Functionalization of adamantane and other bridged cycloalkanes

Charles University in Prague

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Habilitation Thesis

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This habilitation thesis is a collection of published work related to the presented topic, supplemented by original comments.

In Prague, 22. 2. 2021 Radim Hrdina

Content

Summary

My habilitation thesis summarizes the results in the field of functionalization of the adamantane framework present in tricyclo [3.3.1.1^{3,7}] decane and other diamondoids. Developed procedures to create 1,2-substitution pattern on this class of compounds were applicable in some cases also on other bridged cycloalkanes. Designed disubstituted derivatives were used as building blocks for the construction of bifunctional compounds used in regioselective catalysis.

The first goal of the work was to prepare disubstituted compounds from mono-substituted starting materials (with substituent at bridgehead position), which lack the reactivity of C=C double bond. This part of the work is separated into two main streams. Directed functionalization of cycloalkanes *via* intramolecular insertion of nitrenes (electrophilic organic species) and directed catalytic C–H functionalization reactions with palladium C–H activation as the intermediate catalytic step.

The second objective was the application of disubstituted compounds in the development of new catalysts. A new route to rhodium(II) complexes was developed, allowing the preparation of a wide variety of multifunctional catalysts.

Abstrakt

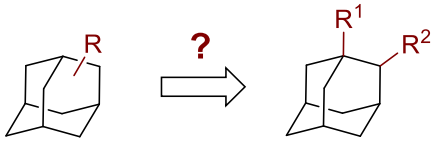
Moje habilitační práce shrnuje výsledky v oblasti funkcionalizace adamantanového skeletu přítomného v tricyklo [3.3.1.1^{3,7}] dekanu a dalších diamantoidech. Vypracované postupy ku 1,2-disubstituovaným derivátům byly v některých případech použitelné i na jiné přemostěné cykloalkany. Navržené disubstituované deriváty byly použity jako stavební bloky pro konstrukci bifunkčních sloučenin používaných jako katalyzátorů v regioselektivních organických reakcích.

Hlavním cílem práce bylo připravit disubstituované sloučeniny z monosubstituovaných výchozích látek (se substituentem na můstkovém atomu), které postrádají reaktivitu dvojné C=C vazby. Tato část práce je rozdělena do dvou hlavních proudů. Řízená funkcionalizace cykloalkanů prostřednictvím intramolekulární inzerce nitrenů (elektrofilní organické species) a palladiem katalyzované C–H aktivace.

Dalším cílem byla aplikace disubstituovaných sloučenin při vývoji nových katalyzátorů. Byl vyvinut nový způsob přípravy komplexů rhodia(II), který umožňuje syntézu široké škály multifunkčních katalyzátorů.

1. Introduction

1.1 Functionalization of alkanes



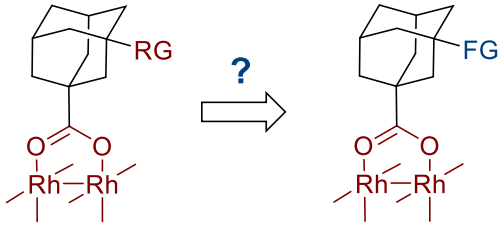
The earth provides us the feedstock of pure alkanes in such a large quantity that man uses it for uncontrolled oxidation with atmospheric oxygen to get the thermal energy. The chemist´s wish is to keep the part of this still immense supply to use it as a starting material for controlled oxidation reactions, for the preparation of simple building blocks, which can be used further in the synthesis of complex functional molecules.

The taming of oxidation reactions still remains a challenge for the chemical community. In the case of C–H bond oxidation the reason is the small difference in reactivity of present, chemically similar, C–H bonds and the fact that the first reaction (in some cases) can activate the molecule for the subsequent reaction event.

In the case of bridged cycloalkanes, which do not possess the reactivity of the C=C double bond (or the corresponding alkene is not stable enough for further derivatisation) one of the big challenges is to reach 1,2-substitution pattern from mono-substituted compounds. Theoretically there are four options to reach this goal using one of the electrophilic reactions. Intramolecular hydrogen abstraction reactions, insertion reactions of electron deficient organic species, carbometalation reactions and formal hydride transfer reactions. In the case of intramolecular insertion reactions and hydride transfer reactions, by definition, it is easy to control the number of reaction steps. In the case of hydrogen abstraction reactions and carbometalations the multiple reactivity might be difficult to control.

The properties of mono-substituted adamantane molecule, especially the symmetry, enables to take this compound as a model and to study (“easy” analysis of the reaction mixture) the directed and undirected oxidation processes from both aspects, regioselectivity and number of oxidation steps. An extended *introduction* is provided in my short review on the directed C–H bond functionalization of the adamantane skeleton (enclosed publication 1).

1.2 Postfunctionalization of dirhodium(II,II) carboxylates



The search for optimal catalysts relies on the subtle variation of a substitution pattern of the lead structure in positions responsible for the interaction with substrates. Late stage functionalization of ligands or directly metal complexes represents attractive strategy for fast approach to a broad variety of active compounds, which can be screened in selected organic reactions as catalysts, to improve the product yield, enantiopurity and efficiency of the catalytic reaction.

Catalytically active transition metal complexes are typically produced in two steps, with the synthesis of a ligand from commercially available starting materials and the complexation reaction with a metal containing precursor. The structural variability of the catalyst depends on the modularity of the key reaction. The later this reaction takes place in a multi-step catalyst synthesis, the less effort and energy has to be invested. In the case of metal complexes, post-functionalization enables the implementation of functionalities, which would not be possible to incorporate by other means (the functional group is not tolerated during the ligand synthesis or during the complexation reaction).

Dirhodium(II,II) complexes found a number of applications in catalysis, especially as nitrenoid or carbenoid transfer catalysts for insertion reactions. Typically, these compounds are prepared by thermal anion exchange between the rhodium acetate and designed carboxylic acid in the last step of their synthesis. This method does not tolerate variety of acid (Lewis or Brønsted) sensitive functional groups. Attractive approach is the design and synthesis of suitable organic spacer for the preparation of bench stable precursor with the defined geometry, which will be easy to post-functionalize by uncatalyzed “click” reaction or by reaction, whose reaction conditions do not change the structure of the starting material. Just few examples, including the work of my group, appear in the literature and are mentioned in my review on this topic, which extends this *introductory* part (enclosed publication 2).

2. Summary of results

2.1 Functionalization of adamantane and its derivatives

My habilitation thesis is focused on the development of synthetic methods, which enable preparation of complex organic molecules with the adamantane framework.[1] The selected approach to the new class of compounds is based on the subsequent directed functionalization of C–H bonds[2] of this tricyclic structure and is so far limited to 1,2-substitution pattern with an outlook to continue to more complicated structures (Figure 1). Compounds generated using this procedure contain functional groups in positions, where previous methods failed, or these compounds were prepared in many steps.

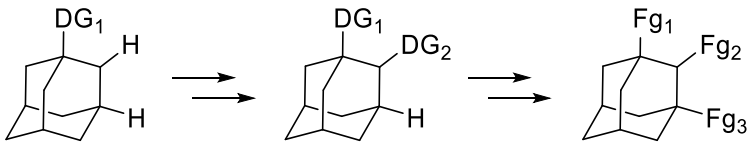


Figure 1. Subsequent (walking) functionalization of the adamantane framework

This approach opens venue to new class of compounds and expands the scope for applications as building blocks in the synthesis of bioactive compounds,[3] ligands and organocatalysts (Figure 2).[4]

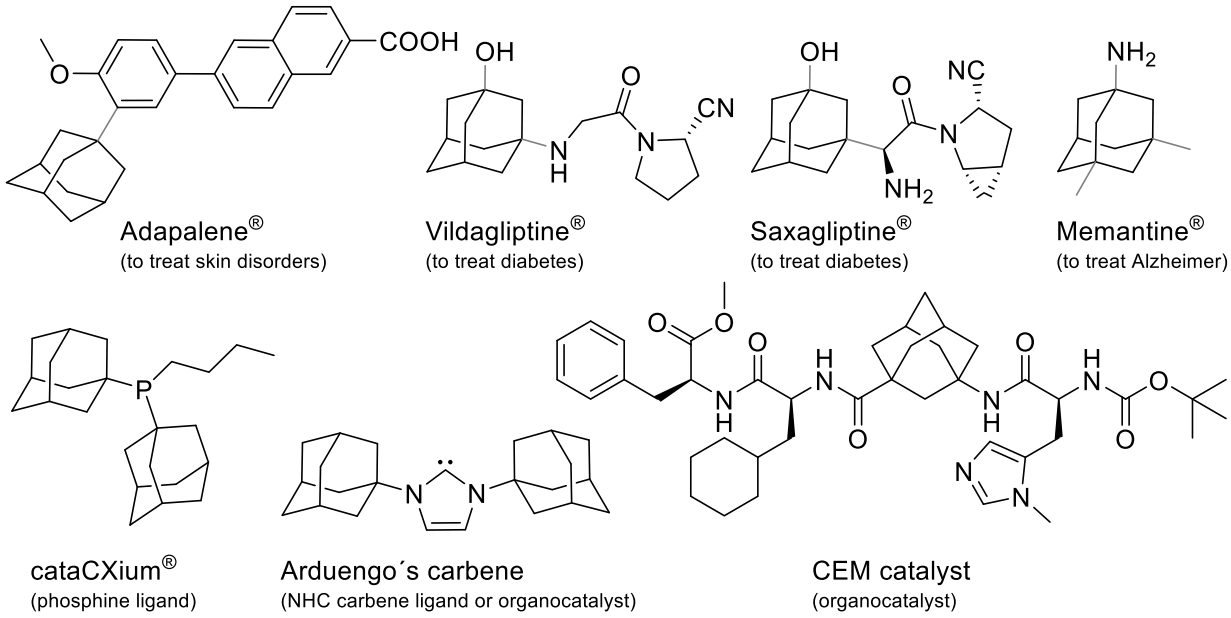


Figure 2. Adamantane based drugs, ligands and organocatalysts. Substitution pattern at positions 1,3 and 5 is a result of undirected oxidation of the adamantane molecule

It is already 88 years when the adamantane was isolated from the crude oil of Hodonín by the group of Landa.[5] Thanks to the unique structure and properties, which are discussed in detail, this molecule has permanent attention of a broad chemical community. Adamantane itself was first synthesized in 1941 in the group of V. Prelog from acyclic compounds in overall 0.16 % yield.[6] This was enough to compare the physical properties of the substance with the isolated one and thus to confirm the structure. First synthetically useful preparation was introduced in 1956 by Schleyer and Donaldson based on the hydrogenation of cyclopentadiene dimer and subsequent Lewis acid catalyzed isomerization.[7] Since that time is adamantane prepared on industrial scale as one of the basic cycloalkanes and serves as a precursor for number of derivatives.[8] Compounds with repetitive adamantane framework are called diamondoids and are extracted from crude oil as well (Figure 3).[9] Only molecule of diamantane was made synthetically from this class of compounds, the others as triamantane, tetramantane and higher diamondoids are separated from oil by column chromatography.[10] Three main features characterize diamondoids. First is their thermodynamic stability, second is the conformational rigidity, which allows to design molecules with local defined shape and third is their lipophilicity, which substantially increases solubility of these compounds in organic solvents or induce lipophilic domains, when incorporated in complex molecules as for example peptides.[11] Strength of dispersion forces grows with number of adamantane subunits in higher diamondoids as well as the size. [12] Size may play a role in host guest interactions not just through the week forces, but also entropically, by replacing the small molecules in enzymatic cavities, *e.g.* water from the original system.[13]

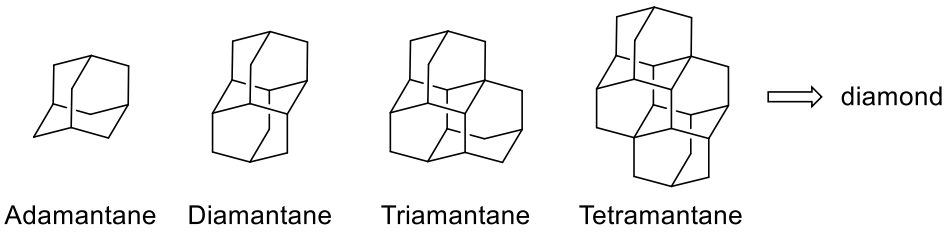
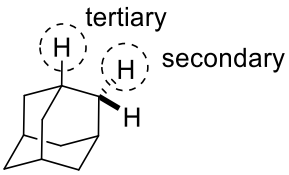


Figure 3. Selected examples of diamondoids

The structure of adamantane (Figure 4), where tertiary carbon atoms are repetitively bonded with secondary ones in the tricyclic system, defines its reactivity, and is a typical example for description of Bredt rule.[14] Monosubstituted derivatives are prepared by the direct oxidation of adamantane.[15] First functionalization reaction usually proceeds at more reactive tertiary position depending on the oxidant.[16]



C−H Dissociation energies
tertiary C−H 96 kcal/mol
secondary C−H 98 kcal/mol

For comparison:
Methane C−H 105 kcal/mol
Toluene (benzylic C−H) 90 kcal/mol
Isobutane (tertiary C−H) 96 kcal/mol

Figure 4. Oxidation of the adamantane molecule typically occurs at the tertiary C–H bond

The most common reaction is the introduction of the hydroxy group,[17] amination reactions[18] or halogenation of the framework.[19] Elimination reactions are not feasible, as double bond cannot be formed on this bridgehead system using this pathway (Bredt rule). Unstable adamantene (containing formal C=C double bond) is possible to prepare as was demonstrated on 1,2-dihalogenated precursor, but its reactivity is close to the biradical system and undergoes dimerization.[20] Secondary functionalization relies again on the oxidation reactions. These proceed again at more reactive tertiary positions and produce 1,3-disubstituted compounds. Undirected oxidations of adamantane derivatives substituted on secondary carbons are used just rarely,[21] as number of possible stereoisomers may be formed (Figure 5) or are the oxidation takes place on the same atom as the substituent.

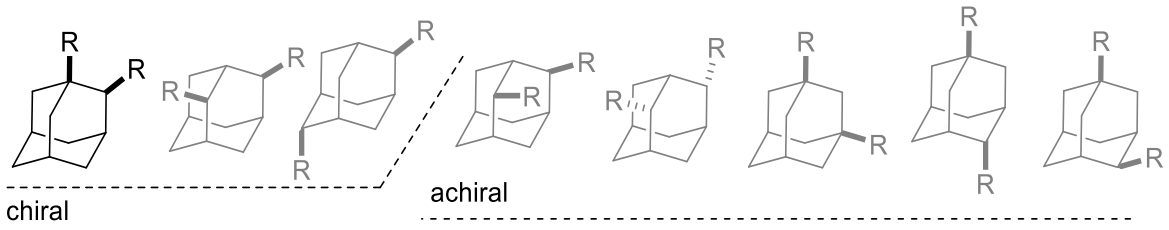


Figure 5. All possible stereoisomers of adamantane with two substituents

Traditional approach to the substituted derivatives is based on the building up the tricyclic structure *de novo* and subsequent modification of the functional groups. This strategy is often used in the case of total synthesis of natural products, as executed on plukenetione A, when number of synthetic steps does not play a main role.[22] Historically, Böttger's group was the first who synthesized poly-substituted compound with adamantane skeleton (Figure 6).[23] Pyrrolidine catalyzed condensation of malonic ester with formaldehyde produces bicyclic structure, so called Meerwein´s ester, which was by double nucleophilic substitution converted to the poly-substituted adamantane derivative. Lately was this protocol used to prepare the pure adamantane,[6] as the functional groups were reduced using at that time developed methods *i.e.* Wolff-Kishner reduction[24] and Hunsdiecker decarboxylation.[25]

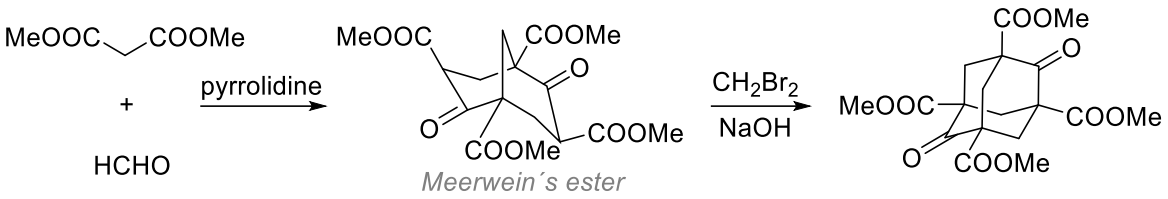


Figure 6. Synthesis of adamantane framework from acyclic compounds

Up to date when we entered the field the most frequent pathway to 1,2-disubstituted adamantane derivatives proceeded through the adamantane cage opening step (Figure 7).[26] As an example, preparation of 2-oxo-adamantane-1-carboxylic acid is shown. Adamantan-1-ol is in the first step oxidized to protoadamantanone, subsequently converted to an epoxide by Corey-Chaykovsky reaction and in the last sequence of reaction steps promoted by Jones reagent (intramolecular rearrangement with subsequent addition of a water, followed by oxidation of both hydroxy groups to 2-oxo carboxylic acid) transformed into 1,2-substituted adamantane.[27] This approach is limited to the synthesis of adamantane derivatives and was not applied or is not applicable on higher diamondoids and noradamantane (adamantane without one methylene unit) derivatives.

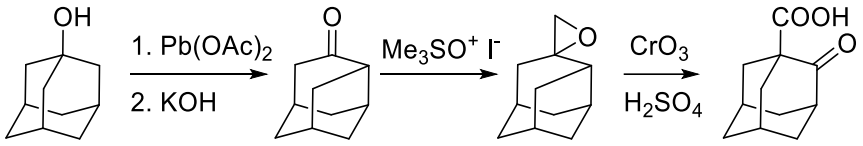


Figure 7. Selected example of adamantane derivatisation via protoadamantanone

Modular approaches either based on: 1. intramolecular insertion reactions of electron-deficient species;[28] 2. transition metal catalyzed C–H activations;[29] 3. hydrogen radical abstraction reactions[30] or 4. hydride shift reactions[31] were rather undeveloped (Figure 8). The protocols were product oriented and lacked the substrate scope.

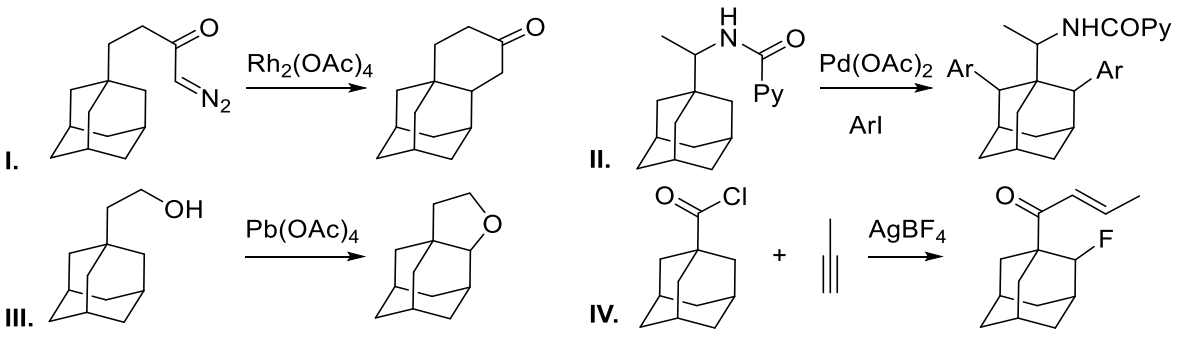


Figure 8. Selected examples of 1,2-functionalization of the adamantane scaffold

2.2 Intramolecular insertion reactions of metal-nitrenoids on adamantane derivatives

The first contribution of my group (enclosed publication 3) to the field of adamantane derivatisation was the development of a new approach to 1,2-disubstituted diamondoids based on intramolecular nitrenoid insertion reaction[32] of sulfonamide derivatives catalyzed by rhodium acetate (Figure 9). Especially we were interested in the synthesis of 2-amino-adamantane-1-carboxylic acid. We envisioned that the approach *via* cyclic sulfonamides has potential to be modular and scalable. The insertion protocol was introduced by Du Bois group on simple alkanes[33] and we were curious, if this method is applicable for such rigid compounds as adamantane derivatives. Next question was, if we find a method, how to deprotect stable sulfonamide group on such neopentylic system.

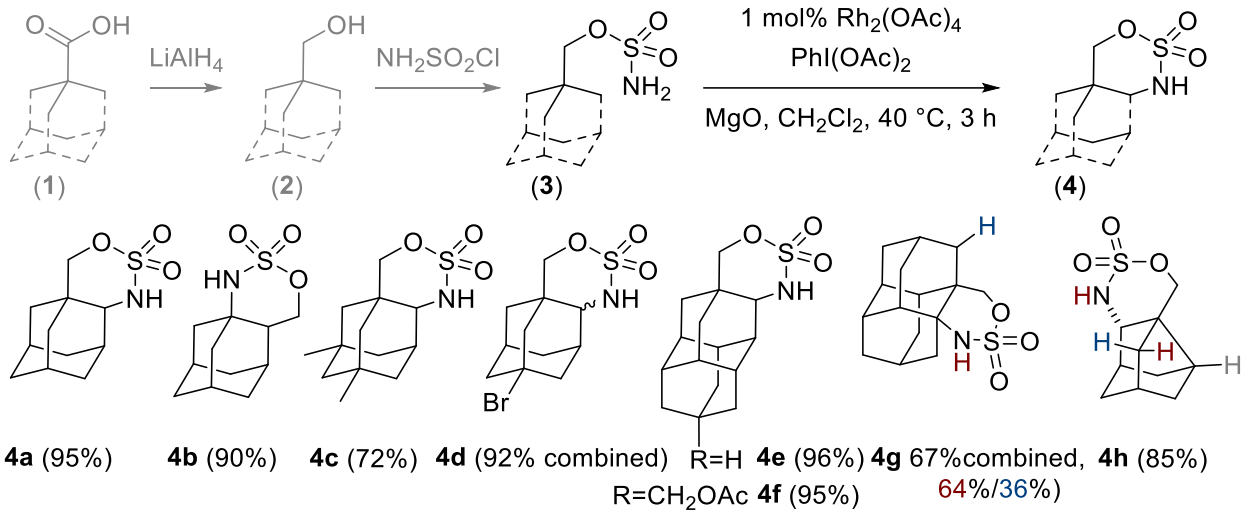


Figure 9. Rhodium acetate catalyzed insertion reaction of nitrenes derived from sulfonamides and scope of the reaction (yield of the isolated product in parentheses)

Readily available carboxylic acids served as a starting material for the three-step synthesis of cyclic sulfamidates. In the first step, starting material a carboxylic acid or an ester of this carboxylic acid was reduced using $LiAlH_4$ to corresponding alcohol. In the next step sulfonamide moiety was introduced using one-pot two-step procedure. The reactive chlorosulfonamide was generated *in situ* by mixing formic acid with chlorosulfonyl isocyanate. The amide formation reaction with alcohol was performed in pyridine as a solvent. The key reaction, intramolecular insertion reaction, was performed in dichloromethane as a solvent, with phenyl iodoacetate as an oxidant in the presence of MgO, which served as a base to trap releasing acetic acid.

The insertion reaction was catalyzed by rhodium acetate, which is typically used for this class of reactions. The generality of the protocol was demonstrated on the preparation of 8 structurally different substrates. Insertion reactions proceeded with excellent selectivity, according to the electronic effects of the substituents, with low loading of the transition metal catalyst (1 mol %) with good to excellent yields. Surprising regioselectivity was achieved with substrate **3c**, compound **4c** was isolated as a single regioisomer. This is explained that both methyl groups due to hyperconjugation have positive effect on stabilization of a partial positive charge created during the course of the insertion reaction of the electrophilic species in the C–H bond. Diamantane derivative **3g** with inserting group located on the so-called belt of the diamantane cage gave mixture of two regioisomers with preference for more electron rich tertiary C–H bond. Compound **4g** was isolated as a major isomer. Another remarkable selectivity was observed with noradamantane derived substrate **3h.** In this case just one isomer **4h** was isolated as well. Taking in account that three different C–H bonds are neighboring with inserting group this reaction is very sensitive to electronic and steric effects. In this case the tertiary C–H bond (in grey) on the strained noradamantane bridge has higher dissociation energy than the secondary C–H bond. Because of the geometry of the methylene sulfonamide unit on the noradamantane cage one set of the CH_2 hydrogens (in red) are geometrically more accessible than the hydrogens directing inwards the cage (in blue). Structure of **4h** was confirmed by X-ray crystallography. High crystallinity of these compounds in diethylether or ethylacetate facilitated the sample preparation for their röntgenographic analysis.

Compound **4a** was then prepared on gram scale to start experiments with the cleavage of the sulfonamide group. Typically, is this group removed using basic or acidic conditions with the first cleavage occurring on the C–O bond.[34] In case of compound **4a** this position is neopentylic, which sterically hinders the attack of the nucleophile at that position, in case of acidic conditions the resulting carbocation would be unstable primary. In both of these cases we failed to find out conditions, which would lead to the isolation of desired amino alcohol. Under basic conditions or with various nucleophiles the starting material was obtained or under harder conditions complex mixture of products as a result of subsequent condensation reactions. Under acidic conditions we were able to observe formation 1-bromo-2-amino adamantane as a result of heating of the starting material in the concentrated hydrobromic acid under microwave irradiation at 140 °C. Clearly these attempts did not lead to desired results,

that is why we turned our effort to cleave this group reductively or oxidatively (Figure 10).

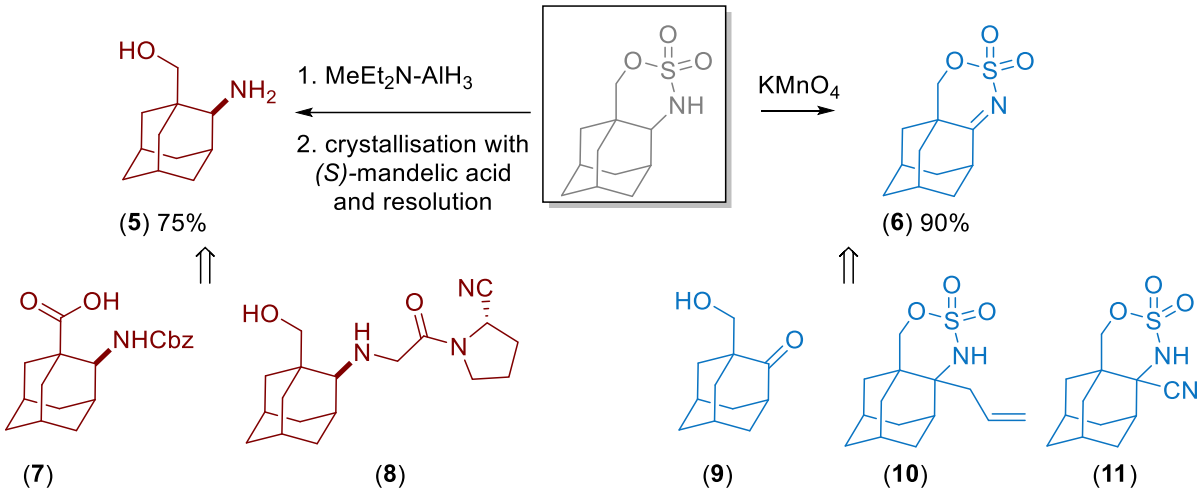


Figure 10. Reductive and oxidative cleavage of the sulfonamide group and further derivatisation

First, we have developed oxidation of the sulfonamide group to sulfonimide using potassium permanganate under basic conditions. It is important to note that amides derived from carboxylic acids do not undergo such oxidation. The imide **6** was isolated in excellent 90% yield and served later as starting material for hydrolysis to compound **9** or for addition of nucleophile to compounds **10** and **11**. Then we followed literature protocol to reduce this protecting group using alane tertiary amine complex[35] and applied it on the compound **4a**. The cleavage proceeded well and the desired racemic amino alcohol **5** was isolated in good 75% yield. Out of the whole study in this chapter this part of the research concerning the deprotection was the most time consuming. Racemic compound **5** was resolved on enantiomers using co-crystallisation with enantiopure mandelic acid. Individual enantiomers were then used to prepare target compound amino acid **7.**

To demonstrate the synthetic utility of our new protocol two bio-isosters **8** of commercial DPP-4 inhibitor[36] Vildagliptin® were prepared in just 5 steps from adamantane-1-carboxylic acid. Both diastereomers **8** were tested *in vitro* on corresponding essay and displayed similar activity to original Vildagliptin.[37]

Intramolecular insertion reactions towards cyclic carbamates and their decarboxylation using triflic acid in the presence of a nucleophile and in the absence of a nucleophile

While sulfonamides provide access to six membered heterocycles, nitrenes derived from carbamates insert in the C–H bond to form five membered cycles.[38] This gave us opportunity to use hydroxy adamantane derivatives as starting material and use these cyclic carbamates **13** first as a precursor for 1,2-amino alcohols and later for other transformations involving decarboxylation of this moiety (enclosed publication 4). Compounds **12** were prepared from corresponding alcohols using protocol developed by Kočovský[39] *i.e.* trichloroisocyanate was used as the starting material to add on the hydroxy group and in the second step basic hydrolysis provided acyclic carbamates **12**. Insertion reaction was catalyzed by rhodium acetate and the protocol was optimized to use the catalyst loading between 0.5% – 1%. Solvent of choice was 1,2-dicholorethane, phenyl iodoacetate as an oxidant and MgO as a base to neutralize releasing acetic acid in the formation of imido-iodinane reaction intermediate. Cyclic carbamates **13** were obtained in good yields, typically without any side products, and after the reaction were separated from the starting material (Figure 11). Compound **13b** was obtained in low 49% yield, the reason is the formation of a side product adamantane-2-one as a result of insertion of the nitrene in the C–H bond in position 2.

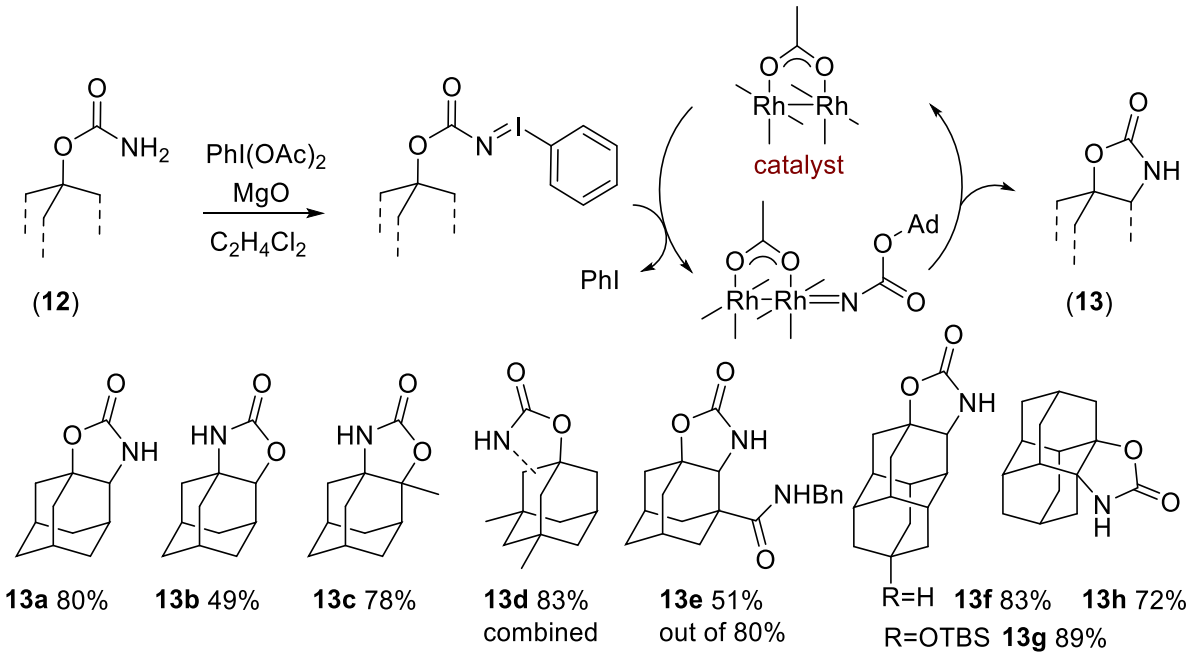


Figure 11. Insertion reactions of nitrenes derived from carbamates; progress of the reaction and scope

The regioselectivity of the insertion reaction is different as compared to the insertion of nitrenes derived from sulfonamides. Product **13d** was obtained as a mixture of three isomers, which were not separable by column chromatography. On the other hand compound **13h** was obtained as a single isomer formed in the reaction. Insertion in the secondary CH_2 group was not observed. Interesting result was obtained with **12e** as a starting material. Compound **13e** was obtained as a major product even if carboxylic acid derivatives evince negative inductive effect and reduce electron density of the neighboring C–H bond. This result indicates that amide group in position 3 has a directing effect on the insertion process. We plan to pursue the research in this direction in future. The compound **13a** was prepared on multigram scale and used for further transformations.

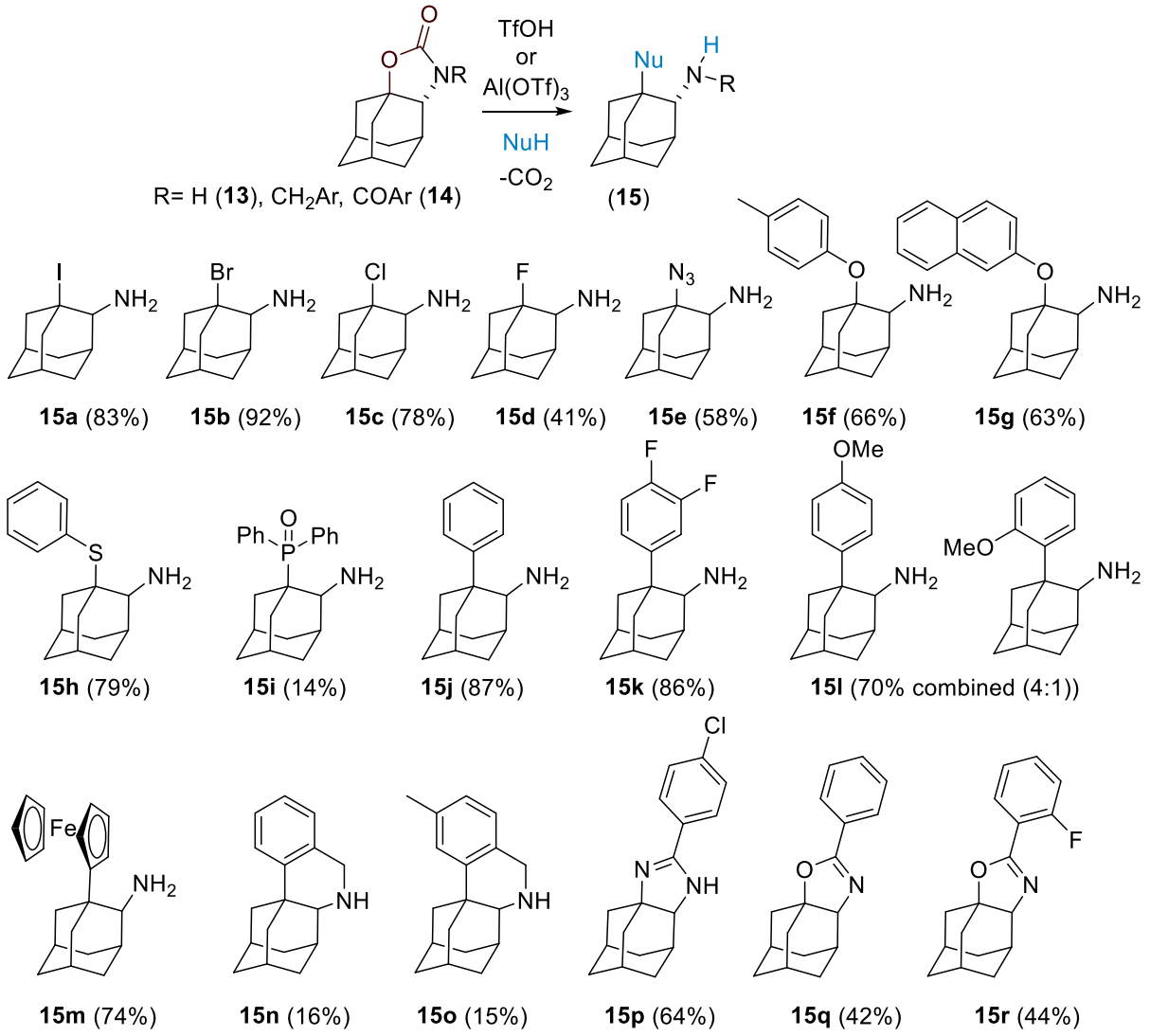


Figure 12. Decarboxylation of cyclic carbamates with triflic acid or aluminium triflate in the presence of a nucleophile

Basic hydrolysis of **13a** leads to the formation of 1-hydroxy-2-amino-adamantane and this compound served as a starting material for the research in the field of organocatalysts preparations. Acidic hydrolysis led to the formation of interesting side products, so we decided to study and optimize this new reaction channel. The plan was to decarboxylate the carbamate moiety on this starting material in the presence of nucleophile, having in mind that tertiary carbocations on adamantane framework are relatively stable and intramolecular aziridine formation is geometrically hindered (Figure 12). Usage of more than 1 equivalent of triflic acid (resulting amine is protonated and corresponding salt formed) catalyzed the decarboxylation of **13a** in the presence of various nucleophiles. The solvent of choice for low temperature transformations is dichloromethane, for higher temperatures 1,2,4-trichlorobenzene is used. These solvents are stable under acidic conditions and do not react with the starting material. In some cases the reactant was used as solvent, for example benzene for corresponding Friedel-Crafts reaction.[40] In some cases triflic acid was replaced by $Al(OTf)_3$ to slow down the decomposition of the starting material, such as ferrocene. Overall 18 compounds were prepared in relatively good yield. For compounds **15n** and **15o** the yield was unsatisfactory and we developed different approach to this class of compounds (see Figure 16 in following section).

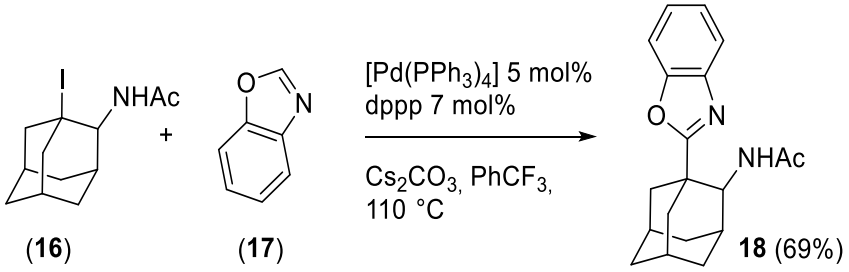


*Figure 13. Coupling reaction of N-protected compound **16** with 1,3-benzoxazol **17***

Compound **15a** was protected on nitrogen and used as a starting material for C–C coupling reactions (Figure 13). This is still ongoing project as many reactions failed. Reaction described in figure 13 is the first success in this area. It is coupling reaction catalyzed by Pd(0) with 1,3-benzoxazole as a coupling partner. The original protocol was developed in Hierso group[41] and was applicable on our starting material as well.

To get approach to enantiopure products we have separated compound **13a** using chiral auxiliary according to Evan's method (Figure 14).[42] Both enantiomers of **13a** were prepared and their enantiopurity controlled using HPLC with chiral stationary column. To our big surprise the developed decarboxylation reaction undergoes racemization. In some cases, just partial racemization ocurred as in the case of compound **15j**, which was prepared in 86% *ee* purity.

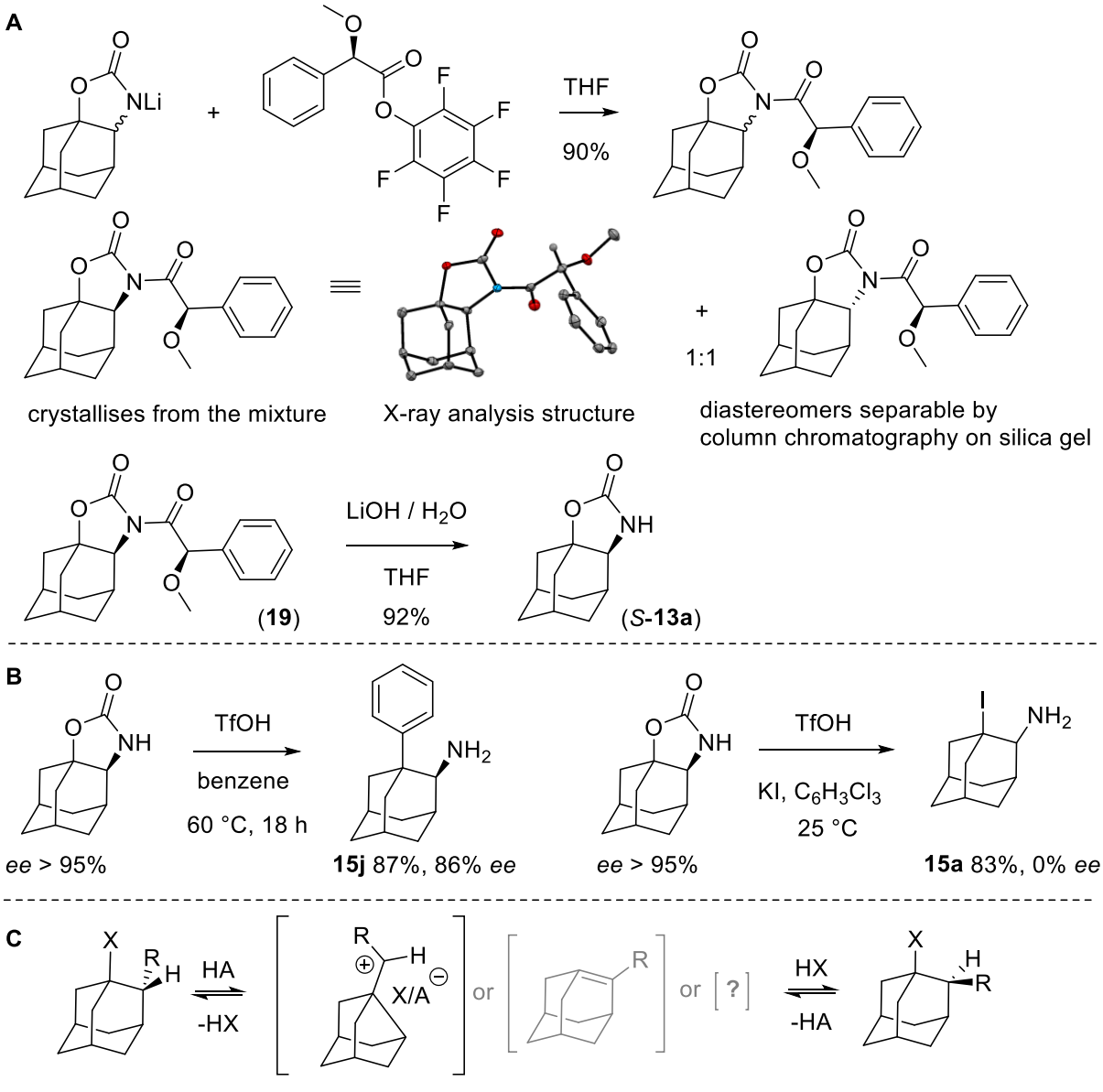


Figure 14. ***A****: Resolution of the racemic compound* ***13a*** *into individual enantiomers;* ***B****: racemization event during the course of triflic acid catalyzed decarboxylation reaction in the presence of a nucleophile;* ***C****: Nature of the racemization event*

In some cases, the racemization was complete as for the compound **15a**. At this stage we can just speculate about the nature of the racemization process (Figure 14). Two options are discussed, either the racemization process is a result of C–C bond cleavage related to 1,2-alkyl shift or other process as C–N bond cleavage (carbocation formation) or “double bond” formation is involved. The C–C bond cleavage was studied separately for synthetic purposes. Even if we now know the thermodynamic profile of the intermediates in the rearrangement reaction we cannot relate it to the racemization process as the other reaction pathways were not studied in detail. The decarboxylation reaction of **13a** using triflic acid in the absence of a nucleophile in 1,2,4-trichlorobenzene as a solvent was producing complex mixture of products. Detailed analysis of the fate of the adamantane framework revealed that ring-contraction reaction occurred to form compounds with noradamantane scaffold. To suppress subsequent side reactions (condensation reactions of the product) we have decided to protect the nitrogen with an alkyl and test the reaction with this starting material **20**. We have observed formation of the methyl iminium salt, which did not undergo further transformations of the iminium unit. This compound was hydrolysed under basic conditions in the next step to the noradamantane carbaldehyde (Figure 15). This result motivated us to optimize the reaction conditions and to test other substrates **20** in the reaction. Desired compounds **21** were obtained in relatively good yield and thus we can call this reaction as a new pathway to noradamantane derivatives, carbaldehydes or ketones. New cages as well as classical one’s as protoadamantanone[43] **21e** can be made using this method. Further ring contraction using substrate **20g** as a starting material is not possible under these conditions. The starting material was recovered indicating that the stability of the cation at the bridgehead position[44] is crucial for this type of transformation.

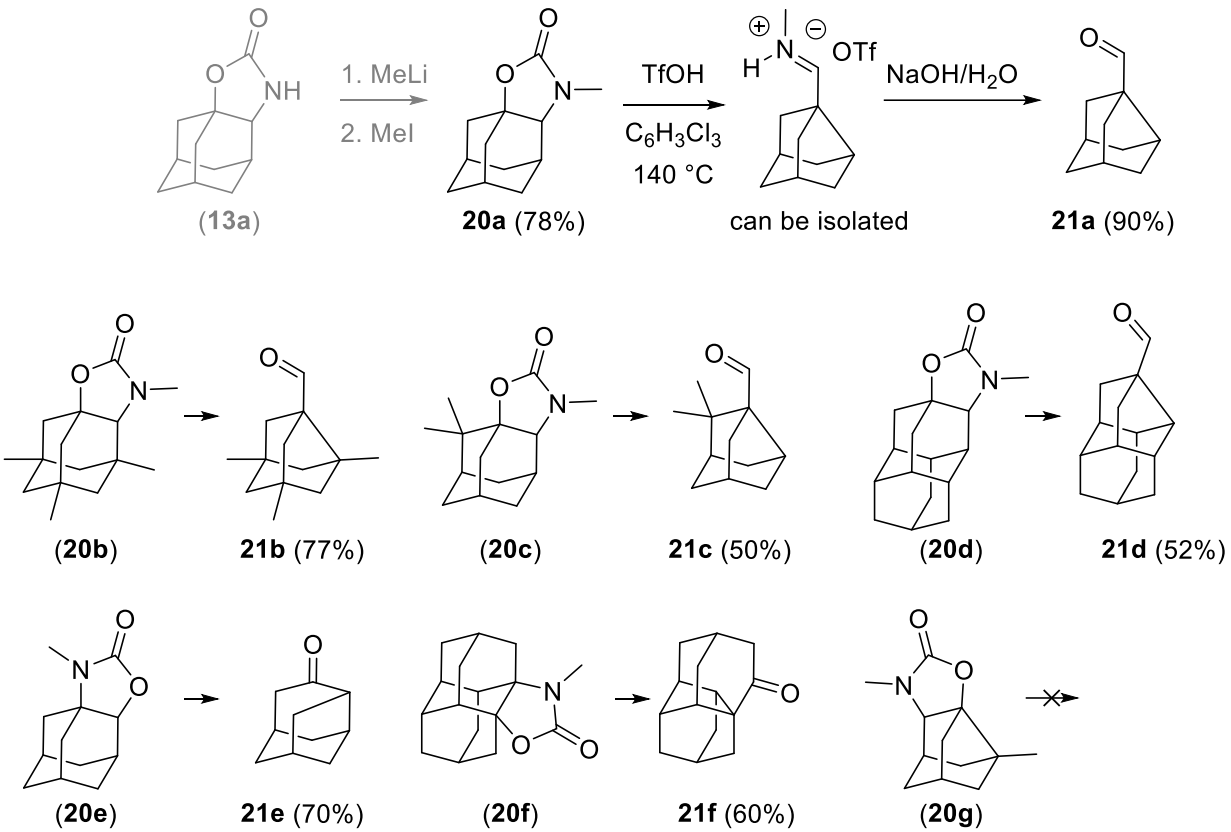


*Figure 15. Decarboxylation of N-Me carbamates **20** using triflic acid in absence of the nucleophile leads to the formation of noradamantane derivatives **21***

Synthesis of heterocycles with annulated adamantane skeleton

The experience gained in the decarboxylation study led us to the question, if it is possible to start the reaction from the plausible intermediate, *i.e.* to prepare noradamantane carbiminium salt and subject it to the reaction conditions (enclosed publication 5). Simple condensation reaction of noradamantane carbaldehyde with a benzyl amine or aniline or aryl ethyl amine provides corresponding imine, which can be in the next step isolated and protonated with a triflic acid. This is starting material for cascade reaction composed of nucleophilic 1,2-alkyl shift and subsequent Friedel-Crafts reaction. Initial experiments were positive, which motivated us to optimize the reaction protocol and study the reaction mechanism.

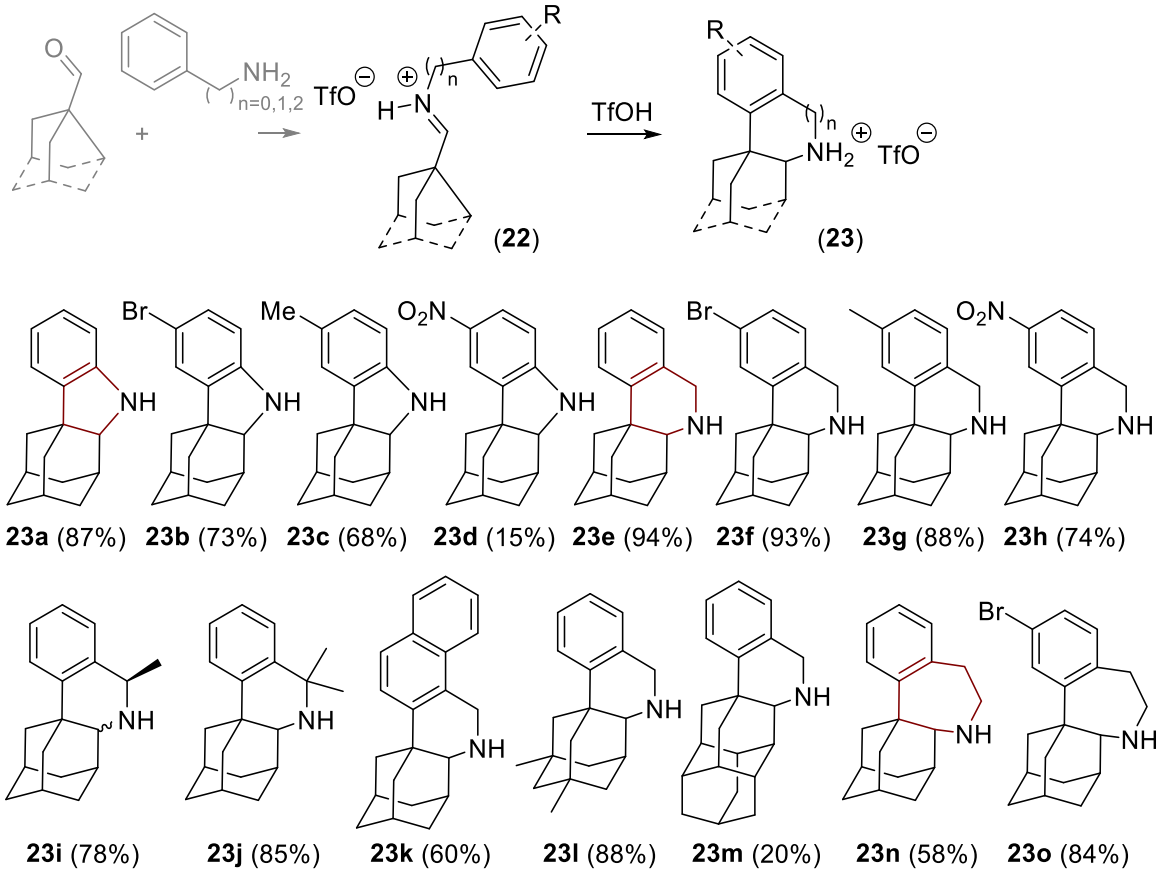


Figure 16. Scope of the cascade reaction composed of 1,2-alkyl shift, followed by intramolecular Friedel-Crafts reaction

The cascade reaction is possible to make intramolecularly to form five-, six-, and seven-membered heterocycles (Figure 16). The attempts to prepare eight-membered ring were not successful, the reaction with phenyl propylamine derivative provided complex mixtures as a result of presumably intermolecular reactions.

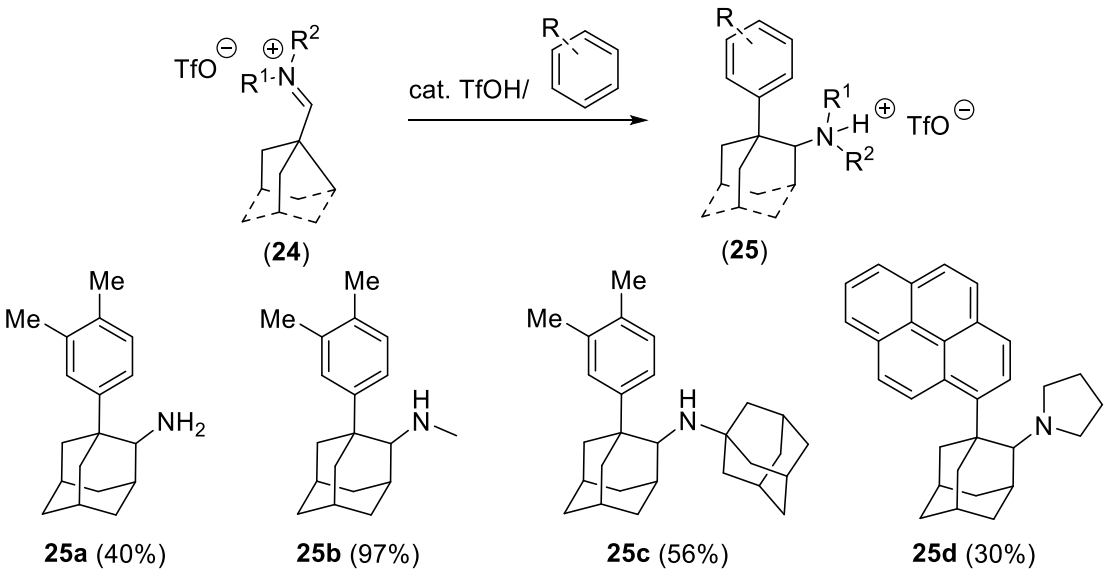


Figure 17. Scope of the cascade reaction composed of 1,2-alkyl shift, followed by extramolecular Friedel-Crafts reaction

The cascade reaction is possible to perform also extramolecularly (Figure 17) using compounds **24** as a starting material to obtain primary **25a** (starting material *tert*-butyl amine), secondary **25b** and tertiary amines **25d**. This procedure is an alternative to other methods, which deal with preparation of bulky amines similar to **25c**.

Based on our experimental and computational studies we have proposed following mechanism (Figure 18). Iminium salt **22** undergoes the thermal rearrangement to the intermediate **Int-1**, which is thermodynamically unstable and rearranges back to the staring material **22** unless is protonated with a catalyst (triflic acid) to form an intermediate **Int-2**. This protonation hinders the reverse reaction to **Int-1** and then to starting material **22**. In the next step of the cascade intermediate **Int-2** undergoes Friedel-Crafts reaction and forms the product **23**.

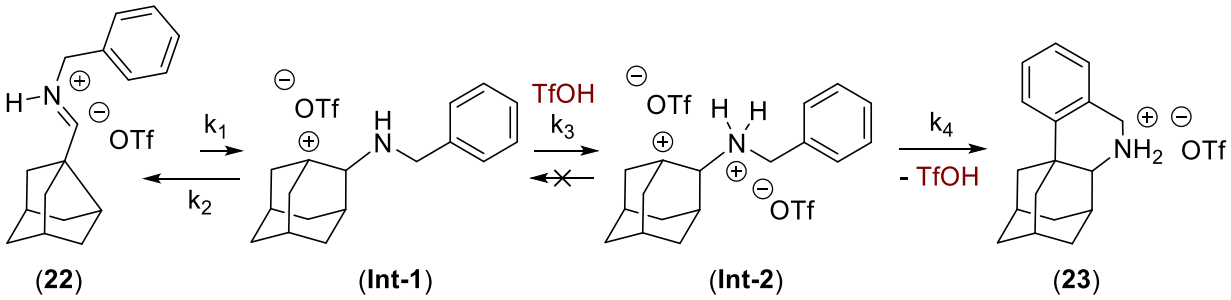


Figure 18. Proposed mechanism of the cascade reaction on the basis of mechanistic experiments, kinetic studies and calculations.

First, we focused on the last reaction in the cascade and generated **Int-2** from precursor **26** by protonation of hydroxy group with triflic acid and subsequent water elimination. We found out that the barrier of this reaction is lower than for the first reaction step (Figure 19). The Friedel-Crafts reaction proceeds already at 80 °C with full conversion after 16 h, the reaction cascade requires temperatures over 120 °C to reach completion in the same time.

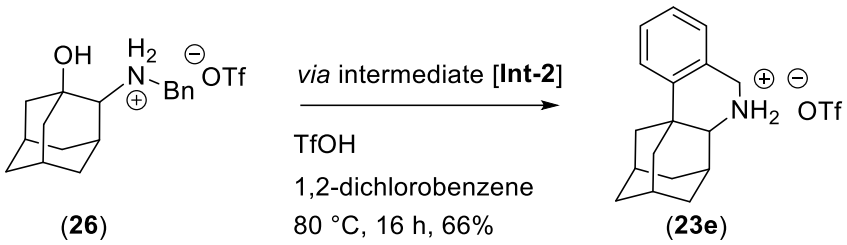


*Figure 19. Mechanistic experiments: Generation of intermediate **Int-2** from **26**.*

Second, we have compared relative stability of the starting material **22e** and intermediate **Int-1**, to facilitate the computational study just corresponding cations were calculated. Computed difference in enthalpy between these two species was found to be 24.1 kcal/mol (Figure 20). If we take in account that kinetic barrier of the rearrangement is higher than this difference and knowing the kinetic profile of the last reaction in the cascade we can state that this thermal rearrangement is the rate limiting step in the cascade.

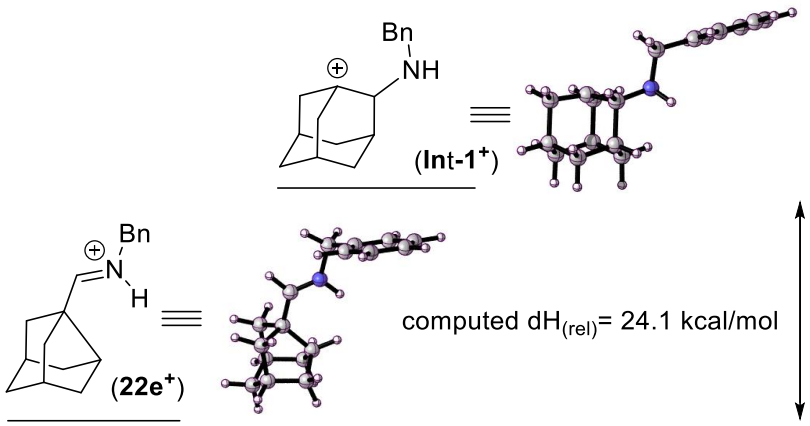


*Figure 20. Mechanistic experiments: Comparison of thermodynamic stabilities of cations **22e** and **Int-1**using DFT calculations.*

Third, we have studied the reversibility of the rearrangement reaction (1,2-alkyl shift) and tried to generate the starting material **22e** from precursors **27** and **28** using silver triflate, which role is to irreversibly replace bromide for triflate and thus generate **Int-1**

from **27** and intermediate **Int-2** from **28** (Figure 21). In the experiment starting from **27** we have observed immediate formation of **22** upon addition of silver triflate at room temperature. When we started with compound **28** formation of **22e** was not observed. Detection of product **22e** was performed using ^{1}H-NMR directly after the experiment.

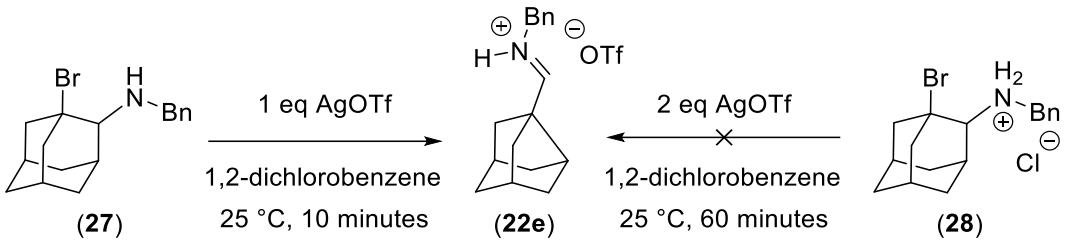


*Figure 21. Mechanistic experiments: Generation of intermediate **Int-1** from precursor **27** at room temperature. Proof that the first reaction step is reversible and that the **22e** is thermodynamically more stable than **Int-1**.*

Last question was, how to experimentally determine that the first step is not catalyzed that means that it is purely thermal rearrangement. For this purpose we invented this experiment (Figure 22): We have mixed starting material **29**, methyl amine derivative, which cannot provide Friedel-Crafts reaction, and mixed it with for equivalents of an aromatic nitrile to perform a Ritter reaction.[45] Reaction proceeded at 140 °C without any additional catalyst to heterocycle **30** in very good yield. In the future we plan to generalize this protocol for more substrates.

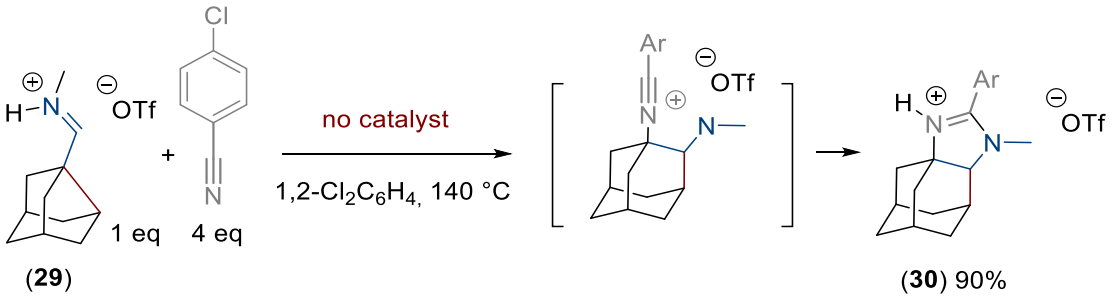


*Figure 22. Mechanistic experiments: trapping of intermediate **Int-1** with an aromatic nitrile to form heterocycle **30**. Proof that the thermal rearrangement does not require any additional catalyst*

This study was accompanied by kinetic study and computational simulation of the reaction progress, which confirmed that the cascade is composed of three events, rate limiting thermal alkyl shift, diffusion-controlled protonation of the first intermediate by the catalyst and subsequent Friedel-Crafts reaction.

This section was focused on the synthesis of amines and nitrogen containing heterocycles with adamantane scaffold prepared using the key intramolecular nitrene insertion reaction and further derivatization of the obtained compounds. In the following section I describe our efforts towards 1,2-substituted carboxylic acids with adamantane skeleton or other bridged cycloalkanes. We changed the key reaction and tried to develop C–H activation process based on palladium(II) catalysis. [46]

2.3 Palladium catalyzed C–H activation reactions

Arylation of the C–H bond next to the directing group on adamantane derivatives

C–H activation studies start typically with the choice of the desired transformation and the choice of the transition metal followed by the screening of the directing groups suitable for the selected catalyst. At the time we entered this field there were no catalytic methods for the directed C–H activation reactions on the adamantane scaffold so we decided to study the arylation process in β-position to the directing group and palladium(II) based methods as the most studied field at that time, estimating high chances for the success. Second choice is the precursor for the directing group, here the application of the final compounds is the guide. In our case we wanted adamantane carboxylic acids as a starting material and 2-substituted adamantane 1-carboxylic acids as a product (enclosed publication 6). Last choice is the nature of the directing group[47] *e.g*. salt of carboxylic acid, monodentate directing group or bidentate directing group. This is very often already the part of the initial screening as it is difficult to predict, which directing groups will enable rather complicated catalytic process. From the first screening of approximately 30 directing groups we detected three, which enabled arylation in the position next to the DG (Figure 23). These are bidenatate groups, amides connected with methylene spacers to pyridine group, which enable intramolecular insertion of palladium into the CH bond of adamantane substrate and formation of five membered palladacycle. The cycle containing the pyridine moiety can be five membered or six membered. The first screening was tested with silver acetate, which role, next to the transmetalation process is very often proposed to coordinate to the oxygen of the amide to induce the right geometry for the critical C–H activation step (Figure 23).

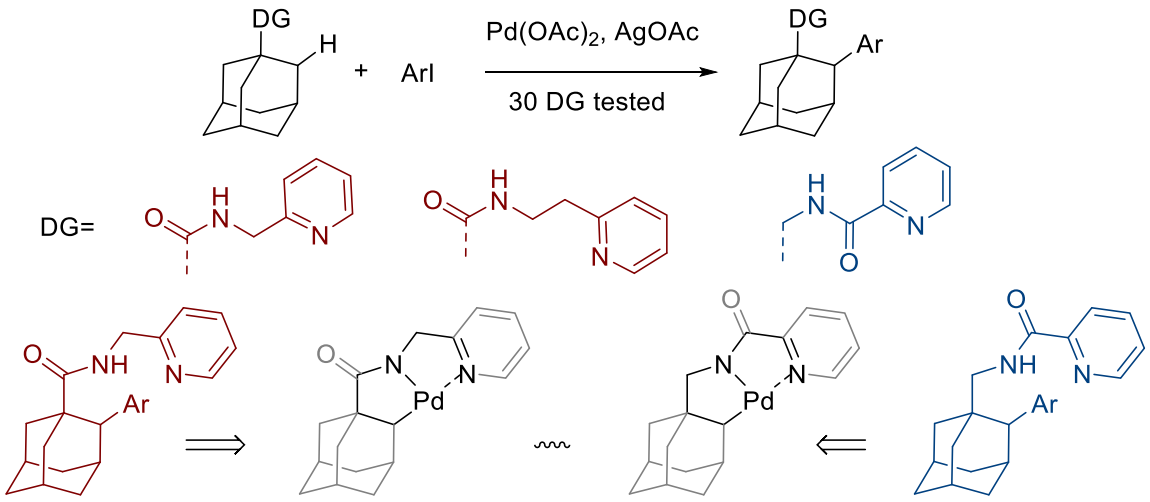


Figure 23. Bidentate directing groups, which enabled arylation of the adamantane framework using catalytic amount of palladium acetate, silver acetate as an additive and ArI as a substrate

2-Picolyl amine was incorporated into the substrates containing adamantane framework and resulting amides **31** were tested using the optimized conditions. Palladium acetate served as a catalyst with 1.3 equivalent of silver acetate and the solvent of choice was in this case polar non-nucleophilic hexafluoro isopropanol (Figure 24).

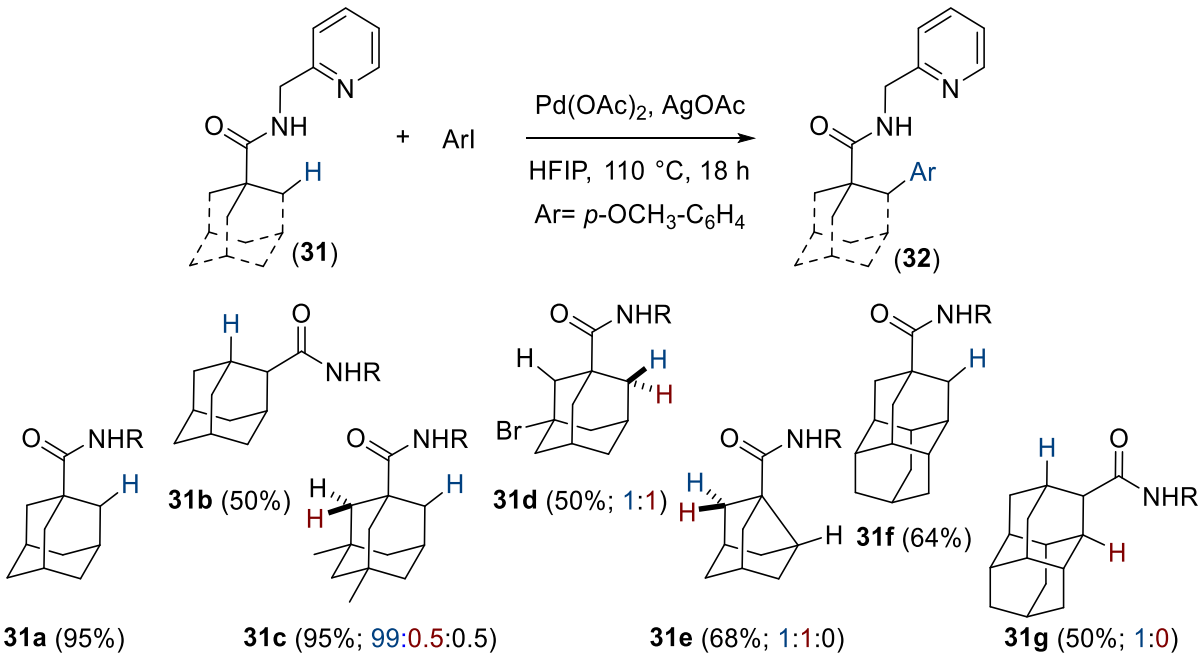


*Figure 24. Palladium(II) catalyzed arylation of adamantane derivatives containing bidentate directing group, conversion of a starting material **31** and selectivity in parentheses.*

Mixtures of *mono*-arylated and *bis*-arylated compounds were separated by column chromatography on silica gel. Conversions of starting materials **31** were in the range from 50% to 95%. Substrates **32c** and **32g** were obtained with remarkable regioselectivity (Figure 24).

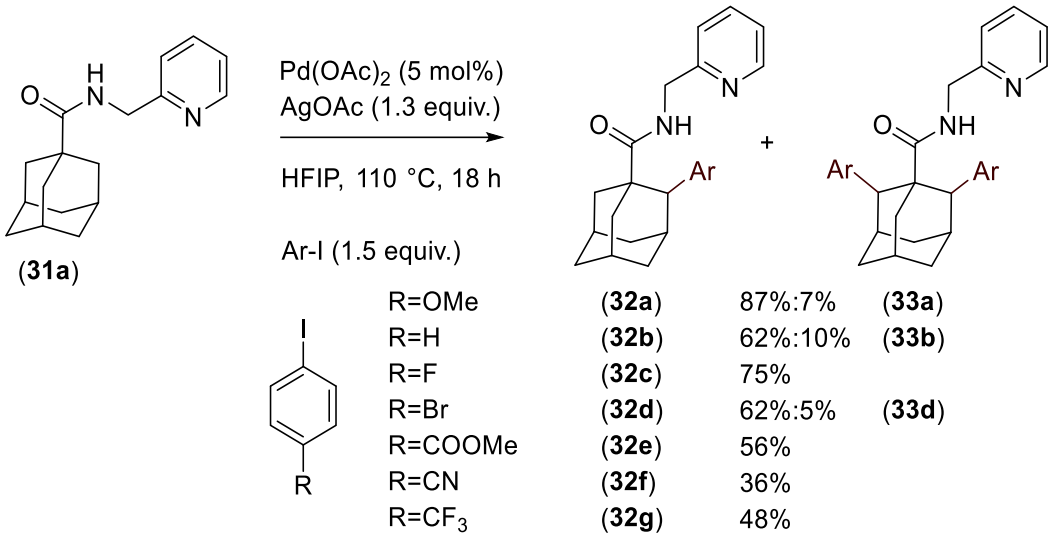


*Figure 25. The scope of aryl-iodides, yields and ratios of mono vs bis-arylated derivatives **32** and **33** are stated.*

In the next step we screened the arylating agents and found out that just aryl iodides provide the product **32**. Aryl chlorides, bromides and triflates do not react and can be incorporated within the substrate, example **32d** (Figure 25). Based on further results (which will be discussed in detail separately) using kinetics, deuterium labelling and mass spectrometry experiments we proposed following mechanism depicted in figure 26: In the first step starting material **31** forms a silver complex **C1** accompanied with release of acetic acid. **C1** then enters the catalytic cycle and reacts with palladium acetate to complex **C2**. In the next step of the catalytic cycle **C2** undergoes C–H activation step to palladacycle **C3.** Then palladacycle **C3** reacts with the aryl iodide to complex **C4**. This step, oxidative addition of aryl iodide is just proposed, there is so far no evidence for intermediate **C4**. Upon reductive elimination step complex **C5** is formed, which transmetalates to form product **32** as a silver salt. This product can compete with the starting material **C1** and undergo second arylation cycle. The incorporated aryl moiety reduces the electrophilicity of the palladium for the next C–H activation step and selectivities 8 to 1 in favor of *mono*-arylated products **32** are observed. Side product **34** was isolated and its structure determined, side product **35** in traces was detected using HRMS, but its structure was not confirmed.

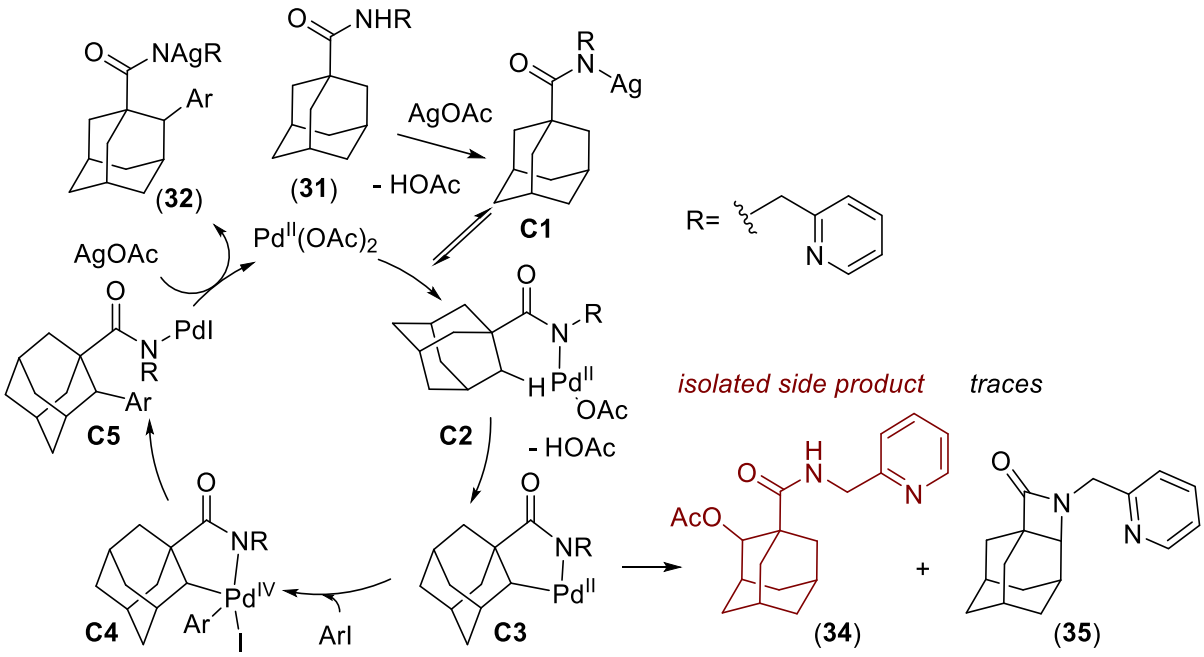


Figure 26. Proposed simplified mechanism of the directed arylation reaction catalyzed by $Pd(OAc)_2$, ligands L on the palladium species are omitted.

Using high resolution ESI-MS experiments we detected and confirmed presence of complexes **C1**, **C2**, **C5** and **32** as silver salt. In the separate experiment (Figure 27, **A**), in which we have removed the acetic acid from the solution we have observed formation of complex **CD**, this dimer does not undergo C–H activation in the absence of acetic acid. In the presence of acetic acid, complex **C2** can be formed from this dimer.

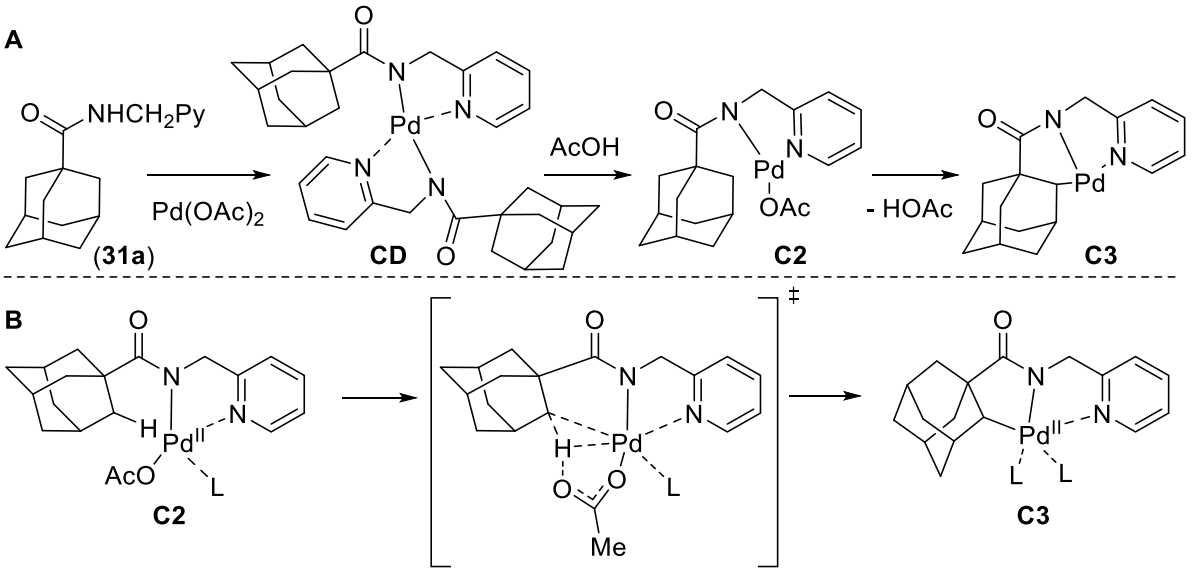


Figure 27. The role of the acetate group in the C–H activation process

This is in accordance with the knowledge that the presence of the acetate group on palladium is crucial for the formation of the palladacycle, C–H activation step (Figure 27, **B**).[48]

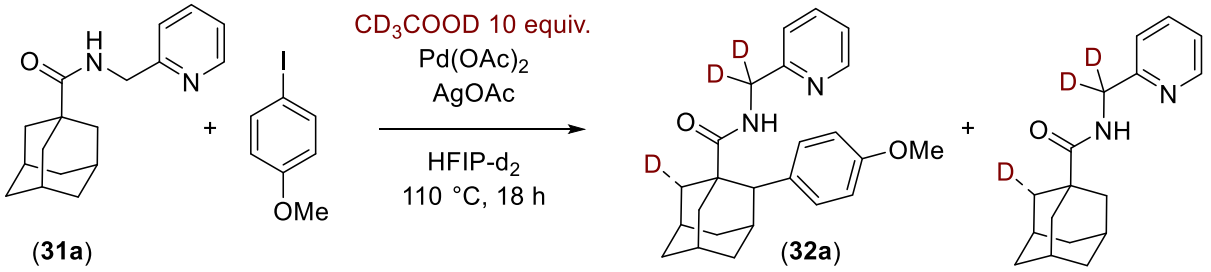


Figure 28. Deuterium labeling experiments, acidic noncatalyzed H/D exchange on the DG and H/D exchange on the adamantane framework as a result of palladacycle acidolysis

Deuterium labelling experiments were performed to answer the question, how fast is the acidolysis of the palladacycle **C3**. Using 10 equivalents of deuterated acetic acid as an additive we observed formation of deuterated starting material **31a** as well as deuterated product **32a** on the carbon (detected using NMR) next to the directing group (Fig. 28). Using *N*–D deuterated starting material **31** did not show any incorporation of deuterium in beta position of product **32** nor starting material **31**. From this experiment we conclude that the acidolysis of the palladacycle is a slow step in this catalytic cycle.

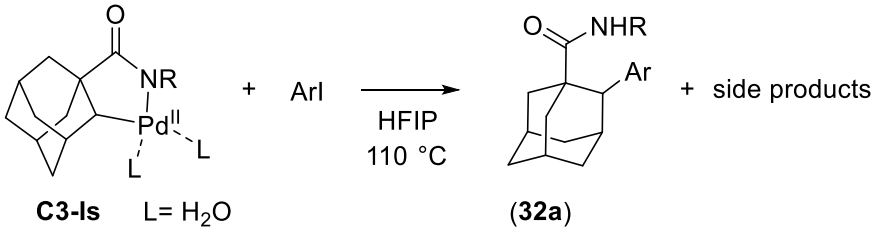


Figure 29. Experiment with the isolated palladacycle, L is presumably water

We succeeded to isolate palladacycle **C3-Is** and characterize it. Unfortunately, we were not able to prepare monocrystal for X-ray analysis. In an experiment (Figure 29), which was recommended to us by a referee, we subjected the isolated palladacycle to a reaction with aryl iodide in hexafluoro isopropanol. Only traces of product **32a** were observed. Palladacycle **C3-Is** subjected to the conditions of the reaction with silver acetate, aryl iodide in hexafluoro isopropanol gave product **32a**. This experiment is not of big value as we don't know the nature of ligand L in the first experiment. In the second experiment the complex formation reactions are reversible and it more less just tells that we put Pd(II) into the reaction mixture.

Kinetic experiments (Figure 30, **A**) revealed first order kinetics for aryl iodide and palladium acetate, zero order for the starting material **31a** which means, taking in account all other experiments, that process from **C3** to **C5** is the rate limiting step of the catalytic cycle.

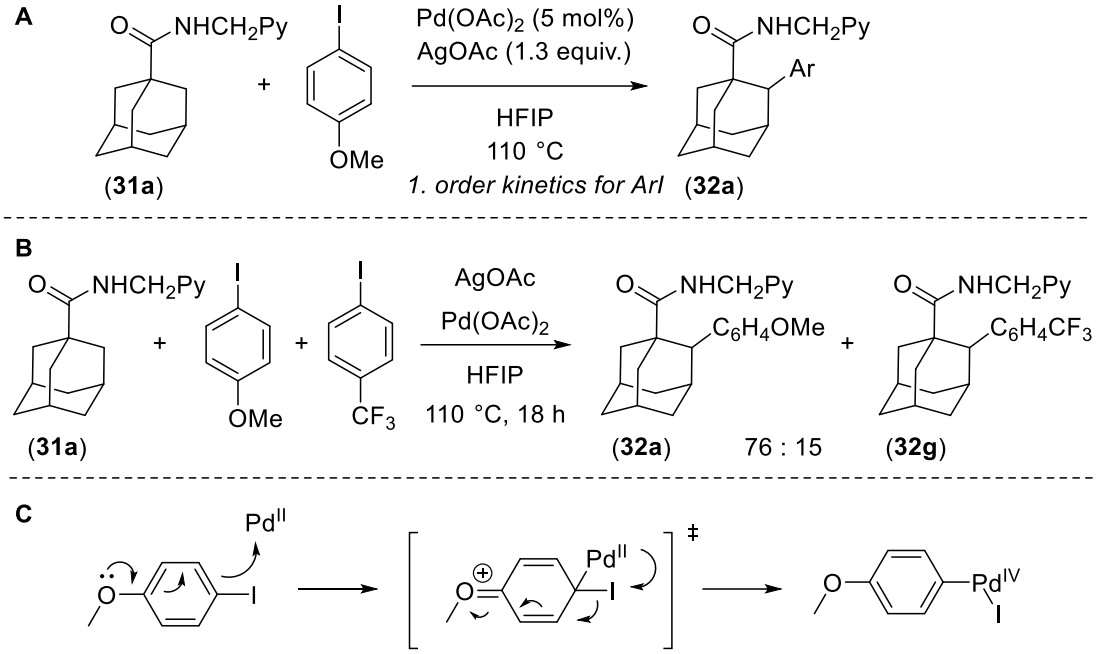


Figure 30. Proposed mechanism of the arylation step

Competitive experiment using stechiometric amounts of aryl iodides with electron withdrawing group -CF_3 and electron-donating (M+ effect) group -OMe showed preferential formation of product **32a** containing electron donating group. Accordingly, oxidative addition of aryl iodide on the palladacycle is proposed to resemble *ipso*-oxidative process as depicted in figure 30, **C**.

Finally, we demonstrated that the directing group can be removed (acidic cleavage) from the product **32a** to get the desired compound **36**. This compound was crystallized and subjected to röntgenographic analysis (Figure 31).

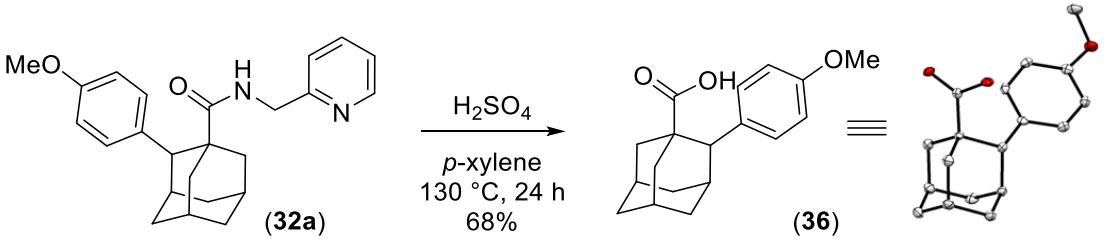


*Figure 31. Cleavage of the directing group and X-ray analysis of the final product **36***

Acetoxylation of the C–H bond next to the directing group on bridged cycloalkanes

In the previous work dealing with directed arylation of adamantane framework we observed formation of the acetoxy side product **34,** as a result of directed oxidation at the carbon next to the directing group.[49] As acetoxy group can be converted to hydroxy group and other useful functional groups, we decided to prepare this compound on purpose and to optimize the corresponding oxidation reaction using the same directing group (enclosed publication 7). Phenyl iodoacetate was used as an oxidant, palladium acetate as a catalyst, potassium acetate, acetic acid, acetic anhydride as an additives and xylene as a solvent.

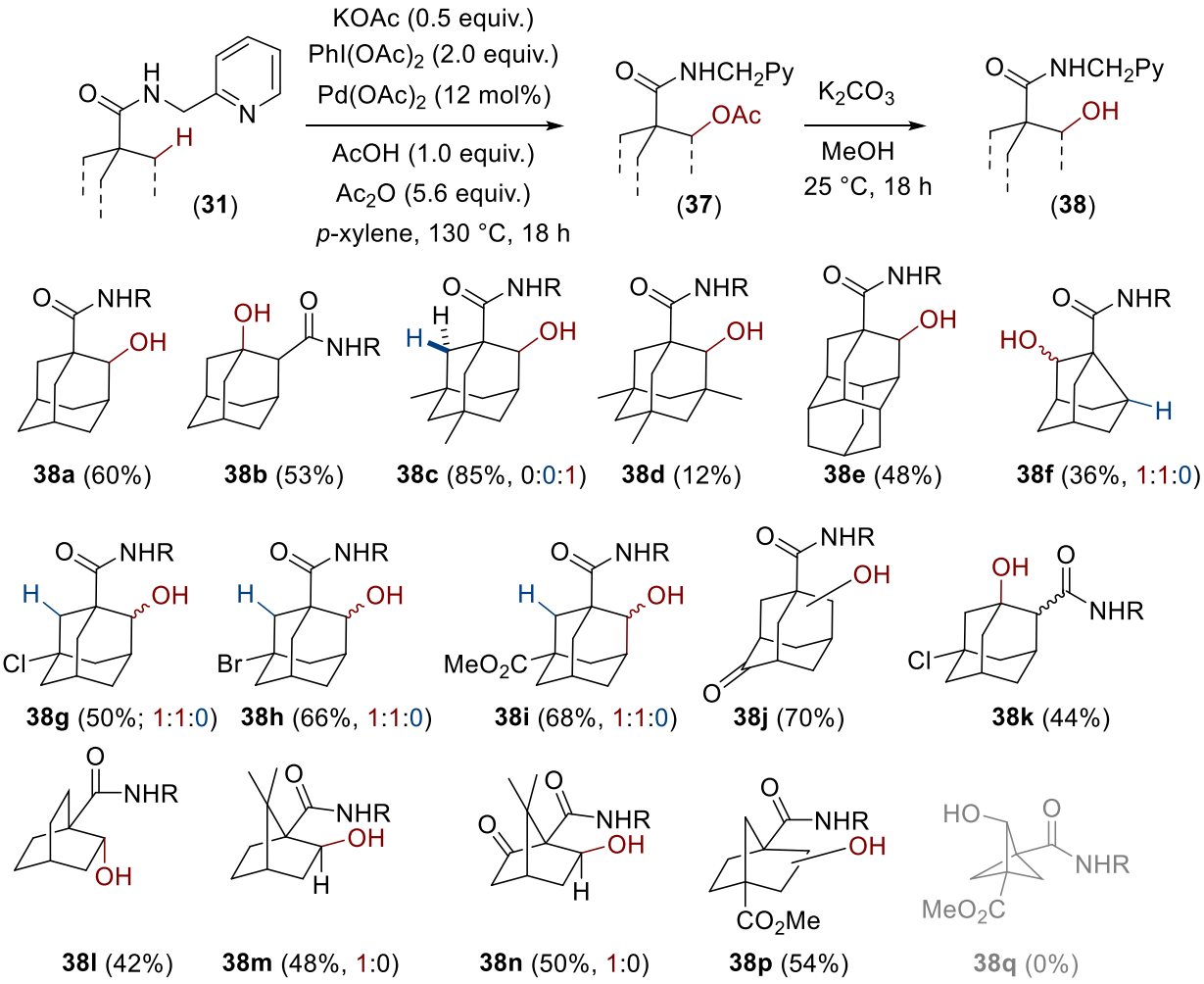


Figure 32. The scope of the acetoxylation reaction using carboxylic acid derived bidentate directing group

The optimized protocol was used for oxidation of compounds with adamantane scaffold and of other bridged cycloalkanes as well. The role of additives is crucial for

the reaction outcome and will be discussed separately. Products of the oxidation reaction **37** containing the acetoxy group were in the same pot hydrolysed to facilitate the separation of the main desired compounds **38**.

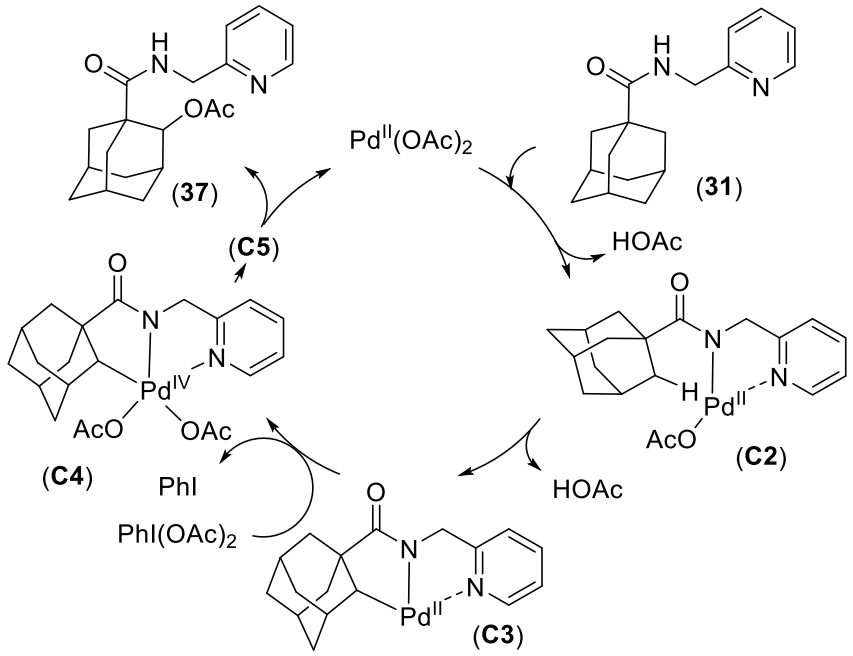


Figure 33. Proposed simplified mechanism of the catalytic acetoxylation directed by an carboxylic acid derived bidentate group, ligands L are omitted

The proposed mechanism (Figure 33) of the catalytic process consists again of two key events, C–H activation to palladacycle **C3** and oxidation of **C3** to **C4** with reductive elimination to **C5** or directly from **C3** to complex **C5** without separation of redox processes in analogy to CMD mechanism (Figure 35).

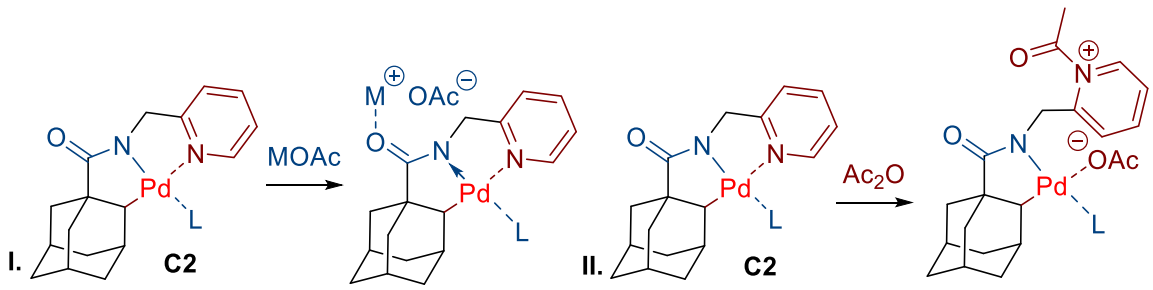


Figure 34. The role of the additives

The reaction mixture contains additives to promote and accelerate the reaction. The presence of oxophylic potassium salt is necessary to induce the proper geometry for the C–H activation step and accelerates the ligand exchange processes on palladium. The role of the acetic anhydride is to form reversibly acyl pyridinium species, which

helps again to accelerate ligand exchange process. Both roles were just proposed, there is no direct evidence so far (Figure 34) except the fact that the reaction does not proceed without KOAc and is slow without acetic anhydride.

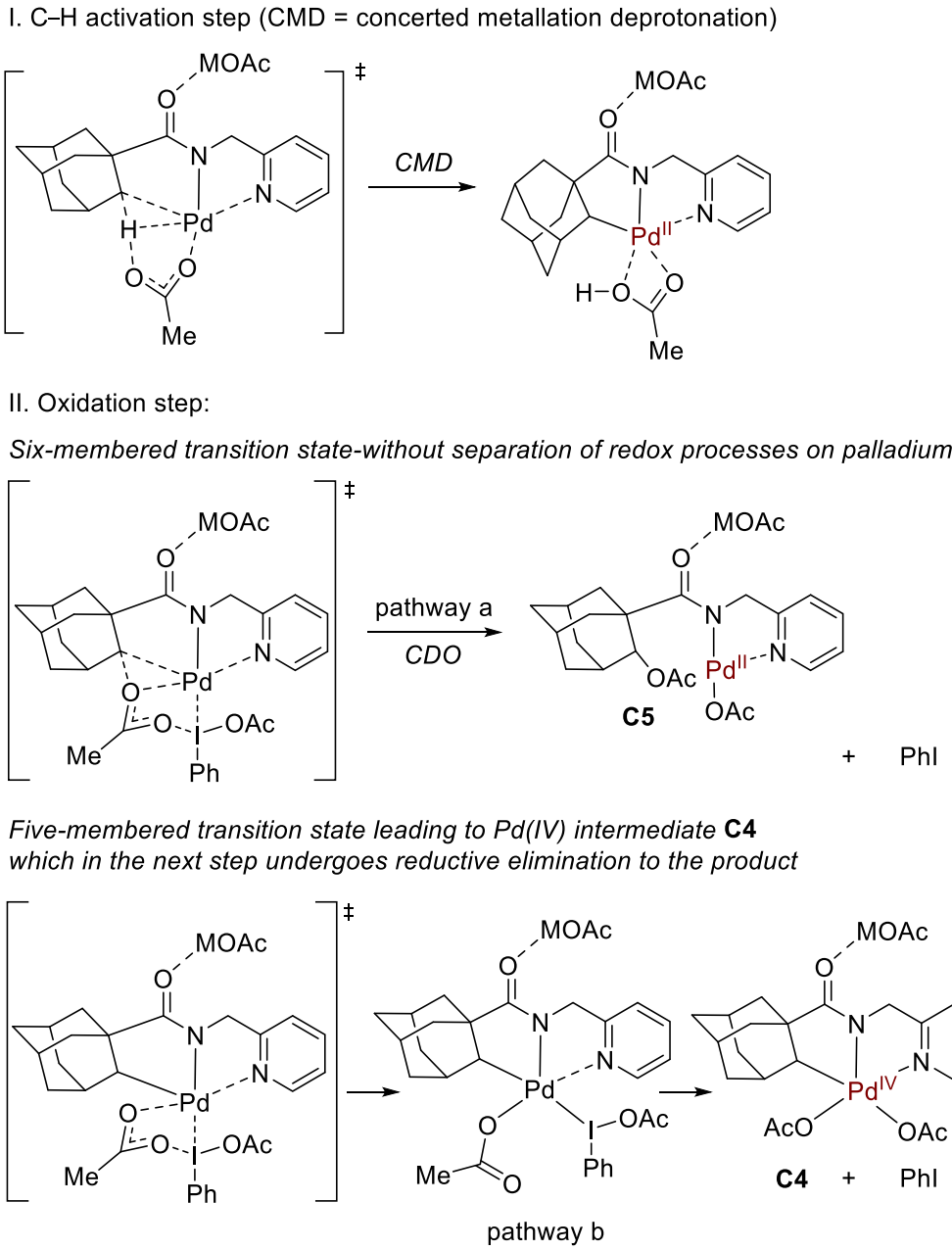


Figure 35. Discussed mechanisms (pathway A and pathway B) of the oxidation event in analogy to the C–H activation process

Deuterium labeling experiments helped us to reveal that in this reaction the acidolysis of the palladacycle competes with the oxidation step. We have subjected fully deuterated starting material **31-D** in the acetoxylation reaction and observed lower D/H ratio in the product **37-D** (Figure 36).

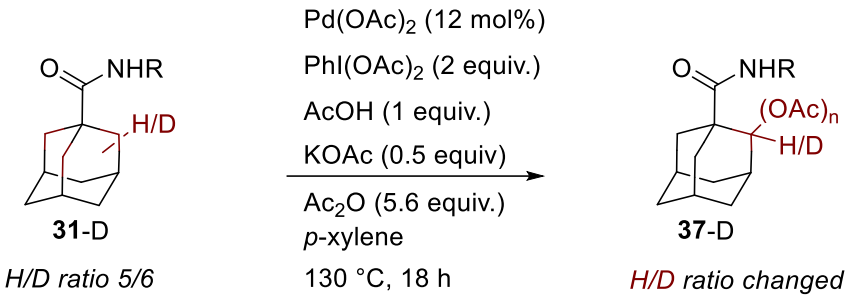


Figure 36. Deuterium labeling experiments, acetoxylation as a competing process to the palladacycle acidolysis

According to the sterochemical outcome of the reaction, obtained on substrates with ketopinic derivatives **38m** and **38n** and according to the outcome on compounds with the adamantane framework we proposed that C–O bond formation has in both cases reductive elimination character, with retention of the configuration (Figure 37).

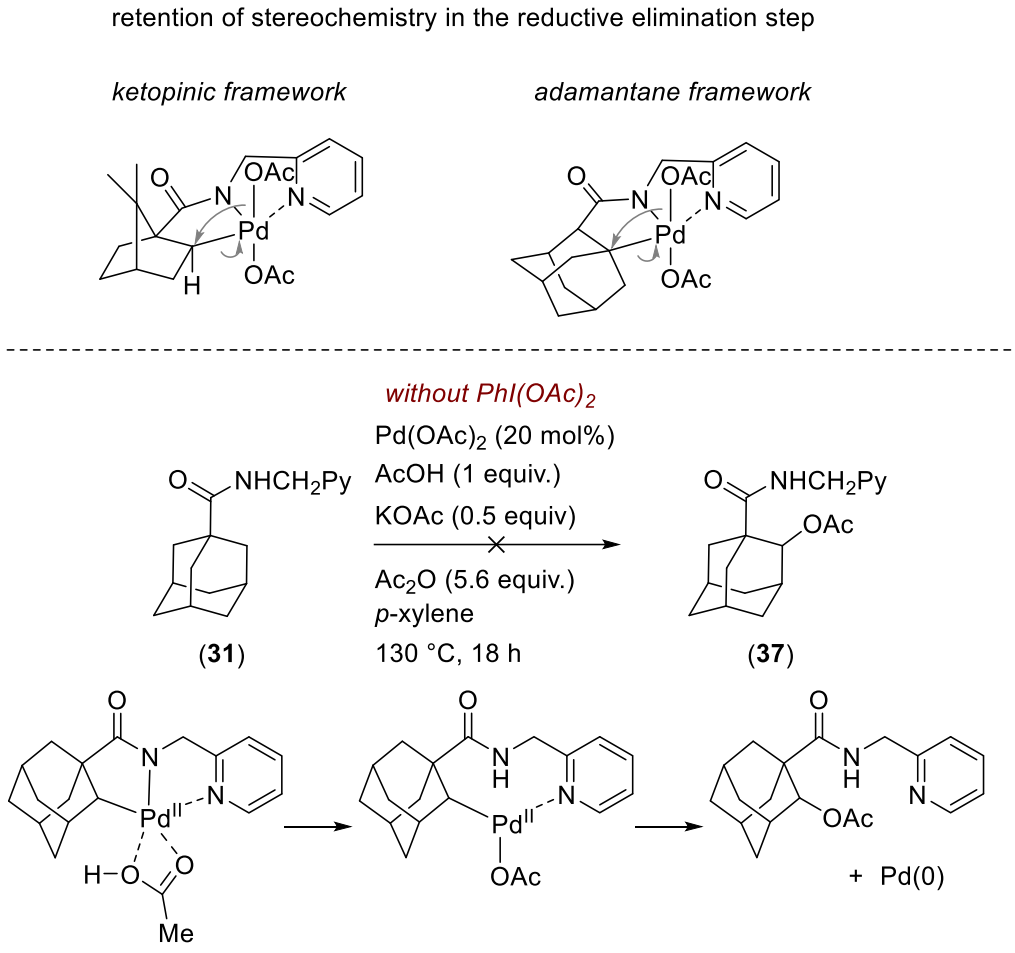


Figure 37. Reductive elimination step and disclosed pathway to C–O bond formation via Pd(0)

No product was detected, when an oxidant (phenyl iodoacetate) was omitted from the reaction mixture. This indicates that reductive elimination from palladacycle to Pd(0) is not involved.

Then we focused on the stereochemical outcome of the reaction towards bis-acetylated **39** and tri acetylated compounds **40**. The second (or third) oxidation reaction is diastereoselective and proceeds in a fashion that two acetyl groups do not face each other on the adamantane framework (Figure 38). Presumably steric effects block the reaction to proceed at that position. The same was observed for the oxidation of the reaction mixture of (*rac*)-di-**39** and (*meso*)-di-**39**. (*Rac*)-di-**39** was oxidized to (*rac*)-tri-**40** and (*meso*)-di-**39** remained in the solution. This reaction can be thus called kinetic resolution of the bis-acetylated isomers **39**. The highlight of this part is the preparation of chiral C_3 symmetric triacetylated derivative tri-**40**.[50]

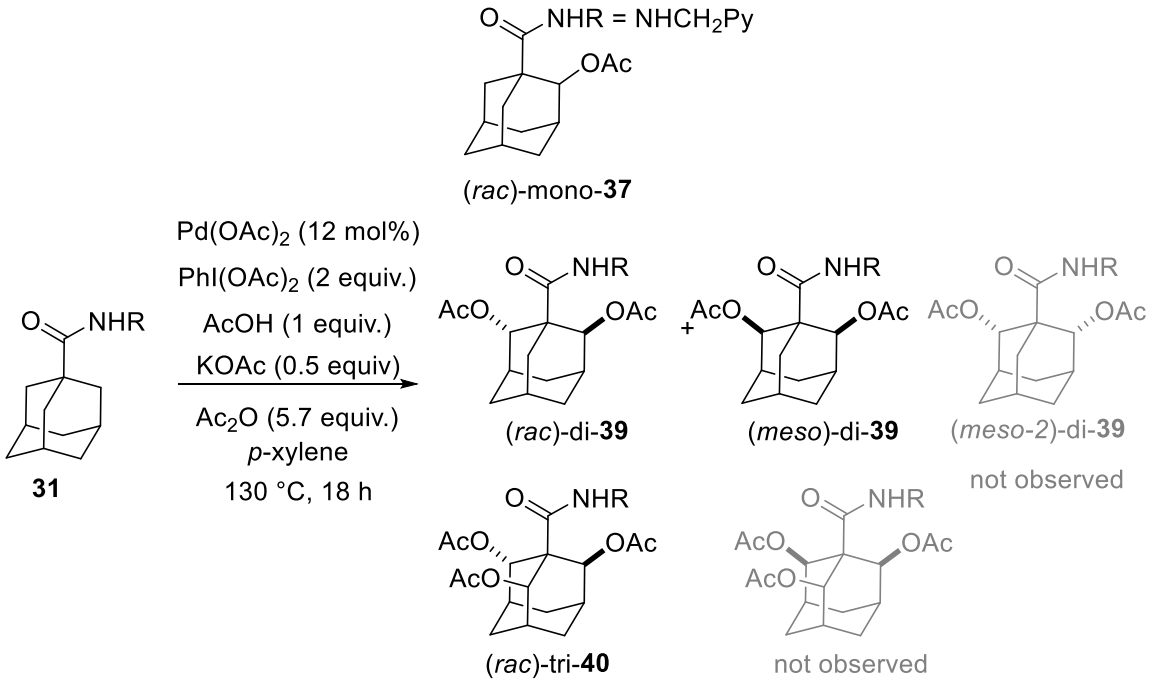


Figure 38. Diastereoselectivity of the second and third oxidation reaction on the adamantane framework

The last part of this study was dealing with the removal of the directing group and with the acetoxy group transformations (Figure 39). 2-Hydroxy-adamantane-1-carboxylic acid **41** was prepared by an acidic hydrolysis in diluted sulphuric acid. 2-Bromo-adamantane-1-carboxylic acid **43** was prepared by an acidic hydrolysis in concentrated hydrobromic acid. And Dess-Martin reagent was used to oxidise compound **38** to the corresponding keto derivative **42**.

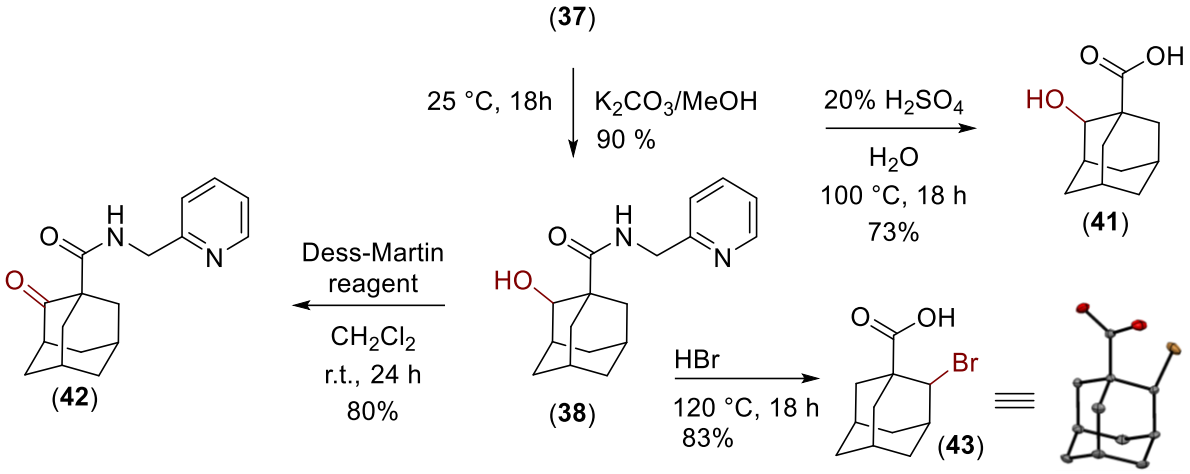


*Figure 39. Cleavage of the directing group, derivatization reactions and crystallographic analysis of 2-bromo-adamantane-1-carboxylic acid **43***

2.4 Application of disubstituted adamantane derivatives in catalysis

Postfunctionalization of dirhodium(II,II) carboxylates and their application in selective amination reactions

Having already experience with rhodium(II) catalyzed insertion reactions, we decided to use disubstituted adamantane derivatives as building blocks for the construction of bifunctional dirhodium(II,II) carboxylates (enclosed publication 8).[51] The main idea was to create a bench stable precursor, dirhodium carboxylate, which would contain a group for connection of any additional chain/functional group *via* "click" reaction or *via* reaction, which does not decompose the initial complex. We envisioned that adamantane based spacer containing amino group (to connect moieties *via* amide bond) would fulfill these conditions. At the beginning to avoid complications with stereochemistry we chose achiral 3-amino-adamantane-1-carboxylic acid as our desired spacer (Figure 40).

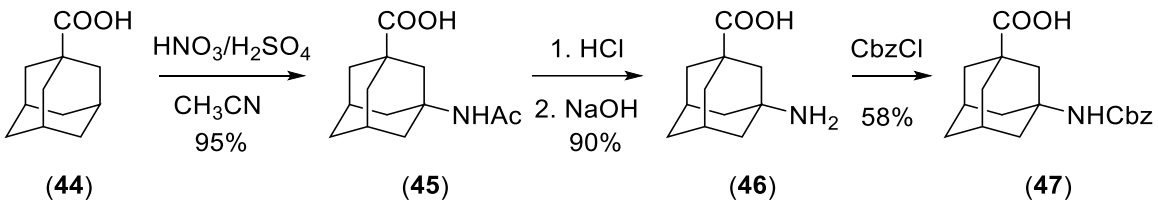


*Figure 40. Synthesis of the ligand **47** for the exchange reaction with dirhodium acetate*

For this purpose, we prepared in three reaction steps Cbz protected compound **47**. This compound was used for the ligand exchange with dirhodium acetate to form dirhodium(II,II) complex **48**. In the next step we tested, if the reductive cleavage of Cbz group will provide us desired complex **49** and if this complex is separable and bench stable. To our delight this was the case.

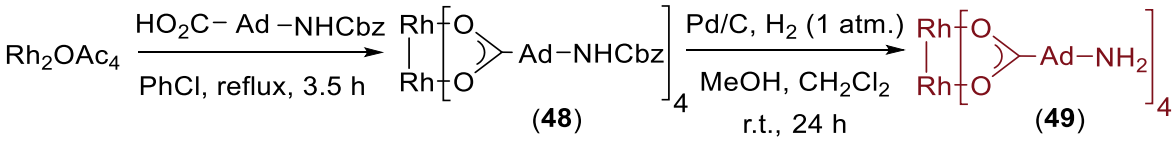


*Figure 41. Synthesis of the dirhodium(II,II) complex **49** containing an unprotected amine group*

With the stable precursor **49** in hand we performed envisioned click reactions using active esters containing compounds or isocyanates as coupling partners. Compounds **50**-**55** containing various functional groups, which would be difficult to prepare by standard ligand exchange reaction, were prepared and isolated in good yields ranging from 41% to 83%.

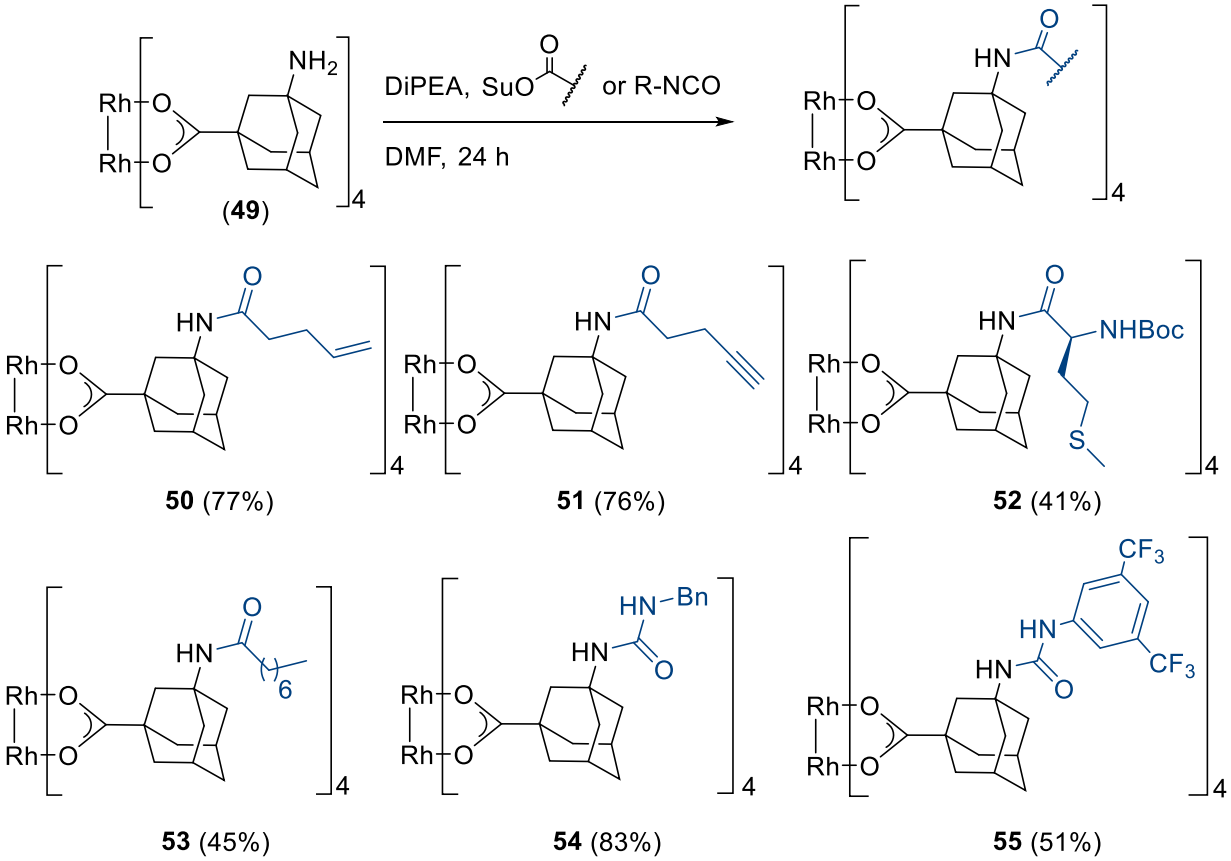


Figure 42. Postfunctionalization of the dirhodium(II,II) complex via amide bond formation

Compound **55**, our designed future catalyst, was crystallised and subjected to crystallographic analysis to have imagination about spatial distances within the molecule, especially the distance between the Lewis acidic rhodium atom and urea moiety. This moiety was implemented to the molecule to bind the substrates *via* hydrogen bonding.[52]

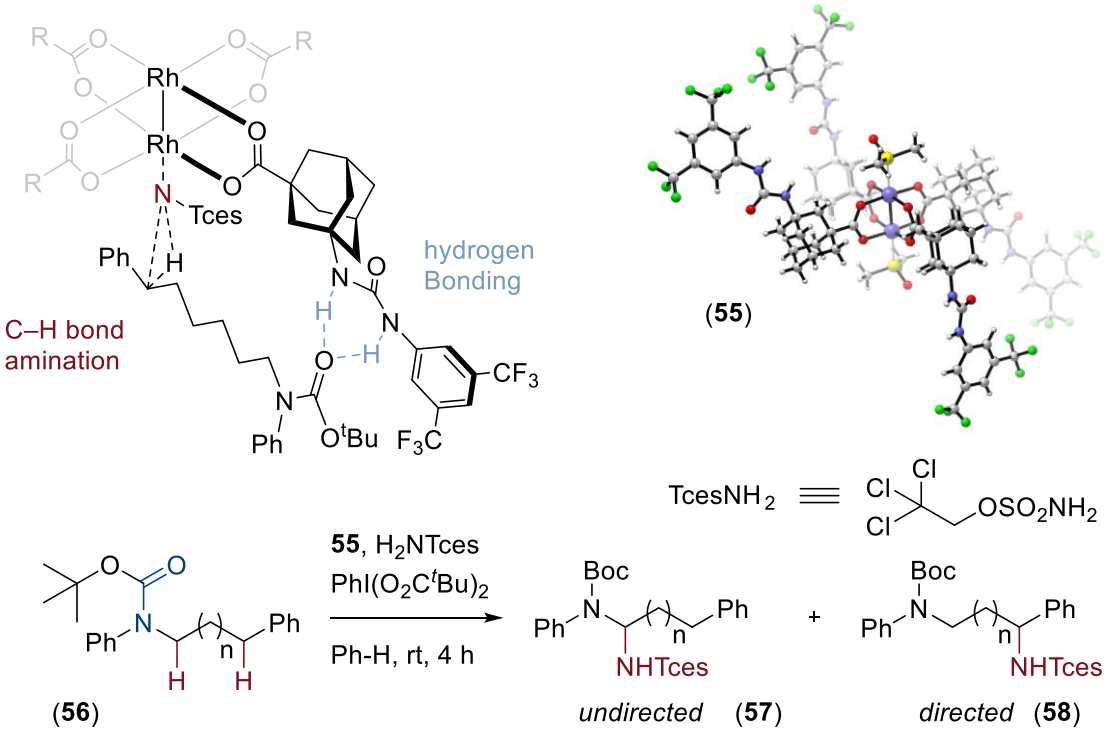


*Figure 43. Selective C–H amination reaction of **56** using bifunctional catalyst **55** (x-ray analysis structure of **55**)*

To estimate the distance between the mode of action on the rhodium atom (nitrene insertion into the C–H bond[53] in this particular case) and hydrogen bonding site for the substrate, we have screened model compounds with variable chain length **56** (Figure 43). For compound with 6 methylene units (n=4) we obtained the best ratio for desired nitrene insertion into the benzylic C–H bond (compound **58**) versus undesired insertion next to the amide bond (compound **57**). The control experiments were performed with catalysts dirhodium acetate and dirhodium Espino complex,[54] which do not possess the hydrogen bonding moiety.

Having rough idea about the optimal distance between the hydrogen bonding site and site of transformation, we tried to apply this method on aziridination[55] of natural product farnesol containing three by flexible chain separated C=C double bonds.

First, we converted the hydroxy group of farnesol to the carbamate, to create the hydrogen bond acceptor on the substrate and then we tested common dirhodium catalysts, which lack additional functionality for hydrogen bonding. The nitrene addition proceeded in all cases unselectively on the double bond A and B with the slight preference for aziridination of A to **60**, double bond C did not undergo insertion reaction, most probably because of sterics (Figure 44). With the catalyst **55** we observed 5:1 selectivity in favor of aziridination of the double bond B to get **61** as the major product. To control that this selectivity is connected to the hydrogen bonding of the substrate by the catalyst **55** we performed an experiment, in which we added an additive, 10 equivalents of ethyl-*N*-ethyl carbamate, to the reaction mixture and observed then drop of selectivity of the aziridination reaction to 1 to 1.3 mixture of aziridine at position A and B, compounds **60** and **61**.

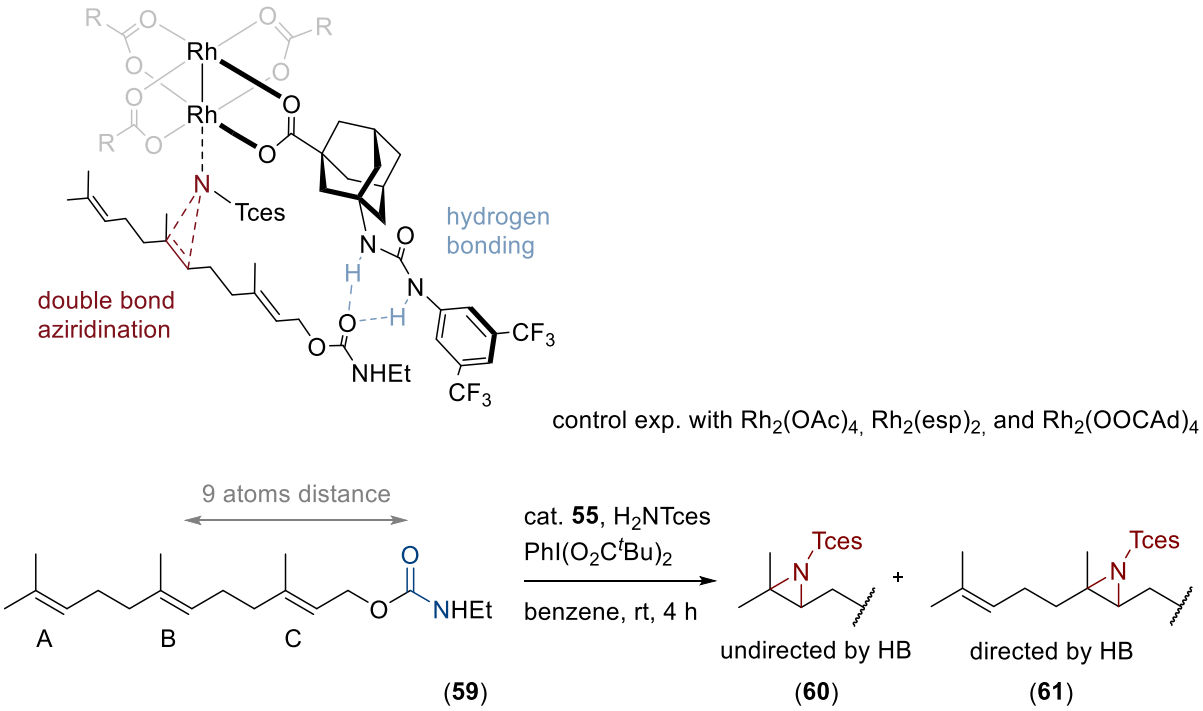


*Figure 44. Selective aziridination reaction of farnesol derivative **59** catalyzed by bifunctional catalyst **55***

In this part of the research we showed that it is possible to prepare transition metal complexes with additional functionalities by post-functionalization of the precursor complex and use them as catalysts in site-selective reactions.[56] Two applications demonstrated that it is possible to direct insertion reactions of electrophilic species using hydrogen bonding of the substrate to the catalyst.

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Conclusions

The main objective was to contribute to the basic knowledge of the transition metal catalysis connected with the reactivity of bridged cycloalkanes and to broaden the pool of easily available materials by the directed C–H functionalization reactions. Generated compounds, amines and acids, can now serve as a building blocks for the synthesis of new biologically active compounds (drug candidates), as a building blocks for the synthesis of chiral ligands and organocatalysts.

Two main approaches were studied: Intramolecular C–H insertion processes and metal C–H activation processes. The first approach leads to the development of protocols for selective synthesis of 1,2-disubstituted cycloalkanes *via* internal C–H insertion reactions. We have focused on the synthesis of C–N derivatives using insertion reaction of known internal groups and development of following transformations, which now allow straightforward access to nitrogen containing derivatives, amines and heterocycles.

The second approach deals with the synthesis of substituted cycloalkanes *via* key metal-carbon bond formation. We focused on the Pd(II) catalyzed C–C bond formation and C–O bond formation reactions using carboxylic acids as starting material and were among the first to show that these reactions occur on bridged cycloalkanes with rigid framework.

To demonstrate application of disubstituted adamantane derivatives (to avoid the stereoselectivity issues, we have chosen at the beginning achiral starting material) we have shown that it is possible to build complex organic structures with defined geometry from a transition metal complex. We have shown that we can control the incorporation of additional functional motifs and apply the combination of their functions in catalysis. A number of further applications are arising.

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