derivative receptive for nucleophilic attack. Nucleophiles such as water, alcohols, amines and organometallic reactants can attack the acylpalladium species to afford carboxylic acids, esters, amides and ketones, respectively. Less nucleophilic organometallics can still produce ketones by transmetalation to the acyl-Pd, followed by a reductive elimination (Figure 13. More about carbonylations in Section 3).

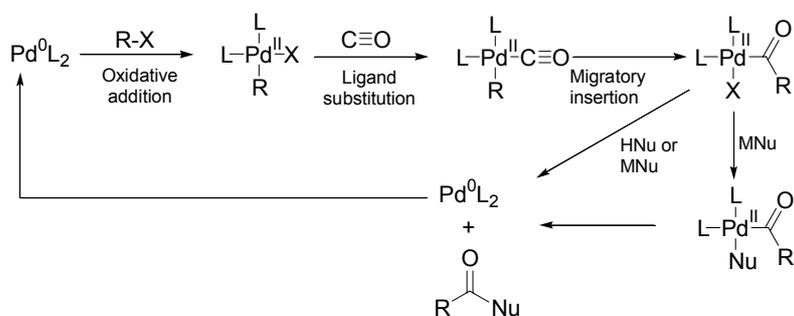


Figure 13. General catalytic cycle for carbonylation reactions

1.3 Microwaves as a Tool in Drug Discovery

Electromagnetic radiation with a frequency of 0.3-300 GHz ($\lambda = 1-0.001$ m) is called microwave radiation. The microwave part of the electromagnetic spectrum lies between the more energetic infrared radiation and the less energetic radiowaves (Figure 14). Microwaves are used in radar, satellite

communication, in land-based communications links spanning moderate distances (cell phones) and in other applications, not forgetting microwave ovens.

Microwave assisted synthesis has recently emerged as a productivity-enhancing tool for the medicinal chemist. Reaction times can often be reduced from hours to minutes or seconds and chemistry previously considered impractical or unattainable can now be accessed.^{94,95}

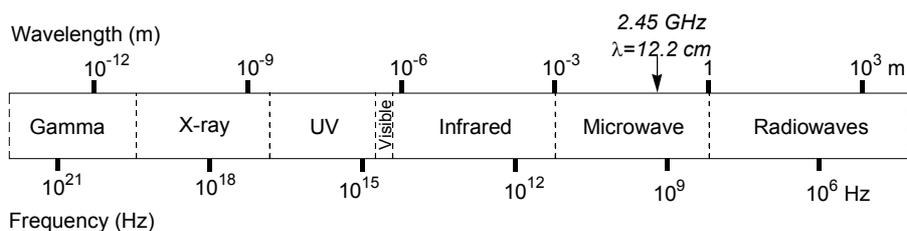


Figure 14. The electromagnetic spectrum

1.3.1 Heating Mechanisms

Microwaves are able to heat a chemical reaction mixture (or food) by two general mechanisms, dipolar polarization and ionic conductance. All matter that contains dipoles and/or charged species can absorb microwave energy and convert it into heat. This is due to the fact that dipoles and ions are constantly trying to align themselves to the electric component of the oscillating electromagnetic field, resulting in rotation of molecules and oscillation of ions. The electromagnetic energy absorbed in this process is hence first converted to kinetic energy, which is then lost as heat through molecular friction.^{96,97}

To achieve efficient heating it is important that the frequency of the applied radiation is within certain limits. If it is too low the dipoles have time to realign too quickly with the electric field and completely follow the field fluctuations, resulting in poor heating. If it is too high the dipoles do not have time to realign themselves at all to the alternating field, which means no motion is created and therefore no heat. The frequency used by domestic microwave ovens and microwave synthesizers (2450 MHz, $\lambda = 12.24$ cm) is located between these extremes where dipoles have time to partly realign with the oscillating electric field but are not quite able to follow the field fluctuations. The result of this is effective generation of heat.^{94,95,98}

1.3.2 Microwaves in Drug Discovery

From its humble beginnings in the middle of the 1980s,^{99,100} microwave heated organic synthesis has evolved rapidly in the last ten years. From being a curiosity, the technology is now conquering new ground at a steady

pace. The popularity has grown in parallel with the improvements in performance, control, reproducibility and safety of the dedicated microwave synthesizers developed in recent years. Competition between the manufacturers has also led to a reduction of instrument prices. If this trend continues, microwave equipment will probably live up to the phrase “Bunsen burners of the 21st century”¹⁰¹ and become the standard tool or technique for heating organic reactions, both in industry and academia.¹⁰²

The generally accepted advantages of microwave assisted organic synthesis compared to conventional heating techniques are speed, convenience and energy efficiency. If at least one component of the reaction mixture can interact with microwaves, a very high heating rate can be accomplished. A consequence of the direct bulk heating generated by microwave irradiation is an energy-efficient and uniform heating of the whole reaction system. In conventional heating, energy must first be transferred from the heat source to the wall of the reaction vessel and then to the reaction medium. The temperature gradient created can lead to so-called wall effects, for example catalyst deactivation on the hot vessel wall. Microwaves can be exploited for selective heating of different multi-phase systems. One example is the use of a two-phase system where one layer absorbs microwaves more efficiently than the other and therefore becomes heated more rapidly.¹⁰³ Ideally, the reactants will be soluble in the “hot” layer and the product in the cold, thereby avoiding possible thermal decomposition and simplify purification. Another example is the selective heating of the surfaces of heterogeneous catalysts with the generation of ‘hotspots’.

Solvents irradiated by microwaves can generally be heated well above their boiling points at atmospheric pressure. This is a result of the heating being faster than the convection to, and loss of heat from, the surface of the solvent/reaction mixture. A higher temperature is reached before bubbles form. This superheating alone (up to 20 °C above the boiling point) can increase reaction rates considerably. One should remember that according to the rate law, a 10 °C increase in reaction temperature will roughly double the reaction rate. If closed vessel conditions are used the ‘pressure cooker’ effect can lead to even more dramatic rate enhancements.^{97,104}

When dedicated microwave synthesizers were developed, the chemists in the pharmaceutical industry were among the first to benefit from the new technology. Time is money, so also in drug discovery and development. “Big Pharma” will therefore quickly evaluate any new time saving tool or technique. Combined with expedient purification techniques (e.g. scavengers and reagents on solid support and solid phase extraction techniques), microwave-assisted synthesis is leading the way towards genuine high-throughput chemistry that will hopefully ease the chemistry-related bottleneck in the drug development process.^{102,105,106}

2 Aims of the Present Study

The severity of the AIDS epidemic, the high cost of antiretroviral drugs and the rapid development of drug resistant viral strains make a continued interest in the development of less expensive and unique anti-HIV/AIDS drugs essential.

Microwave assisted organic synthesis has become an extremely useful tool for the medicinal chemist. Reaction times can often be reduced from hours to minutes or seconds and chemistry previously considered impractical or unattainable can now be accessed.

This study is a part of a research project aimed at the development of novel HIV-1 protease inhibitors.

The specific objectives of this study were:

- To develop practical, microwave promoted, palladium-catalyzed carbonylation methods suitable for small-scale medicinal chemistry applications without the direct use of carbon monoxide gas.
- To demonstrate the scope and limitations of the developed methods by applying the protocols to drug-like molecular scaffolds.
- To exploit the new carbonylation methodologies and other palladium-catalyzed coupling reactions in microwave-assisted syntheses of unique HIV-1 protease inhibitors.
- To establish structure-activity relationships (SAR) of the new HIV-1 protease inhibitors synthesized.

3 Mo(CO)₆ as a Carbon Monoxide Source in Carbonylation Chemistry

3.1 Background to Carbonylation Chemistry

Carbon monoxide (CO) is a highly toxic, colorless, odorless gas with a density comparable to air, primarily produced by partial combustion of carbon containing material in an oxygen-deprived environment. Carbon monoxide is flammable and burns with a characteristic blue flame and forms explosive mixtures with air between 13 and 74 % of CO by volume.

The poisonous effect of carbon monoxide is due to its ability to bind to the hemoglobin of the erythrocytes in the blood about 200-250 times harder than oxygen. When exposed to CO, the hemoglobin quickly becomes saturated with carbon monoxide, rendering it incapable of transporting oxygen to the tissues and thereby causing cellular hypoxia. The symptoms related to exposure to low concentrations of carbon monoxide are dizziness, headache, loss of coordination and nausea. More severe cases may lead to loss of consciousness, respiratory- and circulatory collapse, brain damage and death.^{107,108}

As mentioned, carbon monoxide can be obtained by incomplete combustion of carbon-based material, but the main industrial sources of carbon monoxide are steam reformation of natural gas (methane) and coal gasification (Figure 15). In the steam reformation process, methane and steam (H₂O) are reacted at elevated temperature and pressure with the aid of a nickel catalyst to produce a mixture of carbon monoxide and hydrogen gas called synthesis gas or syngas. Syngas is also the product of coal gasification where white-hot coal or coke is reacted with steam. Syngas can be separated into its components, it can be directly burned as fuel and it can be used in the production of synthetic petroleum via the Fischer-Tropsch process or in the production of methanol (Figure 15). The Monsanto process, a reaction of carbon monoxide and methanol in the presence of a rhodium/iodide catalyst, generates most of the acetic acid produced in the world. Olefins, carbon monoxide and hydrogen produce higher order aldehydes in the presence of a transition metal catalyst in the industrially important hydroformylation reac-

tion (the OXO process). If desired, the aldehydes can be reduced with H₂ to the corresponding alcohols (Figure 15).¹⁰⁹

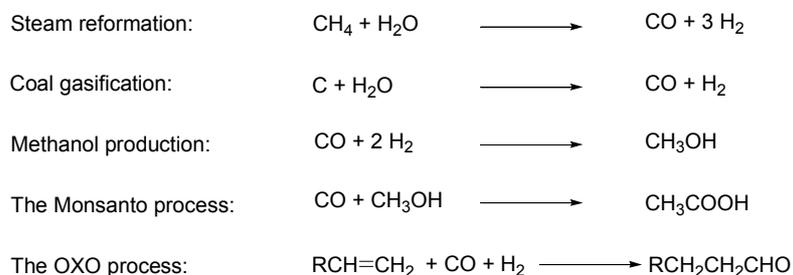


Figure 15. Important industrial processes involving carbon monoxide

The Use of CO (g) in Chemical Synthesis

In synthetic organic chemistry, carbon monoxide has found its use primarily in the field of transition metal catalyzed carbonylations⁹¹⁻⁹³ (e.g. hydroformylations, aminocarbonylations and carbonylative cross-couplings) and in the catalytic Pauson-Khand reaction,^{110,111} a [2+2+1] cycloaddition reaction producing cyclopentenones.

3.1.1 Alternative Sources of Carbon Monoxide

Carbon monoxide is clearly a useful chemical building block, especially in industrial processes. There are however some definite disadvantages with the use of toxic, gaseous reagents in a laboratory environment. Not only the administration of CO to the reaction medium has to be safe, but safety considerations must also be taken for the transport and storage of pressurized carbon monoxide containers. This reduces the utility of carbon monoxide, particularly in small-scale synthetic applications.

A convenient way of avoiding many of these problems would be to exploit a liquid or solid reagent with the ability to release carbon monoxide *in situ* during a reaction. The number of reports of successful applications of condensed CO-sources in organic chemistry is increasing at a steady pace.¹¹² The majority of reports fall into one of the general strategies presented below.

Decarbonylation of Formic Acid or Formic Acid Derivatives

One strategy for performing carbonylations without the direct use of carbon monoxide is to use formic acid derivatives as the source of CO. For example, alkylformates and formamides are known to thermally decompose in the presence of an alkoxide base to carbon monoxide and the corresponding alcohol or amine. Transition metals (e.g. ruthenium) are also known to decarbonylate formic acid derivatives.¹¹³ The carbon monoxide released in

these manners has been used in for example palladium-catalyzed carbonylations (Figure 16).¹¹⁴⁻¹¹⁶ The nucleophile involved can either be the alcohol or amine derived from the CO-source or it can be externally added. Other recent, related examples involve the combination of a formate salt and acetic anhydride. A mixed anhydride is generated *in situ* and subsequently undergoes thermal decomposition to CO and acetic acid. The generated CO was used in hydroxycarbonylations of aryl iodides to the corresponding benzoic acids¹¹⁷ (Figure 16) and in hydroformylations to the corresponding aldehydes.¹¹⁸

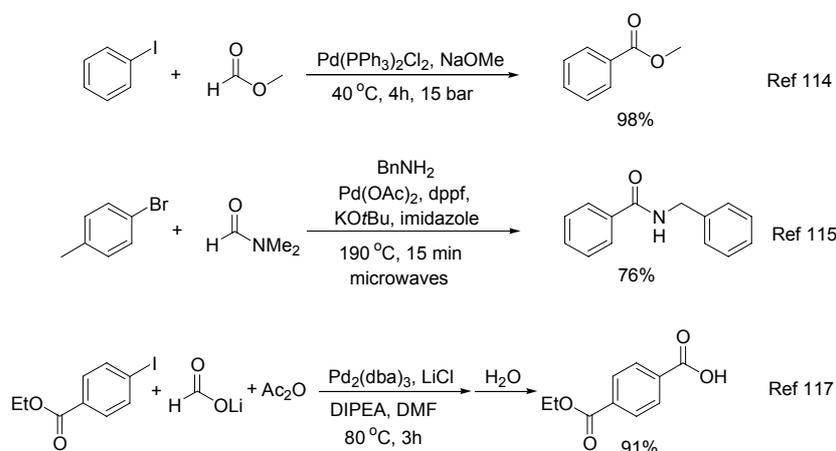


Figure 16. Examples of reactions with formic acid derivatives as the sources of CO

Transition Metal-Catalyzed Decarbonylation of Aldehydes

Some transition metals are known to mediate the decarbonylation of aldehydes. Especially rhodium catalysts have been used successfully in carbon monoxide-free catalytic Pauson-Khand reactions where the carbonyl moiety was derived from various aldehydes.^{119,120} The aldehyde concept was later extended to include intramolecular rhodium-catalyzed aminocarbonylations to afford lactams of different ring-sizes (Figure 17).¹²¹

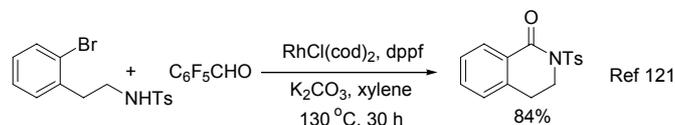


Figure 17. Intramolecular aminocarbonylations using an aldehyde as a CO source

Metal Carbonyls as CO-Releasing Reagents

$\text{Co}_2(\text{CO})_8$ and other metal carbonyl complexes have been used as reagents in the stoichiometric Pauson-Khand reaction since the early 1970s. It is how-

ever only recently that metal carbonyls have generated interest as non-catalytic sources of carbon monoxide in catalytic carbonylations. The interest in molybdenum hexacarbonyl as a solid CO-source began while developing a user-friendly protocol for molybdenum catalyzed enantioselective alkylations.¹²² The active catalyst in this process was formed *in situ* by the substitution of CO-ligands on molybdenum by a chiral ligand. The observation that carbon monoxide was released into the reaction medium inspired the first investigation into the potential use of metal carbonyls as solid sources of carbon monoxide in palladium-catalyzed carbonylation chemistry. Kaiser and Larhed exploited the thermal decomposition of $\text{Mo}(\text{CO})_6$ to carbon monoxide and molybdenum at temperatures above 150 °C for amino- and hydroxycarbonylations of aryl halides (Figure 18).¹²³



Figure 18. The first example of the use of $\text{Mo}(\text{CO})_6$ as a carbon monoxide source

3.1.2 Properties of Metal Carbonyls

The German-born British chemist Ludwig Mond (1839-1909) discovered the first metal carbonyl, the highly toxic nickel tetracarbonyl in 1890. He later developed a process for the isolation of pure nickel based on this discovery. Volatile nickel carbonyl forms when carbon monoxide passes over nickel ore. Nickel carbonyl is subsequently decomposed to yield pure metallic nickel (the Mond process).

Metal carbonyl complexes are compounds where carbon monoxide acts as coordinating ligands to a (transition) metal center. Homoleptic metal carbonyls can be formed from all group 6-9 transition metals (plus V and Ni) by reacting powdered metal with carbon monoxide. The carbon monoxide ligand is simultaneously a σ -donor and π -acceptor (Figure 19). The first

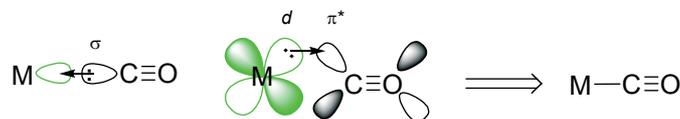


Figure 19. The components of M-CO interaction

component involves a two-electron donation of the CO carbon lone-pair to an empty metal “dsp” orbital. The σ -donation increases the electron density on the metal and the electron density is diverted by the second component of the binding, the π -back-bonding (π -back-donation). A filled d-orbital on the

metal interacts with an empty π orbital (π^*) on the carbonyl ligand. A consequence of this ‘back-bonding’ is a decrease in C-O bond-strength and an increase in C-O bond-length (Figure 19). These complexes generally decompose back to metal and carbon monoxide upon heating. Combined with their relatively high volatility, this makes them ideal for metallic coating of surfaces and particulates. Metal carbonyls are also used as precatalysts in transition metal catalyzed reactions and as a carbonyl source in the stoichiometric Pauson-Khand reaction mentioned above.

3.2 Palladium(0)-Catalyzed Aminocarbonylations (Paper I)

Within an ongoing medicinal chemistry project aimed at identifying novel HIV-1 protease inhibitors, we wanted to examine the effect of different P1/P1’ side chain substitutions in order to efficiently map the tolerance of larger groups in the S1/S1’ subsites of the enzyme. Previously, the impact of P1 and/or P1’ *para*-substitutions have been examined and atazanavir^{124,125} constitutes a representative example of a *para*-substituted compound. Our group found that small substituents (e.g. fluorine) are well tolerated not only in the *meta*- and *para*-positions but also the *ortho*-position when utilizing our mannitol-derived dihydroxyethylene scaffolds.¹²⁶ No information about the impact of larger *ortho*- or *meta*-substituents on the biological activity was available when this work started.

By introducing a halogen (Br or I) in the *ortho* or *meta* positions of the benzyloxy side chain of our C₂-symmetric, C-terminally duplicated HIV protease inhibitor scaffold, a handle for substitutions by palladium(0)-catalyzed reactions was obtained. With the progress made at our department in the field of microwave-heated, ‘carbon monoxide-free’ carbonylation protocols, we envisioned the high-speed synthesis of libraries of carbonylated HIV-1 protease inhibitors (Figure 20).

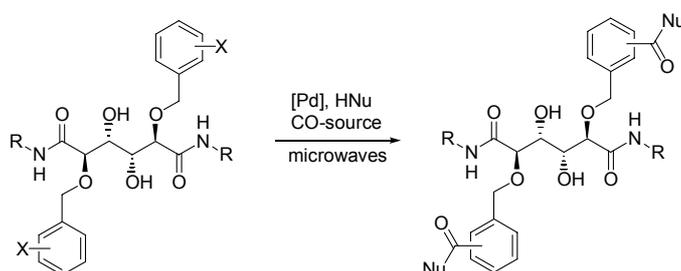


Figure 20. Strategy for the rapid carbonylative synthesis of *ortho*- and *meta* functionalized HIV-1 protease inhibitors

Initial attempts to convert the aryl halide-containing inhibitor derivatives to the corresponding benzamides were however not problem free. The strong base (*tert*-butoxide) and high temperatures needed in the protocols using formamides^{115,116} as the carbon monoxide source was found to be incompatible with the structural integrity of the inhibitor scaffold. Attempts where molybdenum hexacarbonyl (Mo(CO)₆)¹²³ served as the carbon monoxide source were a little more encouraging but still only low yields of the corresponding benzamides were obtained with highly nucleophilic amines and only trace amounts of product were detected when less reactive amines such as aniline were used. Upon realizing that there was room for improvements of the reported protocol, a study on high-speed aminocarbonylations using anilines and other sluggish amines was commenced.

A set of model substrates was selected for the reaction development. Aniline was chosen as an example of a weakly nucleophilic amine and moderately sterically hindered 2-iodotoluene was investigated as an aryl halide mimicking the appearance of an *ortho*-iodo substituted inhibitor (Figure 21).

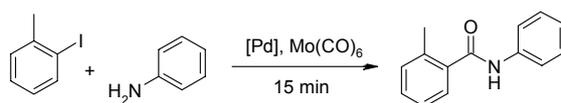


Figure 21. The model reaction selected for the optimization

The aim of the initial study was to arrive at a protocol where full conversion of 2-iodotoluene to the corresponding anilide was achieved within 15 minutes and reaction temperatures were adjusted accordingly. All reactions were conducted under air with controlled microwave heating in sealed borosilicate vessels. In addition to reaction temperature, the following variables were examined:

The base. The choice of base had dramatic effects on the reactivity. Inorganic carbonate bases and tertiary aliphatic amines were not useful in aminocarbonylations with aniline as a nucleophile, at least not at temperatures up to 150 °C. When using the nucleophilic catalysts imidazole or 4-dimethylaminopyridine (DMAP) as bases, full conversion of 2-iodotoluene could be achieved at high temperatures (150 °C). Another effect noted from the pressure curves recorded by the microwave synthesizer was that when adding imidazole, pyridine or DMAP to the reaction mixture, the release of gaseous carbon monoxide was substantially faster than from pure thermal decomposition. Pyridines and other compounds containing electron lone-pairs on unsaturated nitrogens are known to be good ligands to molybdenum. Apparently ligand substitutions on molybdenum accelerate the release of carbon monoxide. This chemical liberation of CO also occurred at temperatures below 150 °C although full conversion of the aryl halide was not ob-

served. Literature precedence for the use of the strong base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in conventional carbonylations with aniline was identified.¹²⁷ When employing DBU as a base an extremely rapid release of CO was observed with formation of bubbles clearly visible even at room temperature. Moreover, complete consumption of 2-iodotoluene was achieved at much lower temperatures. Evidently DBU functions both as an effective carbon monoxide releasing agent and as an efficient base in the aminocarbonylation reactions.

The solvent. The previously reported *in situ* aminocarbonylation protocol was conducted with diglyme as a coordinating solvent.¹²³ This reduced the risk for precipitation of molybdenum metal on the wall of the borosilicate vessel and thereby reducing the risk for subsequent microwave-induced thermal cracking and vessel rupture. The high-boiling and water-soluble diglyme was difficult to remove and complicated the purification of the products. The optimal solvent would preferably have a low enough boiling point to allow convenient evaporation, it should not facilitate ‘metal mirror’ formation on the reaction vessel wall and additionally, the solvent should be readily available in dry form. The etherous solvents diglyme, DME, dioxane and THF were all more efficient than DMF, MeCN or toluene, although the differences between the solvents were moderate. THF was chosen because it was easily removed from the reaction mixture and we had constant and convenient access to freshly distilled, dry solvent.

The palladium-source. A number of phosphine containing and phosphine free palladium pre-catalysts were investigated. Gratifyingly, the ‘old-fashioned’ and relatively inexpensive palladium acetate, Pd(OAc)₂, was found to be equally good or better than the other (pre)catalysts examined.

Running a reaction with 2-iodotoluene, aniline (3 equiv), Pd(OAc)₂ (10 mol%), DBU (3 equiv) and Mo(CO)₆ (1 equiv) in THF at 100 °C for 15 minutes afforded complete consumption of aryl iodide and an 84% isolated yield of 2-methyl-*N*-phenylbenzamide.

The effect of DBU on the release of CO is clearly demonstrated in the temperature-pressure profiles provided in Figure 22. In the presence of both DBU and Mo(CO)₆ (A), the pressure increases to almost 4 bar upon heating to 100 °C. Control experiments revealed that the pressure without Mo(CO)₆ (C) or DBU (D) never exceeded 2.0 bar. For the preparative palladium-catalyzed reaction (B) the pressure increased extremely rapidly and then slowly declined, consistent with a gradual consumption of carbon monoxide (Figure 22).

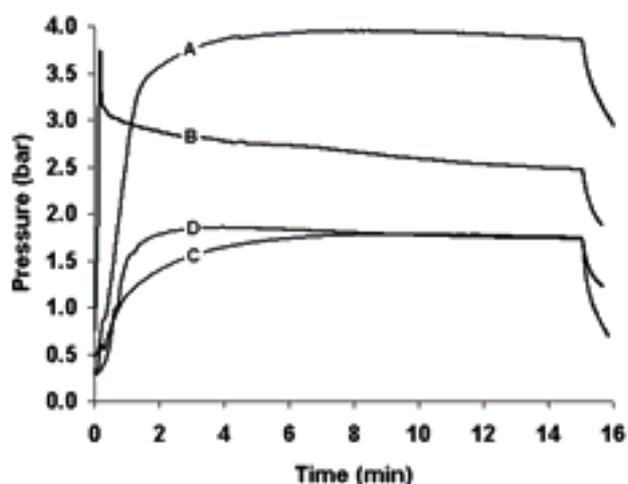


Figure 22. Pressure vs. time-plots from microwave heating at 100 °C: (A) Mo(CO)₆ (0.40 mmol), DBU (3 equiv.) in THF (1 mL). (B) Preparative synthesis at 0.40 mmol scale. (C) As B but without Mo(CO)₆. (D) As B but without DBU.

The selected conditions were investigated with other potential solid sources of carbon monoxide (Table 2). Pressure curves from these reactions indicated gas release in all cases. All of the Group 6 metal carbonyls (Cr(CO)₆, Mo(CO)₆ and W(CO)₆) turned out to be effective sources of carbon monoxide although Mo(CO)₆ produced the highest yield. The use of iron carbonyls were unproductive and reactions with Co₂(CO)₈ produced some product but aryl halide starting material was also consumed in a side reaction forming 2,2'-dimethyl-benzophenone.¹²⁸

Table 2. Reactions performed according to the general procedure, but with different metal carbonyl complexes.

Entry	Metal carbonyl	Isolated yield (%)
1	Cr(CO) ₆	80
2	Mo(CO) ₆	84
3	W(CO) ₆	77
4	Fe(CO) ₅	0
5	Fe ₃ (CO) ₁₂	0
6	Co ₂ (CO) ₈	28

The optimized Mo(CO)₆-based aminocarbonylation protocol was applied on the synthesis of a variety of benzamides. Both electron-rich and electron-

poor aryl iodides proved to be efficient coupling partners. In the set of amines examined in this reaction, the previously investigated piperidine produced improved yields,¹²³ and aniline and benzylamine also coupled easily (Table 3, entries 1-4, 6, 9 and 11). The sterically hindered *tert*-butylamine and the heat sensitive 2-aminothiazole afforded lower yields of products (entries 8, 13, 15 and 20).

Table 3. Rapid Palladium-Catalyzed Aminocarbonylation Reactions with Mo(CO)₆ as a CO Source.

1a-g

2a-i

3a-p

1a Ph-I
1b 4-MeO-Ph-I
1c 4-MeO-Ph-Br
1d 2-Me-Ph-I
1e 2-Me-Ph-Br
1f 4-CF₃-Ph-I
1g 4-CF₃-Ph-Br

2a Piperidine
2b Aniline
2c Benzylamine
2d *tert*-Butylamine
2e 2-Aminothiazole
2f H-Gly-*tert*-Bu · HCl
2g H-Gly-OH
2h H-L-Leu-OH

Entry ^a	Starting material	Product	Method	Yield ^b (%)	Entry ^a	Starting material	Product	Method	Yield ^b (%)
1	1a 2a		A	81	13	1d 2d		A	53
2	1a 2b		A	84	14	1e 2d		B	39
3	1b 2a		A	88	15	1d 2e		A	42
4	1b 2c		A	81	16	1e 2e		B	<5
5	1c 2c		B	92	17	1g 2c		B	95
6	1b 2b		A	87	18	1f 2b		A	86
7	1c 2b		B	68	19	1g 2b		B	53
8	1c 2d		B	44	20	1g 2d		B	35
9	1d 2c		A	83,87 ^c	21	1a 2f		A	64 ^d
10	1e 2c		B	83	22	1a 2g		A	50 ^d
11	1d 2b		A	84,81 ^c	23	1a 2h		A	46 ^{d,e}
12	1e 2b		B	85					

^aThe reactions were performed in 0.40 mmol scale. Method A: A reaction vessel was charged with dry THF (1.0 mL), Ar-I (1.0 equiv), amine (3.0 equiv), Mo(CO)₆ (1.0 equiv), DBU (3.0 equiv) and Pd(OAc)₂ (10 mol%). The reaction mixture was thereafter microwave heated to 100 °C for 15 min. Method B: As method A but with Ar-Br (1.0 equiv), palladacycle (5.0 mol%) and microwave heating to 150 °C for 15 min. ^bIsolated yield, >95% pure according to GC-MS or ¹H NMR. ^cSynthesized with conventional heating (metal heating block, 100 °C, 15 min). ^dDBU (6.0 equiv). Acids **3o** and **3p** purified by RP-LC-MS ^eNo racemization detected.

Protected and non-protected glycines were also used as nucleophiles and were successfully benzoylated by reaction with iodobenzene (entries 21 and 22). Even non-protected L-leucine was benzoylated without racemization under these conditions although the yields of the acidic products were relatively low.

Aryl bromides were also examined as coupling partners. In these aminocarbonylations, Herrmann's palladacycle^{129,130} was an effective palladium(0) catalyst at 150 °C. The change of catalytic system and reaction temperature to 100 °C delivered reaction conditions B. These conditions were applied with good results on a selection of aryl bromides and amines (Table 3). The results followed the same trend as for the corresponding aryl iodides with yields from 35% to 92% although a useful yield could not be obtained with 2-aminothiazole.

Aminocarbonylations of aryl iodides were also performed with traditional heating in standard glass vessels using preheated metal blocks (100 °C, 15 min). Yields comparable to the microwave heated reactions were observed. The practical convenience, excellent reaction control and safety reasons were, however, supporting the microwave approach. We did not investigate the 150 °C sealed procedure with aryl bromides using conventional heating with standard glass vessels due to the risk of explosions at these high temperatures and pressures.

Finally, resin bound 4-iodobenzenesulfonamide **4** (Polystyrene-Rink amide)¹³¹⁻¹³³ was exposed to the aminocarbonylation conditions (Figure 23). Microwave heating (30 min) followed by cleavage from the resin (20% TFA in CH₂Cl₂) produced the carbonic anhydrase II inhibitor **5**¹³⁴ in 64 % yield (calculated from the loading of the resin).

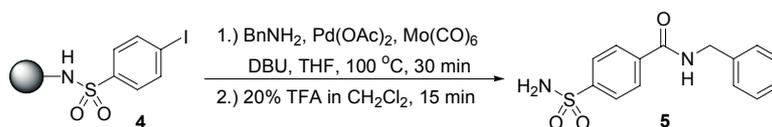


Figure 23. Aminocarbonylation on solid support

3.3 Hydrazidocarbonylations (Paper II)

In parallel with the publication of the aminocarbonylation protocol, a closely related protocol for the alkoxy carbonylation of aryl halides using Mo(CO)₆ was reported from our department.¹³⁵ The satisfying results obtained in the carbonylation projects prompted further interest in the exploration of less common nucleophiles with this convenient high-speed strategy. Since the acylpalladium intermediate in the catalytic cycle of carbonylation reactions can be considered as an activated carboxylic acid derivative, any nucleophile

capable of attacking an acyl chloride or acid anhydride might be of interest for this type of reaction.

Hydrazides are nucleophilic compounds that are able to react with activated carboxylic acid derivatives to form *N,N'*-diacylhydrazines. These structures have several interesting features. They serve as important starting materials for the preparation of various heterocycles, for example oxadiazoles and thiadiazoles.^{136,137} The nitrogens are generally easily deprotonated (pH >10-11) and alkylated. *N,N'*-diacylhydrazines are used as insecticides^{138,139} and can also be found in different protease inhibitors (Figure 24).^{140,141}

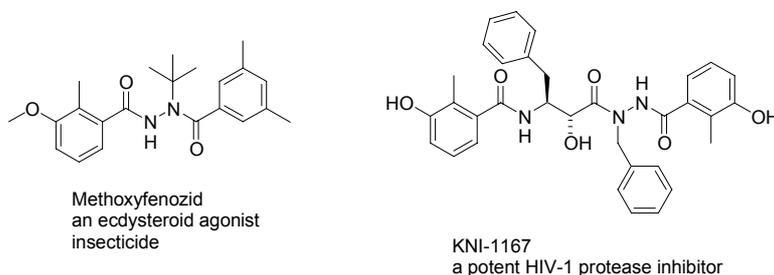


Figure 24. Examples of biologically active *N,N'*-diacylhydrazines

Surprisingly few reports can be found in the literature concerning direct carbonylation of aryl or vinyl halides to the corresponding *N,N'*-diacylhydrazines.^{142,143} The intention was to modify our previously reported *in situ* aminocarbonylation protocol for the carbonylative synthesis of *N,N'*-diacylhydrazines. Exploiting *tert*-butyl carbazate (boc-hydrazine) as a nucleophile would also be interesting for the conversion of aryl halides to boc-protected aryl hydrazides.

Aryl iodides

Aryl iodides (0.40 mmol) were reacted with hydrazides (3 equiv) in dry THF using palladium acetate (10 mol%) as the precatalyst, DBU (3 equiv) as the base and Mo(CO)₆ (1 equiv) as the CO-source. As earlier, the reactions were heated for 15 min using microwave irradiation in sealed vessels under air. In order to achieve full conversion with all aryl iodides the reaction temperature was increased to 110 °C. *N,N'*-diacylhydrazine products **6a-6l** were isolated in moderate to good yields (30-71%). The protected hydrazides **6c**, **6f**, **6i** and **6l** were isolated in rather low yields (30-43%). Since complete consumption of the aryl iodides was observed, loss of material somewhere in the process must occur. GC- and LC-MS analysis of reaction mixtures indicated that primary benzamide and benzonitrile biproducts were formed in most cases. Dehalogenation of the aryl iodides did not seem to be the problem, however. We concluded that thermal (reductive or base-mediated) decomposition of *N,N'*-diacylhydrazine products **6** and/or loss of material in the purification

were the most likely causes for the moderate yields. If decomposition of products was the problem, the lowering of reaction temperatures or shortening of reaction times might improve yields. Unfortunately, lower temperatures resulted in a need for undesirably long reaction times. However, by keeping the temperature at 110 °C and by shortening reaction times stepwise, we observed that all reactions were completed within 5 minutes except with the electron rich 4-iodoanisole (and entry 6). The shorter reaction times presented in Table 4 generally improved the isolated yields (36-78%).

Table 4. Hydrazidocarbonylation of aryl iodides with adjusted reaction times

Entry	Ar-I	Hydrazide	Time (min)	Product	Isolated Yield (%)
1			11		6a 65
2			11		6b 58
3			13		6c 44
4			5		6d 78
5			5		6e 59
6			7		6f 40
7			5		6g 53
8			5		6h 54
9			5		6i 36
10			5		6j 57
11			5		6k 48
12			5		6l 45

Most notable, the reaction between 2-iodotoluene and phenylacetic hydrazide delivered a 54% yield of **6h** after 5 min of heating compared to 30% with 15 min heating.

Aryl bromides

Analogous to the previous aminocarbonylations, we also wanted to explore the use of aryl bromides as substrates. Unfortunately, but not unexpectedly, the high temperature protocol (150 °C) using Herrmann's palladacycle as the precatalyst was not useful for these transformations due to massive side-product formation. For aryl bromides to be useful coupling partners, the reaction temperature and time must be reduced considerably. The primary aim was to find a more active catalytic system.

Bulky, electron rich phosphine ligands have been found to generate extremely catalytically active palladium complexes.¹⁴⁴ One such example is *tert*-butylphosphine, ^tBu₃P.^{145,146} Unfortunately, ^tBu₃P oxidizes quickly in air, but Fu's robust phosphonium salt, [(^tBu)₃PH]BF₄, is designed to liberate free ^tBu₃P *in situ* under basic reaction conditions.¹⁴⁷ The Fu salt was examined with several palladium sources (e.g. PdOAc₂, Pd₂dba₃, Pd(PPh₃)₂Cl₂). These catalytic systems were active at low temperatures but unfortunately the reactions generally stopped at less than 80% conversion of aryl bromide, even at high temperatures. The solution was to apply the Fu salt in combination with Herrmann's catalyst as the palladium source. This generated a system affording full conversion of aryl bromide within 5 minutes at 130 °C. The protocol was examined by the reaction of three different aryl bromides with benzhydrazide. This produced slightly reduced isolated yields (43-57%) of **6a**, **6d** and **6j** compared to the corresponding reaction with aryl iodides (Figure 25).

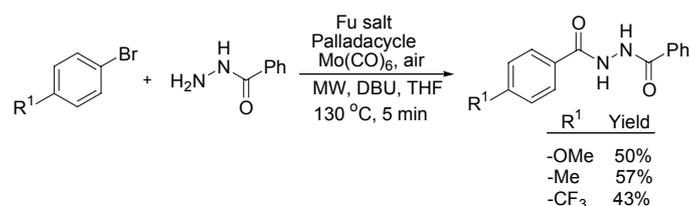


Figure 25. Hydrazidocarbonylation of aryl bromides

Fluorous recycling of catalyst

Within this hydrazidocarbonylation project it was decided to investigate a commercially available fluorous version of triphenylphosphine (tris(4-(1H,1H,2H,2H-perfluorodecyl)phenyl)phosphine), in an organic/fluorous biphasic system. The aim was to enable recycling of the palladium-phosphine catalyst by utilizing the same principle as in fluorous extraction techniques.^{148,149}

Perfluorinated solvents are generally poorly soluble in organic solvents or aqueous mediums and form distinct separate layers. However, at higher tem-

peratures the fluoruous and organic layers can be partly or completely soluble in each other. Here a perfluorinated solvent (FC-84) and the fluoruous-tagged triphenylphosphine were added to the reaction mixture to form a biphasic system. Upon heating, the layers are mixed and the reaction occurred in an apparent homogenous solution. Cooling of the reaction mixture induces phase separation with the fluoruous ligand coordinated to palladium dissolved in the fluoruous phase while the other reagents and product stay in the THF layer. The fluoruous layer was then easily transferred to a new palladium-free reaction mixture with a Pasteur pipette and was heated again. The extent to which the catalytic fluoruous layer could be recycled was studied using 4-iodotoluene and benzhydrazide as reactants, essentially employing identical microwave conditions as with the organic parent reaction but also including the fluoruous-tagged phosphine and the perfluorinated solvent FC-84 (Figure 26).

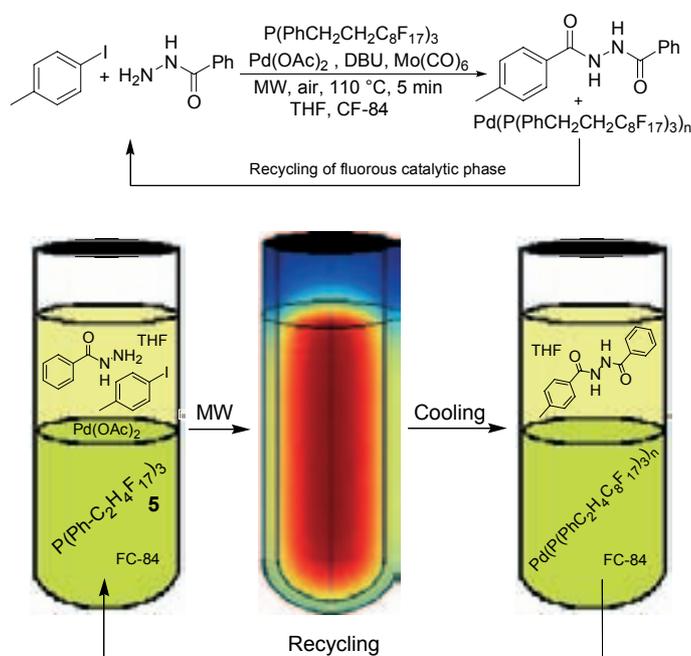


Figure 26. Fluoruous recycling fluoruous phosphine-palladium complex

After five recyclings of the catalytic system, full conversion of 4-iodotoluene was still obtained in the sixth reaction mixture and as indicated in Figure 27, we only observed a modest decrease in isolated yields of **6d** between the cycles (64-79%). A seventh reaction failed after leaving the fluoruous phase in the fume-hood for a week. This multiple carbonylation protocol may represent the first example of recycling of a fluoruous metal catalyst in a microwave heated biphasic reaction system.¹⁵⁰

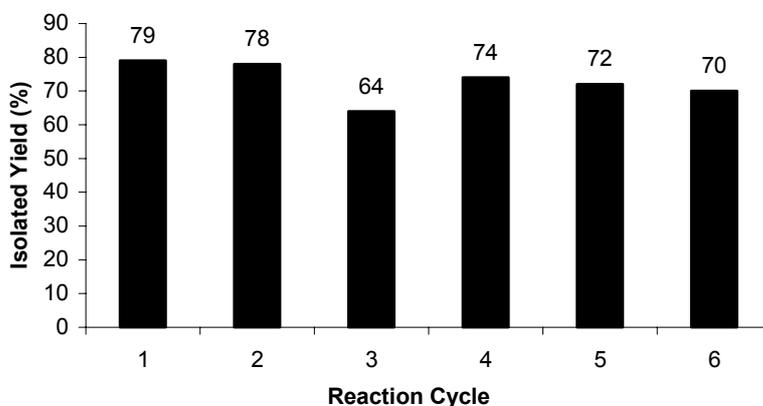


Figure 27. Results of fluororous recycling of palladium-phosphine complex

One-pot 1,3,4-oxadiazole synthesis

Finally, we envisioned the possibility to perform a one-pot, two-step generation of a 1,3,4-oxadiazole substituted aromatic starting from an aryl halide. The first step was the hydrazidocarbonylation of 4-bromobenzotrifluoride with benzhydrazide to *N,N'*-diacylhydrazine **6j**. The cyclization/dehydration of *N,N'*-diacylhydrazines can be performed by many different reagents.^{136,137} Here we added an excess of phosphoroylchloride (POCl_3) and heated the mixture in a metal heating block. The HCl released during the dehydration resulted in partial acid-catalyzed polymerization of THF when using pure THF as solvent, which made product isolation difficult. This could be avoided by using only a small amount of THF in toluene as an alternative solvent.

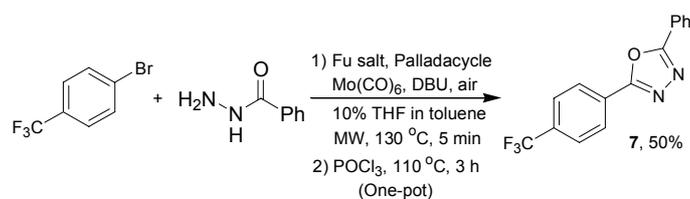


Figure 28. The two-step one-pot synthesis of a 1,3,4-oxadiazole

After purification, 1,3,4-oxadiazole **7** could be isolated in 50% yield which is more than the one-step yield of diacylhydrazine **6j** presented in Table 4. This is an indication of the problems in purifying the free *N,N'*-diacylhydrazine products by flash chromatography.

4 Applications to the 4-Aryl-Dihydropyrimidone Template (Paper III)

Compounds containing the dihydropyrimidone (DHPM) scaffold are easily accessed through the acid-catalyzed three-component cyclocondensation known as the Biginelli reaction.^{151,152} Drug-like DHPM derivatives have been reported to exert various pharmacological effects. Examples include antihypertensive compounds (calcium channel modulators), α_{1a} -adrenergic receptor agonists (for treatment of benign prostatic hyperplasia) and mitotic kinesin Eg5 inhibitors (anti-cancer leads) (Figure 29).¹⁵³

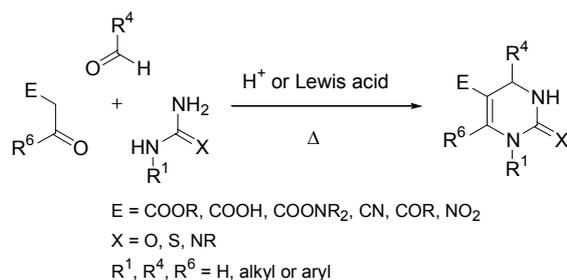


Figure 29. The Biginelli reaction

Despite the numerous reports dealing with combinatorial diversification of this template, transition metal-catalyzed derivatizations have been poorly explored. In a collaborative effort with the group of C. O. Kappe at Karl-Franzens Universität Graz (Austria) we intended to investigate high-speed transition metal-catalyzed functionalizations of this important scaffold.

Three different bromo-substituted aldehydes (*o*-, *m*- and *p*-bromobenzaldehyde) were used in microwave-assisted Biginelli condensations to provide *ortho*-, *meta*- and *para*-substituted 4-(bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-ones **8a-c** by employing a previously reported yttrium triflate-catalyzed protocol (Figure 30). These aryl bromide-substituted DHPMs were considered suitable starting materials for the evaluation of our carbonylation methodology on a more drug-like scaffold.

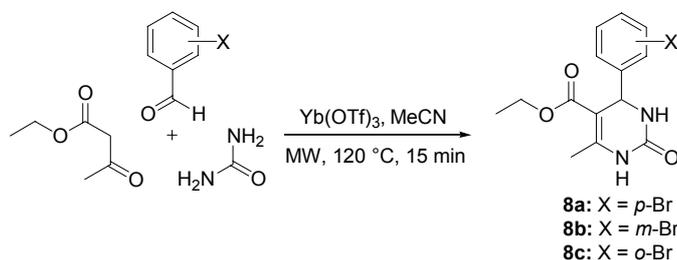


Figure 30. Synthesis of three 4-(bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-ones

The microwave-heated carbonylation protocols using $\text{Mo}(\text{CO})_6$ as a carbon monoxide source were examined at 0.15 mmol scale. Although our initial aminocarbonylation protocol for aryl bromides (Herrmann's palladacycle, 150 °C, Paper I) was performing well also with this scaffold, an addition of Fu's salt ($\text{HP}(\text{tBu})_3\text{BF}_4$) according to the hydrazidocarbonylation protocol (Paper II), allowed a reduction in reaction temperature (in most cases from 150 °C to 130 °C).

Table 5. Preparative results for palladium-catalyzed aminocarbonylations of 4-(bromophenyl)-DHPMs using $\text{Mo}(\text{CO})_6$ as the CO source

Ar-Br	NuH (equiv)	Temp (°C)		Product	Yield (%) ^a
8a	<i>n</i> -Butylamine (3)	130	<i>p</i> -	9a	87
8a	Aniline (3)	130	<i>p</i> -	9b	83
8a 8b	Benzylamine (3)	130	<i>p</i> - <i>m</i> -	9c 9d	78 65
8a 8b 8c	Morpholine (3)	140	<i>p</i> - <i>m</i> - <i>o</i> -	9e 9f 9g	56 71 21

^a Isolated yields after chromatographic purification (> 95% purity by ¹H NMR).

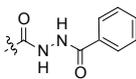
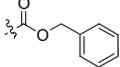
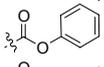
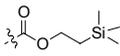
Good to excellent yields were obtained in the aminocarbonylations of *meta*- and *para*-bromo compounds **8a** and **8b** with *n*-butylamine, aniline, benzylamine and morpholine as nucleophiles. Carbonylations of *ortho*-bromo substrate **8c** were less productive. A mere 21% of the *ortho*-amide product could be isolated in the aminocarbonylation using morpholine. The

main component of the complicated reaction mixture was hydrodehalogenated starting material.

These positive results encouraged us to expand the carbonylation efforts to include other nucleophiles. The use of benzhydrazide as a nucleophile afforded *N,N'*-diacylhydrazine **9h** after a 5 min reaction. Unfortunately the problems of purification and product decomposition in these hydrazidocarbonylations only allowed a moderate 35% isolated yield (Table 6).

In addition we decided to explore the use of alcohols in alkoxy-carbonylations. A molybdenum hexacarbonyl-based protocol for the alkoxy-carbonylation of aryl halides has been disclosed in a previous report from our department.¹³⁵ Unfortunately, this protocol requires high temperatures when using aryl bromide substrates (180-190 °C) and for this reason we attempted to apply our successful conditions from the amino- and hydrazidocarbonylations to the carbonylative synthesis of esters.

Table 6. Hydrazido- and alkoxy-carbonylation reactions on the DHPM scaffold

Ar-Br	NuH (equiv)	Temp (°C)		Product	Yield (%) ^a
8a	Benzhydrazide (3)	130	<i>p</i> - 	9h	35 ^b
8a 8b 8c	Methanol (solvent)	110	<i>p</i> - 	9i	77
		120	<i>m</i> - 	9j	71
		120	<i>o</i> - 	9k	24
8a	Benzyl alcohol (5)	140	<i>p</i> - 	9l	45
8a	Phenol (5)	140	<i>p</i> - 	9m	42
8a	2-TMS-ethanol (5)	140	<i>p</i> - 	9n	52

^a Isolated yields after chromatography (> 95% purity by ¹H NMR).

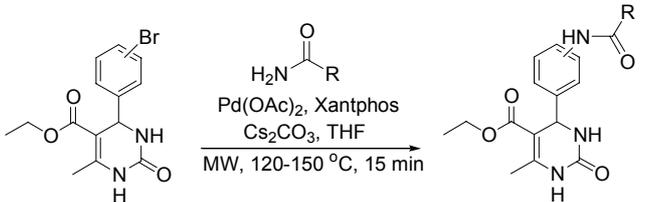
^b Reaction time reduced to 5 min.

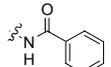
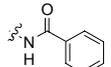
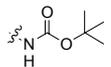
To our delight, the simple change of the nucleophile to an alcohol gave very promising results although the reactions were slightly more sluggish. By adding a larger excess of alcohol (5 equiv) and a slightly higher reaction temperature (140 °C) full conversion of **8a** to the corresponding ester-protected carboxylic acids could be obtained using benzyl alcohol, phenol and 2-trimethylsilyl-ethanol (Table 6). The relatively low yields obtained might be a result of carboxylic acid formation in the reaction mixture. The use of methanol as a combined solvent and nucleophile resulted in a very rapid conversion to the corresponding methyl ester. In fact, the reaction temperature could be reduced as far as to 110 °C in the methoxycarbonylation of *para*- and *meta*-substituted **8a** and **8b** while maintaining high yields (77-

77%). The reaction with *ortho*-derivative **8c** was still fast but the reaction mixture contained mainly debrominated starting material.

Amide N-arylation reactions. There was also an interest in preparing the inverse amide analogs to the aminocarbonylation products. To accomplish this, it was decided to explore the scope of the palladium-catalyzed version of the Goldberg amide *N*-arylation reaction. The conditions reported by Yin and Buchwald^{154,155} were modified to provide a successful microwave protocol. Benzamide and acetamide were *N*-arylated using **8a** or **8b** with Pd(OAc)₂ as the Pd source, Xantphos as the ligand and cesium carbonate as the base in dry THF. The reaction temperatures were adjusted to allow full conversion within 15 min of microwave heating. These clean reactions provided 72-88% yield of amide products **10a-d**. An interesting feature of this reaction was the prospects of *N*-arylations of *tert*-butylcarbamate.¹⁵⁶ This would be useful for the direct conversion of aryl halides to boc-protected aniline derivatives. By employing this strategy, **8a** was converted to the corresponding boc-protected aniline **10e** in 62% yield by 15 min of heating at 150 °C.

Table 7. Preparative results for palladium-catalyzed *N*-arylation using 4-(bromophenyl)-DHPMs as aryl source



Ar-X	Reagent	Temp (°C)		Product	Yield (%) ^a
8a	Acetamide	140	<i>p</i> - 	10a	85
8b	Acetamide	140	<i>m</i> - 	10b	79
8a	Benzamide	120	<i>p</i> - 	10c	72
8b	Benzamide	120	<i>m</i> - 	10d	88
8a	<i>tert</i> -Butyl-carbamate	150	<i>p</i> - 	10e	62

^a Isolated yields after flash chromatography (> 95% purity by ¹H NMR).

Intramolecular Heck cyclization. Important information regarding bioactive conformations can often be obtained by rigidifications of pharmacologically active compounds. Hence, the prospects of rigidification of privileged structures like DHPMs are always of interest in medicinal chemistry projects.¹⁵⁷

Here, we envisioned the use of an intramolecular Heck reaction¹⁵⁸ for the cyclization between the 4-aryl and the dihydropyrimidone ring. A requisite for this type of reaction was the introduction of a vinylic moiety somewhere in the DHPM ring. A starting material for the planned intramolecular Heck reaction was prepared by the selective *N*3-acylation of 4-(*o*-bromophenyl)-dihydropyrimidone **8c** with acryloyl chloride by a previously reported microwave-assisted acylation protocol.¹⁵⁹

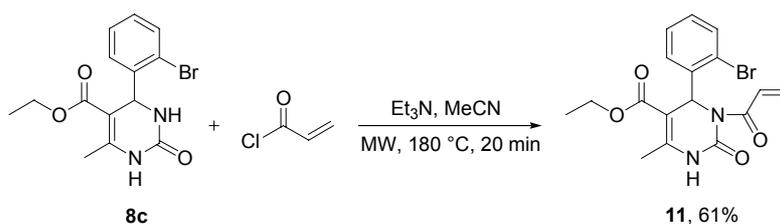


Figure 31. *N*3-acylation of **8c**

By applying relative standard conditions and with a quick time/temperature optimization it was revealed that **11** could be conveniently converted to benzoazepine **12** within 15 min in an uncommon Heck *endo*-cyclization.^{158,160,161} DHPM **11** was heated at 150 °C in MeCN/H₂O (9:1) using Herrmann's palladacycle as the precatalyst and *N,N*-diisopropylethylamine (DIPEA, Hünig's base) as base to afford 78% of ring closed **12**. The structure of this new tricyclic system was confirmed by NMR.

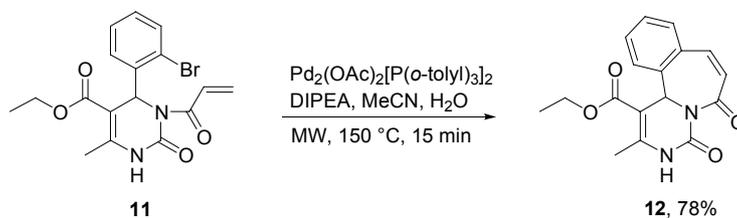


Figure 32. Intramolecular seven-membered Heck *endo*-cyclization

In addition to being a new ring system, further Heck modifications might be possible at the vinylic carbon β to the carbonyl.

Goldberg-type *N*3 arylations

In a significant contribution from the Graz laboratory, the first protocol for direct *N*3-arylation of the DHPM scaffold was developed. *N*3 arylated DHPM analogs are unavailable by classical Biginelli condensation strategies involving *N*-arylureas. Instead the corresponding *N*1-substituted derivatives will be formed exclusively. In fact, database searches (Scifinder Scholar) failed to reveal a single *N*3 arylated DHPM derivative in the literature. In

order to introduce novel diversity in the *N3*-position of the DHPM scaffold the team from Graz first attempted to carry out palladium-catalyzed *N3*-arylations. Disappointingly, the protocol for amidation of 4-bromophenyl-DHPMs (Table 7) provided no product in the attempted *N3*-arylations of *N1*-blocked **13** using aryl iodides. Instead the copper-catalyzed Goldberg reaction¹⁶²⁻¹⁶⁴ was explored. Inspired by the conditions reported by Lange and coworkers,¹⁶⁵ a number of reaction parameters were screened. The most general Goldberg protocol used a concentrated mixture of 20 mol % of CuI as catalyst, 1.5 equiv of Cs₂CO₃ as base and 5 equiv of DMF as solvent. The reactions were conducted at 180 °C for 40 min with a set of eight differently substituted aryl iodides. *N3* arylated DHPMs **14a-j** were isolated in low to excellent yields (13-83%).

Table 8. Preparative results for Goldberg *N3*-arylation of DHPMs with aryl iodides

13a: R¹ = Me
13b: R¹ = H

14a-j

Starting material	R	Ar	Product	Yield (%)
13a	Me		14a	63
13a	Me		14b	34
13a	Me		14c	69
13b	H		14d	36
13a	Me		14e	70
13a	Me		14f	83
13a	Me		14g	80
13b	H		14h	13
13a	Me		14i	67
13a	Me		14j	49

5 Synthesis of HIV-1 Protease Inhibitors (Paper IV and V)

The HIV-protease is essential for the replication of the AIDS-causing HIV virus (Section 1.1). Substantial research efforts have been allocated for this ‘drugable’ target and HIV-1 protease inhibitors are, as mentioned earlier, integral parts in current treatment of HIV/AIDS. The inhibitors used in clinic are for the most part rather large compounds that require complex synthetic routes. Our ongoing HIV-1 protease inhibitor project has the general aim of allowing fast, convenient and inexpensive routes to new and potent HIV-1 protease inhibitors.

In an earlier work from our department, Alterman and coworkers presented an expedient, three-step synthesis of C₂-symmetric, C-terminally duplicated inhibitors.⁷⁶ A commercially available derivative of L-mannitol, L-mannonic- γ -lactone, was the basis for compounds where a dihydroxy ethylene unit served as a transition state mimicking fragment and benzyl ethers as P1/P1’ side chains. In this first report, different amines were used in order to explore the impact of different P2/P2’ side chains. Several highly active compounds were identified (Figure 33).⁷⁶

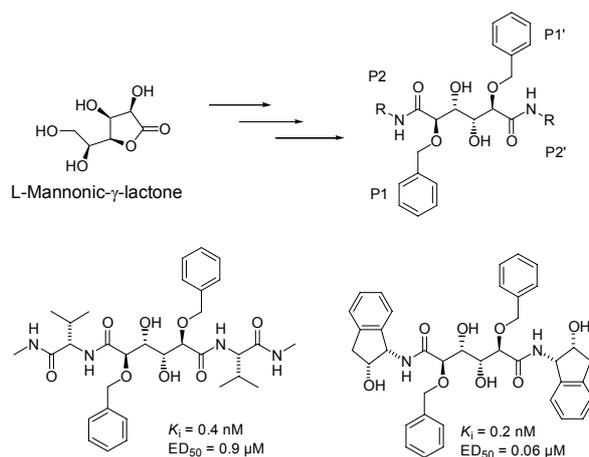


Figure 33.

In a subsequent report, the same synthetic route was used to prepare a core structure containing a *para*-bromo substituted P1/P1’ benzyloxy side

chain. Palladium-catalyzed coupling reactions were used to prepare a series of compounds where the bromines were substituted for different functionalities, also yielding some very potent compounds (Figure 34).¹⁶⁶

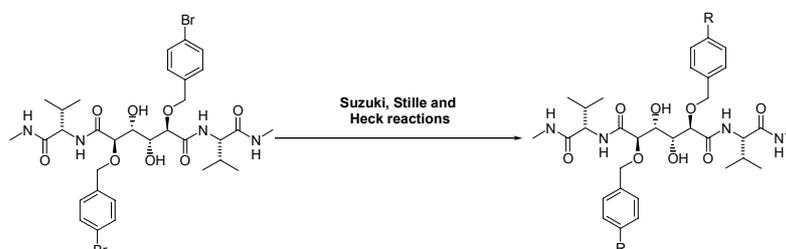


Figure 34.

X-ray structures of enzyme-inhibitor complexes revealed that the *para*-substituted benzyloxy side chains occupied both the S1/S1' and S3/S3' subsites of the native C₂-symmetric protease, reaching water at the boundary of the active site channel. Computer modeling suggested that it might be possible to extend the *meta*-position of the P1/P1' side chain to afford potent compounds. However, an extension of the *ortho*-position with large groups seemed less likely to furnish good inhibitors. There was still an interest in examining the effect of both *meta*- and *ortho*-substitution in order to get a complete picture of the binding possibilities of our inhibitor scaffold in the S1/S1' and S3/S3' subsites. As far as we know, inhibitors containing large substituents in the *ortho*-positions of aromatic P1 and/or P1' side chains have previously not been reported.

5.1 Aminocarbonylations

The aminocarbonylation methodology presented in Paper I was developed with the intention of applying it in laboratory-scale medicinal chemistry, more precisely to enable the fast generation of new HIV-1 protease inhibitors containing different size *ortho*- or *meta*-amido substituents in the P1/P1' benzyloxy groups. The idea was that the microwave-promoted bis-functionalizations of our C₂-symmetric dihydroxy ethylene based inhibitor scaffold would quickly generate compounds that could help us map the impact of *ortho*- and *meta*-amide substituents on the HIV-1 protease inhibiting capacity. The introductions of two new amide bonds are generally not advisable from a drug development perspective¹⁶⁷ but the ambition was that these compounds would provide information useful for the future design of potent HIV-1 protease inhibitors with unique characteristics.

The aryl halide-containing key intermediates **18** and **19** were prepared in close analogy with the previously published procedure (Figure 35).^{76,166}

Hence, L-mannonic- γ -lactone was oxidized with HNO_3 to the corresponding bis-lactone **15**. The hydroxyl groups of the bis-lactone were alkylated under acidic conditions with *o*-iodobenzyl-2,2,2-trichloroacetimidate or *m*-bromobenzyl-2,2,2-trichloroacetimidate to produce the corresponding benzylic ethers. The benzylated bis-lactones **16** and **17** were thereafter treated with L-valine methyl amide to afford the halogen containing bis-amides **18** and **19**, respectively.

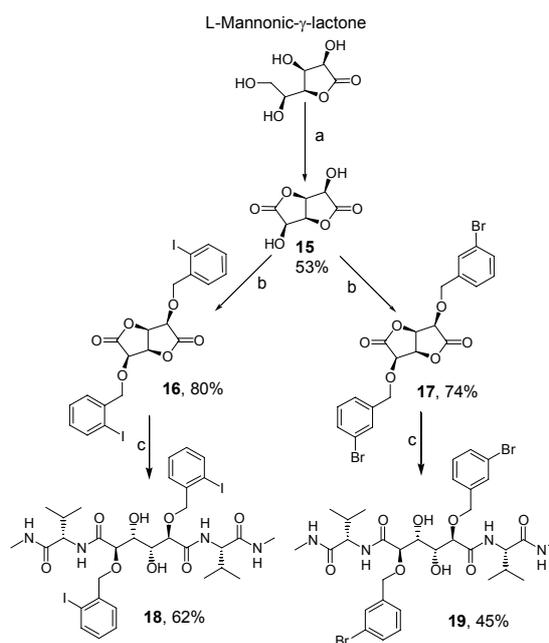


Figure 35. Reagents and conditions: (a) HNO_3 , 90 °C, 5 h; (b) *o*-Iodobenzyl-2,2,2-trichloroacetimidate or *m*-bromobenzyl-2,2,2-trichloroacetimidate, $\text{BF}_3 \times \text{Et}_2\text{O}$, rt, 18 h; (c) L-Valine methylamide, dichloroethane, 50 °C, 18 h.

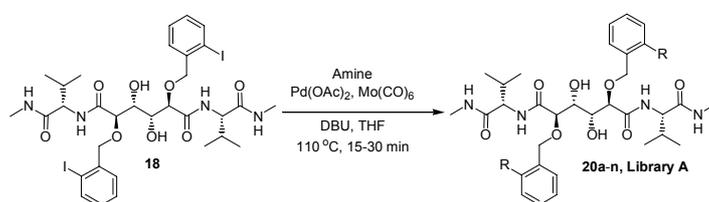
The substitutions of the halogen groups were performed in sealed vessels under non-inert palladium-catalyzed aminocarbonylative microwave conditions. The strategy was to use a number of in-house amines in small-scale reactions with 10-15 mg (~0.015 mmol) of **18** or **19**. The reactions that were deemed successful (by RP-LC-MS analysis) were purified by reverse-phase preparative RP-LC-MS using UV-triggered fraction collection. Providing enough pure material was obtained, the inhibitors were sent for biological testing in an enzyme assay where their ability to inhibit the HIV-1 protease (K_i values) were determined.^{168,169}

Library A

The iodo-substituted **18** was used as precursor in the synthesis of the *ortho*-benzamide series of inhibitors (Library A). A total of 14 compounds were isolated in sufficient amounts after aminocarbonylations under ligandless

conditions ($\text{Pd}(\text{OAc})_2$) and with a large excess of the respective amine and 15 or 30 min of microwave heating at 110 °C. The more severe conditions used compared to those originally presented were necessary in order to obtain full conversion of **18** under these diluted circumstances. Special precautions were taken to avoid contamination of the product with potentially active side products such as mono-functionalized, mono-dehalogenated or bis-dehalogenated products. Fortunately, sufficient separation of these side products from the desired inhibitors could be obtained. All but one of the inhibitors in library A were isolated in more than 95% purity. The biological results are presented in Table 9.

Table 9. Synthesis of Library A and results of first screening of HIV-1 protease inhibition.^a



Inhibitor	R	K _i (nM)	Inhibitor	R	K _i (nM)
20a		>5000	20h		7
20b		700	20i		70
20c		600	20j		800
20d		400	20k		200
20e		>5000	20l		6
20f		200	20m		2000
20g		700	20n		800

^aThe isolated yields of pure **20a-n** varied between 15% and 53%

The compounds tested displayed a wide range of activity but showed no evident structure-activity trend. The high activity of **20h** and **20l** seem to indicate favorable interactions for the *ortho*-anilide type of substituents.

Library B

The aryl bromide-containing **19** was used as precursor in the synthesis of Library B, analogous to Library A but using a higher reaction temperature

and employing a more advanced catalytic system. At 150 °C (Ar-Br conditions from Paper I) complex reaction mixtures were observed, probably due to partial decomposition of starting material and/or product. Applying the modified conditions for aryl bromides presented in Paper II (Fu's salt, 130 °C), afforded much 'cleaner' reactions while allowing full conversion within 15 minutes. Seven inhibitors were prepared in high purity (>95%) (Table 10).

Table 10. Synthesis of Library B and results of first screening of HIV-1 protease inhibition.^a

Inhibitor	R	K_i (nM)	Inhibitor	R	K_i (nM)
21a		20	21e		20
21b		3	21f		7
21c		200	21g		2
21d		300			

^aThe isolated yields of pure **21a-g** varied between 18% and 45%

All compounds in Library B were highly active (K_i , 2-300 nM) as predicted. The secondary amides proved to be particularly potent (K_i , 2-20 nM).

Re-synthesis of selected compounds

Compounds regarded as particularly interesting were chosen for re-synthesis on a larger scale with thorough chemical characterization of the isolated inhibitors. These compounds would then be tested again to establish with certainty the initial results.

In order to decrease the formation of side product detected in the initial library syntheses, it was decided to protect the central vicinal diols of the aryl halide starting materials **18** and **19** as acetonides (Figure 36). This would most likely simplify purification and increase the yields. Also, the larger scale involved higher concentrations and CO pressure, which had a beneficial impact on the reaction.

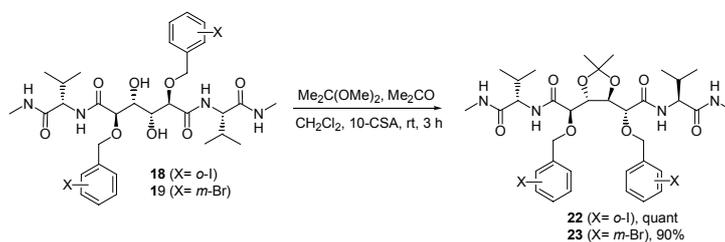


Figure 36.

The re-synthesis of inhibitors **20f**, **20h**, **20i**, **20l**, **20m**, **21b** and **21g** was conducted from the 1,3-dioxolanes **22** and **23** on 0.050 mmol scale. The protected inhibitors generated by the aminocarbonylations were purified by flash chromatography and subsequent treatment with HCl/ether in MeOH afforded the desired structures in satisfying yields. The re-testing of the compounds showed a good correlation with the initial results, confirming the high potencies of *ortho*-anilide substituted compounds **20h** and **20l** (Table 11).

Table 11. Isolated yields and inhibitory activity of re-synthesized compounds

Starting material	Inhibitor	Isolated Yield (%) ^a	K _i (nM)	Starting material	Inhibitor	Isolated Yield (%) ^a	K _i (nM)
22	6f	69	196	23	7b	40	6.5
22	6h	67	20	23	7g	39	2.9
22	6i	32	118				
22	6l	24	8.5				
22	6m	69	1332				

^aTwo-step yield after aminocarbonylation and deprotection. >95% pure by ¹H-NMR.

The information obtained in this study suggested that *ortho*-substitution of P1 and/or P1' benzyl side chains might provide a promising new approach in the search for unique HIV-1 protease inhibitors.

5.2 Palladium-Catalyzed C-C Bond Forming Reactions

In the previous section it was found, rather unexpected, that large anilide substituents in the *ortho*-position of the P1/P1' benzyloxy group were well tolerated by the enzyme (Figure 37). These inhibitors with no less than six amide bonds and two hydroxyl groups severely violate Lipinski's 'rule-of-five',¹⁶⁷ making them rather unattractive from a drug-development perspective. However, these inhibitors could still serve as valuable lead structures and guide the optimization process towards more drug-like molecules.

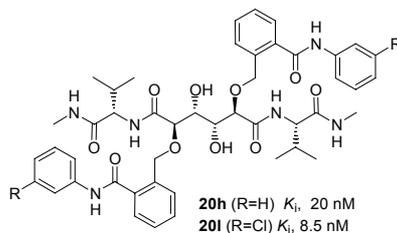


Figure 37. Inhibitors with *ortho*-anilide P1/P1' substituents

We intended to further explore the *ortho*-concept by introducing alternative substituents *via* microwave-accelerated and chemoselective carbon-carbon bond coupling reactions.¹⁷⁰ By avoiding the introduction of amide groups utilized in our previous investigation we intended to obtain more drug-like inhibitors. In order to further reduce the peptide character it was decided to exploit the from indinavir well-known *N*-(1*S*,2*R*)-2-hydroxy-1-indanyl group as P2/P2' substituents. These two operations would lead to target compounds with two rather than six amide bonds.

The synthesis of the C_2 -symmetrical aryl palladium precursor **24** was carried out according to the procedure developed by Alterman and coworkers.^{76,166} The bis-lactone **16** (see Section 5.2) was stirred with (1*S*,2*R*)-2-hydroxy-1-indanol in 1,2-dichloroethane at 50 °C for 4 h conveniently affording bis-amide **24** in 55% isolated yield and high purity (Figure 38).

With the aryl iodo substrate **24** in hand, an abundance of possibilities to explore palladium(0)-catalyzed carbon-carbon bond forming reactions in order to produce new HIV-1 protease inhibitors were recognized.⁸²

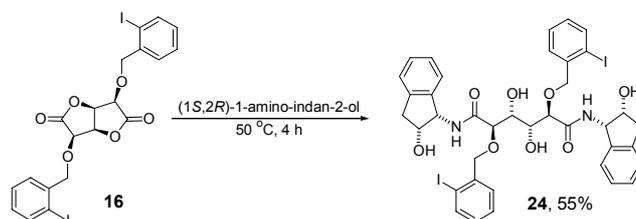


Figure 38. Preparation of aryl iodide containing inhibitor **24**

The indanolamino compound **25** was synthesized by aminocarbonylation of unprotected **24** with aniline as nucleophile according to the protocol of Paper IV in order to obtain a basis for comparisons between the compounds containing the valine methylamide group in the P2/P2' and the indanolamine compounds planned in this series (Figure 39). The *ortho*-anilide **25** proved to be a practically equipotent inhibitor to **20h** (**20h**, $K_i = 20$ nM; **25**, $K_i = 18$ nM), encouraging us to proceed with the synthetic efforts as planned.

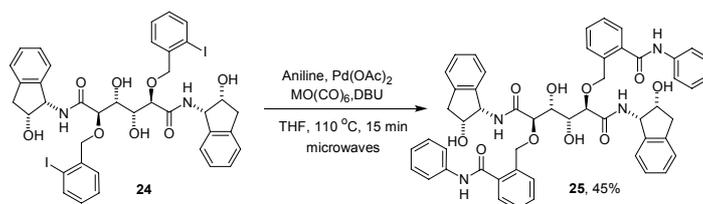


Figure 39. Synthesis of **25** by aminocarbonylation of **24** with aniline

In the planning of the carbon-carbon bond couplings, the specific reactants were selected both according to commercial availability and in order to furnish some degree of diversity in the size and flexibility of the isolated P1/P1'-modified inhibitors. In addition, the styrene and benzofuran group of *ortho*-substituents may be viewed as isosteres to the active *ortho*-anilides.

The introduction of a non-functionalized vinyl group by substitution of an aryl halide could be achieved by different palladium-catalyzed methods, the most common perhaps being the Stille cross-coupling with tributyl(vinyl)tin or the Heck reaction using ethene under pressure. The employments of toxic tin reagents or the need for a reactive gas are obvious drawbacks of these strategies. A more attractive alternative would be to use a vinylboronic acid derivative in a Suzuki reaction. Monomeric vinylboronic acid is relatively unstable but the bench stable derivative 2,4,6-trivinylcyclo-triboroxane-pyridine complex has been described as a useful coupling partner.¹⁷¹ This commercially available reagent was utilized in a Suzuki-coupling to produce styrene derivative **26a** in 51% yield after only 15 min of irradiation. The swift and straightforward Suzuki-microwave methodology was also applied to produce **26d** (53%), **26e** (29%) and **26i** (45%) (Table 12). Offsetting the advantages of the Suzuki reaction there are some detractions. With non-

gaseous olefins and acetylenes, direct Heck and Sonogashira reactions are performed with higher atom-efficiency avoiding the usage of organometallic reactants. The difficulty in introducing benzylic groups by the Suzuki methodology is another drawback. Therefore, continued modifications of the P1/P1' side chains were conducted with complementary reaction protocols.

Table 12. Synthesis and biological evaluation of inhibitors **26a-i**

Compound	Reactant	Time (min)	Temp (°C)	R	Isolated yield (%)	K _i (nM)
24	-	-	-		-	33
26a		15	100		51 ^a	14
26b		30	100		90 ^b	193
26c		5	120		57 ^c	658
26d		30	120		53 ^a	105
26e		30	120		29 ^a	448
26f		5	100		25 ^d	14
26g		10	120		62 ^c	218
26h		5	120		63 ^c	4.1
26i		30	120		45 ^a	224

^aPd(OAc)₂, (tBu)₃PHBF₄, K₂CO₃, DME, H₂O ^bPd(OAc)₂, DPPP, TIOAc, (iPr)₂EtN, DMF, H₂O ^cPd₂(OAc)₂(P(o-tol)₃)₂, (iPr)₂EtN, DMF, H₂O ^dPd(OAc)₂, (tBu)₃PHBF₄, THF.

The methyl ketone derivative **26b** was obtained in two steps. A regio-selective internal Heck-coupling of 2-hydroxyethyl vinyl ether with **24** afforded the 1,3-dioxolane protected ketone. After an acidic deprotection of the 1,3-dioxolane, methyl ketone **26b** could be isolated in an excellent 90% two-step yield. Reactions of methyl acrylate and styrene with **24** under standard Heck conditions produced methyl cinnamate derivative **26c** (57%) and stilbene derivative **26h** (63%). A Negishi coupling of **5** with benzylzinc bromide delivered **26f** in a disappointing 25% yield but without detected

epimerization or water elimination. Finally, 2-bromothiazole was initially reacted with the 2,4,6-trivinylcyclotriboroxane-pyridine complex in a Suzuki reaction. After a quick workup, the formed 2-vinylthiazole was subsequently reacted with **24** under Heck conditions to produce **26g** in 62% yield.

In total, 11 novel HIV-1 protease inhibitors were synthesized and tested in the same enzyme assay as in Section 5.1. From this collection of compounds of varying size and flexibility some structure-activity conclusions were drawn. Small lipophilic *ortho*-substitutions of the P1/P1' benzyloxy side chains provided inhibitors of high potency, probably adapting a binding mode similar to inhibitors with unsubstituted P1/P1' benzyloxy groups. In contrast, the potency of compounds containing large *ortho*-substituents showing single- or double-digit nanomolar activity (e.g. **26h**) could not be easily explained by the binding mode of related compounds displayed in previously reported crystal structures. Computational efforts (docking studies) were applied in order to decipher the binding-modes and SAR of these HIV-1 protease inhibitors.

5.3 Computational Chemistry

X-ray crystal structures are the experimental basis of docking simulations. Therefore, the selection and preparation of the crystal structure is of great importance. The choice of structure greatly influences the outcome of the simulation studies, since the size and the shape of the inhibitors/substrates bring about corresponding conformational changes in the protein. There exist more than 700 X-ray structures of HIV-1 protease co-crystallized with various inhibitors/substrates in the Protein Databank (PDB)¹⁷². We chose 1EC0 since the co-crystallized inhibitor in this X-ray crystal structure most closely resembled the compounds under investigation¹⁷³. The structure was subjected to minimization to refine structural discrepancies that may have existed. After minimization, the resulting structure had a heavy atom root-mean-square deviation (rmsd) of 0.26 Å compared to the heavy atoms of the starting structure. A low rmsd suggested no significant change in the crystal structure.

Most of our inhibitors docked in HIV-1 protease were bound in the enzyme active site in an extended conformation so that when they were superimposed upon one another, their functional elements aligned quite well. The dihedral angles in the backbone of all the inhibitors were also maintained. The contacts between the backbone atoms of all the inhibitors and the protease were consistent for all the complexes. Following a similar pattern, the hydrogen bonds were seen mostly between the backbone atoms of the enzyme and the inhibitor. It has been shown before that the C₂-symmetric inhibitors bind to the protease in an asymmetric fashion.¹⁷⁴ We found similar results with our inhibitors. One of the hydroxyls of the diol was positioned

between the Asp25/25' carboxyls of the protease, within hydrogen bonding distance to at least one oxygen of each aspartate. A feature common to almost all complexes of the HIV-1 protease, a structural water molecule (WAT00) that bridges the P2 and P2' carbonyl groups of the inhibitors with the amide nitrogens of Ile50/50', was also observed with the docked inhibitors (Figure 40).

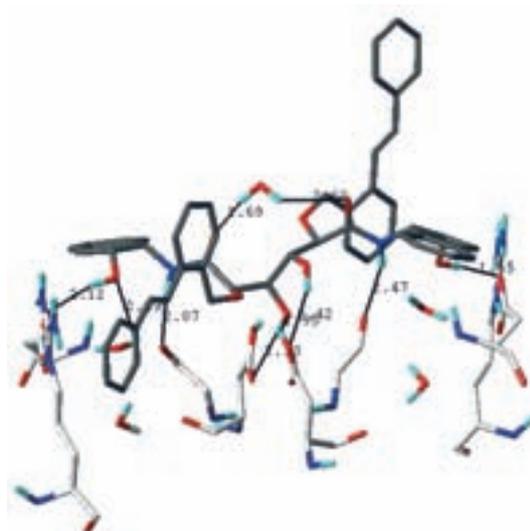


Figure 40. Hydrogen bonding network between representative compound **26h** and the protease with structural waters. The carbon atoms of the inhibitor are colored dark grey while all other atoms are colored according to Sybyl atom types. Only polar hydrogens are displayed for clarity reasons.

Interestingly, the different *ortho*-substituents of the inhibitors could be accommodated in three different areas of the enzyme. When studying the different docking poses it was seen that all inhibitors could position their *ortho* substituents in these areas with closely matching binding energies. Upon closer visual inspection it was revealed that the observed poses corresponded to the observed binding mode of co-crystallized inhibitors reported earlier in the PDB, which further suggested that any one of the binding poses could be the most probable one.

The stilbene derivative **26h** was used as a representative compound to describe the observed binding modes. In pose one, the terminal phenyl rings could be seen occupying the space between Phe53/53' and Pro81/81' in a similar fashion as did the substituted pyridine on the P1 piperazine of indinavir (PDB entry: 1C6Y)¹⁷⁵ and the *para*-substituted pyridines in the P1 and P1' positions of 1EC2¹⁷⁶ (Figure 41).

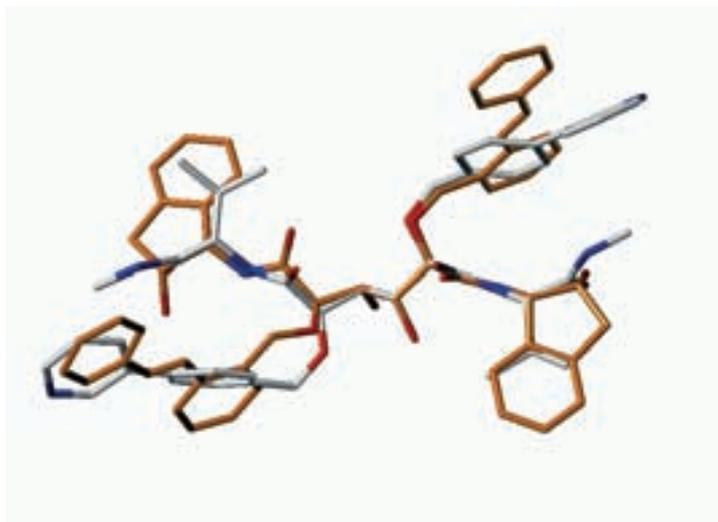


Figure 41. Compound **26h** superimposed over the symmetric inhibitor co-crystallized with HIV-1 protease (PDB entry: 1EC2). Carbon atoms of **26h** are colored orange all other atoms are colored according to Sybyl atom types. Only polar hydrogens are displayed for clarity reasons.

The second pose placed the phenyl rings within a radius of 2.1 Å from Arg8/8' and was also seen at a distance of 1.7 Å from the P2 and P2' substituents. This binding mode was consistent with the X-ray structure of the cyclized tripeptides analogs found in PDB entry, 1B6J¹⁷⁷ (Figure 42).

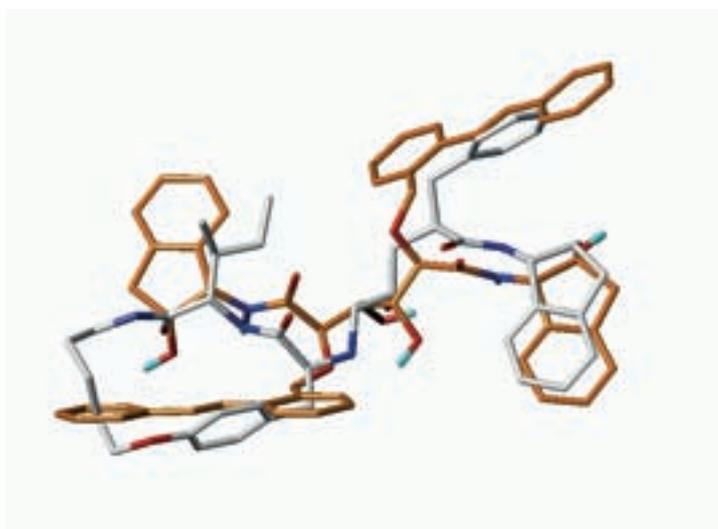


Figure 42. Compound **26h** superimposed over the macrocyclic inhibitor co-crystallized with HIV-1 protease (PDB entry: 1CPI). Carbon atoms of **26h** are colored orange all other atoms are colored according to Sybyl atom types. Only polar hydrogens are displayed for clarity reasons.

In the third binding mode, the phenyl ring was seen lying in the groove formed by the hydrophobic side chains of Arg8/8', Leu10/10', Leu23/23', Val82/82'. Figure 43 shows the various poses for the *ortho*-substituted stilbene analog **26h**.

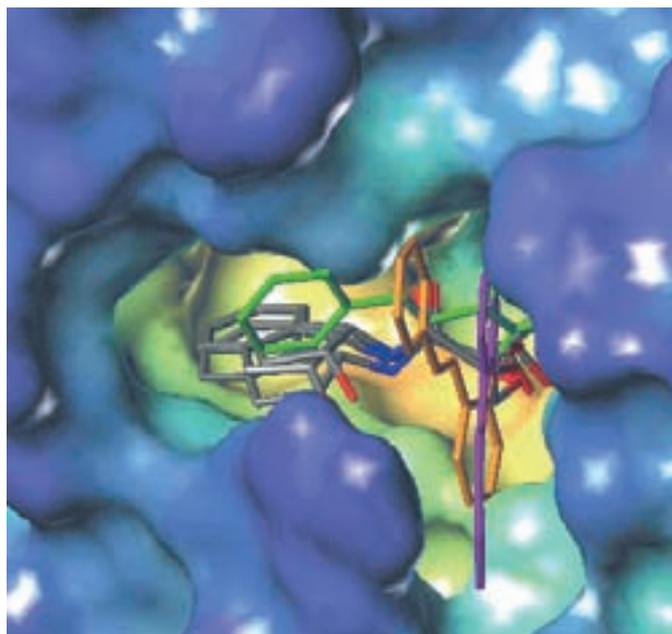


Figure 43. Connolly surface color-coded with cavity depth is shown with the three probable binding regions for the P1 and P1' substituents of **26h**, colored in green, purple and orange.

Further computational evaluations including an enlarged set of compounds are currently under way.

6 Concluding Remarks

This thesis has described the development of new palladium-catalyzed carbonylations methods and the application of these and other methods for fast syntheses of new potent HIV-1 protease inhibitors.

The specific results and conclusions are summarized below:

- A rapid microwave-promoted aminocarbonylation protocol where $\text{Mo}(\text{CO})_6$ functions as a safe and convenient source of carbon monoxide has been developed. Both highly and poorly nucleophilic amines participated in the conversion of aryl halides to benzamides. It was also demonstrated that the aminocarbonylations could be performed with a solid-phase supported aryl iodide as substrate.
- The above mentioned protocol was modified to include the use of hydrazides as nucleophiles in similar carbonylations. Aryl halides were converted to the corresponding *N,N*-diacylhydrazines or boc-protected arylhydrazides, in most cases within 5 minutes of microwave irradiation.
- The carbonylation methodology and other palladium-catalyzed and copper-catalyzed reactions were applied in decorations of the Biginelli-derived dihydropyrimidone scaffold.
- The aminocarbonylations were utilized for the synthesis of two novel series of HIV-1 protease inhibitors. The *o*-iodo- and *m*-bromobenzyloxy P1/P1' substituted, C_2 -symmetric, 1,2-dihydroxyethylene based core structures were transformed to 21 different benzamide analogs. The potency of P1/P1' *ortho*-substituted anilide derivatives indicated that larger groups than previously expected were tolerated in the space spanning the S1-S3 and S1'-S3' pockets.
- An additional series of novel HIV-1 PRIs was synthesized. Microwave-heated, palladium-catalyzed carbon-carbon bond forming reactions were executed to obtain more drug-like inhibitors. Potent compounds were identified and computer-aided docking experiments suggested plausible binding-modes for these inhibitors.

7 Acknowledgements

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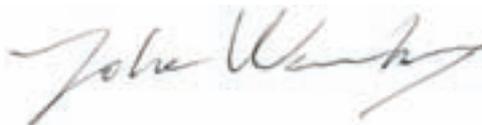
Det finns ju också många utanför den kemiska världen som jag vill tacka av olika anledningar.

Jag vill så klart tacka de vänner och bekanta som har bidragit till ett liv utanför BMC också. Särskilt tack till grabbarna grus: Anders, Bengt, C-M, Dr. Henke, Jesper, Marcus och Mattias. Tyvärr hade jag ganska mycket avhandling i tankarna vid tiden för ditt bröllop, Anders. Hoppas det inte märktes allt för mycket. Tack till Lotta F. för alla fester. Annas vänner, jag har fått er på köpet men ni är, som tur är, väldigt trevliga.

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