



UPPSALA
UNIVERSITET

*Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Science and Technology 156*

[¹¹C]Carbon Monoxide in Rhodium-/Palladium-Mediated Carbonylation Reactions

JULIEN BARLETTA



ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2006

ISSN 1651-6214
ISBN 91-554-6500-5
urn:nbn:se:uu:diva-6654

Dissertation presented at Uppsala University to be publicly examined in Room B22, BMC, Husarsgatan 3, Uppsala, Friday, April 28, 2006 at 09:00 for the degree of Doctor of Philosophy. The examination will be conducted in English.

Abstract

Barletta, J. 2006. [^{11}C]Carbon Monoxide in Rhodium-/Palladium-Mediated Carbonylation Reactions. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology* 156. 50 pp. Uppsala. ISBN 91-554-6500-5.

Methods for the ^{11}C -labeling of carbonyl compounds applicable in the preparation of radiotracers for Positron Emission Tomography (PET) are described. To this end [^{11}C]carbon monoxide at low concentration was used in transition metal-mediated reactions.

Stille couplings were employed in the synthesis of [^{11}C]ketones from methyl and aryl halides with [^{11}C]carbon monoxide. The synthesized [^{11}C]ketones were obtained from the corresponding organostannanes with analytical radiochemical yields up to 98%.

A number of synthetic routes were designed using [^{11}C]carbon monoxide and rhodium complexes. Nitrene intermediates were generated from azides and reacted via a rhodium-mediated carbonylation reaction as a general synthetic route to [^{11}C]isocyanates, versatile precursors. [^{11}C]Isocyanate reacted via nucleophilic attack of an amine to form *N,N*-diphenyl[^{11}C]urea in 82% analytical radiochemical yield, ethyl phenyl[^{11}C]carbamate was synthesized by the same route, using ethanol as the nucleophile, in 70% radiochemical yield. [^{11}C]Isocyanate was also able to react in a [2+3] cycloaddition with ethylene oxide to form 3-phenyl[^{11}C]oxazolidin-2-one in over 80% analytical radiochemical yield. This method was applied to the synthesis of a potential efflux system tracer [^{11}C]hydroxyurea in 38% isolated radiochemical yield and the derivative 1-hydroxy-3-phenyl[^{11}C]urea in 35% isolated radiochemical yield. Carbene intermediates, generated from diazo compounds, were reacted with [^{11}C]carbon monoxide in the rhodium-mediated synthesis of [^{11}C]ketenes. [^{11}C]Ketene intermediates were utilized in the synthesis of diethyl[^{11}C]malonate, from ethyl diazoacetate and ethanol. The product was obtained with a 20% isolated radiochemical yield. Alkylation of diethyl[^{11}C]malonate, with ethyl iodide and tetrabutylammonium fluoride, was successfully accomplished and diethyl diethyl[^{11}C]malonate was synthesized in 50% analytical radiochemical yield. Several (^{13}C)compounds were also synthesized using the described methods as a way of characterizing the position of the label using ^{13}C -NMR.

Keywords: carbonylation reaction, carbon monoxide, PET, ^{11}C -labelling, rhodium, palladium

Julien Barletta, Department of Biochemistry and Organic Chemistry, BMC, Box 576, Uppsala University, SE-75123 Uppsala, Sweden

© Julien Barletta 2006

ISSN 1651-6214

ISBN 91-554-6500-5

urn:nbn:se:uu:diva-6654 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-6654>)

Articles included in this thesis

- I. **Synthesis of ^{11}C -labelled N,N' -diphenylurea and ethyl phenyl-carbamate by rhodium-promoted carbonylation reaction via $[^{11}\text{C}]$ isocyanatobenzene using phenyl azide and $[^{11}\text{C}]$ carbon monoxide.** Hisashi Doi, [Julien Barletta](#), Masaaki Suzuki, Ryoji Noyori, Yasuyoshi Watanabe and Bengt Långström. *Org. Biomol. Chem.*, 2004, 2, 3063-3066.
- II. **Palladium-mediated ^{11}C -carbonylative cross-coupling of alkyl/aryl iodides with organostannanes: an efficient synthesis of unsymmetrical alkyl - aryl [*carbonyl*- ^{11}C]ketones.** Farhad Karimi, [Julien Barletta](#) and Bengt Långström. *Eur. J. Org. Chem.*, 2005, 2374-2378.
- III. **Synthesis of [*carbonyl*- ^{11}C]hydroxyureas by a rhodium-mediated carbonylation reaction using $[^{11}\text{C}]$ carbon monoxide.** [Julien Barletta](#), Farhad Karimi and Bengt Långström. *J. Labelled Compd. Radiopharm.*, 2006. Accepted.
- IV. **Synthesis of diethyl[*carbonyl*- ^{11}C]malonate from $[^{11}\text{C}]$ carbon monoxide by rhodium-promoted carbonylation and its application as a reaction intermediate.** [Julien Barletta](#), Farhad Karimi, Hisashi Doi and Bengt Långström. Submitted
- V. **Synthesis of 3-phenyl[*carbonyl*- ^{11}C]oxazolidin-2-one using $[^{11}\text{C}]$ carbon monoxide via rhodium-mediated carbonylation reaction and [*carbonyl*- ^{11}C]isocyanate intermediate.** [Julien Barletta](#), Farhad Karimi, Hisashi Doi and Bengt Långström. Manuscript.

Reprints were made with permission from the publishers: John Wiley & Sons Ltd. (I & III), The Royal Society of Chemistry (II).

Related patent applications:

Julien Barletta, Hisashi Doi, Farhad Karimi, Masaaki Suzuki, Ryoji Noyori, Yasuyoshi Watanabe and Bengt Långström. **Methods for Carbon Isotope Labeling Synthesis by Rhodium-Promoted Carbonylation via Isocyanate Using Azides and Carbon-Isotope Monoxide.** *Filed patent application.* PH0389, 2004.

Julien Barletta, Hisashi Doi, Farhad Karimi and Bengt Långström. **Methods for Carbon Isotope Labeling Synthesis by Transition Metal-Promoted Carbonylation via Ketene Using Diazo Compounds and Carbon-Isotope Monoxide.** *Filed patent application.* PH0511, 2005.

Contents

1	Introduction.....	7
1.1	Positron Emission Tomography – A molecular imaging technology	7
1.2	Synthetic aspects	8
1.2.1	Synthetic Strategies	8
1.2.2	Specific radioactivity - Sensitivity	10
1.2.3	Analysis, characterization and purification	10
1.3	Labeled precursors.....	11
1.3.1	Labeling with ^{11}C	11
1.3.2	Production and handling of [^{11}C]carbon monoxide.....	12
1.3.3	[^{11}C]Carbon monoxide in carbonylation reactions	13
1.4	Objectives.....	15
2	Palladium-mediated synthesis of [<i>carbonyl</i> - ^{11}C]ketones from [^{11}C]carbon monoxide (Paper II)	16
2.1	Stille coupling using [^{11}C]carbon monoxide	16
2.2	Synthesis of aryl[<i>carbonyl</i> - ^{11}C]ketones (Paper II)	18
3	Rhodium-mediated synthesis of ^{11}C -labeled carbonyl compounds (Paper I, III-V).....	26
3.1	Synthesis of ^{11}C -labeled compounds via isocyanate (Paper I, III, V)	26
3.1.1	Properties of isocyanates	26
3.1.2	Rhodium-mediated synthesis of isocyanates.....	27
3.1.3	Synthesis of <i>N,N'</i> -diphenyl[^{11}C]urea and ethyl phenyl[^{11}C]carbamate (Paper I).....	28
3.1.4	Proposed reaction mechanism	31
3.1.5	Synthesis of [^{11}C]hydroxyurea (Paper III)	32
3.1.6	Synthesis of 3-phenyl[<i>carbonyl</i> - ^{11}C]oxazolidin-2-one (Paper V)	34
3.2	Synthesis of ^{11}C -labeled compounds via ketene (Paper IV).....	36
3.2.1	Properties of ketenes	36
3.2.2	Rhodium mediated synthesis of ketenes	37
3.2.3	Synthesis of diethyl[<i>carbonyl</i> - ^{11}C]malonate (Paper IV)	38

Abbreviations

AsPh ₃	Triphenylarsine
BBB	Blood Brain Barrier
Bq	Becquerel (decay per second)
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-bis (diphenylphosphino)ethane
dppf	1,1'-bis (diphenylphosphino)ferrocene
dppp	1,2-bis (diphenylphosphino)propane
eV	Electron volt
HCl	Hydrochloric acid
IR	Infra-Red
LC	Liquid Chromatography
LC-MS	Liquid Chromatography – Mass Spectrometry
Bu ₃ SnI	Tributyltin iodide
NMP	<i>N</i> -methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Tomography
PMP	1,2,2,6,6- Pentamethylpiperidine
Pd ₂ dba ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd(Ph ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
P(<i>o</i> -tol) ₃	Tri(<i>ortho</i> -tolyl) phosphine
PhSnBu ₃	Tributylphenylstannane
PPh ₃	Triphenylphosphine
PPh ₃ PO	Triphenylphosphine oxide
RCY	Radiochemical Yield
[RhCl(cod)] ₂	Chloro(1,5-cyclooctadiene)rhodium(I) dimer
SnMe ₄	Tetramethylstannane
SPE	Solid Phase Extraction
TBAF	Tetrabutylammonium fluoride
TE	Trapping Efficiency
TFP	Tri-2-furyl phosphine
THF	Tetrahydrofurane
UV	Ultra-Violet

1 Introduction

This thesis is focusing on the development of new synthetic methods for introducing ^{11}C into target compounds via a metal-mediated carbonylation reaction, and applying such reactions for tracer applications using Positron Emission Tomography (PET).

1.1 Positron Emission Tomography – A molecular imaging technology

Molecular imaging combines new molecular agents with traditional imaging tools to capture pictures of specific molecular pathways or events in the body, particularly those that are targets in disease processes. Molecular imaging holds the unique potential of simultaneously being able to find and diagnose disease *in vivo*, as well as the ability to depict how well a particular treatment is working.

PET is a non-invasive molecular imaging *in vivo* technique permitting external monitoring of specific radioactive tracers labeled with a positron (β^+ particle) emitting radionuclide¹. Positron emitting radionuclides are neutron deficient and decay by conversion of a proton into a neutron with the emission of a positron. The positron is annihilated by a collision with an electron in tissue, this process generates two high-energy photons (511 keV) that travel in opposite directions. These photons can be detected in coincidence by detectors on opposite sides of the PET-camera. In a PET-scan, a tracer labeled with a β^+ -emitting radionuclide is introduced into a living organism. Several such decay events occur, and the recorded data can be reconstructed to give three-dimension digital images. This technique allows thus detection of the temporal and spatial distribution of positron emitting tracers in the human body. The tracer may allow the studies of a certain biochemical process in a sufficient low amount to not disturb the studied process, with a very low radiation dose for the human patient.

Some common radionuclides used for PET are presented in Table 1:

Table 1: Some common radionuclides used in PET-imaging.

Radio-nuclide	Half-life	Nuclear Reaction	Positron Energy (MeV)	Theoretical Specific Radioactivity (GBq/ μ mol)
^{11}C	20.3 min	$^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$	1.0	3.4×10^5
^{15}O	2.07 min	$^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$	1.7	3.4×10^6
^{18}F	109.7 min	$^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$	0.6	6.3×10^4
^{68}Ga	67.8 min	$^{68}\text{Ge} \rightarrow ^{68}\text{Ga}$	1.9	1×10^5
^{76}Br	16 h	$^{76}\text{Se}(\text{p},\text{n})^{76}\text{Br}$	3.4	7.2×10^3

Over the past decades, advances in synthetic chemistry and PET instrumentation have merged to make PET a powerful scientific tool for studying biochemical transformations and a pharmacokinetics tool² during the development of tracers for distribution studies of lead compounds in the human brain as well as other organs in the body³. PET has found numerous applications in medical diagnosis, investigating ways to image cancer⁴, neurological pathologies and disorders such as Alzheimer's disease⁵, epilepsy⁶ and Parkinson's disease⁷. PET has also found some applications in drug development, PET investigations of a drug labeled with β^+ -emitting radionuclide provides information on the drug distribution and concentration *in vivo* in subpharmacological doses.⁸

1.2 Synthetic aspects

1.2.1 Synthetic Strategies

Time is an important parameter in the synthesis of compounds labeled with short-lived radionuclides. While the formation of the product is governed by the kinetics or thermodynamics of the chemical reaction, the competing decay of the radionuclide has to be considered. The total radiochemical yield is a compromise between these two parameters⁹ (Figure 1). It is usually not the chemical yield that is critical but rather the amount of radioactivity obtained at the end of the synthesis. A rule of thumb is that the total synthesis time including purification should not exceed three half-lives of the radionuclide. In this thesis, a standard reaction time of 5 min was chosen for simplicity.

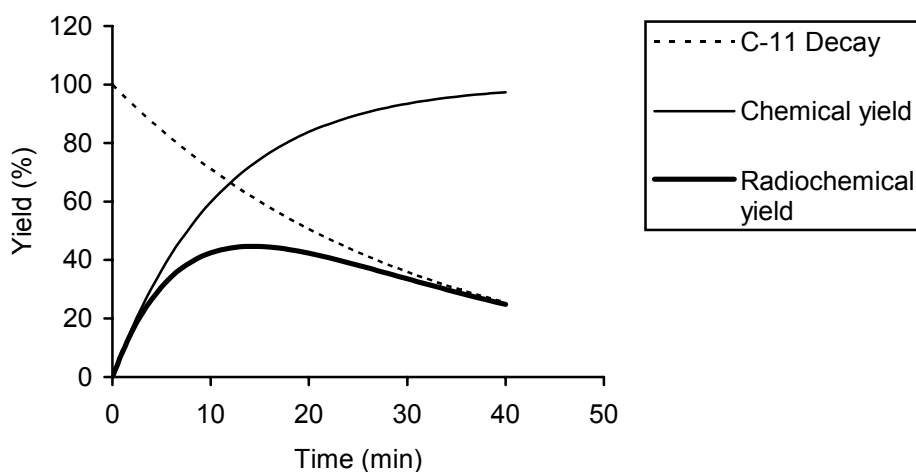


Figure 1: Relationship between chemical yield, radioactive decay, and radiochemical yield for a theoretical ^{11}C -labeling reaction.

Practically, the radiochemical yield is determined by measuring the radioactivity at the start of the synthesis and the radioactivity of the purified product. The yield is corrected for the radioactive decay and presented in this thesis as the isolated radiochemical yield. The analytical radiochemical yield or conversion yield is based on a sample withdrawn from the reaction mixture and determined by LC. The trapping efficiency is defined as the amount of radioactivity trapped to the reaction mixture. This factor is particularly important so as to quantify the reliability of a reaction when working with volatile reagents such as $[^{11}\text{C}]$ carbon monoxide. It is dependant on several parameters such as reaction conditions (including temperature, concentration of reagents or nature of the solvent) and experimental and technical apparatus. The trapping efficiency is determined by measuring the amount of radioactivity present before and after flushing the reaction mixture with nitrogen gas. In this thesis, the analytical radiochemical yields in Papers I & II were based on a sample withdrawn from the reaction mixture. In Papers III-V, the analytical radiochemical yields were decay-corrected and calculated from the total amount of radioactivity present in the reaction mixture at the start of the synthesis.

Some experimental techniques can be employed to increase reaction rates, for example microwave heating has been successfully used for accelerating the labeling process of different organic molecules with ^{11}C or ^{18}F .¹⁰ The building of automated synthetic devices has been a focus since it permits both the significant reduction of synthesis time and minimization of the radioactive dose received by the operating chemist.

Syntheses with short-lived radionuclides such as ^{11}C are performed on a microscale. Other reagents can be used in stoichiometric quantities and up to 1000 fold excess or more. This excess of mass can be used to increase reaction rates in some syntheses.

1.2.2 Specific radioactivity - Sensitivity

The specific radioactivity is defined as the amount of radioactivity per unit of mole of labeled compound. Theoretically, the value of specific radioactivity for ^{11}C is $3.4 \times 10^5 \text{ GBq}/\mu\text{mol}$ but in practice, an isotopic dilution by natural unlabeled substance always occurs. This mainly originates from the target material, delivery lines or chemical reagents. In fact almost everything introduced into the system is a potential source of stable carbon, causing isotopic dilution. In this thesis, the value of specific radioactivity at the end of the synthesis for a ^{11}C -labeled compound synthesized using [^{11}C]carbon monoxide is of the order 120-700 $\text{GBq}/\mu\text{mol}$, and the amount of unlabeled product is in the range of 3-9 nmol. The requirements for high specific radioactivity are due to the possible biological interactions of the unlabeled material such as saturation of a limited amount of receptors or pharmacological side effect of the substance.

1.2.3 Analysis, characterization and purification

The most common techniques used for purification of the labeled products are semi-preparative LC and SPE. The analysis and preliminary characterization of the labeled products can be performed fast and efficiently using LC equipped with both radioactivity- and mass-absorption (i.e. UV) detectors. Characterization of the labeled product is performed by co-elution of the UV-peak of an authentic cold reference sample and radioactive peak. LC-MS can directly provide a spectrum of an isolated sample without addition of a cold reference, and fragmentation patterns give information for the identification of the substance. The position of the ^{11}C -labeled carbon can be characterized by ^{13}C -NMR analysis. For this purpose, a combined labeling experiment with ^{11}C and ^{13}C is performed. The [^{11}C]/(^{13}C)compound is isolated, and after decay the residual (^{13}C)compound can be analyzed by ^{13}C -NMR. The ^{13}C signal obtained is compared with that from the spectrum of an authentic isotopically unmodified compound.

This is illustrated in Figure 2 where [^{11}C]hydroxyurea and (^{13}C)hydroxyurea have been synthesized simultaneously. In these reactions the concentration of (^{13}C)carbon monoxide is much higher, and the reagents concentrations and reaction time are increased subsequently.

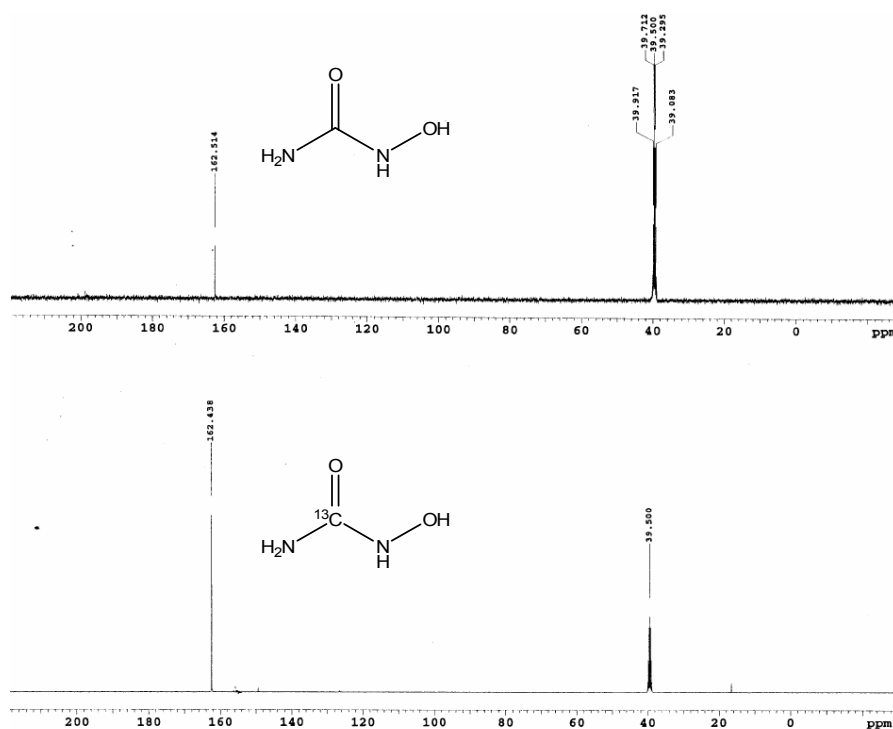
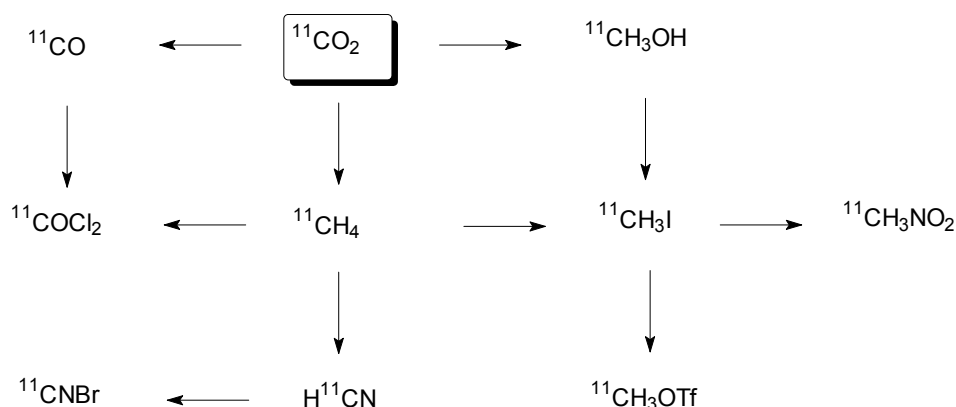


Figure 2: ^{13}C -NMR analysis of (^{13}C)hydroxyurea (lower) and an isotopically unmodified compound (upper). Internal standard: d^6 -DMSO.

1.3 Labeled precursors

1.3.1 Labeling with ^{11}C

^{11}C ($t_{1/2}=20.3$ min) is a positron emitting radionuclide commonly used in PET investigations.¹¹ It was discovered in 1934 by Crane and Lauritsen¹² and became the first radioactive isotope of carbon to be used for chemical and biochemical tracer studies¹³. However, the limitations imposed by the 20.3 min half-life delayed the development of ^{11}C labeling, until the beginning of the seventies.¹⁴ The most frequently used method today for producing ^{11}C is by the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ nuclear reaction. This reaction is performed by proton irradiation of a target filled with nitrogen gas. The formed ^{11}C is highly reactive and reacts with oxygen gas (0.1 %) present in the target to produce [^{11}C]carbon dioxide as the main radioactive product.



Scheme 1: ^{11}C -labeled precursors possibly synthesized from ^{11}C carbon dioxide by simple on-line or batch procedures.

The primary precursor ^{11}C carbon dioxide is transferred to the laboratory where it can be transformed by various routes to other ^{11}C -labeled intermediates (Scheme 1), for example ^{11}C methanol¹⁵, ^{11}C methyl iodide¹⁵, ^{11}C carbon monoxide¹⁶, ^{11}C methane¹⁶, hydrogen ^{11}C cyanide¹⁶, ^{11}C phosgene¹⁷, ^{11}C cyanogen bromide¹⁸, ^{11}C nitromethane¹⁹ or ^{11}C methyl triflate²⁰ using simple on-line procedures.

1.3.2 Production and handling of ^{11}C carbon monoxide

^{11}C Carbon monoxide was the first labeled compound applied in PET experiments on humans.²¹ Carbon monoxide has the great advantage of not being naturally present in large amount in the atmosphere, thus isotopic dilution can be avoided, compared to for example ^{11}C carbon dioxide. However, its low solubility and reactivity had restricted its use in labeling chemistry. This problem has partly been solved by a semi-automated system recirculating the ^{11}C carbon monoxide and trapping it in molecular sieves²² or by reacting the ^{11}C carbon monoxide with a borane-tetrahydrofurane complex, making another complex ready to further react²³.

The presented method is based on pre-concentrating and trapping of ^{11}C carbon monoxide in a micro-autoclave. This technique has solved the problems with low solubility and now permits an easier use²⁴ (Figure 3). The ^{11}C carbon dioxide is produced and directly transferred using nitrogen (N_2) as a carrier gas from the cyclotron to the hotcell where it is trapped on silica. After collection, the ^{11}C carbon dioxide is passed using a stream of helium gas through a quartz tube filled with zinc granules heated at 400 °C reducing it to ^{11}C carbon monoxide, which is then trapped and concentrated on silica.

The unreacted [^{11}C]carbon dioxide is trapped using ascarite material while the [^{11}C]carbon monoxide is transferred to the micro-autoclave (200 μL), followed by addition of the reagents introduced via an injection loop by an HPLC pump and organic solvent, the reaction can proceed.

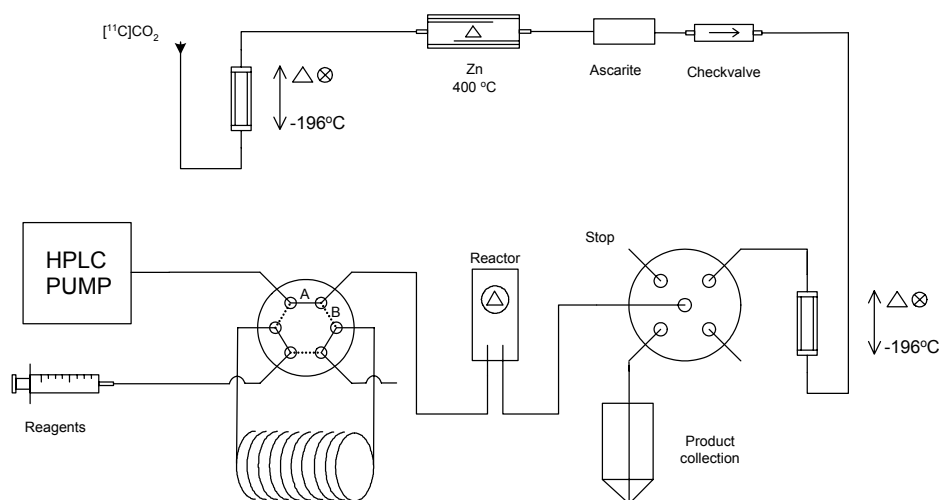


Figure 3: Schematic drawing of the experimental setup used for reactions involving [^{11}C]carbon monoxide.

This synthetic system concentrating [^{11}C]carbon monoxide and the other reagents in a small volume at high pressure has permitted increases of the radiochemical yield and the specific radioactivity of the labeled products.

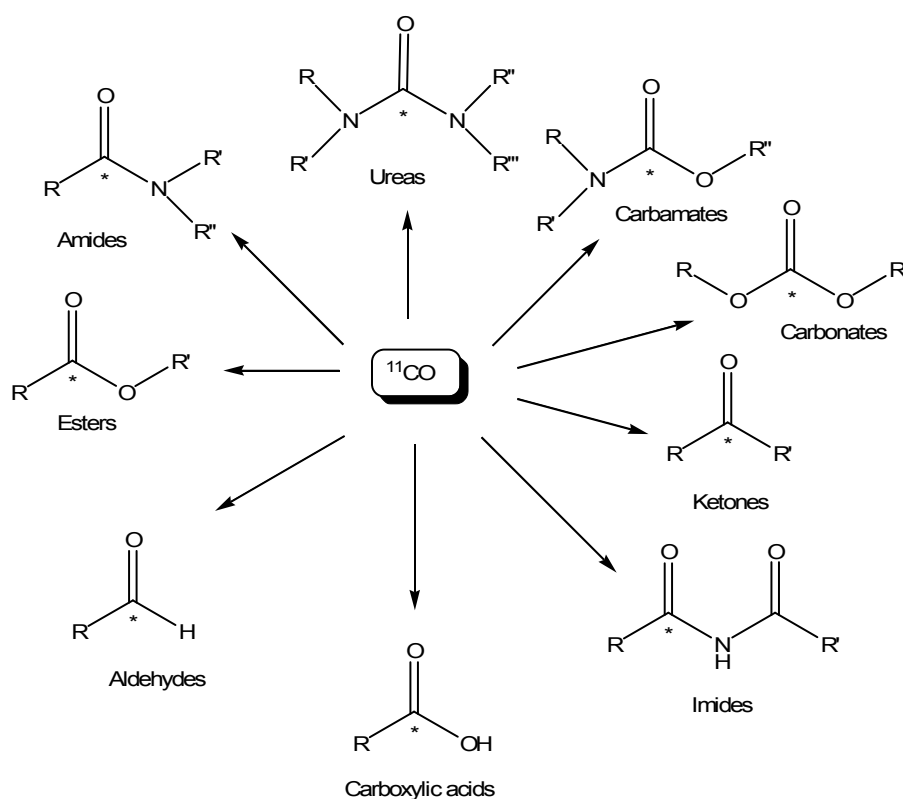
1.3.3 [^{11}C]Carbon monoxide in carbonylation reactions

The possibilities offered by organometallic chemistry have inspired search for applications of metal-catalyzed reactions for the synthesis of PET tracers. For example, applications for the formation of C-C bonds using palladium-promoted coupling reactions such as Stille²⁵, Heck²⁶ or Suzuki reactions²⁷ with [^{11}C]methyl iodide have been described.

Carbon monoxide reacts efficiently in a palladium-catalyzed carbonylative coupling reaction using halides²⁸ or triflates²⁹. The reliable access to [^{11}C]carbon monoxide has facilitated its use to label compounds with ^{11}C in the *carbonyl* position. A wide variety of [*carbonyl*- ^{11}C]compounds have been synthesized using this approach (Scheme 2). This strategy has allowed the syntheses of [*carbonyl*- ^{11}C]amides from halides³⁰ or triflates³¹, [*carboxyl*- ^{11}C]acids³², [*carbonyl*- ^{11}C]imides³³, [*carbonyl*- ^{11}C]esters³⁴, [*carbonyl*-

^{11}C]aldehydes³⁵, or [*carbonyl- ^{11}C*]ketones using carbonylative Stille³⁶ or Suzuki³⁷ couplings. The limitations related to beta-hydride eliminations can be overcome by changing strategy and using [^{11}C]carbon monoxide in a photoinitiated radical carbonylation reaction. Alkyl iodides containing an hydrogen in a beta-position have been successfully used to synthesize aliphatic [*carbonyl- ^{11}C*]amides³⁸, [*carbonyl- ^{11}C*]esters³⁹ and [*carboxyl- ^{11}C*]acids⁴⁰. Transition-metal mediated processes are employed in a key-step for the synthesis of [^{11}C]alkyl halides labelling precursors such as [1- ^{11}C]ethyl iodide⁴¹. The carbonylation reaction have been employed in the key-step of this synthesis and improved the specific radioactivity compared to previous labeling methods.

Following the method proposed by Sonoda⁴², selenium was successfully applied as a mediating agent in the synthesis of ^{11}C -labeled carbamoyl compounds⁴³ such as [*carbonyl- ^{11}C*]ureas, [*carbonyl- ^{11}C*]carbamates and [*carbonyl- ^{11}C*]carbonates from amines and/or alcohols.



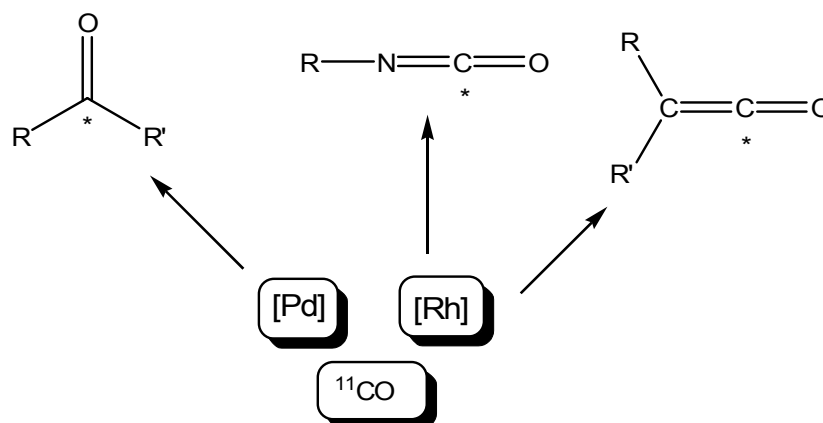
Scheme 2: Some examples of target molecules obtained from [^{11}C]carbon monoxide.
* = ^{11}C .

1.4 Objectives

The work presented in this thesis is aimed at further exploring the synthetic possibilities of [^{11}C]carbon monoxide, focusing on the following transition metal-mediated reactions (Scheme 3):

- Palladium in C-C bond formation reaction. A synthetic methodology for [*carbonyl*- ^{11}C]ketones was designed.
- Rhodium was used for reactions with the intermediates nitrenes and carbenes. Synthetic pathways involving the versatile ^{11}C -labeled precursors [*carbonyl*- ^{11}C]isocyanate and [*carbonyl*- ^{11}C]ketene was designed and proof of concept obtained.

Both of these strategies are intending to expand the field of compounds labeled with ^{11}C with a high specific radioactivity and thus open new routes for the synthesis of potential PET-tracers.



Scheme 3: Synthetic strategies in this thesis. * = ^{11}C .

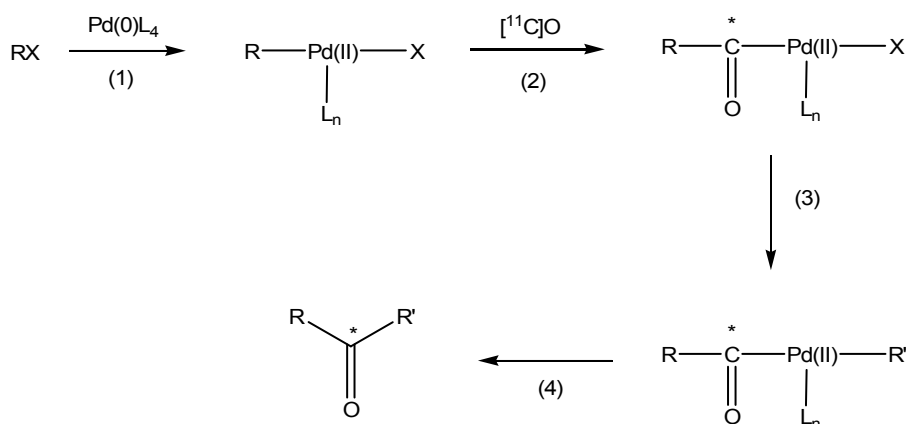
2 Palladium-mediated synthesis of [*carbonyl*-¹¹C]ketones from [¹¹C]carbon monoxide (Paper II)

The value of palladium in catalytic carbonylation reactions from halides or triflates and carbon monoxide at high concentration is well known,⁴⁴ and a wide variety of carbonyl compounds can be obtained by reaction of different nucleophiles. Ketones are obtained by the addition of a transmetallation reagent and in the Stille coupling, organostannanes are used.⁴⁵ In this report, the [¹¹C]carbon monoxide is used in very low concentration and is introduced in the *carbonyl* position via a palladium-mediated reaction from the corresponding iodide.

2.1 Stille coupling using [¹¹C]carbon monoxide

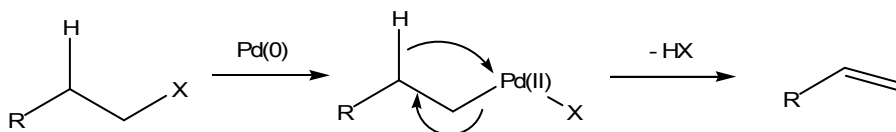
The large concentration excess of other reagents compared with [¹¹C]carbon monoxide should not allow the description of the reaction mechanism as a catalytic cycle as originally reported⁴⁶. Under the low [¹¹C]carbon monoxide concentration conditions used, the palladium catalyst may not be regenerated (Scheme 4) and can be considered as a stoichiometric reagent⁴⁷. Four basic steps are proposed to be involved in this mechanism:

- 1) Oxidative addition: The halide or triflate, RX reacts with the palladium(0) species, and the carbon-halide bond breaks to form two σ -bonds with the palladium atom. The palladium is oxidized to palladium(II) in this process.
- 2) Insertion of [¹¹C]carbon monoxide.
- 3) Transmetallation. Alkyl or aryl groups (R') are transferred from the organostannane to the palladium.
- 4) Reductive elimination. The alkyl or aryl (R') group migrates from the palladium-acyl complex to the carbonyl group.



Scheme 4: Mechanistic steps of the palladium-mediated synthesis of [^{11}C -carbonyl]ketones: (1). Oxidative addition. (2) Insertion of [^{11}C]O. (3) Transmetalation. (4) Reductive elimination. * = ^{11}C .

This method is limited to organic halides or triflates without hydrogens on sp^3 carbons in β -positions to avoid unwanted β -hydride elimination (Scheme 5). This side reaction competes with the insertion of carbon monoxide into the palladium-alkyl complex and is a barrier to the full completion of the carbonylation reaction.



Scheme 5: β -hydride elimination of a σ -alkyl palladium(II) complex.

In a few cases, the competition between β -hydride elimination and [^{11}C]carbon monoxide insertion has been studied, and the desired compound 1-(2-phenyl-[carbonyl- ^{11}C]propanoyl)pyrrolidine was obtained as the main product.⁴⁸

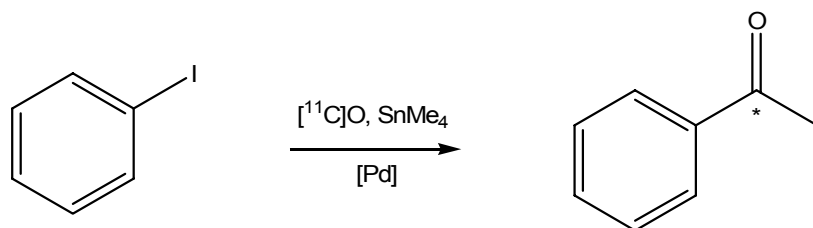
Several palladium-mediated syntheses of [carbonyl- ^{11}C]ketones have been reported. Carbonylative Stille coupling was used in one method based on bubbling [^{11}C]carbon monoxide into the reaction mixture³⁶ and gave a trapping efficiency lower than 10 %. Another method in which [^{11}C]carbon monoxide is bubbled into a reaction mixture was a palladium(II)-mediated reaction starting from diaryl-iodonium salts coupled with organostannanes.⁴⁹ The radiochemical yields were determined up to 98% but with extremely low trapping efficiency. The same procedure starting from iodides was still not successful.⁵⁰ This problem was partially solved by recirculating the [^{11}C]carbon monoxide in the reaction mixture.⁴⁷ This technique was em-

ployed for a palladium-mediated carbonylation of ^{11}C -labeled aromatic ketones and trapping efficiencies over 95 % were obtained.

An alternative was to use the Suzuki coupling⁵¹, giving [*carbonyl*- ^{11}C]benzophenone in 69% radiochemical yield^{37,52}. The micro-autoclave system using aryl triflates gave radiochemical yields up to 68% and specific radioactivities up to 642 GBq/ μmol ⁵³. This synthetic method could be further exploited in the reductive amination of the synthesized [*carbonyl*- ^{11}C]ketones⁵⁴.

2.2 Synthesis of aryl[*carbonyl*- ^{11}C]ketones (Paper II)

The synthesis of [*carbonyl*- ^{11}C]acetophenone was chosen as a model reaction. Phenyl iodide and SnMe_4 were chosen as starting materials together with [^{11}C]carbon monoxide (Scheme 6).



Scheme 6: Synthesis of [*carbonyl*- ^{11}C]acetophenone. * = ^{11}C .

In all syntheses, the major labeled by-product was the corresponding carboxylic acid, which can be explained by the competing nucleophilic attack of water on the palladium-acyl complex, thus anhydrous conditions are required.

Table 2: The impact of various ligands and palladium complexes on the radiochemical yields in the synthesis of [*carbonyl*-¹¹C]acetophenone.

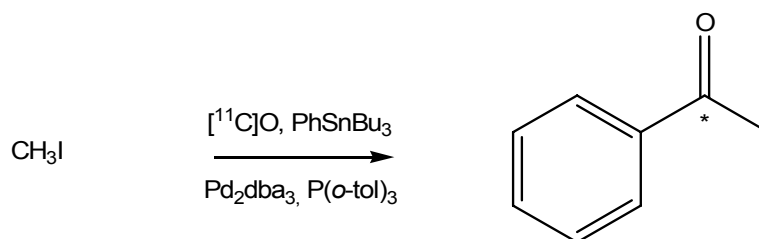
Entry	Palladium complex	Ratio [Pd] : L	Solvent	TE (%) (n) ^a	RCY [*] , % (n) ^a
1	PdCl ₂ (dppe) ₂	-	THF / NMP	85 ± 3 (2)	5 ± 2 (2)
2	Pd(PPh ₃) ₄	-	THF	91 ± 2 (4)	7 ± 2 (4)
3	PdCl ₂ P(<i>o</i> -tol) ₂	-	THF / NMP	92	6
4	Pd ₂ (dba) ₃ : AsPh ₃	1 : 4	THF	95 ± 2 (2)	50 ± 3 (2)
5	Pd ₂ (dba) ₃ : dppf	1 : 1	THF	92	40
6	Pd ₂ (dba) ₃ : P(<i>o</i> -tol) ₃	1 : 4	DMF	90	8
7	Pd ₂ (dba) ₃ : P(<i>o</i> -tol) ₃	1 : 4	DMSO	95 ± 1 (2)	49 ± 1 (2)
8	Pd ₂ (dba) ₃ : P(<i>o</i> -tol) ₃	1 : 12	DMSO	98 ± 1 (7)	72 ± 3 (7)

* The radiochemical analytical yield is based on a sample withdrawn from the reaction mixture. ^a The figure in brackets is the number of runs.

Several parameters were systematically evaluated to find the reliable procedure. In the synthesis of [*carbonyl*-¹¹C]acetophenone (Table 2), the most efficient palladium complex was found to be the complex formed by the *in situ* mixture of Pd₂(dba)₃ and P(*o*-Tol)₃ (entry 8) with DMSO as the solvent, giving an analytical radiochemical yield of 72% with a variation of ± 3%. A key detail in the efficiency of this synthesis was the dependence of the radiochemical yield of having a large excess of the ligand P(*o*-Tol)₃ to the palladium(0) source Pd₂(dba)₃. This fact can be explained by the need of a stable saturated palladium(0) complex to conduct the reaction under optimal conditions. The choice of P(*o*-tol)₃ was justified by its lower electron-donating character, compared to PPh₃, which may enhance the transmetallation rate. The bulkiness of P(*o*-tolyl)₃ (cone angle: 194 °) is presumed to improve the reactivity of the palladium complex.

Optimal results were obtained with temperatures around 100-125 °C. At reduced temperatures, the insertion of carbon monoxide into the palladium complex and transmetallation does not occur cleanly and at higher temperatures, the formation of unwanted carboxylic acids was increased.

An alternative synthetic route was tested using iodomethane and tributylphenyltin under the same conditions (Scheme 7) resulting in an improved radiochemical yield and trapping efficiency of 91% and 98% respectively, which is probably due to a higher relative transfer rate of aryl to alkyl groups from tin to palladium⁵⁵.



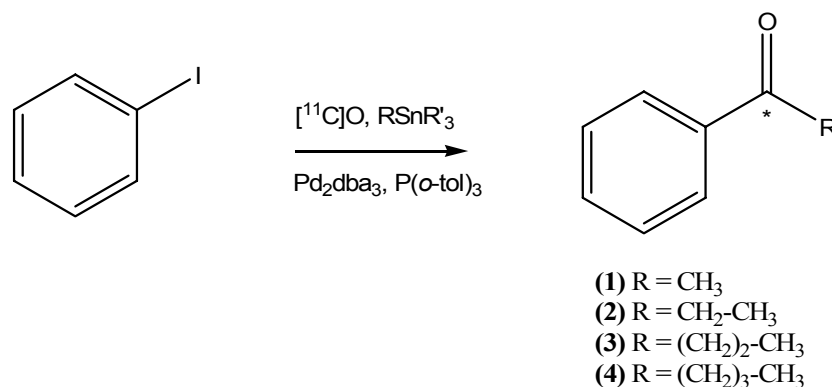
Scheme 7: Alternative route for the synthesis of [*carbonyl*-¹¹C]acetophenone. * = ¹¹C.

This synthetic methodology was successfully applied to the synthesis of twenty different [*carbonyl*-¹¹C]ketones. In the synthesis of these [*carbonyl*-¹¹C]ketones many different parameters were investigated:

- Different organostannanes were tested with phenyl iodide.
- Different organostannanes were tested with methyl iodide.
- Phenyl iodides with different substituent in para position were tested with SnMe₄.
- Different heterocyclic and alkyl iodides were tested with SnMe₄.

1. Reactivity of phenyl iodide with different organostannanes.

Several alkyl-donor organostannanes were reacted with phenyl iodide (Scheme 8).



Scheme 8: Synthesis of [*carbonyl*-¹¹C]ketones from phenyl iodide. * = ¹¹C.

Trapping efficiency of [¹¹C]carbon monoxide was in all cases almost quantitative. 1-Phenyl- [*carbonyl*-¹¹C]propan-1-one (**2**) was synthesized in 60% RCY and 98% TE under the same conditions, but in the cases of 1-phenyl [*carbonyl*-¹¹C]butan-1-one (**3**) and 1-phenyl [*carbonyl*-¹¹C]pentan-1-one (**4**), an increase in temperature to 150 °C was required.

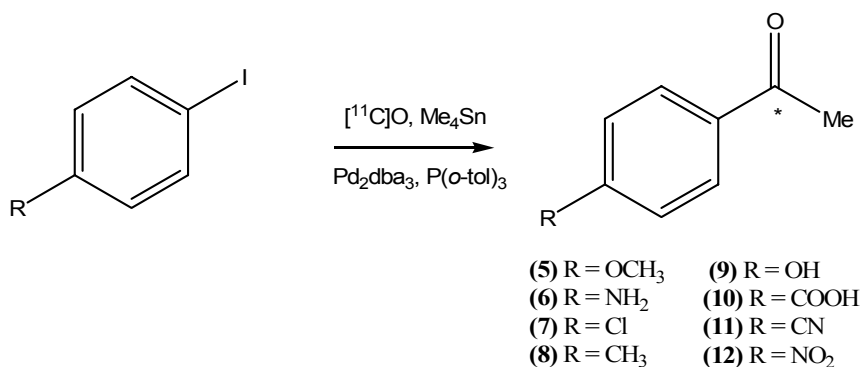
Table 3: Reaction conditions and RCY for the synthesized [*carbonyl*-¹¹C]ketones.

Entry	Product	T (°C)	TE (%) (n) ^b	RCY ^a (%) (n) ^b
1	1	100	98 ± 1 (7)	72 ± 3 (7)
2	2	100	98 ± 1 (3)	60 ± 1 (3)
3	3	150	97 ± 1 (3)	65 ± 2 (3)
4	4	150	97 ± 1 (3)	37 ± 1 (3)

^a RCY: radiochemical analytical yield, based on a sample withdrawn from the reaction mixture. ^b Numbers in brackets show the number of runs.

2. Reactivity of para-substituted phenyl iodides with tetramethylstannane

Eight substituted aryl halides were tested with the present method in order to observe the influence of functional groups on reactivity (Scheme 9).



Scheme 9: Synthesis of para-substituted phenyl[*carbonyl*-¹¹C]ketones. * = ¹¹C

The corresponding methyl [*carbonyl*-¹¹C]ketones were synthesized (Table 4), giving improved radiochemical yields in the range of 49 to 75%. The synthesis of 4'-hydroxy[¹¹C-*carbonyl*]acetophenone (**9**) gave best results when starting from the protonated 4-iodophenol generated from HCl. The reverse phenomenon was observed for the synthesis of 4-acetyl[*carboxyl*-¹¹C]benzoic acid (**10**) where the protonated 4-iodobenzoic acid decreased the radiochemical yield.

Table 4: Radiochemical yields for the synthesized [*carbonyl*-¹¹C]ketones.

Entry	Product	T (°C)	TE(%) (n) ^b	RCY ^a (%) (n) ^b
1	5	100	96 ± 2 (3)	68 ± 2 (3)
2	6	100	96 ± 1 (3)	75 ± 1 (3) ^c
3	7	100	98 ± 1 (3)	62 ± 5 (3)
4	8	100	95 ± 2 (3)	73 ± 2 (3)
5	9 ^d	100	91 ± 3(3)	75 ± 4 (3)
6	10	100	94 ± 1 (3)	56 ± 1 (3)
7	11	100	88 ± 1 (2)	49 ± 1 (2)
8	12	80	92 ± 1 (2)	49 ± 1 (2)

^a RCY: radiochemical analytical yield, based on a sample withdrawn from the reaction mixture. ^b Numbers in brackets show the number of runs. ^c The isolated RCY was determined at 69%. ^d Reaction made using HCl salt of the halide 4-iodophenol.

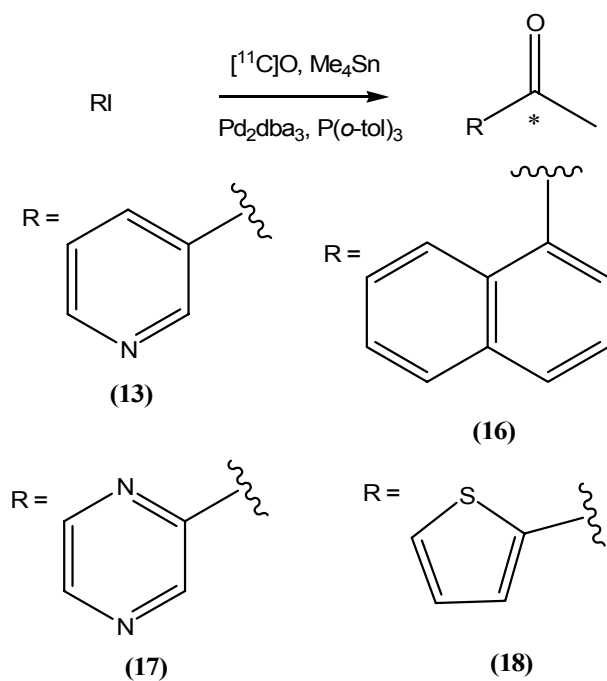
The effects of temperature and reaction time were explored for the synthesis of 1-(4-nitrophenyl)[*carbonyl*-¹¹C]ethanone (**12**) (Table 5). Increasing the temperature only had a moderate influence on the RCY and decreasing temperature slightly affected the trapping efficiency (Table 5, entries 4-7). However, by increasing the reaction time it was possible to partly overcome this problem (Table 5, entry 6).

Table 5: Effects of temperature and reaction time in the synthesis of 1-(4-nitrophenyl)[*carbonyl*-¹¹C]ethanone (**12**).

Entry	Product	T (°C)	TE(%) (n) ^b	RCY ^a (%) (n) ^b
1	12	140	82	40
2	12	100	87	41
3	12	80	92 ± 1 (2)	49 ± 1 (2)
4	12	60	88 ± 1 (2)	41 ± 4 (2)
5	12	30	66	40
6 ^c	12	30	76 ± 4 (2)	28 ± 1 (2)
7	12	r.t.	41	65

^a RCY: radiochemical analytical yield, based on a sample withdrawn from the reaction mixture. ^b Numbers in brackets show the number of runs. ^c Reaction time: 8 min.

3. Reactivity of heterocyclic iodides with tetramethylstannane



Scheme 10: Synthesized heterocyclic [*carbonyl*- ^{11}C]ketones. * = ^{11}C

Several heterocyclic [*carbonyl*- ^{11}C]ketones were successfully synthesized (Scheme 10) starting from the corresponding heterocyclic iodides. The lower RCY of 1-(pyrazin-2-yl)[*carbonyl*- ^{11}C]ethanone (**17**) (Table 6, entry 3) could be explained by the lower purity of the precursor 2-iodopyrazine, and higher temperatures could favour competitive side-reactions.

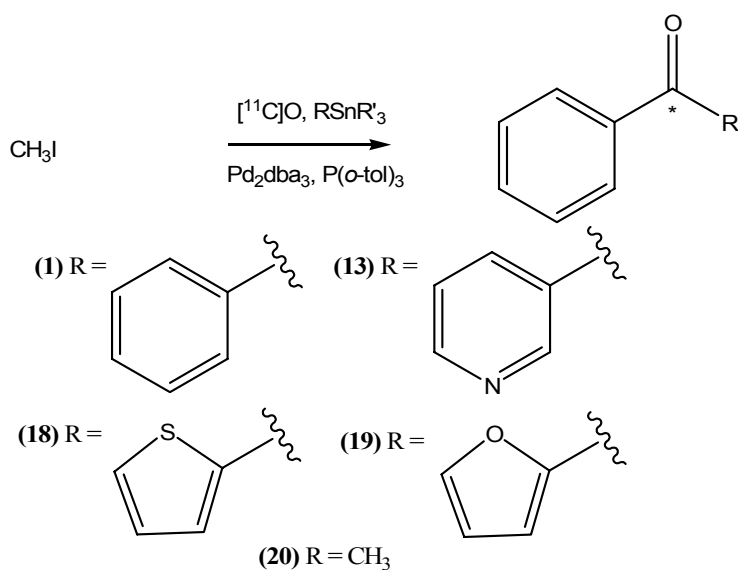
Table 6: Radiochemical yields for the synthesized [*carbonyl*- ^{11}C]ketones.

Entry	Product	T (°C)	TE(%) (n) ^b	RCY ^a (%) (n) ^b
1	13	100	91 ± 3 (4)	61 ± 1 (4)
2	16	150	92 ± 1 (2)	63 ± 2 (2)
3	17	50	68 ± 3 (5)	46 ± 10 (5)
4	18	100	98 ± 1 (3)	71 ± 1 (3)

^a RCY: radiochemical analytical yield, based on a sample withdrawn from the reaction mixture. ^b Numbers in brackets show the number of runs.

4. Reactivity of methyl iodide with different organostannanes.

The synthetic use of methyl iodide was investigated (Scheme 11). As previously mentioned, methyl iodide can be considered as an alternative starting material when the rate of the alkyl transfer from tin to palladium is insufficient.



Scheme 11: Synthesis of [*carbonyl*- ^{11}C]ketones from methyl iodide. * = ^{11}C .

Using this strategy [*carbonyl*- ^{11}C]acetophenone (**1**), [*carbonyl*- ^{11}C]3-acetylpyridine (**13**), [*carbonyl*- ^{11}C]2-acetylthiophene (**18**) and [*carbonyl*- ^{11}C]2-acetylfuran (**19**) can be obtained almost quantitatively, starting with methyl iodide and the corresponding organostannanes (Table 7). [*carbonyl*- ^{11}C]Acetone (**20**) was also synthesized (entry 5, Table 7) from the readily available precursors methyl iodide and SnMe_4 . This result is reproducible which makes possible further exploitation of this versatile compound.

Table 7: Radiochemical yields for the synthesized [*carbonyl*-¹¹C]ketones.

Entry	Product	T (°C)	TE(%) (n) ^b	RCY ^a (%) (n) ^b
1	1	100	98 ± 1 (3)	91 ± 1 (3)
2	13	100	97 ± 1 (3)	93 ± 2 (3)
3	18	100	95 ± 1 (4)	98 ± 1 (4)
4	19	100	96 ± 1 (4)	95 ± 1 (4)
5	20	100	95 ± 1 (2)	97 ± 1 (2)

^a RCY: radiochemical analytical yield, based on a sample withdrawn from the reaction mixture. ^b Numbers in brackets show the number of runs.

In general, the radiochemical yields obtained are dependant on the relative transfer rate for the different groups from tin to palladium⁵⁵ alkynyl > alkenyl > aryl > benzyl > alkyl.

3 Rhodium-mediated synthesis of ^{11}C -labeled carbonyl compounds (Paper I, III-V)

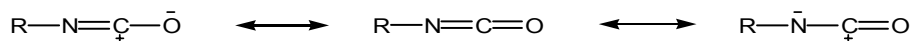
Isocyanates⁵⁶ and ketenes⁵⁷ are well known intermediates in organic synthesis. Rhodium has been used in carbonylation reactions involving [^{11}C]carbon monoxide to design a synthetic methodology from [*carbonyl*- ^{11}C]isocyanate and [*carbonyl*- ^{11}C]ketene and both model compounds and biologically active compounds were successfully.

3.1 Synthesis of ^{11}C -labeled compounds via isocyanate (Paper I, III, V)

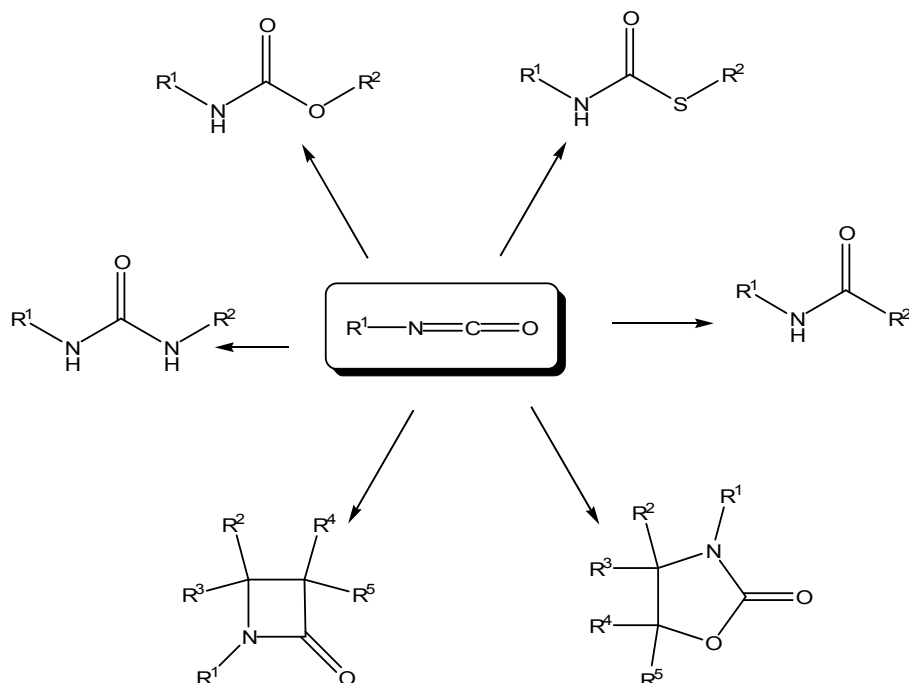
3.1.1 Properties of isocyanates

Aliphatic and aromatic isocyanates are widely used as building blocks for more complicated molecules and are considered as versatile precursors in organic synthetic chemistry. Many are produced using Isocyanates intermediates are involved in the industrial production of polymers and agricultural or pharmaceutical compounds⁵⁸. There are methods for synthesizing isocyanates but the syntheses from sodium azides and acyl chloride compounds⁵⁹, or from phosgene and amines⁶⁰ have been of a great importance.

Some synthetic functional groups obtained from isocyanates are presented in Scheme 13. Isocyanates readily undergo nucleophilic addition yielding products almost quantitatively. The reactivity of an isocyanate to nucleophilic attack can be explained by understanding the electronic structure of the isocyanate group (Scheme 12), the charge density is greatest on the oxygen and lowest on the carbon.



Scheme 12: Resonance form of the isocyanate group.



Scheme 13: Potential compounds obtained from isocyanate groups.

The isocyanate electron π -system allows several types of cycloaddition reactions to occur such as [2+2], [2+3] and [2+4] in the synthesis of heterocyclics.

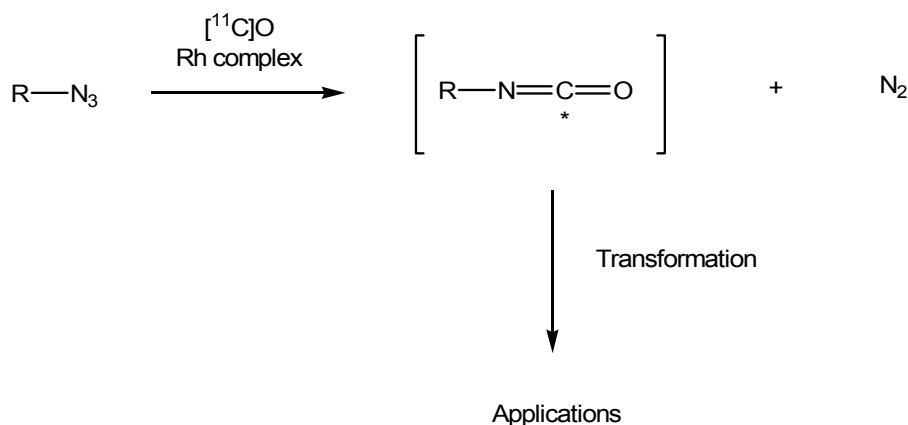
3.1.2 Rhodium-mediated synthesis of isocyanates

Nitrene intermediates can complex with transition metals to form metal complexes of molecular nitrogen.⁶¹ In contrast to the well-defined reactivity of diazo compounds with transition-metal complexes, activation of azide derivatives to produce nitrene metal species is not as common⁶², although both reactions involve the loss of nitrogen. However, recent studies have shown the feasibility of preparing imido complexes from organic azides and manganese complexes⁶³. Metal nitrene complexes have found synthetic applications in both aziridination reactions⁶² and C-H amination insertion reactions.⁶⁴

Collman has reported a synthesis of isocyanate from azides and carbon monoxide in the presence of iridium complexes⁶⁵. Collman stated⁶⁶: “in the absence of a metal complex, CO and organic azides do not react at a measurable rate”. However in 1968, Bennett and Hardy published a synthesis of

phenyl isocyanate, based on the formation of nitrene from an azide compound, which reacted together with carbon monoxide⁶⁷ at high temperature (160-180°C) and high pressure (200-300 atm). Phenyl azide has also been shown to undergo a carbonylation reaction by a catalytic process involving the action of rhodium complexes and carbon monoxide at high pressure (150-300 atm) and high temperature (160-180°C) resulting in the corresponding isocyanate⁶⁸.

The presented method deals with the characteristics of rhodium complexes when reacting with carbon monoxide in the presence of a nitrogen atom. In order to form the ¹¹C-isocyanate we assumed that the nitrene, as a reaction intermediate produced from an azide, would react with [¹¹C]carbon monoxide in the presence of a transition metal complex such as the rhodium complex to yield the [*carbonyl*-¹¹C]isocyanate (Scheme 14).

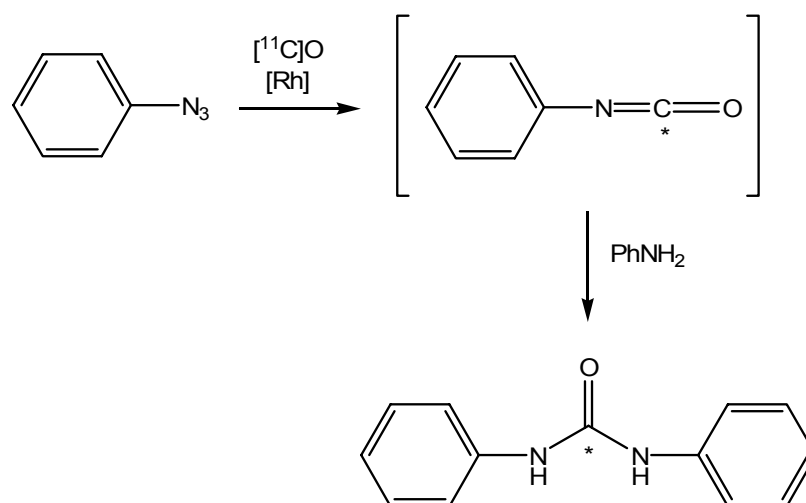


Scheme 14: Plan for the synthesis of [*carbonyl*-¹¹C]isocyanate. * = ¹¹C.

The [*carbonyl*-¹¹C]isocyanate could then be utilized as a synthetic intermediate which may undergo several transformations via different processes.

3.1.3 Synthesis of *N,N'*-diphenyl[¹¹C]urea and ethyl phenyl[¹¹C]carbamate (Paper I)

The synthesis of *N,N'*-diphenyl[¹¹C]urea was chosen as a model reaction. The formation of the phenyl isocyanate intermediate occurred by the reaction of phenyl azide in the presence of a rhodium complex, and [¹¹C]carbon monoxide. The final product was formed by the nucleophilic attack of aniline (Scheme 15).



Scheme 15: Synthesis of *N,N'*-diphenyl[^{11}C]urea. * = ^{11}C .

A one-pot synthesis of *N,N'*-diphenyl[^{11}C]urea was developed, in which aniline was directly placed with the other reagents in the micro-autoclave. The first observation was that the reaction proceeded without the addition of a transition metal complex (Table 8, entry 1). These results are in agreement with Bennett and Hardy's conclusions. The character of the rhodium complex which allows the coordination of [^{11}C]carbon monoxide and controls the reactivity of the nitrene was explored, the results are shown in Table 8. The first complex tested was rhodium(II) acetate which did not give the anticipated results, despite confirming that the reaction could proceed at a lower temperatures. Rhodium(I) complexes were then tested, starting with Wilkinson's catalyst $\text{RhCl}(\text{PPh}_3)_3$. An important observation at this stage was the yield dependence on the amount of rhodium complex. A catalytic amount (0.01 equiv.), with respect azide, of rhodium complex was found to be necessary. This fact can be explained by the formation of a stable ^{11}CO -coordinated rhodium complex. Interestingly, this system also proceeded at 60°C . After extensive studies, the best conditions were obtained by using a coordinatively unsaturated rhodium(I) complex formed *in situ* by mixing $[\text{RhCl}(\text{cod})_2]$ and two equivalents of dppe. This system gave the *N,N'*-diphenyl[^{11}C]urea in 85% RCY (entry 10, Table 8).

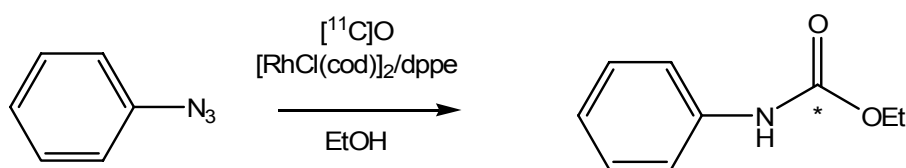
Table 8: Radiochemical yields and trapping efficiency of the synthesized *N,N'*-diphenyl[¹¹C]urea.

Entry	Rh Complex	Ratio azide:Rh	T (°C)	TE (%) (n) ^b	RCY (%) ^a (n) ^b
1	-	-	190	33	67
2	[Rh(OCOCH ₃) ₂] ₂	1:0.2	120	30	71
3	RhCl(PPh ₃) ₃	1:0.1	120	60	74
4	RhCl(PPh ₃) ₃	1:0.01	120	63 ± 1 (2)	89 ± 1 (2)
5	RhCl(cod) ₂ / 4 P(<i>o</i> -tolyl) ₃	1:0.01	80	50	70
6	[RhCl(cod)] ₂ / 4 PPh ₃	1:0.01	120	80	74
7	[RhCl(cod)] ₂ / 4 AsPh ₃	1:0.01	120	24	80
8	[RhCl(cod)] ₂ / 2 dppp	1:0.01	120	69	70
9	[RhCl(cod)] ₂ / 2 dppf	1:0.01	120	69 ± 3 (3)	79 ± 6 (3)
10	[RhCl(cod)] ₂ / 2 dppe	1:0.01	120	85 ± 6 (6)	85 ± 4 (6)

^a RCY: radiochemical analytical yield, based on a sample withdrawn from the reaction mixture. ^b Numbers in brackets show the number of runs.

PPh₃, dppp and dppf were also proved to be relatively effective ligands for this reaction (entries 6, 8 and 9, Table 8). However, the use of an excess of phosphine ligands, based on the associative mechanism of rhodium chemistry, was found to be totally ineffective.

This methodology was applied to the synthesis of ¹¹C-labeled carbamates, choosing ethyl phenyl[¹¹C]carbamate as the model (Scheme 16).



Scheme 16: Synthesis of ethyl phenyl[¹¹C]carbamate. * = ¹¹C.

The same procedure was used as the synthesis of *N,N'*-diphenyl[¹¹C]urea but using ethanol instead of aniline as the nucleophilic reagent. This reaction gave the desired ethyl phenyl[¹¹C]carbamate with 70% trapping efficiency and 22% radiochemical yield (Table 9, entry 2). This result can be explained by the weaker nucleophilicity of ethanol compared to aniline. However, small improvements in trapping efficiency and radiochemical yield were observed when using 3eq. of dppe to [RhCl(cod)]₂. Increasing of tempera-

ture to 150 °C improved the RCY (70%) (entry 3, Table 9). The addition of lithium salts, focusing on the enhancement of the reactivity of ethanol on [*carbonyl*-¹¹C]isocyanate, did not give satisfying results and was abandoned. The direct addition of alkali metal ethoxides increased the RCY and the trapping efficiency. Among the different ethoxides tested, lithium ethoxide was the most efficient and gave the best RCY (Table 9, entry 6).

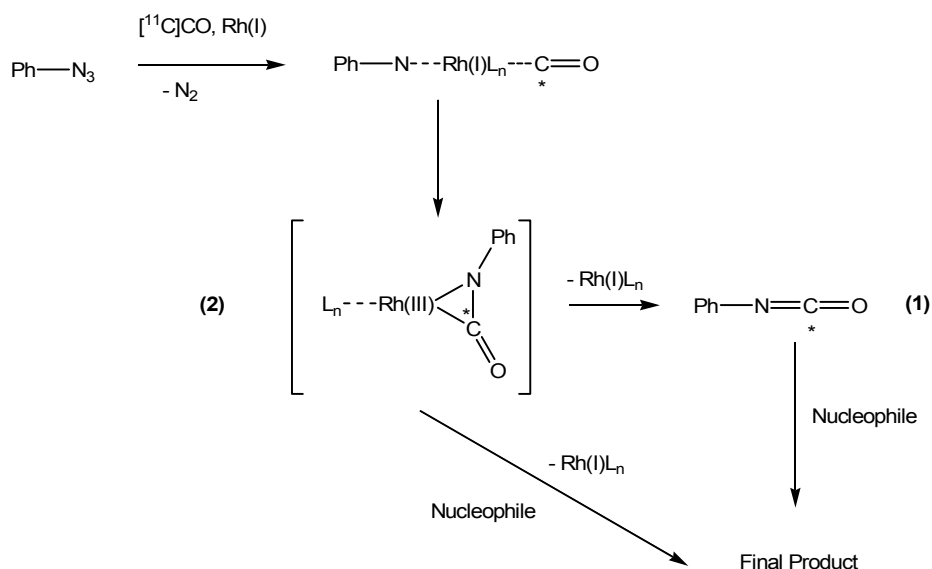
Table 9: Radiochemical yields for ethyl phenyl[¹¹C]carbamate

Entry	Rh Complex	Additive	TE (%) (n) ^c	RCY (%) ^b (n) ^c
1	RhCl(PPh ₃) ₃	–	27	34
2	[RhCl(cod)] ₂ / 2dppe	–	70 ± 2 (2)	22 ± 3 (2)
3 ^a	[RhCl(cod)] ₂ / 3dppe	–	70 ± 2 (2)	70 ± 3 (2)
4	[RhCl(cod)] ₂ / 4dppe	–	50	50
5	[RhCl(cod)] ₂ / 3dppe	LiBr	76 ± 5 (2)	35 ± 5 (2)
6	[RhCl(cod)] ₂ / 3dppe	EtOLi	90 ± 2 (4)	74 ± 4 (4)
7	[RhCl(cod)] ₂ / 3dppe	EtONa	90	54
8	[RhCl(cod)] ₂ / 3dppe	EtOK	94	60

^a The reaction was conducted at 150°C. ^b RCY: radiochemical analytical yield, based on a sample withdrawn from the reaction mixture. ^c Numbers in brackets show the number of runs.

3.1.4 Proposed reaction mechanism

Since the isocyanate functional group (**1** in Scheme 17) normally undergoes nucleophilic attack by ethanol to give ethyl phenylcarbamate formation⁶⁹, this may indicate that the ¹¹C-isocyanate-coordinated rhodium complex (**2** in Scheme 17) is the main intermediate present in the reaction mixture in excess compared to [*carbonyl*-¹¹C]isocyanatobenzene.⁷⁰ The reaction might also be concerted⁷¹ and so the presence of a stronger nucleophile is required. Since isocyanates can complex with transition metal to give isocyanate-metal complexes, an equilibrium between the two species could occur⁷⁰ and slow down the reaction process.



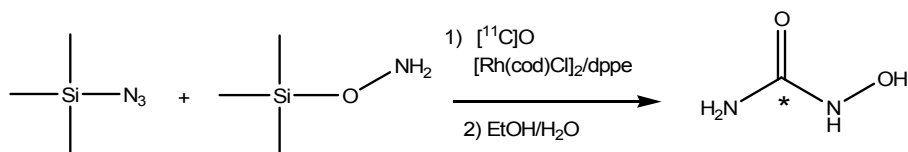
Scheme 17: proposed mechanism for the synthesis and reactivity of [*carbonyl*- ^{11}C]isocyanate. * = ^{11}C .

This may be the explanation of the data indicating that the nucleophilicity of aniline is sufficient in the previous *N,N'*-diphenyl[^{11}C]urea synthesis, but that ethanol is inadequate to produce the ethyl phenyl[^{11}C]carbamate properly under similar conditions.

3.1.5 Synthesis of [^{11}C]hydroxyurea (Paper III)

[^{11}C]Hydroxyurea was the first biologically active compound synthesized with this method. Hydroxyurea is a commonly used anti-cancer drug⁷². Hydroxyurea has previously been labeled with [^{11}C]carbon in the *carbonyl* position using [^{11}C]cyanate and hydroxylamine hydrochloride⁷³ in 72% radiochemical yield, but it was impossible to obtain a pure fraction. The penetration of hydroxyurea into the brain through the Blood Brain Barrier (BBB) has not been studied with PET yet.

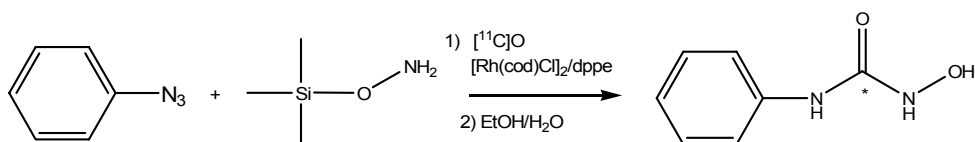
A two-pot synthesis of [^{11}C]hydroxyurea was designed, starting from the commercially available compounds azidotrimethylsilane, $[\text{Rh}(\text{cod})\text{Cl}]_2$, the ligand dppe, *o*-(trimethylsilyl) hydroxylamine as the nucleophile and [^{11}C]carbon monoxide (Scheme 18).



Scheme 18: Synthesis of [^{11}C]hydroxyurea. * = ^{11}C .

The same procedure developed for the synthesis of *N,N'*-diphenyl[^{11}C]urea was used, deprotection of the trimethylsilyl groups was done using ethanol. After purification and formulation, the desired product was obtained in $38 \pm 3\%$ decay-corrected radiochemical yield. The radiochemical purity was measured to be higher than 99%. The compound was identified by a labeling experiment with both ^{11}C and ^{13}C in order to analyze the obtained (^{13}C)hydroxyurea by ^{13}C -NMR and to compare it with a cold reference hydroxyurea. The results agreed with previous published NMR analysis⁷⁴.

The very high polarity of this compound was an obstacle to obtain sufficient retention on a HPLC column.⁷⁵ The low molecular weight of this compound is another problem to perform clear analysis and identification by LC-MS. However, a derivative of hydroxyurea, 1-hydroxy-3-phenyl[^{11}C]urea was synthesized using a similar procedure starting from phenylazide (Scheme 19) in $35 \pm 4\%$ isolated radiochemical yield and identified by LC-MS.

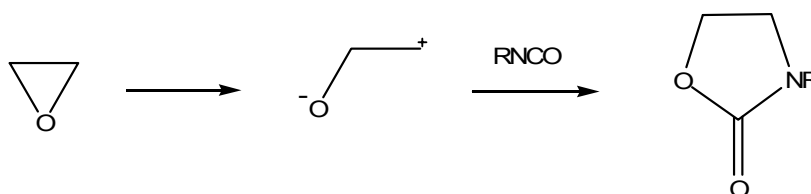


Scheme 19: Synthesis of 1-Hydroxy-3-phenyl[^{11}C]urea. * = ^{11}C .

The availability of [^{11}C]hydroxyurea would allow PET studies on the organ distribution and kinetics of hydroxyurea, especially with respect to access to tumors and normal organs, including transport over the BBB.⁷⁶ Furthermore there is an interest in the evaluation of possible pharmacokinetic interactions by other pharmacological agents, e.g. acting on the efflux systems.

3.1.6 Synthesis of 3-phenyl[*carbonyl*- ^{11}C]oxazolidin-2-one (Paper V)

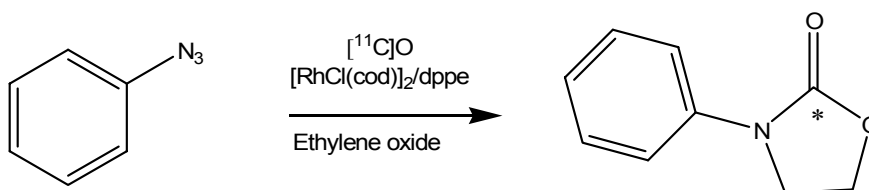
The reactivity of [*carbonyl*- ^{11}C]isocyanate in [2+3] cycloadditions with epoxides was also explored. This reaction affords five-membered heterocycles, generally the [2+3] cycloaddition reaction occurs across the CN double bond to give 2-oxazolidinones⁷⁷ and is catalyzed by lithium salt phosphine adducts, aluminum trichloride and calcium ethoxide. The reaction proceeds *via* interception of thermally generated 1,3-dipolar intermediates and it has been shown that the reaction does not take place unless the catalysts initiate the ring opening of the epoxides⁷⁸ (Scheme 20).



Scheme 20: Mechanism for the [2+3]cycloadditions of epoxides with isocyanates.

It has also been demonstrated that $\text{Bu}_3\text{SnI}\cdot\text{Ph}_3\text{PO}$ causes the complete reaction of aryl isocyanates with epoxides to give 2-oxazolidinones in good yields.⁷⁹ Unsymmetrically substituted 1,2-epoxides give mixtures of isomeric oxazolidinones.⁸⁰ These cycloaddition reactions usually proceed across the CN double bond of the isocyanate, but examples of addition across the CO double bond are also known.⁸¹

The synthesis of 3-phenyl[*carbonyl*- ^{11}C]oxazolidin-2-one was chosen as a model reaction, starting from [^{11}C]carbon monoxide, the rhodium complex $[\text{Rh}(\text{cod})\text{Cl}]_2$, the ligand dppe, phenyl azide and ethylene oxide (Scheme 21).



Scheme 21: Synthesis of 3-phenyl[*carbonyl*- ^{11}C]oxazolidin-2-one. * = ^{11}C .

For the first test reaction, the same conditions as previously described were used, with ethylene oxide and THF as the solvent. Although the radiochemical yield was low (Table 10, entry 1), the results obtained under these conditions showed that the reaction was possible. Inorganic salts were introduced into the reaction media in order to perform the epoxide ring opening

under mild conditions. Tetrabutylammonium iodide (represented as QI in Table 10) coupled with the change of solvent to dioxane and an increase of temperature to 190°C, improved the radiochemical yield to 49%. The addition of a second solvent DMF to help the solubility of tetrabutylammonium iodide was able to improve the radiochemical yield up to over 80 %. However, the reproducibility of these results is highly related to anhydrous conditions, the reaction was found to be highly sensitive to moisture, the 1,3-dipolar intermediate shown in Scheme 20 was found to be very sensitive to attack by water.

Table 10: Radiochemical yields for 3-phenyl[*carbonyl*-¹¹C]oxazolidin-2-one.

Entry	Solvent	T (°C)	Additives	RCY (%) ^a	TE (%) ^b
1	THF	120	-	2.5 ± 1 (2)	80 ± 2 (2)
2	Dioxane	190	QI	49	50
3	Dioxane	190	QI in DMF	>80	>90
4	THF	160	LiBr	60 ± 5 (4)	90 ± 5 (4)

^a RCY: decay-corrected analytical radiochemical yields, calculated from the total amount of radioactivity present in the reaction mixture at the start of the synthesis. ^b Numbers in brackets show the number of runs.

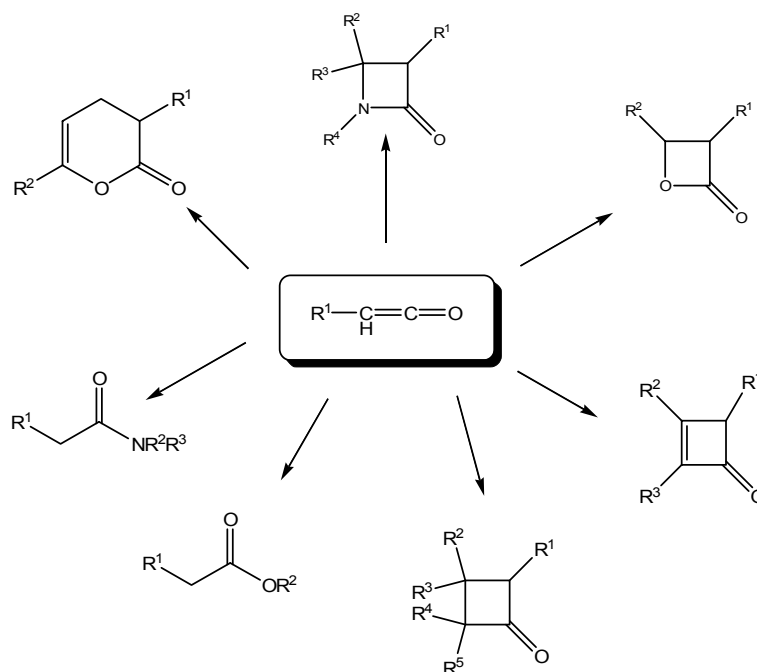
2-Iodoethanol was used instead of ethylene oxide but gave no product. 3-Phenyl[*carbonyl*-¹¹C]oxazolidin-2-one could only be synthesized in a 30% RCY by the addition of a mild base, PMP. A key step for good reproducibility appears to be the oxazolidinone ring closure, more than the ethylene oxide ring opening.

3.2 Synthesis of ^{11}C -labeled compounds via ketene (Paper IV)

The results obtained on the synthesis of [*carbonyl*- ^{11}C]isocyanate from azide compounds and [^{11}C]carbon monoxide suggested the possibility of obtaining [*carbonyl*- ^{11}C]ketene using the same strategy. The starting diazo compounds would complex with rhodium to form a rhodium-carbenoid complex.

3.2.1 Properties of ketenes

The first ketene synthesis reported was made in 1905 by Staudinger when synthesizing diphenylketene.⁸² This preparation involved the reaction of α -chlorodiphenylacetyl chloride with zinc. The chemical utility of ketenes was recognized quickly and these species became a popular topic of investigation. For many years, the hydration of ketene was a major industrial process in the preparation of acetic acid.⁸³

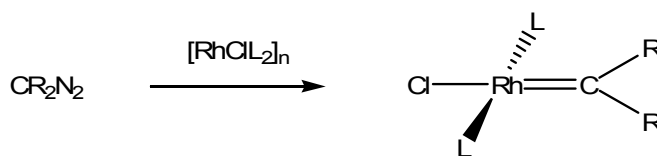


Scheme 22: Potential compounds obtained from ketene groups

Ketenes have been also of major importance in organic synthesis, for example in the formation of β -lactams leading to penicillins⁸⁴ by [2+2]cycloadditions with imines, the formation of prostaglandin precursors⁸⁵, and syntheses of quinones⁸⁶. Some potential target compounds⁸³ obtained from ketenes are shown in Scheme 22.

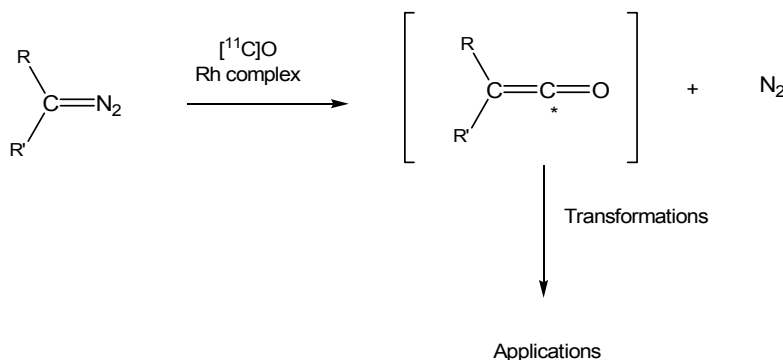
3.2.2 Rhodium mediated synthesis of ketenes

Diazo compounds are an important class of reagents in organometallic chemistry especially regarding formation of metallocarbene complexes⁸⁷. The reactivity of these complexes has found interests in cyclopropanation of olefins⁸⁸ and C-H bond activation⁸⁹. Divalent rhodium such as $[\text{Rh}(\text{OCOCH}_3)_2]_2$ are among the most efficient catalysts for the formation of disubstituted cyclopropanes from ethene and diazoalkanes derivatives⁹⁰. Synthesis and isolation of carbene-rhodium(I) complexes prepared from diazoalkanes have also been described⁹¹ (Scheme 23).



Scheme 23: Typical formation of carbene-rhodium(I) complex from diazoalkane.

Concerning the carbonylation of carbenes, Rüdhardt and Schrauzer have examined the reactivity of some diazo compounds with tetracarbonylnickel⁹², finding that the final product was the corresponding ketene. The initial step of the reaction possibly involves an attack on $\text{Ni}(\text{CO})_4$ by the basic carbon of the diazoalkane, leading to carbonyl substitution. Elimination of nitrogen yielded a highly unstable metallocarbene complex, which decomposes to a ketene compound via insertion of carbon monoxide into the carbene-metal bond. Insertion of free carbon monoxide into a carbene-rhodium bond has also been reported, in the isolation of a η^1 -ketenyl rhodium complex.⁹³



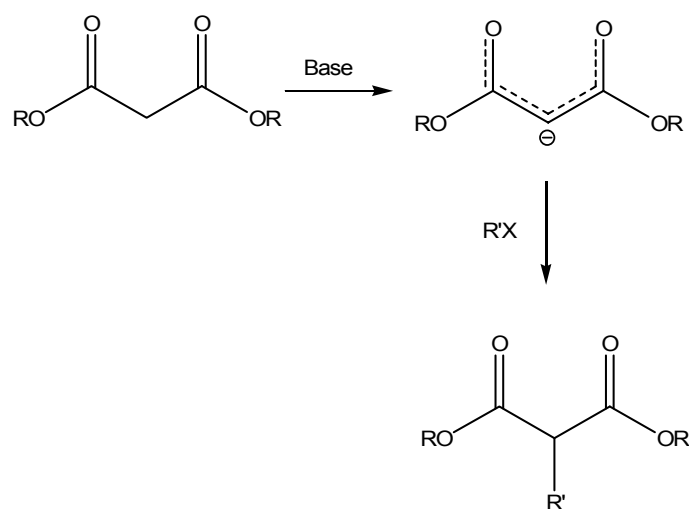
Scheme 24: Plan for the synthesis of [carbonyl-¹¹C]ketene. * = ¹¹C.

This information pointed towards the possibility to synthesize a carbene-rhodium complex from a given diazo compound and rhodium where

$[^{11}\text{C}]$ carbon monoxide could insert into the rhodium-carbon bond and yield the desired [*carbonyl*- ^{11}C]ketene (Scheme 24), indicating that [*carbonyl*- ^{11}C]ketene might be a versatile precursor for further applications.

3.2.3 Synthesis of diethyl[*carbonyl*- ^{11}C]malonate (Paper IV)

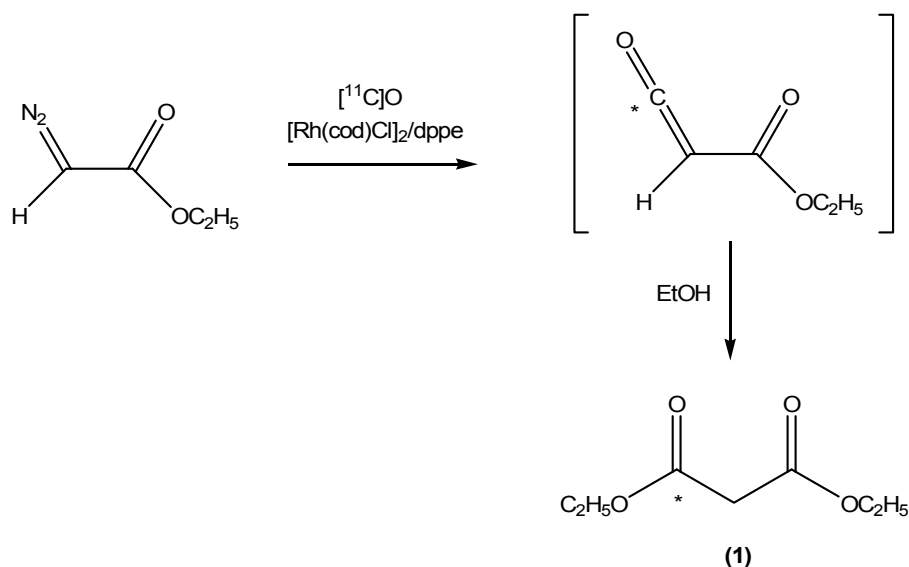
Diethyl malonate is a natural compound, found in grapes and strawberries with an apple-like odor. The malonic esters have also widely been used in organic synthesis as a two-carbon nucleophilic synthon⁹⁴. The synthetic utility of this class of compounds is shown in Scheme 25. The electron withdrawing effect of the two esters groups make the methylene proton easy to remove under basic conditions. Alkylation reactions can occur via an electrophilic attack, for example with an alkyl halide.



Scheme 25: Reactivity of malonic esters towards alkylation reactions.

Several malonic esters have been labeled with $[^{11}\text{C}]\text{H}_3\text{I}$ using this alkylation strategy, although the radiochemical yields were satisfying, this synthesis is limited to compounds containing the ^{11}C -label on an alkyl group⁹⁵.

Labeling with $[^{11}\text{C}]$ carbon monoxide could solve this problem and a more general methods for labeling malonic esters in the carbonyl position is possible. The availability of [*carbonyl*- ^{11}C]ketene as an intermediate was explored for the synthesis of diethyl[*carbonyl*- ^{11}C]malonate (**1**) in Scheme 26. The starting material was the commercially available ethyl diazoacetate (Scheme 26) and ethanol was used as the nucleophilic agent.



Scheme 26: Synthesis of diethyl[*carbonyl*- ^{11}C]malonate via [*carbonyl*- ^{11}C]ketene intermediate. * = ^{11}C .

Rhodium(II) acetate was the first complex tested in this reaction (Table 11, entry 1) yielding the wanted product in 25% radiochemical yield. The results were improved by using the complex made *in situ* by mixing $[\text{RhCl}(\text{cod})]_2$ and dppe giving diethyl[*carbonyl*- ^{11}C]malonate in 44% radiochemical yield (Table 11, entry 2). The late addition of ethanol in the reaction mixture permitted an improvement of the radiochemical yield to 75% (Table 11, entry 3), probably due to the decomposition of ethyl diazoacetate in the presence of ethanol.⁹⁶

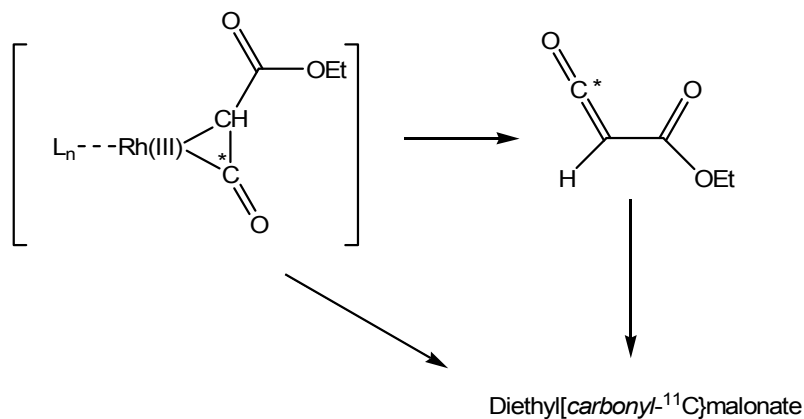
Table 11: Different experiment conditions and RCY for the synthesis of diethyl[1- ^{11}C]malonate.

Entry	Rhodium complex	T (°C)	RCY ¹ (%) ²	TE (%) ²
1	$\text{Rh}(\text{OAc})_2$	100	25	38
2	$[\text{Rh}(\text{cod})\text{Cl}]_2/\text{dppe}$	100	44	78
3	$[\text{Rh}(\text{cod})\text{Cl}]_2/\text{dppe}$ ³	150	75 ± 4 (5)	85 ± 5 (5)

¹ RCY: decay-corrected analytical radiochemical yields, calculated from the total amount of radioactivity present in the reaction mixture at the start of the synthesis. ² Numbers in brackets show the number of runs. ³ Late addition of EtOH.

In a pathway similar to the formation of [*carbonyl*- ^{11}C]isocyanate from azide (Papers I,III,V), the free [*carbonyl*- ^{11}C]ketene might not be the reaction intermediate, but a ketene-rhodium complex⁹⁷ (Scheme 27). An equilibrium between the two species can be considered since it has been shown that sta-

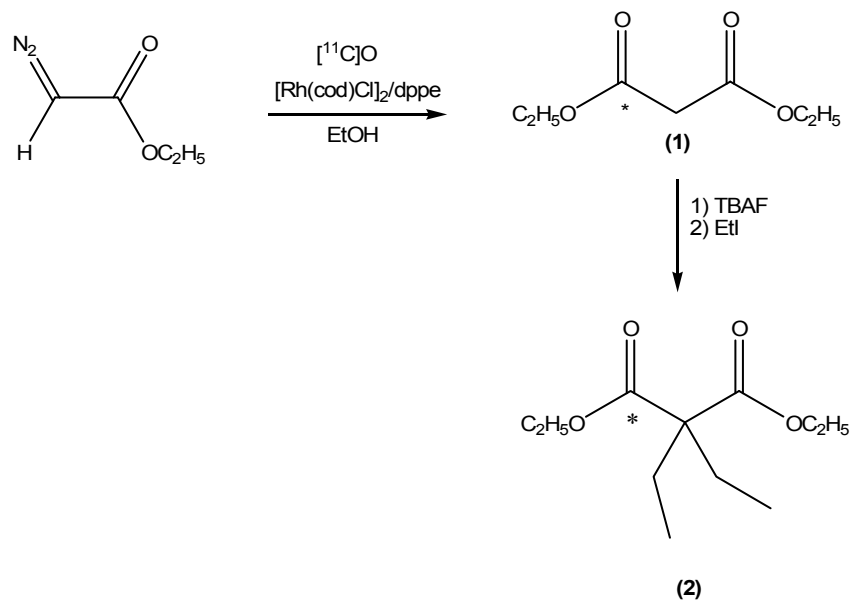
ble ketene-metal complexes can be obtained by the addition of ketenes on unsaturated organometallic complexes.⁹⁸



Scheme 27: Proposed reaction intermediates. * = ¹¹C.

The ketene-rhodium complex is expected to have the same reactivity than the ketene itself.⁹⁹

An alkylation reaction on this compound was performed using ethyl iodide to synthesize diethyl diethyl[carbonyl-¹¹C]malonate (**2**) in Scheme 28, in order to test the availability of diethyl[carbonyl-¹¹C]malonate as a potential precursor and intermediate for biologically active PET-tracers.



Scheme 28: Synthesis of diethyl diethyl[carbonyl-¹¹C]malonate. * = ¹¹C.

Alkylation reaction on malonic esters usually involves the use of a strong base such as sodium hydride in order to generate the carbanion. In this synthesis, tetrabutyl ammonium fluoride was used to remove the methylene proton under milder conditions¹⁰⁰ to avoid interactions of a strong base with potential substituents. Diethyl diethyl[*carbonyl*-¹¹C]malonate was obtained in 50 % radiochemical yield.

Conclusion

The transition metals rhodium and palladium have been successfully used in carbonylation for the rapid labeling of compounds with ^{11}C in the carbonyl position. Easy and reliable use of [^{11}C]carbon monoxide at low concentration was achieved.

Palladium was used in the design of a route for the general synthesis of aryl [*carbonyl*- ^{11}C]ketones. This method covers several synthetic possibilities and high yields were obtained.

Rhodium has been successfully employed in synthetic pathways involving the precursors [*carbonyl*- ^{11}C]isocyanate and [*carbonyl*- ^{11}C]ketene. Model compounds were synthesized in order to confirm this strategy.

The practical utility of [^{11}C]isocyanate as a reaction intermediate was illustrated by developing the synthesis of a biologically active compound. The potential of [^{11}C]hydroxyurea as a PET-tracer is now under investigation.

The rhodium and palladium carbonylation methods are complementary with respect to the scope of the synthetic targets.

For all methods, high specific radioactivity was obtained. In addition, (^{13}C)compounds were synthesized using the described methods and position of the label was confirmed by ^{13}C -NMR analysis.

The use of these methods are making possible labeling of several interesting endogenous compounds

Acknowledgements

I would like to express my sincere gratitude to the following:

Prof. Bengt Långström, my supervisor, for giving me the chance to start my PhD studies and providing excellent lab facilities but also for his enthusiasm, support and encouragements throughout all these years.

My co-supervisors and co-workers (in order of appearance): Dr Mattias Ögren, for his guidance and help during my first months; Dr Hisashi Doi, for being an excellent scientist and a friend and Dr Farhad Karimi, for sharing his science, cheering me up when needed and always providing a solution to (what I thought was) an unsolvable problem.

This manuscript was checked by Doc Tor Kihlberg, Dr Torben Rasmussen, Dr Farhad Karimi and Jonas Eriksson. Language correction by Dr Ian Munslow and swedish summary by Jonas Eriksson and Ullis Lönngren. Thank you all for your effort, I am really impressed by the time you have spent for me!

The past and present members of the Blå-group! For creating an excellent atmosphere and for good scientific discussion. Jonas for great technical help with the CO system and being such a good friend, Alex, Bettan, Obbe, Ola, Irina, Sven-Åke, Kristina, Linda, Kengo, Koichi, Maria and more. Kram!

Everyone at Uppsala Imanet! Especially the production chemists for always allowing me some time at the cyclotron (and with a smile), Jocke Schultz for keeping the cyclotron in a good shape, Pernilla Frändberg for assistance with LC-MS, Gudrun Nylén for taking great care of me and good psychological assistance, and Viktor Leander for being a good friend and allowing me to relax by speaking french.

Preklin people! For good collaborations and kindness when I failed a delivery: Prof. Mats Bergström for HUR and PIB, Doc Sergio Estrada and Dr Ray Josephsson for PIB, and Stina Syvänen for HUR and being a friend.

Everyone at the Department of Organic Chemistry! I wasn't there very often (especially the last years) but I always felt welcome! Thanks to Eva for

administrative assistance. One word for Prof. Stefan Sjöberg and Dr. Ludvig Eriksson for giving me the opportunity to stay in Uppsala.

Prof. Ryoji Noyori, Prof. Masaaki Suzuki and Prof. Yasuyoshi Watanabe, for good collaboration with the isocyanate-project.

Amersham Fund., Uppsala University and C.F. Liljewachs for financial support.

I would like to thank my parents and family, and all my friends all over the world, for never-ending support, always being there when needed and for helping changing my mind outside chemistry.

Finally to my little bird, Ullis, for all her love, sweetness and everything that makes you the way you are! Puss!

Summary in swedish

Doktorsavhandlingen fokuserar på forskning kring nya syntesmetoder för märkning av molekyler med kol-11 (^{11}C) via övergångsmetall-medierad karbonylering. Dessa metoder möjliggör syntes av en mängd olika spår-molekyler som kan användas vid positronemissionstomografi (PET). PET är en avbildningsteknik som mäter strålningen från en spår-molekyl märkt med en positronemitterande - β^+ -radionuklid. Vid en PET-undersökning introduceras spår-molekylen i en levande organism och genom positronstrålningen avbildas utbredningen och koncentrationen av spår-molekylen i vävnaden. En stor fördel med PET är att de mycket låga koncentrationerna av spår-molekylen möjliggör studier av biokemiska processer utan att dessa störs från normala mönster. Under de senaste årtiondena har framsteg inom synteskemi tillsammans med vidareutvecklingen av utrustning för PET-undersökningar gjort PET till ett kraftfullt verktyg för så väl diagnostik av sjukdomar, utveckling av nya läkemedel som medicinsk forskning.

^{11}C är en vanligt förekommande positronemitterande radionuklid vid PET-undersökningar. Halveringstiden för ^{11}C är 20 minuter vilket ställer krav på att märkningen av spår-molekylen är snabb och effektiv. Produktionen av det radioaktiva materialet sker genom en kärnreaktion och för det används en cyklotron, en typ av partikelaccelerator. Det radioaktiva materialet används sedan i en kedja av av kemiska reaktioner vilka leder fram till den märkta spår-molekylen. Metoden som presenteras här baseras på [^{11}C]kolmonoxid, vilket i sin tur fås från cyklotronproducerad [^{11}C]koldioxid.

Metallorganisk kemi tillhandahåller ett brett spektrum av syntesmetoder vilket har givit tillämpningar för metall-katalyserade reaktioner inom många områden, bl.a. syntes av spår-molekyler för användning vid PET. Arbetet som presenteras i denna avhandling är fokuserat på övergångsmetall-medierad karbonylering och syftar till att utvidga möjligheterna att använda [^{11}C]kolmonoxid som radioaktivt startmaterial vid syntes av spår-molekyler. Palladium har använts tillsammans med [^{11}C]kolmonoxid i reaktioner för bildandet av kol-kol-bindningar. I denna metod för syntes av [*karbonyl*- ^{11}C]ketoner användes Stille-koppling mellan organoiodider och organiska tennföreningar i närvaro av [^{11}C]kolmonoxid. Metoden täcker flera syntes-möjligheter och högt utbyte erhöles. Rodium användes i reaktioner där in-

termediaten nitrener och karbener erhöles vilka sedan omvandlades till de två mångsidiga prekursorerna [*karbonyl*-¹¹C]isocyanat and [*karbonyl*-¹¹C]keten.

Modellföreningar syntetiserades för att konfirmera denna strategi: *N,N'*-Difenyl[¹¹C]urea och etyl fenyl[¹¹C]karbamat syntetiserades från [*karbonyl*-¹¹C]isocyanat via nukleofil attack och 3-fenyl[*karbonyl*-¹¹C]oxazolidin-2-on via [2+3]cycloaddition med epoxider. [*karbonyl*-¹¹C]Keten användes i syntesen av dietyl[*karbonyl*-¹¹C]malonat via nukleofil attack.

Det praktiska användandet av [¹¹C]isocyanat som reaktionsintermediat visades genom att syntetisera [¹¹C]hydroxyurea, en biologiskt intressant förening. Potentialen för [¹¹C]hydroxyurea som spår molekyl vid PET-undersökningar är nu under utredning. De båda metoderna, karbonylering med rodium respektive palladium, kompletterar varandra och kan användas för att syntetisera ett stort antal föreningar märkta med ¹¹C med hög specifik radioaktivitet. Dessa strategier ger därmed möjlighet till att utveckla nya spår molekyler för användning vid PET-undersökningar.

References

-
- ¹ (a) H.N. Wagner, Z. Szabo and J.W. Buchanan in *Principles of Nuclear Medicine*, W.B. Saunders Company (Philadelphia), 1995, ISBN 0-7216-9091-2. (b) J.S. Fowler and A.P. Wolf, *Acc. Chem. Res.*, 1997, 30, 181-188.
- ² M. Bergström and B. Långström, *Prog. Drug Res.*, 2005, 62, 281-317.
- ³ H.L. van Westeene, D.C.P. Cobben, P.L. Jager, H.M. van Dullemen, J. Wesseling, P.H. Elsinga and J.T. Plukker, *J. Nucl. Med.*, 2005, 46, 400-404.
- ⁴ Q.H. Zheng, X. Fei, T.R. DeGrado, J.Q. Wang, K.L. Stone, T.D. Martinez, D.J. Gay, W.L. Baity, B.H. Mock, B.E. Glick-Wilson, M.L. Sullivan, K.D. Miller, G.W. Sledge and G.D. Hutchins, *Nucl. Med. Biol.*, 2003, 30, 753-760.
- ⁵ W.E. Klunk, H. Engler, A. Nordberg, Y. Wang, G. Blomqvist, D.P. Holt, M. Bergström, I. Savitcheva, G.F. Huang, S. Estrada, B. Ausén, M.L. Debnath, J. Barletta, J.C. Price, J. Sandell, B.J. Lopresti, A. Wall, P. Koivisto, G. Antoni, C.A. Mathis and B. Långström, *Ann. Neurol.*, 2004, 55, 306-319.
- ⁶ R. Korinthenberg, C. Bauer-Scheid, P. Burkart, H. Martens-Le Bouar, J. Kassubek and F.D. Juengling, *Epilepsy Res.*, 2004, 60, 53-61.
- ⁷ W.L. Au, J.R. Adams, A.R. Troaino and A.J. Stoessl, *Mol. Brain Res.*, 2005, 134, 24-33.
- ⁸ M. Bergström, A. Grahnén and B. Långström, *Eur. J. Clin. Pharmacol.*, 2003, 59, 357-366.
- ⁹ B. Långström and G. Bergson, *Radiochem. Radioanal. Lett.*, 1980, 43, 47-54.
- ¹⁰ N. Elander, J.R. Jones, S.Y. Lu and S. Stone-Elander, *Chem. Soc. Rev.*, 2000, 29, 239-249.
- ¹¹ B. Långström, T. Kilhberg, M. Bergström, G. Antoni, M. Björkman, B. H. Forngren, T. Forngren, P. Hartvig, K. Markides, U. Yngve and M. Ögren, *Acta Chem. Scandinavica*, 1999, 59(9), 651-669.
- ¹² H.R. Crane and C.C. Lauritsen, *Phys. Rev.*, 1934, 45, 430-432.
- ¹³ S. Ruben, W.Z. Hassid and M.D. Kamen, *J. Am. Chem. Soc.*, 1939, 61, 661-663.
- ¹⁴ (a) D.R. Christmann, R.M. Hoyle and A.P. Wolf, *J. Nucl. Med.*, 1970, 11, 474-478. (b) M.B. Winstead, H.S. Winchell and R. Fawwaz, *Int. J. Appl. Isot.*, 1969, 20, 859-863.
- ¹⁵ (a) B. Långström and H. Lundqvist, *Int. J. Appl. Radiat. Isot.*, 1976, 27, 357-363. (b) B. Långström, G. Antoni, P. Gullberg, C. Halldin, P. Malmberg, K. Någren, A. Rimland and H. Svärd, *J. Nucl. Med.*, 1987, 28, 1037-1040. (c) D. Comar, J.C. Cartron, M. Maziere and C. Marazano, *Eur. J. Nucl. Med.*, 1976, 1, 11-14.
- ¹⁶ D.R. Christmann, R.D. Finn, K.I. Karlstrom and A.P. Wolff, *Int. J. Appl. Radiat. Isot.*, 1975, 26, 435-442.
- ¹⁷ (a) D. Roeda, C. Crouzel and B. van Zanten, *Radiochem. Radioanal. Lett.*, 1978, 33, 175-178. (b) P. Landais and C. Crouzel, *Appl. Radiat. Isot.*, 1987, 38, 297-300.
- ¹⁸ G. Westerberg and B. Långström, *Acta Chem. Scand.*, 1993, 47, 974-978.

- ¹⁹ K.O. Schoeps, S. Stone-Elander and C. Halldin, *Appl. Radiat. Isot.*, 1989, 40, 261-262.
- ²⁰ D.M. Jewett, *Appl. Radiat. Isot.*, 1992, 43, 1383-1385.
- ²¹ C.A. Tobias, J.H. Lawrence, F.J.W. Roughton, W.S. Root and M.I. Gregerson, *Am. J. Physiol.*, 1945, 145, 253-263.
- ²² L. Brichard, C. Del Fiore, A. Lemaire, A. Plenevaux and A. Luxen, *J. Labelled Cpd. Radiopharm.* 2003, 46, S74.
- ²³ H. Audrain, L. Martarello, A. Gee and D. Bender, *Chem. Commun.*, 2004, 558-559.
- ²⁴ T. Killberg and B. Långström, "Method and apparatus for production and use of [¹¹C]carbon monoxide in labelling synthesis"; PCT-International patent. Application number: PCT/SE02/01222.
- ²⁵ M. Björkman, Y. Andersson, H. Doi, K. Kato, M. Suzuki, R. Noyori, Y. Watanabe and B. Långström, *Acta Chem. Scandinavica*, 1998, 52, 635-640.
- ²⁶ M. Björkman and B. Långström, *J. Chem. Soc. Perkin Trans. 1*, 2000, 18, 3031-3034.
- ²⁷ Y. Andersson, A. Cheng and B. Långström, *Acta Chem. Scand.*, 1995, 49, 683-688.
- ²⁸ V.P. Baillargeon and J.K. Stille, *J. Am. Chem. Soc.*, 1986, 108, 452-461.
- ²⁹ G.T. Crisp, W.J. Scott and J.K. Stille, *J. Am. Chem. Soc.*, 1984, 106, 7500-7506.
- ³⁰ (a) T. Killberg and B. Långström, *J. Org. Chem.*, 1999, 64, 9201-9205. (b) F. Karimi and B. Långström, *J. Chem. Soc. Perkin Trans. 1*, 2002, 2111-2115. (c) F. Karimi and B. Långström, *Eur. J. Org. Chem.*, 2003, 2132-2137.
- ³¹ O. Rahman, T. Killberg and B. Långström, *J. Org. Chem.*, 2003, 63, 3558-3562.
- ³² F. Karimi and B. Långström, *J. Chem. Soc. Perkin Trans. 1*, 2002, 2256-2259.
- ³³ F. Karimi, T. Killberg and B. Långström, *J. Chem. Soc. Perkin Trans. 1*, 2001, 1528-1531.
- ³⁴ F. Karimi in "¹¹C]Carbon monoxide in Palladium-/selenium-promoted carbonylation reactions", Acta Universitatis Upsaliensis, Uppsala, 2002. ISBN 91-554-5452-6.
- ³⁵ M. Björkman in "Palladium-promoted synthesis of compounds labeled with ¹¹C", Acta Universitatis Upsaliensis, Uppsala, 2000. ISBN 91-554-4797-X.
- ³⁶ Y. Andersson and B. Långström, *J. Chem. Soc. Perkin Trans. 1*, 1995, 287-289.
- ³⁷ S.K. Zeisler, M.W. Nader, A. Thobald and F. Oberdorfer, *Appl. Rad. Isot.*, 1997, 48, 1091-1095.
- ³⁸ O. Itsenko, T. Killberg and B. Långström, *J. Org. Chem.*, 2004, 69, 4356-4360
- ³⁹ O. Itsenko, T. Killberg and B. Långström, *Eur. J. Org. Chem.*, 2005, 70, 2244-2249.
- ⁴⁰ O. Itsenko, T. Killberg and B. Långström, *J. Org. Chem.*, 2005, 70, 3830-3834.
- ⁴¹ J. Eriksson, G. Antoni and B. Långström, *J. Labelled Cpd. Radiopharm.*, 2004, 47, 723-731.
- ⁴² N. Sonoda, T. Yasuhara, K. Kondo, T. Ikeda and S. Tsutsumi, *J. Am. Chem. Soc.*, 1971, 93, 6344.
- ⁴³ T. Killberg, F. Karimi and B. Långström, *J. Org. Chem.*, 2002, 67, 3687-3692.
- ⁴⁴ V. Farina and G.P. Roth, *Advances in Metal-Organic chemistry*, 1996, 5, 1-53.
- ⁴⁵ J.K. Stille, *Angew. Chem. Int. Ed. Engl.*, 1986, 25, 508.
- ⁴⁶ V. Farina, *Pure Appl. Chem.*, 1996, 68, 73-78.
- ⁴⁷ P. Lidström, T. Killberg and B. Långström, *J. Chem. Soc. Perkin Trans. 1*, 1997, 2701-2706.
- ⁴⁸ F. Karimi and B. Långström, *Org. Biomol. Chem.*, 2003, 1, 541-546.

- ⁴⁹ M.H. Al-Qahtani and V.M. Pike, *J. Chem. Soc. Perkin Trans.1*, 2000, 1033-1036.
- ⁵⁰ M.H. Al-Qahtani and V.M. Pike, *J. Labelled Cpd. Radiopharm.*, 2000, 43, 825-835.
- ⁵¹ (a) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, 95, 2457-2483. (b) A. Suzuki, *J. Organomet. Chem.*, 1999, 576, 147-168.
- ⁵² M.W. Nader and F. Oberdorfer, *Appl. Rad. Isot.*, 2002, 57, 681-685.
- ⁵³ (a) O. Rahman, T. Kilhberg and B. Långström, *Eur. J. Org. Chem.*, 2004, 474-478. (b) O. Rahman, J. Llop and B. Långström, *Eur. J. Org. Chem.*, 2004, 2674-2678.
- ⁵⁴ O. Rahman, T. Kilhberg and B. Långström, *Org. Biomol. Chem.*, 2004, 2, 1612-1616.
- ⁵⁵ J.W. Labadie and J.K. Stille, *J. Am. Chem. Soc.*, 1983, 105, 6129-6137.
- ⁵⁶ S. Ozaki, *Chem. Rev.*, 1972, 72(5), 457-496.
- ⁵⁷ M. Torres, A. Clement and O.P. Strauss, *J. Org. Chem.*, 1980, 45, 2273-2274.
- ⁵⁸ H. Ulrich, in *Chemistry and Technology of Isocyanates*, John Wiley & Sons, 1996, ISBN 0-471-96371-2.
- ⁵⁹ H. Ulrich, B. Tucker and A.A.R. Sayigh, *J. Org. Chem.*, 1969, 34, 3200-3201.
- ⁶⁰ Y. Iwakura and K. Uno, *J. Org. Chem.*, 1965, **30**, 1158-1161.
- ⁶¹ (a) W.J. Chambers, C.W. Tullock and D.D. Collmann, *J. Am. Chem. Soc.*, 1962, 84, 2337-2343. (b) J.P. Collmann, M. Kubota, J.Y. Sun and F. Vastine, *J. Am. Chem. Soc.*, 1967, 89, 169-170.
- ⁶² H. Lebel, K. Huard and S. Lectard, *J. Am. Chem. Soc.*, 2005, 127, 14198-14199.
- ⁶³ M.M. Abu-Omar, C.E. Shields, N.E. Edwards and R.E. Eikey, *Angew. Chem. Int. Ed.*, 2005, 6203-6207.
- ⁶⁴ H.M.L. Davies and M.S. Long, *Angew. Chem. Int. Ed.*, 2005, 44, 3518-3520.
- ⁶⁵ J.P. Collman, M. Kubota, F.D. Vastine, J.Y. Sun and J.W. Kang, *J. Am. Chem. Soc.*, 1968, 90(20), 5430-5434.
- ⁶⁶ J.P. Collman, M. Kubota and J.W. Hoskins, *J. Am. Chem. Soc.*, 1967, 89, 4809-4811.
- ⁶⁷ R.P. Bennett and W.B. Hardy, *J. Am. Chem. Soc.*, 1968, 90(12), 3295-3296.
- ⁶⁸ (a) G. La Monica and S. Cenini, *J. Organomet. Chem.*, 1981, 216, C35-C37. (b) G. La Monica, G. Ardizzoia, G. Maddinelli and S. Tollari, 1986, *J. Mol. Catal.*, 1986, 38, 327-330.
- ⁶⁹ S. Sivakamasundari and R. Ganesan, *J. Org. Chem.*, 1984, 49, 720-722.
- ⁷⁰ S. Hasegawa, K. Itoh and Y. Ishii, *Inorg. Chem.*, 1974, 11, 2675-2679.
- ⁷¹ D.J. Mindola and G.L. Hillhouse, 2002, *Chem. Commun.*, 1840-1841.
- ⁷² (a) I.H. Krakoff, H. Savel and M.L. Murphy, *Cancer Chemother. Rep.*, 1964, 40, 53-55. (b) B.L. Sorg, W.E. Hull, H.C. Kliem, W. Mier and M. Wiessler, *Carbohydr. Res.*, 2005, 340, 181-189.
- ⁷³ M.B. Winstead, C.I. Chern, T.H. Lin, A. Khentigan, J.F. Lamb and H.S. Winchell, *Int. J. Appl. Rad. Isot.*, 1978, 29, 443-447.
- ⁷⁴ K.B. Main, T. Medwick, L.C. Bailey and J.H. Shinkai, *Pharm. Res.*, 1987, 4(5), 412-415.
- ⁷⁵ J. Pluscec and Y.C. Yuan, *J. Chrom.*, 1986, 362, 298-302.
- ⁷⁶ M. Dogruel, J.E. Gibbs and S.A Thomas, *J. Neurochem.*, 2003, 87, 76-84.
- ⁷⁷ (a) M.E. Dyen and D. Swern, *Chem. Rev.*, 1967, 67, 197-246. (b) D. Braun and J. Weinert, *Justus Liebigs Ann. Chem.*, 1979, 200.
- ⁷⁸ G.P. Speranza and W.J. Poppel, *J. Org. Chem.*, 1958, 23, 1922-1924.

- ⁷⁹ (a) A. Baba, I. Shibata, K. Matsuda and H. Matsuda, *Synlett*, 1985, 1144-1146. (b) A. Baba, M. Fujiwara and H. Matsuda, *Tet. Lett.*, 1986, 27(1), 77-80. (c) I. Shibata, A. Baba, H. Iwasaki and H. Matsuda, *J. Org. Chem.*, 51, 2177-2184.
- ⁸⁰ J.E. Herweh, T.A. Foglia and D. Swern, *J. Org. Chem.*, 1968, 33, 4029-4033.
- ⁸¹ K.S. Keshava Murthy and D.N. Dhar, *J. Heterocycl. Chem.*, 1984, 21, 1721-1725.
- ⁸² (a) H. Staudinger, *Ber.*, 1905, 38, 1735-1739. (b) H. Staudinger, *J. Liebigs Ann. Chem.*, 1907, 356, 51-123.
- ⁸³ T.T. Tidwell in *Ketenes*, John Wiley & Sons, 1996, ISBN 0-471-69282-4.
- ⁸⁴ R.D. Carroll and L.L. Reed, *Tetrahedron Lett.*, 1975, 16(40), 3435-3438.
- ⁸⁵ S. Ranganathan, D. Ranganathan and A.K. Merhotra, *J. Am. Chem. Soc.*, 1974, 96(16), 5261-5262.
- ⁸⁶ (a) R.L. Danheiser, D.S. Casebier and J.L. Loebach, *Tetrahedron Lett.*, 1992, 33(9), 1149-1152. (b) R.L. Danheiser and D.D. Cha, *Tetrahedron Lett.*, 1990, 31(11), 1527-1530.
- ⁸⁷ (a) W.A. Hermann, *Angew. Chem. Int. Ed. Engl.*, 1978, 17, 800-812. (b) W.R. Roper, *J. Organomet. Chem.*, 1986, 300, 167-190. (c) R. Cohen, B. Rybtchinski, M. Gandelman, H. Rozenberg, J.M.L. Martin and D. Milstein, *J. Am. Chem. Soc.*, 2003, **125**, 6532-6546.
- ⁸⁸ (a) M.P. Doyle, R.L. Dorow, W.E. Buhro, J.H. Griffin, W.H. Tamblyn and M.L. Trudell, *Organometallics*, 1984, 3, 44-52. (b) M.P. Doyle, J.H. Griffin, V. Bagheri and R.L. Dorow, *Organometallics*, 1984, 3, 53-61.
- ⁸⁹ H.M. Davies and E.G. Antoulinakis, *J. Organomet. Chem.*, 2001, 47, 617-618.
- ⁹⁰ (a) A. Padwa, D.J. Austin, A.T. Price, M.A. Semones, M.P. Doyle, M.N. Protopova, W.R. Winchester and A. Tran, *J. Am. Chem. Soc.*, 1993, **115**, 8669-8680. (b) Z. Qu, W. Shi and J. Wang, *J. Org. Chem.*, 2001, 66, 8139-8144.
- ⁹¹ H. Werner, *J. Organomet. Chem.*, 1995, 500, 331-336.
- ⁹² C Rüchardt and G.N. Schrauzer, *Chem. Ber.*, 1960, 93, 1840-1851.
- ⁹³ E. Deydier, M.J. Menu, M. Dartiguenave and Y. Dartiguenave, *J. Organomet. Chem.*, 1993, 458, 225-228.
- ⁹⁴ As an example in *Organic Syntheses Collective Volumes*, John Wiley & Sons, 1976: I, 245, 250, 267, 272, 290.
- ⁹⁵ T. Gee and B. Långström, *Appl. Rad. Isot.*, 1991, 42, 1195-1198.
- ⁹⁶ J.D. Roberts, C.M. Regan and I. Allen, *J. Am. Chem. Soc.*, 1952, 74, 3679-3683.
- ⁹⁷ L.S. Hegedus, G. de Weck and S. D'Andrea, *J. Am. Chem. Soc.*, 1988, 110, 2122-2126.
- ⁹⁸ G.L. Geoffroy and S.L. Bassner, *Adv. Organomet. Chem.*, 1988, 28, 1-76.
- ⁹⁹ L.S. Hegedus, *Tetrahedron*, 1997, 12, 4105-4128.
- ¹⁰⁰ J.H. Clark and J.M. Miller, *J. Chem. Soc. Perkin Trans. 1* 1977, 7, 1743-1745.

Acta Universitatis Upsaliensis

*Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Science and Technology 156*

Editor: The Dean of the Faculty of Science and Technology

A doctoral dissertation from the Faculty of Science and Technology, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-6654



ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2006