Institute of Pharmaceutical Chemistry
University of Szeged

Structural diversity-driven synthesis of cycloalkane-based heterocycles and 1,3-bifunctional compounds

PhD Thesis
by Árpád Balázs

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Contents

List of publications and lectures related to the thesis

Full papers

[1] Zsolt Szakonyi, **Árpád Balázs**, Tamás A. Martinek, Ferenc Fülöp:
Enantioselective addition of diethylzinc to aldehydes catalyzed by *γ*-amino alcohols derived from (+)- and (-)-α-pinene
Tetrahedron: Asymmetry, **2006**, *17*, 199-204.

[2] **Árpád Balázs**, Zsolt Szakonyi, Ferenc Fülöp:
Synthesis of alicyclic *N*-substituted 1,3-amino alcohols via 1,3-oxazines
J. Heterocyclic Chem., **2007**, *44*, 403-406.

[3] **Árpád Balázs**, Erik Van der Eycken, Ferenc Fülöp:
A novel, microwave-assisted method for the synthesis of alicyclic condensed 5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-ones
Tetrahedron Lett., **2008**, *49*, 4333-4335.

[4] **Árpád Balázs**, Anasztázia Hetényi, Zsolt Szakonyi, Reijo Sillanpää, Ferenc Fülöp:
Solvent-enhanced diastereo- and regioselectivity in the Pd(II)-catalyzed synthesis of six- and eight-membered heterocycles via *cis*-aminopalladation
Chem. Eur. J., **2009**, *15*, 7376-7381.

Scientific lectures

1. Martinek Tamás, Szakonyi Zsolt, **Balázs Árpád**, Fülöp Ferenc: Enantioszelektív katalízis ab initio modellezése monoterpénvázas 1,3-aminoalkoholok alkalmazása során
   MTA, Elméleti kémiai munkabizottság ülése
   Budapest, január 27, 2005.
2. Szakonyi Zsolt, **Balázs Árpád**, Martinek Tamás, Fülöp Ferenc: Monoterpén-vázas 1,3-difunkciós vegyületek szintézise és alkalmazása enantioszelektív átalakításokban
   Vegyészkonferencia
   Hajdúszoboszló, június 28-30, 2005, P-85.
3. **Árpád Balázs**, Zsolt Szakonyi, Tamás Martinek, Ferenc Fülöp: Synthesis of Monoterpene skeleton 1,3-difunctional compounds and their application in enantioselective transformations

Semi-centennial conference of Semmelweis University, Faculty of Pharmacy; Hungarian Academy of Sciences;
Budapest, October 12-14, 2005, P-5.

4. **Balázs Árpád**: Szekunder 1,3-aminoalkoholok előállítása 1,3-oxazinok reduktív transziminálásával
   Szegedi Ifjú Kémikusokért Alapítvány előadóülés
   Szeged, január 17, 2006. Különdíj
5. **Balázs Árpád**: 2-Tozil-amino-ciklohexán-1-karbonsav származékok regioszelektív gyűrűzárási reakciói, palladium(II)-katalizált intramolekuláris oxidative aminálással
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6. **Balázs Árpád**: Ciklohexánnal kondenzált heterociklusok szintézise, Pd(II)-katalizált oxidatív aminálással
   VIII. Clauder Ottó Emlékverseny
   Budapest, április 12-13, 2007. Különdíj
7. **Balázs Árpád**, Szakonyi Zsolt, Hetényi Anasztázia, Fülöp Ferenc: Ciklohexánnal kondenzált heterociklusok szintézise, Pd(II)-katalizált oxidatív aminálással
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   Sopron, május 29-június 1, 2007, SZ-P-2.
8. **Árpád Balázs**, Zsolt Szakonyi, Anasztázia Hetényi, Ferenc Fülöp: Synthesis of cyclohexane-fused six- and eight-member heterocycles via Pd(II)-catalyzed intramolecular oxidative amination
   15th European Symposium on Organic Chemistry
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9. **Balázs Árpád**: Ciklohexánnal kondenzált heterociklusok szintézise, Pd(II)-katalizált oxidatív aminálással
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   Balatonszemes, szeptember 12-14, 2007.
10. **Árpád Balázs**, Erik Van der Eycken, Ferenc Fülöp: Synthesis of Cyclohexane-fused Six- and Eight-Membered Heterocycles via Pd(II)-Catalyzed Intramolecular Oxidative Amination
    11th Sigma-Aldrich Organic Synthesis Meeting
    Spa, Belgium, December 6-7, 2007, P2.

11. **Balázs Árpád**, Erik Van der Eycken, Fülöp Ferenc: Egy új, mikrohullámmal segített módszer aliciklusokkal kondenzált 1,4,6,7-tetrahidro-1,4-diazepin-5-onok előállítására
    MTA, Heterociklusos munkabizottsági ülés
    Balatonszemes, május 21-23, 2008.
12. **Balázs Árpád**, Hetényi Anasztázia, Szakonyi Zsolt, Fülöp Ferenc: Ciklohexánnal kondenzált hat- és nyolctagú heterociklusok szintézise Pd(II)-katalizált oxidatív aminálással. Egy új Pd(II)-katalizált dominó reakció
    MTA, Heterociklusos munkabizottsági ülés
    Balatonszemes, május 20-22, 2009.

List of abbreviations

AP: aminopalladation

Boc: *tert*-butoxycarbonyl

BzONa: sodium benzoate

Cbz: benzyloxycarbonyl

CSI: chlorosulfonyl isocyanate

DMA: dimethylacetamide

DMSO: dimethyl sulfoxide

ee: enantiomeric excess

MAOS: Microwave-Assisted Organic Synthesis

MW: microwave

PMB: *para*-methoxybenzyl

rt: room temperature

sub: substrate

TFA: trifluoroacetic acid

p-TsCl: *para*-toluenesulfonyl chloride

p-TsOH: *para*-toluenesulfonic acid

1. Introduction and aims

Alicyclic β-amino acids and their derivatives, such as 1,3-amino alcohols, 1,3-diamines and β-amino esters, play important roles in both fundamental and applied research. Apart from their proven pharmacological effects (*e.g.* icofungipen and tramadol), they are also interesting from a chemical viewpoint. They can serve as excellent starting materials for the synthesis of diverse *N*-containing heterocycles or, in an enantiomerically pure form, they can be applied as asymmetric auxiliaries or catalysts in enantioselective transformations. The primary aim of the work reported in this thesis therefore, was to develop new procedures for their synthesis and to explore their chemical reactivities.

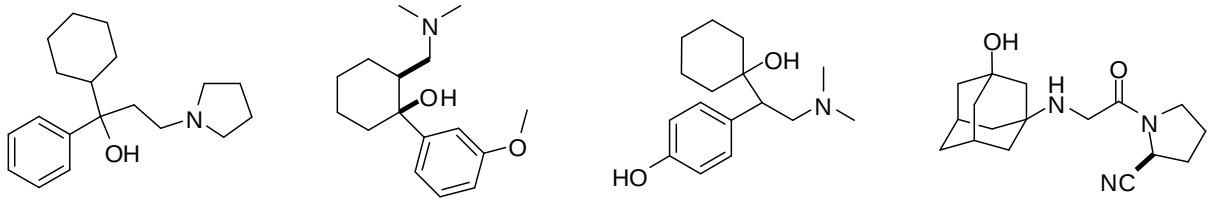
Since monoterpenes are excellent starting materials for the synthesis of enantiomeric alicyclic compounds, our aim was to synthetize new α-pinane-based optically active 1,3-amino alcohols and 1,3-diamines and to apply them as catalysts in the enantioselective addition of diethylzinc to various aldehydes. The major advantage of the chosen α-pinene over other monoterpenes is that both enantiomeric forms are commercially available in bulk. Moreover, due to the highly constrained bicyclic pinane skeleton, a high degree of chiral information transfer can be expected in asymmetric transformations. Besides the synthesis of optically pure 1,3-amino alcohols, an additional aim was to develop a simple and short procedure for the synthesis of alicyclic *N*-substituted 1,3-amino alcohols, since the preparation of such compounds with increased diversity usually requires a time-consuming multistep process.

The synthesis and properties of cycloalkane-based six-membered heterocycles are well established, whereas only limited or no procedures have been reported for the synthesis of seven- and especially eight-membered ones, although the synthesis of such compounds would greatly increase the structural diversity of the family of *N*-containing heterocycles. Accordingly, our aim was to investigate novel reactions of β-amino acid derivatives to prepare such compounds via the utilization of microwave irradiation techniques, for example, and previously little-used methods such as Pd(II)-catalysed transformations.

2. Literature survey

2.1. Preparation, properties and utilization of alicyclic 1,3-amino alcohols

1,3-Amino alcohols are of significance because of their pharmacological and chemical relevance. For instance, procyclidine (Kemadrin®) is administered in the therapy of Parkinson's disease[5], tramadol (Contramal®) is a non-morphine-like μ-opioid receptor agonist analgesic[6], vildagliptin (Galvus®) is a dipeptidylpeptidase-4 inhibitor administered in type II diabetes[7], while desvenlafaxine (Pristiq®) is a serotonin-norepinephrine reuptake inhibitor antidepressant[8] (Scheme 1).



Scheme 1

1,3-Amino alcohols are also interesting from a chemical aspect, since they are suitable starting materials for the synthesis of 1,3-heterocycles[9-14] and in an enantiopure form, they can serve as useful asymmetric auxiliaries[15-19] or asymmetric catalysts[1, 19-23] in enantioselective transformations.

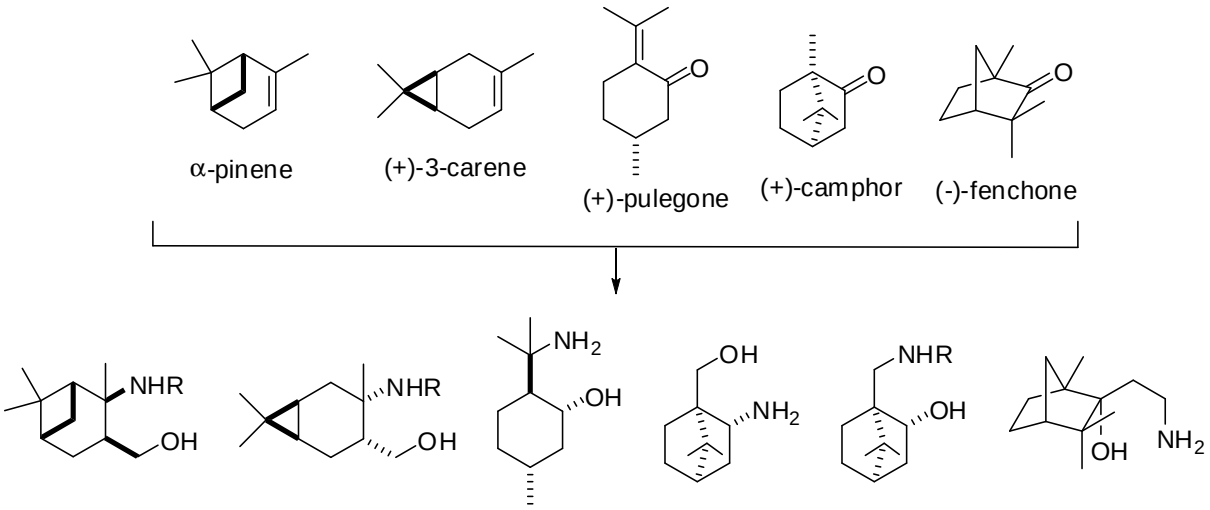
2.1.1. Synthesis and application of 1,3-amino alcohols

Numerous strategies have been developed for the synthesis of optically pure 1,3-amino alcohols, *e.g.*:

- from achiral compounds via asymmetric synthesis, *e.g.* the asymmetric Mannich reaction[24, 25], followed by diastereoselective reduction
- from optically pure compounds, *e.g.* the reduction of enantiopure β-amino acids and their derivatives[26] or utilizing optically pure *N*-sulfinyl imines in the Mannich reaction[24]
- by performing a non-enantioselective synthesis and resolving the product 1,3-amino alcohols

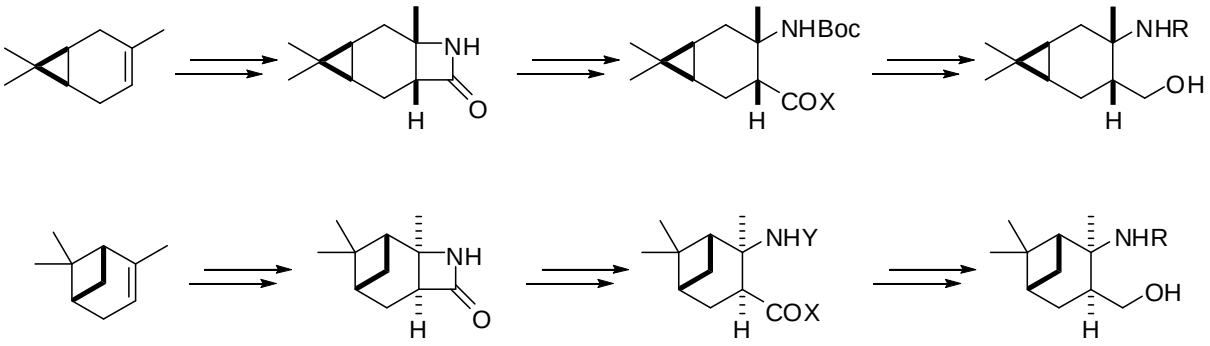
A simple alternative is to use "Nature's laboratory" to establish asymmetry and choose a readily available starting material from the chiral pool. Monoterpenes are small, relatively cheap and non-toxic optically active compounds with a suitable functional group that can be transformed economically to the target 1,3-amino alcohol moiety. For example, Eliel and He

prepared (-)-8-aminomenthol from (+)-pulegone in a three-step process[15], Dimitrov *et al.* synthetized optically active monoterpene-based 1,3-amino alcohols from (+)-camphor and (-)-fenchone[27], Mino *et al.* made the camphor-derived enantiomeric 1,3-amino alcohol from ketopinic acid[21], Li *et al.* prepared a regioisomeric camphor derivative enantiopure 1,3-amino alcohol also from ketopinic acid[28], and in our institute, (+)- and (-)-α-pinene- and (+)-3-carene-based optically pure 1,3-amino alcohols were synthetized by Szakonyi *et al.*[9] and Gyónfalvi *et al.*[10], respectively (Scheme 2).



Scheme 2

Chlorosulfonyl isocyanate (CSI) was added stereo- and regioselectively to (+)-3-carene[10] and (+)- and (-)-α-pinene[9, 11] to prepare new optically active *β*-amino acids, esters and amides (Scheme 3). Simple reduction and functionalization of these precursors led to enantiopure 1,3-amino alcohols. The major advantage of α-pinene-derived compounds over those derived from 3-carene is that both enantiomers of α-pinene are commercially available.



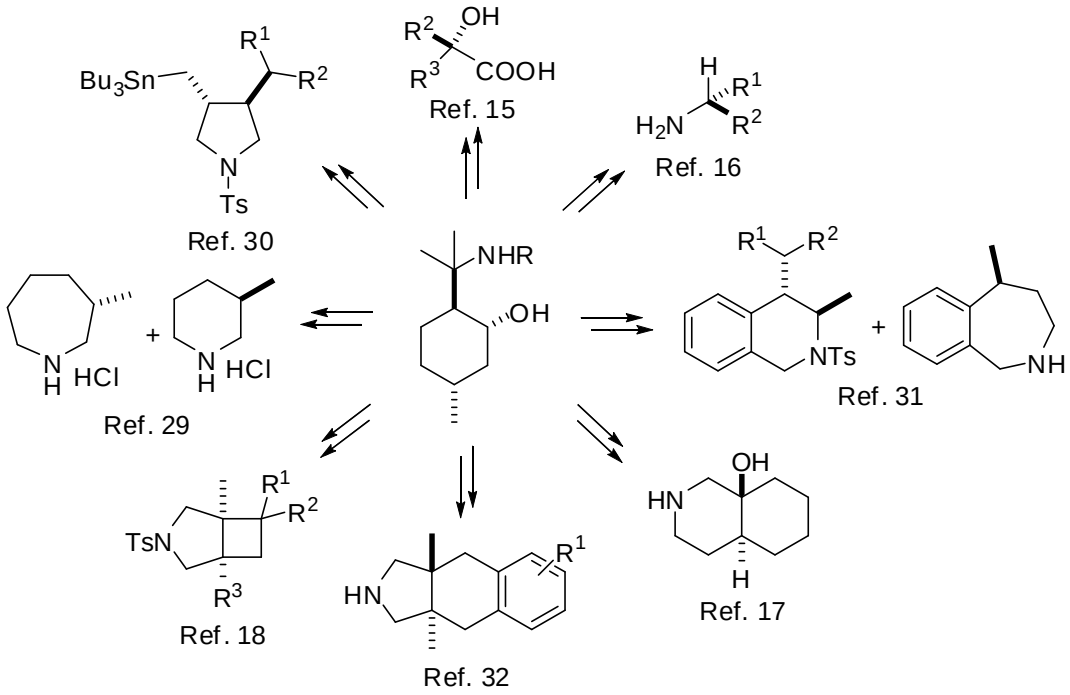
X = OH, OEt, OMe, NH_2 ; Y = H, Boc, COOEt ; R = H, Me

Scheme 3

Enantiomerically pure 1,3-amino alcohols can be utilized as chiral auxiliaries in stoichiometric amounts or as asymmetric catalysts, either in the form of amino alcohols or as their derivatives, such as 1,3-oxazines.

2.1.1.1. Application of 1,3-amino alcohols as chiral auxiliaries

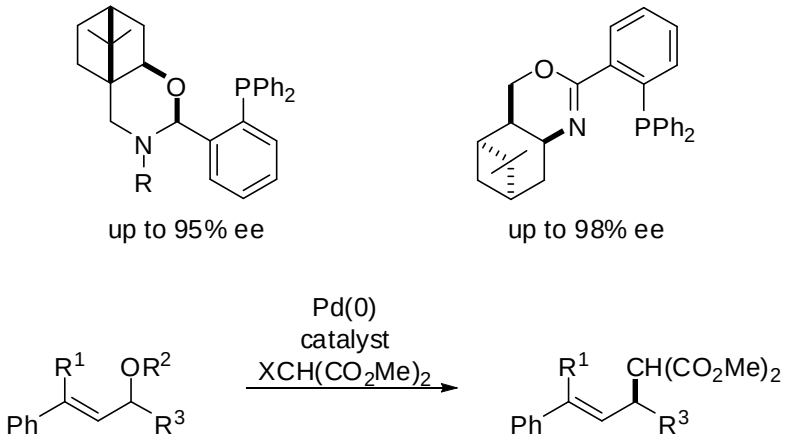
Although, 1,3-amino alcohols have to be used in stoichiometric amounts as chiral auxiliaries in multistep synthetic procedures, there are many applications of them for the synthesis of various valuable compounds, since chirality transfer is generally achieved to a high degree. Among the most widely utilized chiral auxiliaries are (-)-8-aminomenthol and its derivatives (Scheme 4). In their pioneering work, Eliel and He reported the application of (-)-8-aminomenthol in the preparation of enantiomeric α-hydroxy acids[15]. Later, the research group of Pedrosa studied the applications of (-)-8-aminomenthol particularly extensively. They utilized this auxiliary for the preparation of enantiopure primary amines[16] and various enantiomeric heterocycles, such as *trans*-8a-hydroxydecahydro-isoquinolines[17], (*S*)-3-methyl-perhydroazepine and (*R*)-3-methylpiperidine[29], pyrrolidine-derivatives[30], tetrahydroisoquinolines and tertahydrobenzazepines[31], isoindoline derivatives[32] and 3-azabicyclo[3.2.0]heptanes[18].



Scheme 4

2.1.1.2. Application of enantiopure 1,3-amino alcohol derivatives as asymmetric catalysts

Besides 1,3-amino alcohols, their derivatives such as 1,3-oxazines have also been utilized as asymmetric catalysts[19, 33]. For instance, camphor-derived oxazaborinanes were used in the asymmetric reduction of acetophenones, enantioselectivities up to 91% ee being observed[28]. Camphor-derived aminophosphine phosphinite ligands were utilized in the Rh-catalysed asymmetric reduction of dehydroamino acid derivatives with enantioselectivities in the range 77-85% ee[34]. Moreover, optically active camphor-[21] and β-pinene-derived[35] 2'-diphenylphosphinophenyl-substituted 1,3-oxazines were successfully used as ligands in Pd-catalysed asymmetric allylic alkylation reactions, with high enantioselectivities (Scheme 5).

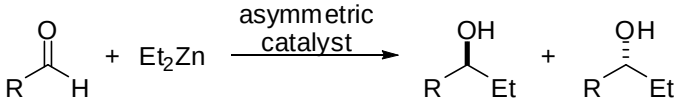


R^1 = H, Ph; R^2 = Ac, vinyl sulfonate, R^3 = alkyl, Ph; X = H, Na

Scheme 5

2.1.1.3. 1,3-Amino alcohols and diamines as catalysts in the enantioselective addition of dialkylzinc reagents to carbonyl compounds

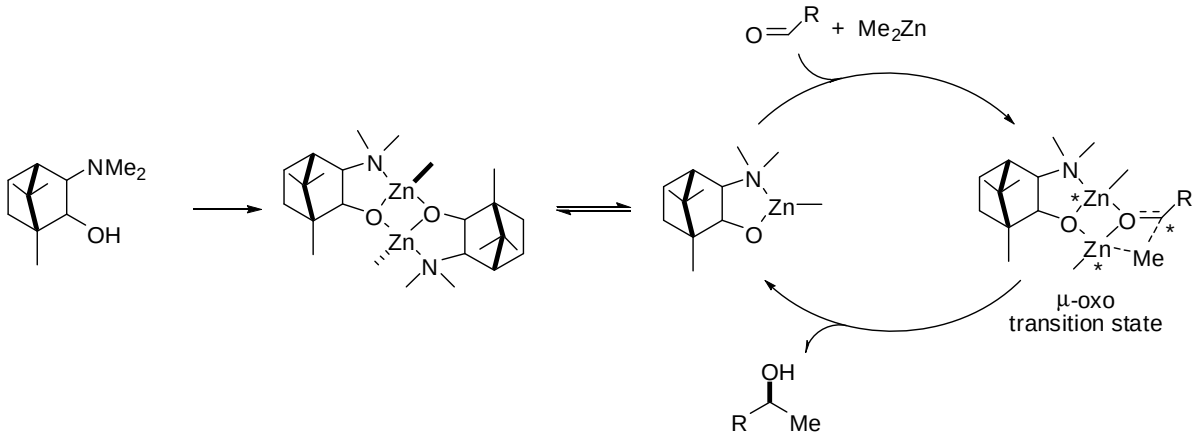
The nucleophilic addition of dialkylzinc reagents to carbonyl compounds is a powerful asymmetric carbon-carbon bond-forming reaction resulting in optically active secondary alcohols (Scheme 6).



Scheme 6

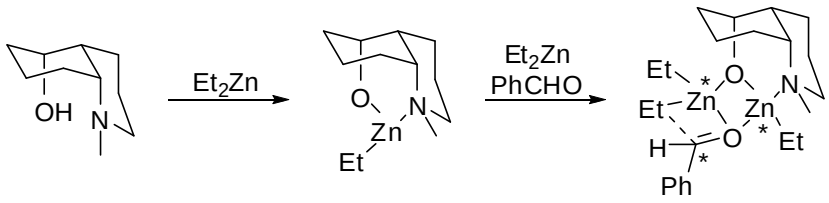
It also proved to be an excellent model reaction for the interpretation of non-linear effects in asymmetric catalysis by Noyori *et al.*[36] and in asymmetric autocatalysis by Soai *et al.*[37]. However, these milestone discoveries were mainly based on the application of 1,2-

amino alcohol or rigid heteroaromatic catalysts. Related to these findings and based on the relatively simple preparation, there are numerous examples in the literature for the application of 1,2-amino alcohol catalysts and auxiliaries[38]. Less attention has been devoted to the analogous 1,3-[19, 22, 23, 27, 39-46], and 1,4-amino alcohol ligands[47-51]. According to the transition state model established by Noyori *et al.*[52], the addition of the zinc reagent takes place first via a dimeric pseudo-five-membered intermediate formed by the 1,2-amino alcohol catalyst and the dialkylzinc reagent, which consequently transforms into the monomeric active species[53, 54] (Scheme 7).



Scheme 7

When the catalyst is a 1,3-amino alcohol, a presumably more flexible pseudo-six-membered intermediate is formed, though this model has been far less studied[23, 49] (Scheme 8).

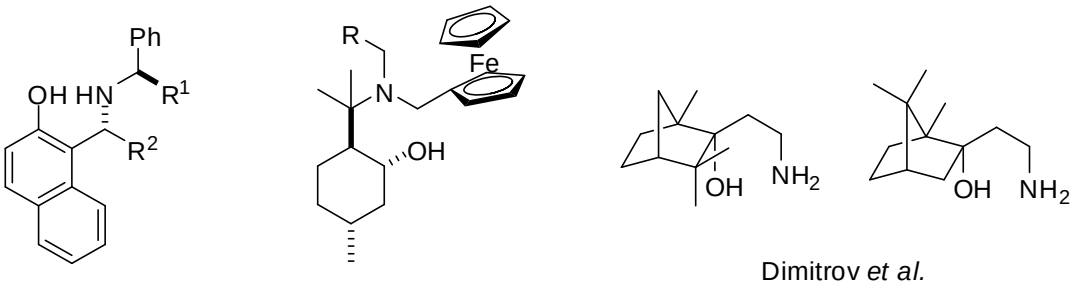


Scheme 8

Moreover, few examples of substituent-dependent product absolute configuration selectivity have been reported for 1,2-amino alcohols[55-57], and none for 1,3- or 1,4-amino alcohols.

1,3-Diamines have also proved to be efficient catalysts in the asymmetric addition of dialkylzinc to carbonyl compounds[56-59].

Selected 1,3-amino alcohols utilized in the enantioselective addition of dialkylzinc to carbonyl compounds are presented in Scheme 9.



Palmieri *et al.*
best ee 89%

Vilaplana *et al.*
best ee 95%

Dimitrov *et al.*
best ee 28% and 9%, respectively

Scheme 9

Cimarelli *et al.* reported the Mannich condensation of 2-naphthol, various aldehydes and optically pure amines for the preparation of enantiopure 1,3-aminonaphthols that were utilized as chiral catalysts in the addition of diethylzinc to aldehydes[25]. The simplicity of the catalyst preparation and the fine tunability of these systems make the 1,3-aminonaphthols an attractive target for catalyst development.

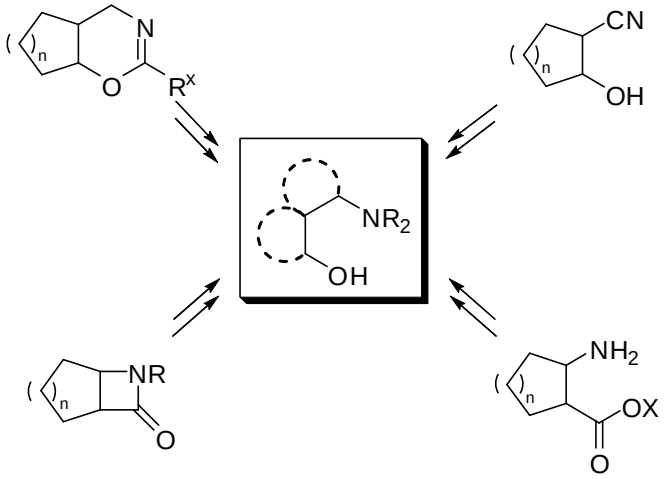
Vilaplana *et al.* reported the synthesis of ferrocene-functionalized 1,3-amino alcohols and utilized them in the addition of diethylzinc to aldehydes[22]. They found noteworthy enantioselectivity (in the range 60-95% ee) for aromatic, aliphatic and ferrocenyl aldehydes.

Dimitrov *et al.* synthetized (+)-camphor- and (-)-fenchone-based 1,3-amino alcohols[27]. However, the application of these catalysts led to only moderate enantioselectivities.

A common drawback of the last two examples is that only one enantiomer can be prepared from commercially available sources, or the other one is far more expensive.

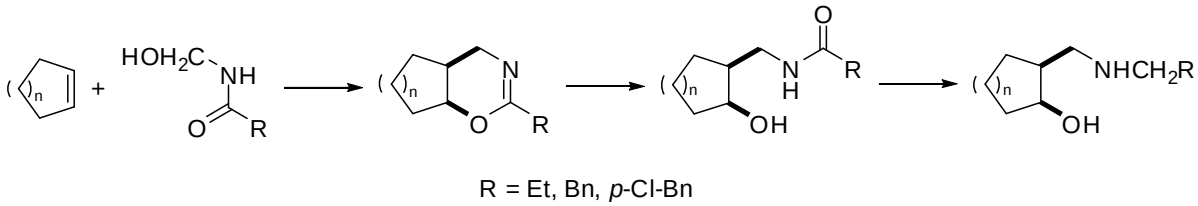
2.1.2. Synthesis of *N*-substituted alicyclic 1,3-amino alcohols

The significance of alicyclic 1,3-amino alcohols has attracted considerable scientific attention, and a number of strategies have been developed for their economical and effective synthesis (Scheme 10). The strategies include the reduction of alicyclic-fused *β*-lactams[60], *β*-amino acids and esters[9], the reduction of 2-hydroxycycloalkanecarbonitriles[61-63], and the catalytic reduction of cycloalkane-fused 1,3-oxazines[64-67].



Scheme 10

The cycloaddition strategies[60, 65-67] seem to be the shortest routes, although the mostly primary 1,3-amino alcohols obtained require further steps to provide substituted compounds and the attainment of higher diversity. Another method[64] gives *N*-monosubstituted alicyclic 1,3-amino alcohols directly in a three-step 1,4-dipolar cycloaddition/hydrolysis/reduction sequence, though the substitution pattern is limited by the *N*-(hydroxymethyl)amide applied (Scheme 11). Since the 1,4-dipolar cycloaddition step is highly stereoselective, *cis*-1,3-amino alcohols can be prepared exclusively.



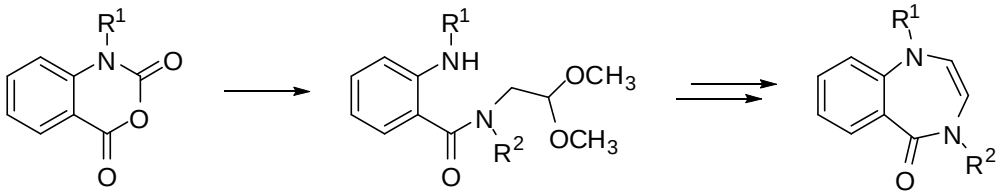
R = Et, Bn, *p*-Cl-Bn

Scheme 11

2.2. Microwave-assisted synthesis of 1,4-diazepin-5-ones

The field of MW-assisted organic synthesis (MAOS) has rapidly been gaining ground since the late 1990s and is still attracting considerable attention due to its proven benefits, as compared to conventional heating, *e.g.* the rapid optimization of reactions, increased yields, enhanced product purities, altered product selectivity and novel chemical reactivities[68-71]. MAOS is based on the MW dielectric heating effects that are responsible for the extremely efficient heating of materials. Besides thermal or kinetic effects, there is clear evidence for the presence of the “specific” or “non-thermal” MW effects responsible for results that cannot be achieved at the same reaction temperature with conventional heating[72].

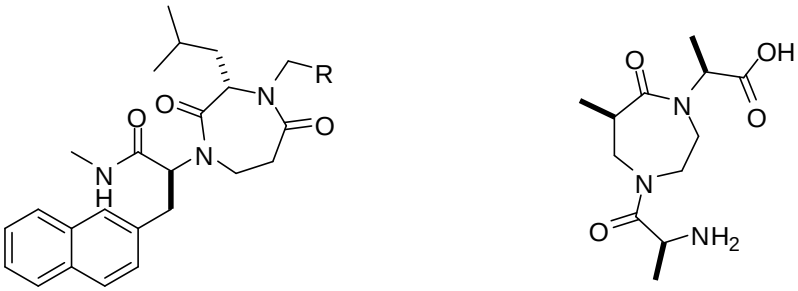
1,4-Diazepines and especially 1,4-benzodiazepines are an extensively studied class of heterocycles due to their pharmaceutical importance[73], and numerous synthetic strategies have therefore been developed, including MW-assisted methods[74]. As an example, a short and efficient synthesis of *N,N'*-disubstituted 1,4-benzodiazepines was devised by Wang and Cloudsdale, from commercially available isatoic anhydride[75] (Scheme 12).



R^1 = Me, allyl, Bn; R^2 = Me, Bn

Scheme 12

There is only one literature report on the synthesis of cycloalkane-condensed 1,4-diazepines[76], though a number of saturated monocyclic 1,4-diazepines exhibit interesting biological properties, such as lymphocyte function-associated antigen-1 (LFA-1) inhibitors[77] and γ-turn-like mimetics[78] (Scheme 13).

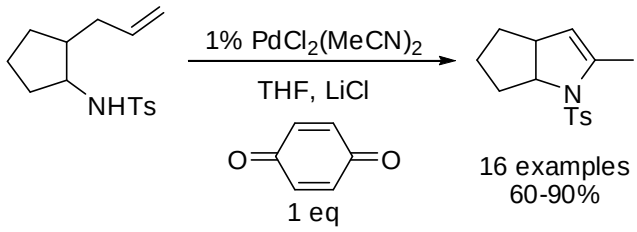


LFA-1 inhibitors γ-turn-like mimetic

Scheme 13

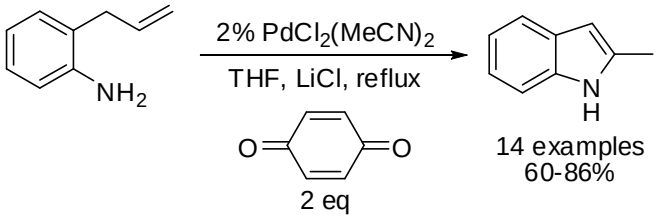
2.3. Synthesis of *N*-heterocycles via Pd(II)-catalysed oxidative amination

Nucleophilic attack on Pd(II)-complexed alkenes is one of the most efficient organo-metallic processes with which to generate valuable organic compounds. A prominent example of them is the Wacker process[79], an industrial method for the preparation of acetaldehyde from ethylene. The pioneering work of Hegedus showed that nitrogen nucleophiles too can be used as reactants in such transformations[80]. In the case of cyclopentylamine derivatives, both the starting amine and the product are good ligands for palladium, though when suitably derivatized in order to decrease their basicity, such transformations can be performed in a catalytic fashion [81-83] (Scheme 14).



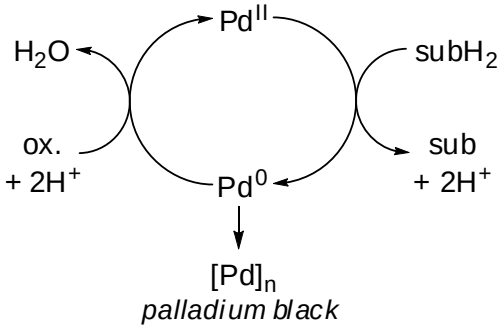
Scheme 14

Since aromatic amines are much less basic than aliphatic ones, these substances readily cyclize to the corresponding indole derivatives without the necessity of *N*-functionalization (Scheme 15).



Scheme 15

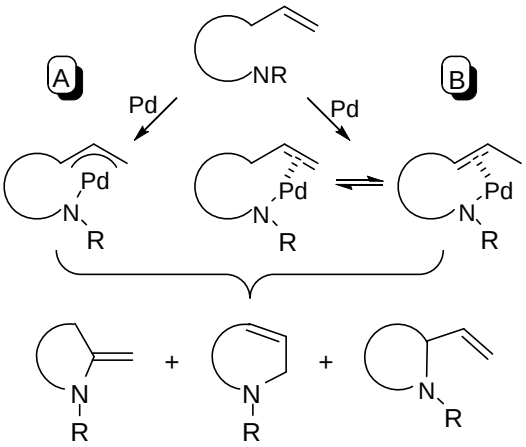
In order to achieve catalysis, not only the character of the amine, but also the re-oxidation of the catalyst should be considered. At the end of each catalytic cycle, the Pd(0) that is formed needs to be re-oxidized to the catalytically active Pd(II) species before aggregation which would lead to inactivation (Scheme 16).



Scheme 16

For this, a number of redox systems have been developed with regard to the stability of the products towards the oxidant. While the $O_2/CuCl_2$ system is used in the classical Wacker process[80], other metal-free systems involving benzoquinone[84], molecular oxygen[85] and even air[86] have been developed. Among these systems, molecular oxygen and air are the most attractive from both economical and environmental viewpoints.

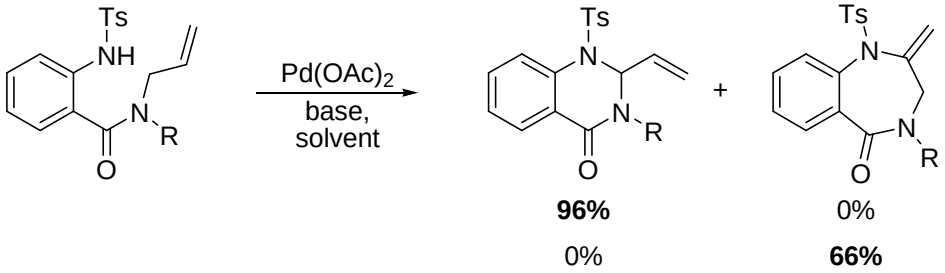
As concerns the underlying mechanism of the oxidative Pd(II)-catalysed formation of *N*-heterocycles, two different pathways are hypothesized (Scheme 17). One proceeds via a η^3-allyl-palladium intermediate (A), while in the other an aminopalladation (AP)/β-hydride elimination route (B) is proposed.



Scheme 17

In the literature, reports can be found that support each of these theories[86-88], but the exact underlying mechanism remains unclear.

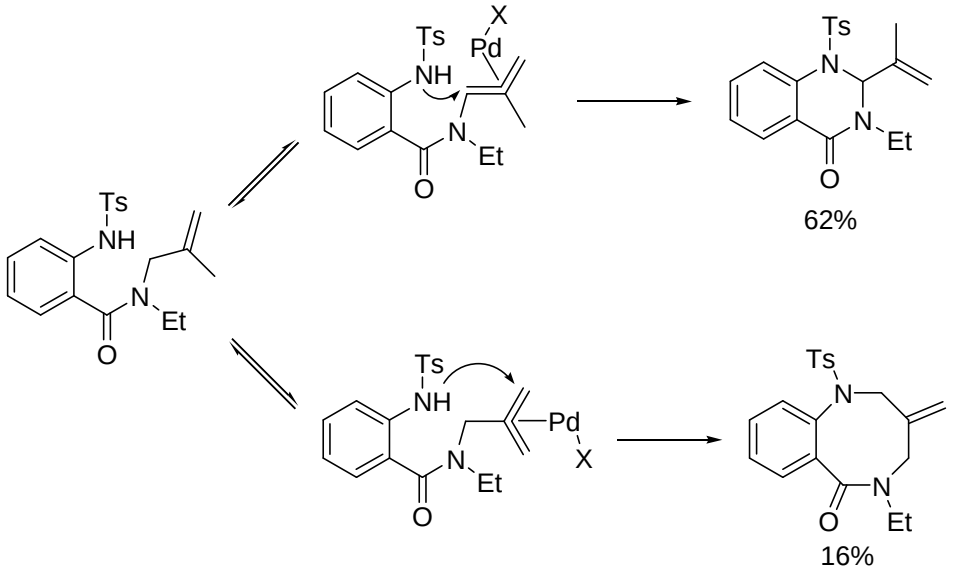
In 2004, Beccalli *et al.* described the aerobic Pd(II)-catalysed cyclization of tosylated *N*-allylanthranilamides[86]. They found that, by using different base and solvent combinations, 2-vinylquinazolin-4-ones and 2-methylene-1,4-benzodiazepin-5-ones could be obtained regio-selectively (Scheme 18).



Scheme 18

By using sodium acetate in DMSO at 100 ºC, quinazolin-4-ones were selectively obtained in up to 96% yield, while in pyridine in xylene in the presence of air at 100 ºC, 1,4-benzodiazepin-5-ones were produced in up to 66% yield. It was proposed that the cyclizations proceed via different intermediates. For the formation of quinazoline-type products, an η^3-allyl-palladium complex was suggested, whereas for the formation of diazepine-type compounds, a π-olefin-complex/β-hydride elimination pathway was postulated. Further support

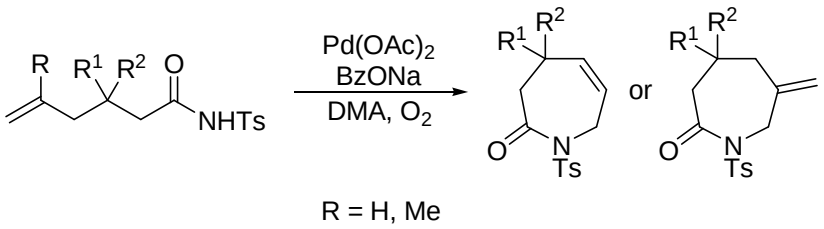
for their η^3-allyl-palladium complex theory was obtained from the reaction of an *N*-(2-methylallyl)amide derivative. Under the optimized conditions for the formation of 1,4-benzodiazepin-5-ones, no product formation was observed, while under the conditions for quinazoline formation, a mixture of two products was obtained. The major one was a quinazoline-type compound, and the minor one was a 1,5-benzodiazocine-type product (Scheme 19).



Scheme 19

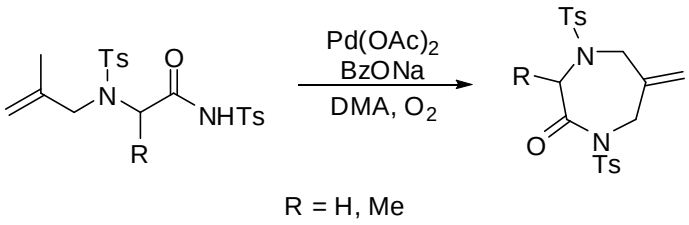
It was assumed that the presence of the methyl group on the allyl group allowed the formation of two isomeric η^3-allyl-palladium complexes, resulting in the distinct structures obtained.

Wu *et al.* recently reported a Bronsted base-modulated, Pd-catalysed intramolecular oxidative amination to obtain seven-membered heterocycles regioselectively[89] (Scheme 20).



Scheme 20

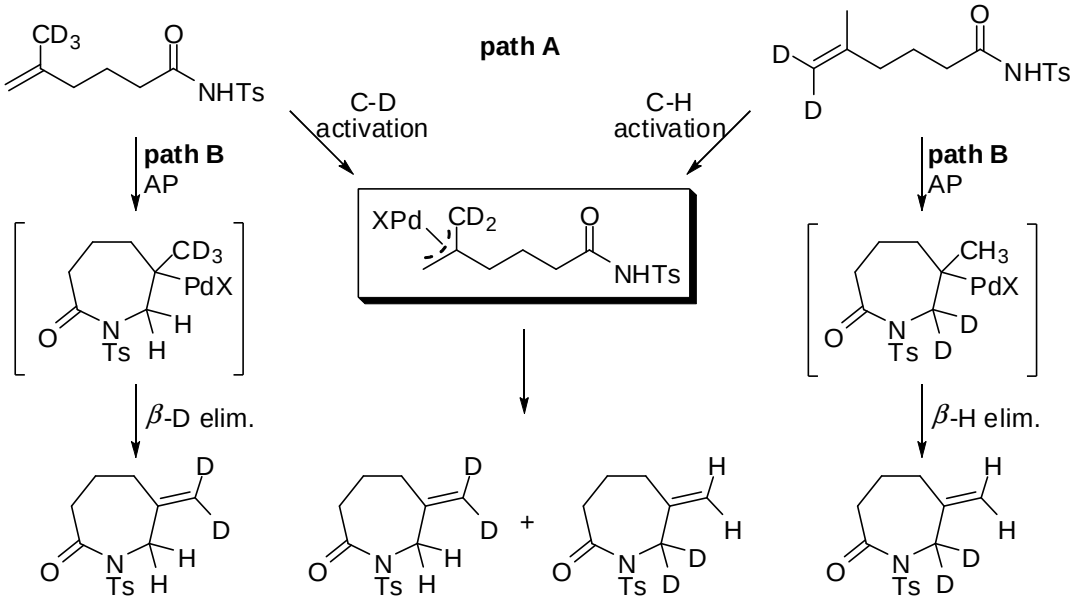
In this study, seven-membered heterocycles are formed exclusively or in a pronounced excess over five-membered ones. Among the chosen substrates, α-amino acid derivatives were also cyclized to the corresponding diazepinones in good yields (Scheme 21).



R = H, Me

Scheme 21

However, when the conditions developed were applied for the synthesis of an eight-membered heterocycle, the regioselectivity was reversed, favouring the formation of the six-membered cycle. It was presumed that the application of a Bronsted base promotes the formation of the C-N bond in an *endo* fashion via a π-allyl-palladium intermediate (path A) instead of an aminopalladation/β-hydride elimination (path B) pathway. This hypothesis was supported the results of by deuterium labelling experiments (Scheme 22).



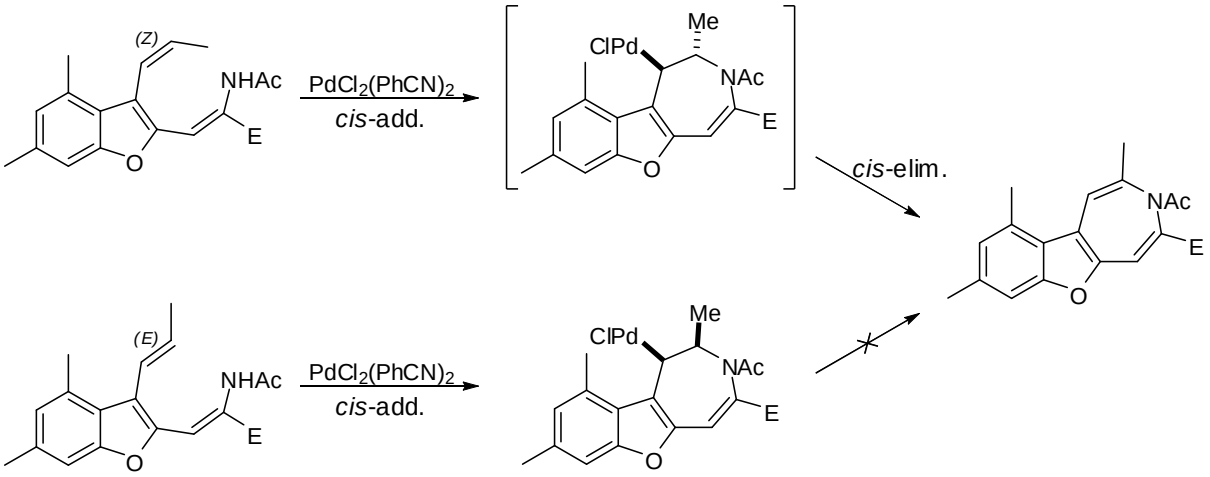
Scheme 22

Both reactions with deuterium-labelled substrates resulted in a mixture of seven-membered products in a close to 1:1 ratio, besides the five-membered products. If the reactions proceeded via the aminopalladation/β-hydride elimination pathway, each deuterated substrate would give the appropriate seven-membered product exclusively, together with the five-membered products. In view of the results, this possibility was ruled out and it was assumed that the outcome supports an allylic C-H activation/reductive elimination pathway.

In contrast, in a number of publications the Stahl group[88, 90-92] and others[93-96] have presented noteworthy examples demonstrating that the aza-Wacker-type oxidative cyclization

of alkenes can proceed via the *cis*- or *trans*-aminopalladation/*β*-hydride elimination pathway, *cis* addition being preferred.

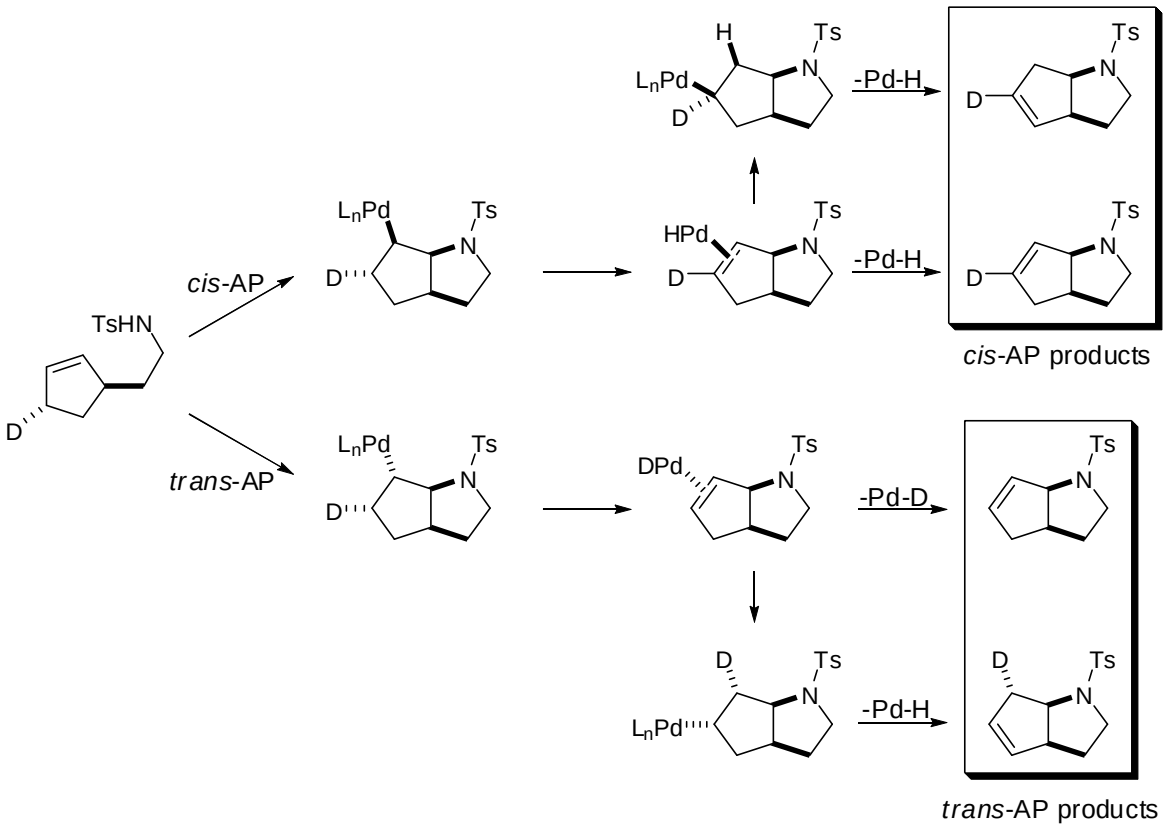
An early, yet outstanding example is a report by Isomura *et al.* on the cyclization of 1-aminohexatrienes with $PdCl_2$[93] (Scheme 23).



Scheme 23

It was found that, while the *Z* substrate readily furnishes the desired benzo-furo[2,3-*d*]azepine derivative under stoichiometric Pd catalysis, the *E* substrate provides only the Pd-σ-complex, which could be isolated and characterized. Since *β*-hydride elimination generally proceeds with *cis* stereochemistry, and in the case of *E* substrate there is no hydrogen *cis* to the palladium, the reaction stops after the addition step. Furthermore, the demonstrated *cis* arrangement of the palladium and methyl groups can originate from an initial *cis* addition to the *E* double bond.

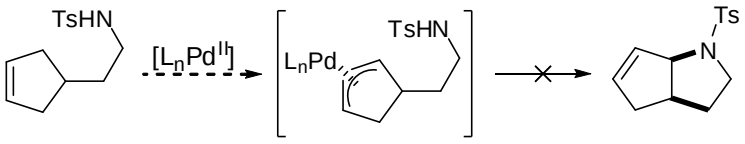
As part of an extensive deuterium labelling mechanistic study on the Pd-catalysed intramolecular aza-Wacker reaction, Liu and Stahl[88] reported important data on the preference for *cis*-aminopalladation over *trans*-aminopalladation (Scheme 24).



Scheme 24

In the testing of five catalyst systems, four yielded *cis*-aminopalladation products exclusively, while an *N*-heterocyclic-carbene catalyst system gave a nearly 1:1 mixture of *cis*- and *trans*-aminopalladation products.

The theory was supported by the experimental result, that no η^3-allyl-palladium mechanism is involved in these transformations (Scheme 25).



Scheme 25

If the reaction proceeded via such a mechanism, the bicyclic product could also be prepared from the double-bond isomeric substrate; when the reaction was performed, however, only unreacted starting material was isolated from the mixture.

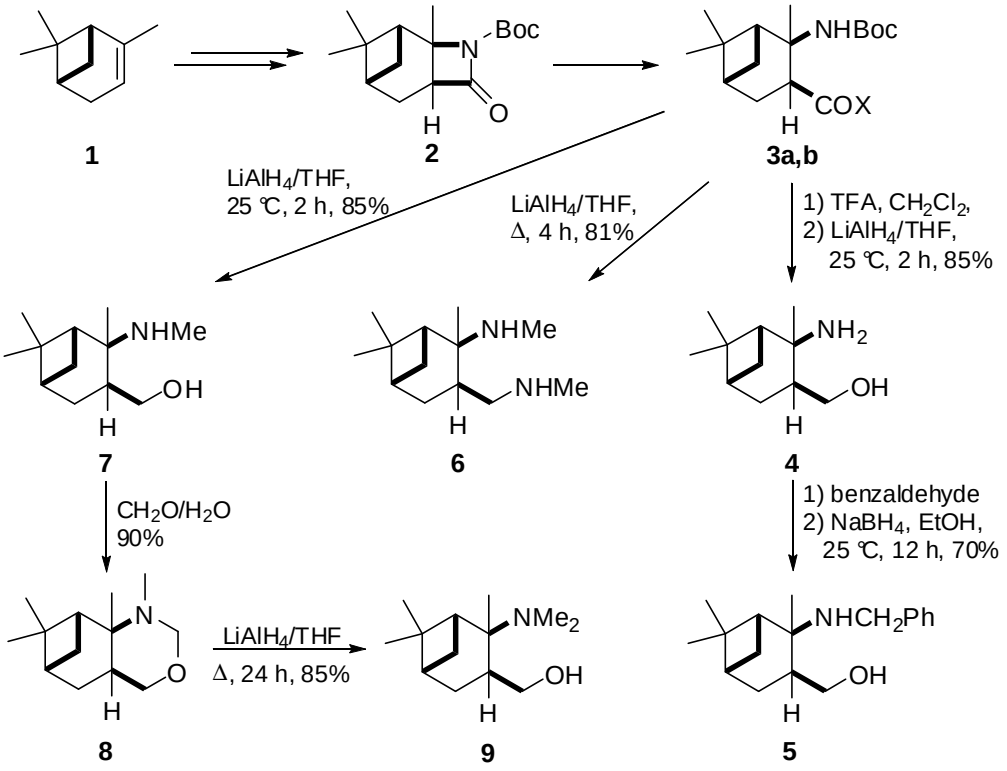
These results, together with the fact that in the case of ethylene in the classical Wacker process practically no η^3-allyl-palladium complex is formed, strongly support the feasibility of the aminopalladation/β-hydride elimination pathway.

3. Results and Discussion

3.1. Synthesis of alicyclic 1,3-amino alcohols

3.1.1. Synthesis of α-pinene-derived 1,3-amino alcohols and their application as chiral auxiliaries [1]

Enantiopure γ-amino alcohols **4**, **5**, **7** and **9** and diamine **6** were synthetized from (+)- and (-)-α-pinene **1**, respectively, according to Scheme 26. Although both enantiomers were prepared, only the compounds derived from (-)-α-pinene are depicted in Scheme 26.



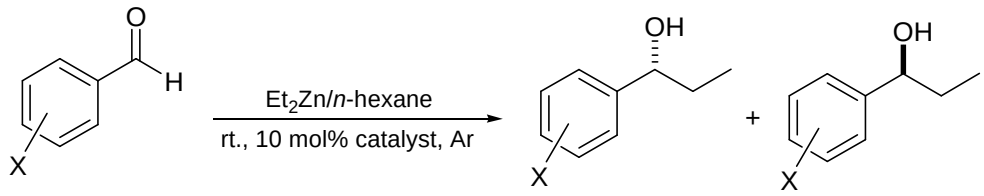
Scheme 26

Amino ester **3a** (X = OMe) and carboxamide **3b** (X = NHMe) were synthetized according to literature methods[9, 11]. The literature data indicate that the cycloaddition of CSI to α-pinene is highly regio- and stereoselective[9], and the optical purity of the compounds obtained is therefore identical to the enantiomeric purity of the starting monoterpenes. Deprotection of **3a**, followed by reduction, resulted in primary amino alcohol **4**, and sequential reductive amination with benzaldehyde gave derivative **5**. Direct reduction of **3a** produced *N*-methyl derivative **7**, while reduction of the carboxamide provided diamine **6**. *N*,*N*-Dimethylamino alcohol **9** was prepared via oxazine **8** by $LiAlH_4$ reduction. Despite all

our efforts, we failed to synthetize the *N*-benzyl-*N*-methyl-substituted amino alcohol derivative by an analogous method. We suggest that, due to the highly constrained bicyclic pinane skeleton, bulkier substituents create so much steric hindrance that this is highly unfavoured. Although a number of different strategies were applied, we also failed to synthetize the *N*-isopropyl derivative of **4**.

The synthetized 1,3-amino alcohols (**4, 5, 7** and **9**) and 1,3-diamine (**6**) can be prepared on a gram scale and in both enantiomeric forms.

Compounds **4-7** and **9** were then used as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes, as test reactions resulting in optically active secondary alcohols (Scheme 27). The enantiomeric excesses of the resulting 1-phenyl-1-propanols were determined by chiral GC (Chirasil-Dex CB column), using a Maestro II Chromatography data system.



10a,b **(*R*)-11a,b** **(*S*)-12a,b**

Scheme 27

Screening of ligands **4-7** and **9** in the enantioselective addition of diethylzinc to aldehydes

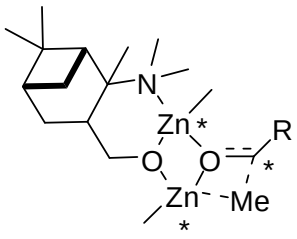
Entry	X	Ligand	Yield (%)	ee (%)	Major configuration
1	H	**6**	88	–	–
2	H	**4**	85	40	*R*
3	3-MeO	**4**	70	22	*R*
4	H	**5**	87	13	*S*
5	3-MeO	**5**	78	32	*S*
6	H	**7**	83	53	*R*
7	3-MeO	**7**	75	20	*R*
8	H	**9**	91	62	*S*
9	**3-MeO**	**9**	**83**	**72**	***S***

Table 1

Unfortunately, diamine **6** underwent no enantioinduction at all in the title reaction. However, when amino alcohol **4** or **7** was used, moderate enantioselectivities were observed, the 1-aryl-1-propanols being obtained with *R* selectivity. In contrast, when the *N*,*N*-dimethyl- (**9**) or *N*-benzyl-substituted (**5**) catalysts were applied, a complete change in selectivity from *R* to *S* was observed, and amino alcohol **9** gave both the highest yields and enantioselectivities

up to 72% ee. To the best of our knowledge, this is the first report on an *N*-substituent-dependent enantioswicth in the field of 1,3-amino alcohol-catalysed asymmetric reactions.

To clarify the observed *N*-substituent-dependent enantioswitch, molecular modelling was performed for the Noyori-type μ-oxo transition states[52] of amino alcohols **4** and **9** (Scheme 28).



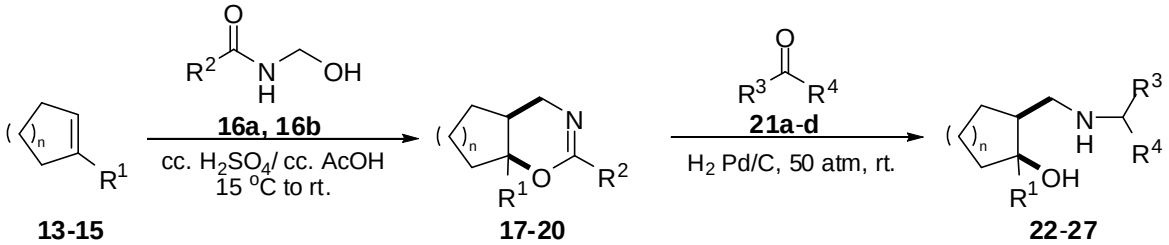
Scheme 28

The calculated lowest-energy transition states were in good accordance with the experimental results. The calculated geometries also allowed an interpretation of the inverted enantioselectivity since the optimum transition state for **9** showed steric hindrance between the bridging methylene of the pinane skeleton and the *N*-methyl group, inhibiting formation of the intermediate diastereomer observed in the case of **4**.

It can be concluded that the rigid, sterically hindered pinane skeleton is an efficient source of chiral induction, though the methyl group next to the nitrogen atom limits the substitution pattern of the nitrogen atom, and as a consequence the fine tuning of the catalyst.

3.1.2. One-pot synthesis of alicyclic *N*-substituted 1,3-amino alcohols [2]

Alicyclic condensed 1,3-oxazines **17-20** were transformed into the corresponding *N*-substituted 1,3-amino alcohols **22-27** in the presence of a ketone **21a-d** in a simple one-pot reductive process (Scheme 29).



Scheme 29

1,3-Oxazines were synthetized by the 1,4-dipolar cycloaddition of *N*-hydroxymethyl-acylamides (**16a**,**b**) to the appropriate cycloalkenes **13-15** in a stereospecific[64, 65], and in the

case of 1-methyl-1-cyclohexene **15** a regiospecific fashion, in full accordance with Markovnikov's rule[66].

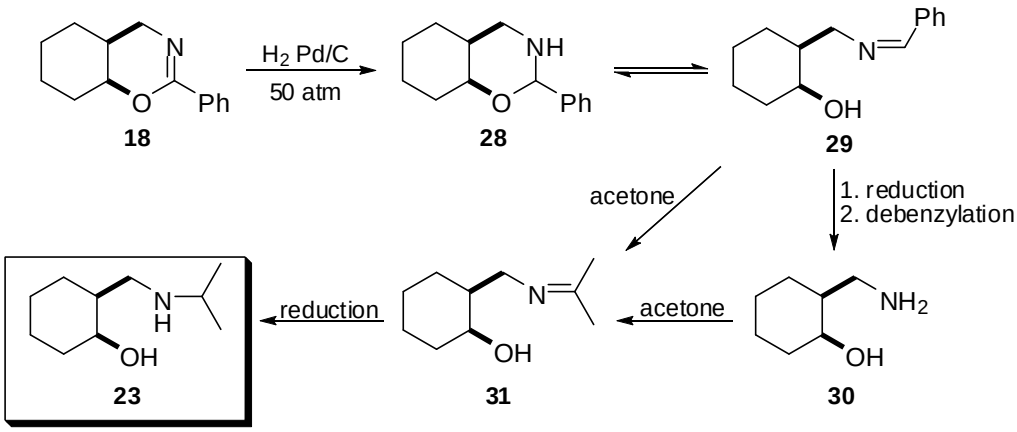
Alicyclic *N*-substituted 1,3-amino alcohols **22-27** obtained from oxazines **17-20**

Compound	n	R^1	R^3	R^4	Yield (%)
22	1	H	Me	Me	37
23	2	H	Me	Me	91
24	2	H	$-(CH_2)_5-$		71
25	2	H	Et	Et	51
26	2	H	Me	Et	50
27	2	Me	Me	Me	43

Table 2

Upon hydrogenation of **18** in the presence of only 1.2 equivalents of acetone and 10% palladium on charcoal under 50 atm of hydrogen at room temperature, *N*-isopropyl 1,3-amino alcohol **23** was isolated in 91% yield (Table 2). However, oxazines **17** and **20** gave lower yields of the corresponding *N*-isopropyl-substituted 1,3-amino alcohols **22** and **27**; the reduction of oxazine **18** in the presence of other aliphatic and alicyclic ketones **21a-d** afforded **24-26** in acceptable to good yields.

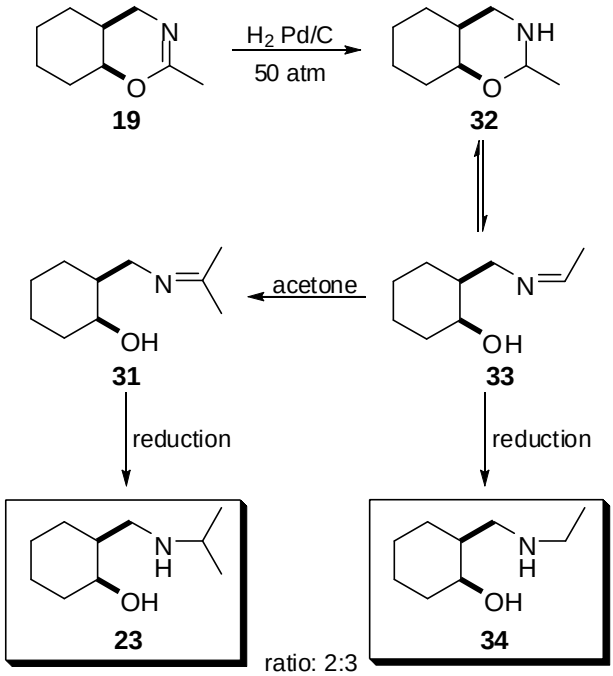
Although the underlying mechanism seems to be rather obvious, two different mechanistic pathways must be considered (Scheme 30).



Scheme 30

Saturation of the C=N double bond takes place first, resulting in **28**, which is in ring-chain tautomeric equilibrium with imine **29**. Next, imine **31** can be formed via two pathways. The reduction and subsequent debenzylation of **29** would furnish **30**, which would form imine **31** with acetone. Alternatively, transimination of **29** by acetone would provide **31** directly. Finally, amino alcohol **23** is formed by the reduction of **31**.

In order to find evidence regarding the alternative transimination pathway, a control experiment was designed where primary amino alcohol could not be formed (Scheme 31). 2-Methyl-substituted oxazine **19** was hydrogenated in the presence of acetone.



Scheme 31

In accordance with our expectations, besides *N*-ethyl-substituted derivative **34**, *N*-iso-propyl-substituted amino alcohol **23** was detected in a ratio of 2:3 in the crude reaction mixture. This experiment clearly supports the proposed competitive pathways depicted in Scheme 30.

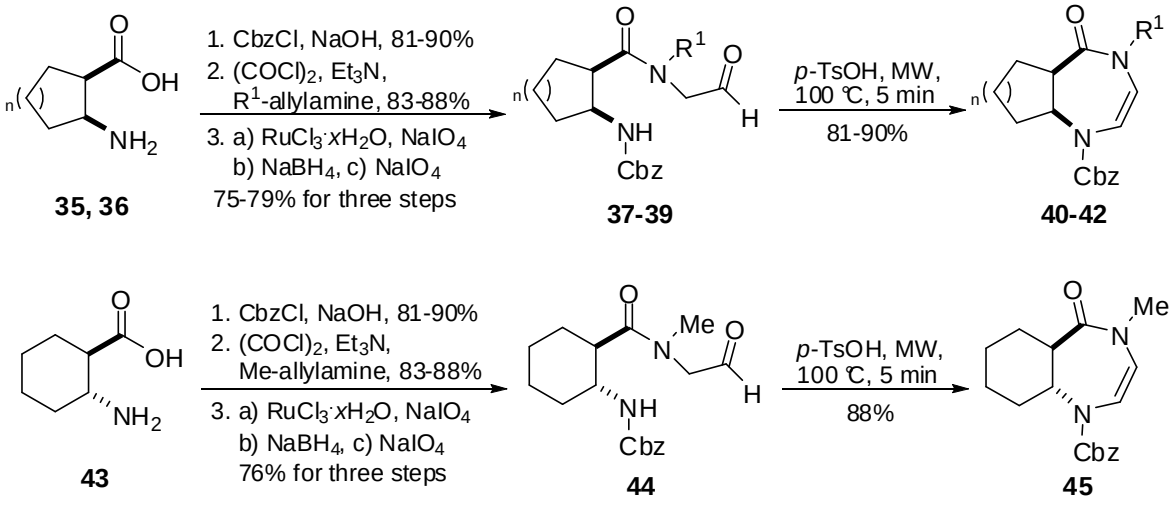
3.2. Synthesis of six-, seven- and eight-membered cycloalkane-fused heterocycles

In order to investigate the cyclization properties of β-amino acid derivatives towards novel alicycle-fused ring systems, we set out to prepare cycloalkane-condensed seven- and eight-membered heterocycles by using state-of-the-art methods such as MW irradiation and transition-metal mediated transformations.

3.2.1. Microwave-assisted synthesis of alicyclic-condensed 1,4-diazepin-5-ones [3]

The application of MW irradiation in organic synthesis is a major field of interest of the research group of Prof. Erik Van der Eycken at the Laboratory for Organic and Microwave-Assisted Chemistry (LOMAC), Katholieke Universiteit Leuven. In the frame of an Erasmus programme, my project there involved the application of MW power to the synthesis of cycloalkane-fused heterocycles.

An efficient, MW assisted method was developed for the cyclization of benzyloxy-carbonyl(Cbz)-protected *cis*- and *trans*-cyclohexane- and *cis*-cyclopentane-formylmethyl carboxamides towards the corresponding 5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-one derivatives **40-42** and **45**. Cbz protection of the starting racemic *cis*- and *trans*-2-aminocyclohexanecarboxylic acids **35** and **43** and cispentacin **36**, followed by amidation with allylmethylamine or allyl(*p*-methoxy)benzylamine and subsequent RuO_4-mediated oxidative cleavage of the olefinic bonds, furnished the corresponding formylmethyl carboxamides **37-39** and **44** (Scheme 32).



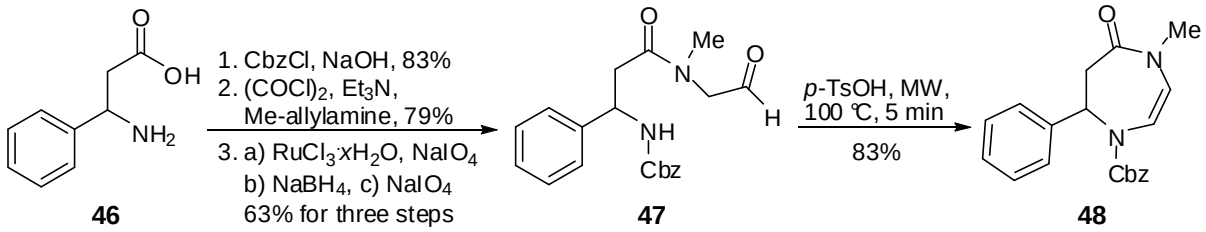
Scheme 32

There are numerous procedures in the literature for the oxidative cleavage of an olefin bond. First, we attempted to perform a one-pot method[97], but the title formylmethyl derivatives could be isolated in only low yields. We therefore decided to utilize a stepwise process instead, to minimize side-reactions[98]. The *in situ* generated RuO_4-catalysed dihydroxylation of the terminal double bond, followed by $NaIO_4$-mediated cleavage of the dihydroxy compound, resulted in a fast, efficient and high-yield (71-79%) preparation of the target molecules **37-39** and **44**.

The very first cyclization was actually the outcome of a failure. When **37** was reacted with benzeneboronic acid in an attempted intramolecular Petasis reaction, only the cyclic ene-carbamate **40** was formed. Since the cyclization was rather sluggish, even under MW irradiation, and the boronic acid acted only as a catalyst to facilitate water elimination, we decided to utilize a stronger acid in order to obtain a better yield and a shorter reaction time. The use of 10 mol% *p*-TsOH in dry CH_2Cl_2 in a MW reactor at 100 ºC resulted in the

corresponding 1,4-diazepin-5-one **40** in 90% yield in only 5 min. For **38** and **44**, the reaction gave similar yields (81% and 88%, respectively). In order to broaden the scope of the transformation, PMB-protected derivative **39** was synthetized and subjected to cyclization, which provided **42** in 83% yield.

As part of the investigation of the scope and limitations of the transformation, phenyl-substituted diazepine **48** was successfully prepared in 83% yield from racemic 3-phenyl-*β*-alanine **46** (Scheme 33).



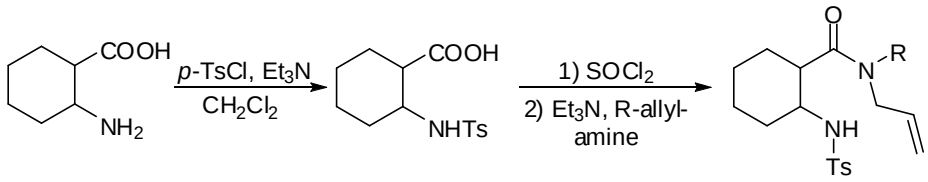
Scheme 33

Unfortunately, our efforts to apply this method to anthranilic acid derivatives failed to give the desired benzodiazepines, most probably because the Cbz-group considerably reduces the nucleophilicity of the aniline-type nitrogen atom.

3.2.2. Pd(II)-catalysed synthesis of cyclohexane-fused 2-vinylpyrimidinones and 1,5-diazocin-6-ones [4]

On the basis of a report by Beccalli *et al.*[86] discussing the Pd(II)-mediated cyclization of tosyl-protected *N*-allylanthranilamides, our aim was to investigate the cyclization properties of the analogous *N*-allyl-2-aminocyclohexanecarboxamides with special attention to the possible stereochemical results of the transformation.

The cyclization of tosyl-protected *cis*- and *trans*-*N*-allyl-2-aminocyclohexane-carboxamides (**53-56, 64**) was carried out in Pd(II)-catalysed oxidative amination reactions. The starting **53-56** and **64** were prepared from the corresponding racemic *cis*- and *trans*-2-aminocyclohexanecarboxylic acids via tosylation, followed by conversion into the acyl chlorides and reaction with allylamines (Scheme 34).



49: *cis*
50: *trans*

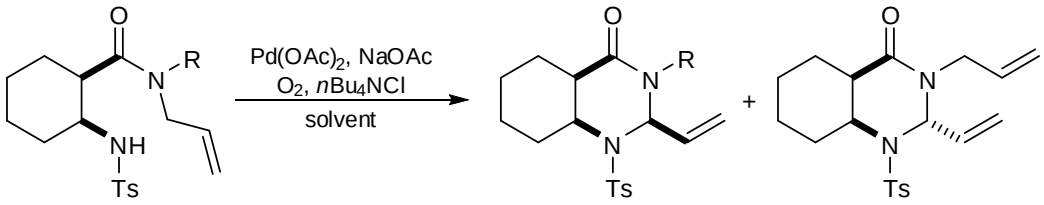
51: *cis*
52: *trans*

53, 54: *cis*
55, 56: *trans*

53, 55: R = allyl, **54, 56**: R = Me

Scheme 34

Although application of the reported cyclization conditions[86] resulted in the formation of Pd black without conversion of the starting material, the systematic use of a phase-transfer catalyst and an oxygen atmosphere on the basis of literature data[99, 100] provided **57** in 69% yield as a single diastereomer (Scheme 35). The *cis*-*N*-allyl-*N*-methyl analogue **54** gave **58** as a single diastereomer, albeit in lower yield (Table 3).



53, 54

57, 58

59

53, **57**: R = allyl; **54**, **58**: R = Me

Scheme 35

Pd(II)-catalysed cyclization of *cis*-*N*-allyl-2-aminocyclohexanecarboxamides **53** and **54**

Entry	Compound	R	T (ºC)	Solvent	Reaction time (h)	Product	Yield (%)
1	**53**	allyl	110	DMSO	4	**57**	69
2	**53**	allyl	110	toluene	1.5	**57+59**	76[a]
3	**54**	Me	130	DMSO	20	**58**	52
4	**54**	Me	110	toluene	2.5	**58**	**84**

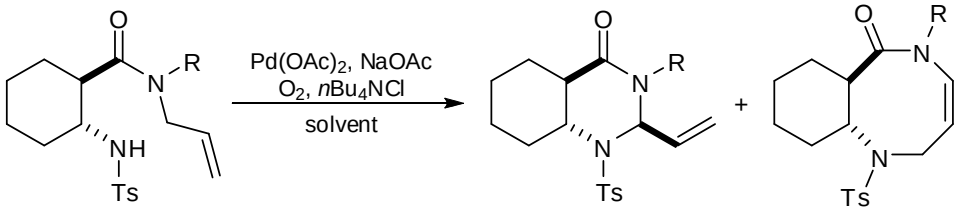
[a]Combined yield of C-2 epimers

Table 3

In view of the reported marked solvent-dependence of such transformations, **53** was reacted in refluxing toluene, which gave a practically 1:1 C-2 epimeric mixture of **57** and **59** in a combined yield of 76%. Under similar conditions, **54** provided **58** in a noteworthy 84%

yield. To investigate the possibility of product isomerization, quinazolinone **57** was submitted to identical conditions as shown in Entry 2, but **59** was not detected in the reaction mixture.

Under the optimized conditions for the cyclization of *trans*-carboxamides **55** and **56**, the reaction was first performed in DMSO (Table 4, Entry 1) and provided a close to 1:1 mixture of two compounds (Scheme 36).



55, **60**, **62**: R = allyl; **56**, **61, 63**: R = Me; **64-66**: R = PMB

Scheme 36

Pd(II)-catalysed cyclization of *trans*-*N*-allyl-2-aminocyclohexanecarboxamides **55, 56** and **64**

Entry	Comp.	R	T (ºC)	Solvent	Reaction time (h)	Yield (%)	
						60, 61, 65	**62, 63, 66**
1	**55**	allyl	110	DMSO	2	42[a] (32)[b]	58 (44)
2	**55**	allyl	110	toluene	0.5	21	79
3	**55**	allyl	**82**	**MeCN**	**4**	**13 (6)**	**87 (72)**
4	**55**	allyl	110	DMF	1.5	45	55
5	**55**	allyl	110	NMP	1.5	33	66
6	**56**	Me	110	DMSO	3	64 (54)	36 (21)
7	**56**	Me	82	MeCN	4	28 (12)	72 (61)
8	**64**	PMB	82	MeCN	4	15 (9)	85 (67)

[a]Calculated ratio based on ^{1}H NMR, [b]isolated yield in parenthesis

Table 4

The first-eluted compound **60** was identified as the *trans* analogue of **57**, while the later-eluted one was identified as *trans*-cyclohexane-fused 1,5-diazocin-6-one **62** on the basis of two-dimensional NMR studies and X-ray crystallography (Figure 1).

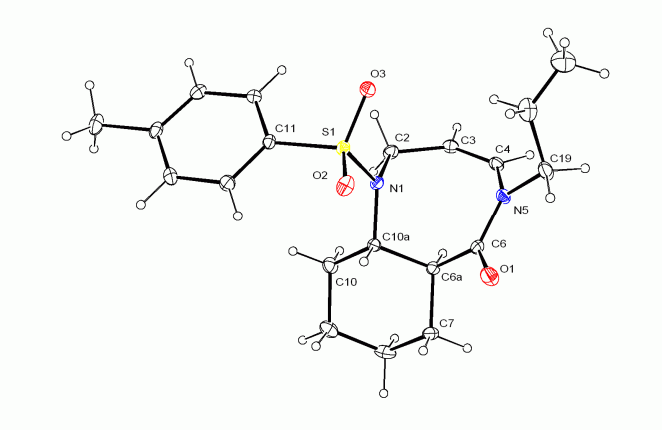
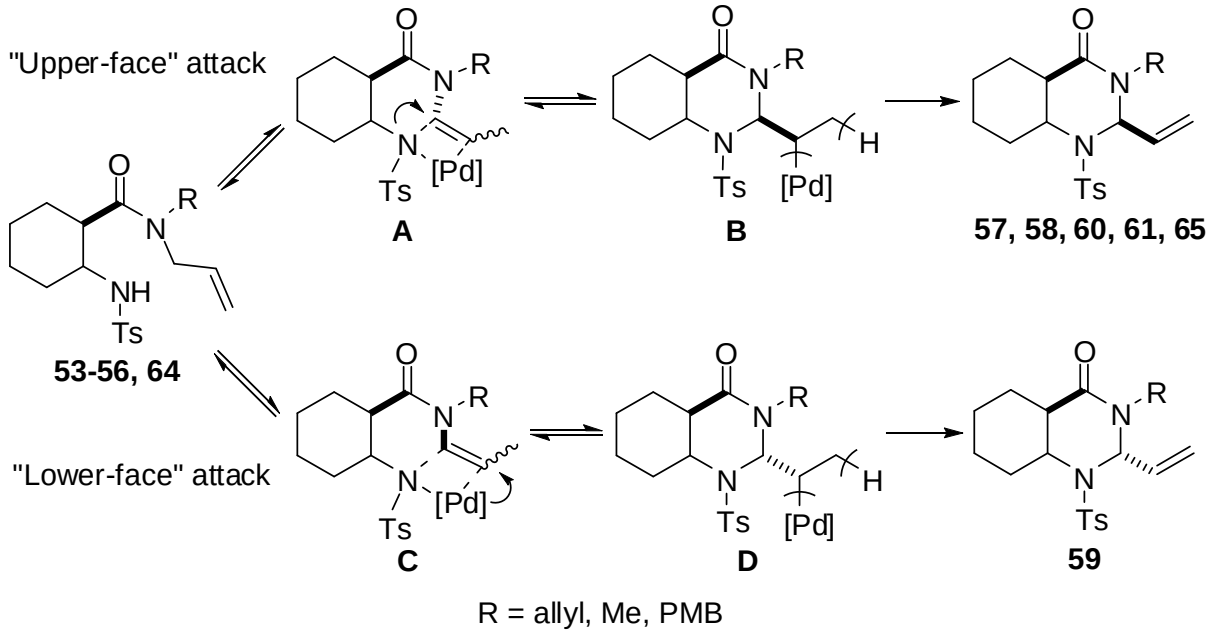


Figure 1

This outcome prompted us to explore the scope and limitations of this transformation, since this uncommon structure can be found in certain spermine alkaloids, such as homaline and dovyalycine[101, 102], and as part of an interleukin-1β synthesis inhibitor peptidomimetic[103].

In a study of the effect of the solvent on the regioselectivity, we found that in toluene diazocinone **62** was formed in a 4:1 ratio with **60**. Moreover, refluxing acetonitrile gave the best ratio of 87:13, together with an isolated yield of 72% of diazocinone **62**. Further efforts to improve the selectivity of the reaction did not succeed. It is interesting that, while the cyclization of **56** in acetonitrile provided **63** in a similar ratio to the diallyl derivative, in DMSO a complete switch was observed, resulting quinazolinone **61** in a ratio of 2:1. In order to increase the value of the products, the *N*-methyl group on the amide moiety was replaced by a PMB group, thus establishing an orthogonal protection of the two nitrogen atoms. The PMB-protected diazocinone **66** was prepared in 67% yield.

In view of these unconventional results, together with recent literature data showing that a π-allyl-palladium transition state does not always support the empirical outcome of certain Pd-mediated transformations[104-107], we took into consideration the concept of *cis- vs. trans*-aminopalladation as another alternative in order to determine which theory best supports our results. Our first doubt about the π-allyl-palladium mechanism was the lack of diazepine-type molecules in the product mixture, albeit theoretical calculations indicate that their thermodynamic stability is comparable to that of the quinazolinones and diazocinones formed. These observations, together with the marked difference between the electron densities of a tosyl-protected aniline-type and a protected cyclohexylamine-type nitrogen atom led us to propose that, after an initial Pd-mediated double-bond migration[106, 107], the ring-closure step takes place via *cis*-aminopalladation, in consequence of the stronger coordination of the cyclohexylamine-type nitrogen to the palladium atom, practically by forming a Lewis base–Lewis acid pair (Scheme 37).

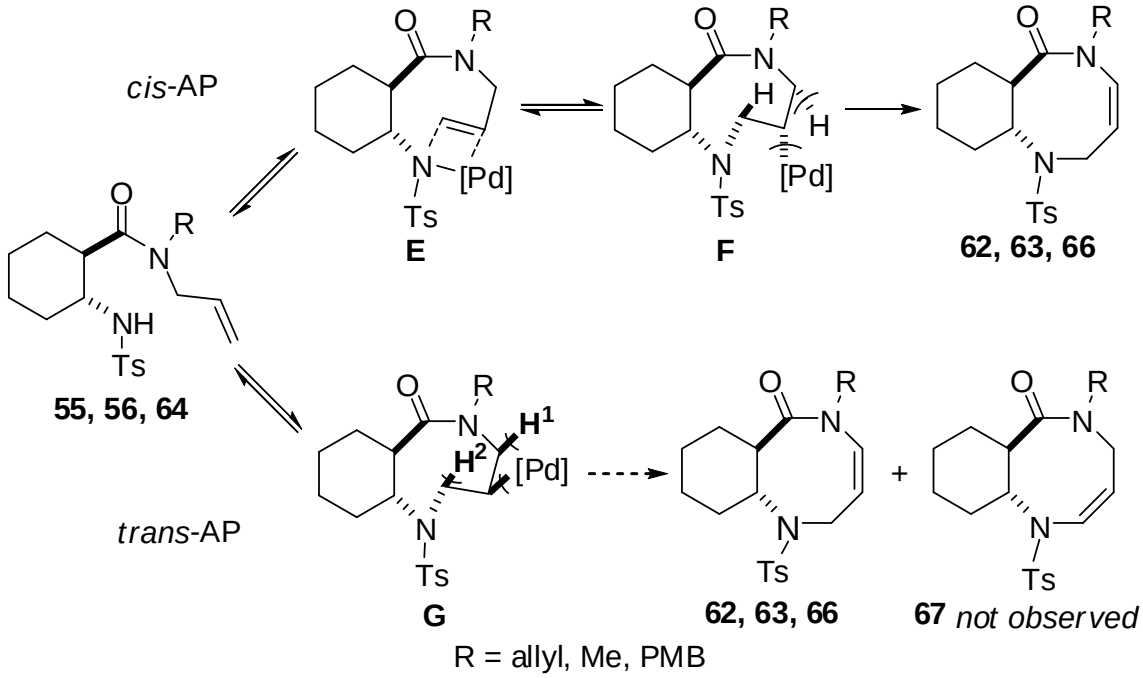


Scheme 37

Hydropalladation of the allylic double bond, followed by β-hydride elimination, provides intermediates **A** and **C**. Consecutively, *cis*-aminopalladation of the isomerized propenylic double bond by either “upper” or “lower-face” attack and final β-hydride elimination from intermediates **B** and **D** would give quinazolinones **57-61** and **65**.

Theoretically, diazocinone-type products could form via a π-allyl-palladium intermediate, but the sole difference as compared to the formation of quinazolinones is the initial stereochemistry of the compounds and not the electron density of the protected nitrogen atom. It is therefore plausible that the underlying mechanism could be similar.

As regards the formation of diazocinones, our proposed catalytic pathway is depicted in Scheme 38.



Scheme 38

Intermediate **E** is formed via *cis*-aminopalladation of the allylic double bond, and a following *syn*-β-hydride elimination from **F** provides **62**, **63** and **66**. If the transformation proceeded via *trans*-aminopalladation, intermediate **G** would form and subsequent *syn*-β-hydride elimination could take place with either $\mathbf{H^1}$ or $\mathbf{H^2}$ giving the double bond isomer product **67** as well, but this was not detected in any of our experiments.

To support the above-mentioned mechanistic theories, gas-phase DFT calculations at the level of B3PW91/lanl2dz were performed for transition states **A** and **C** shown in Scheme 37 and for **E** shown in Scheme 38 (Table 5).

DFT calculations on **53A-56A**, **53C-56C** and **53E-56E** at the level of B3PW91/lanl2dz.

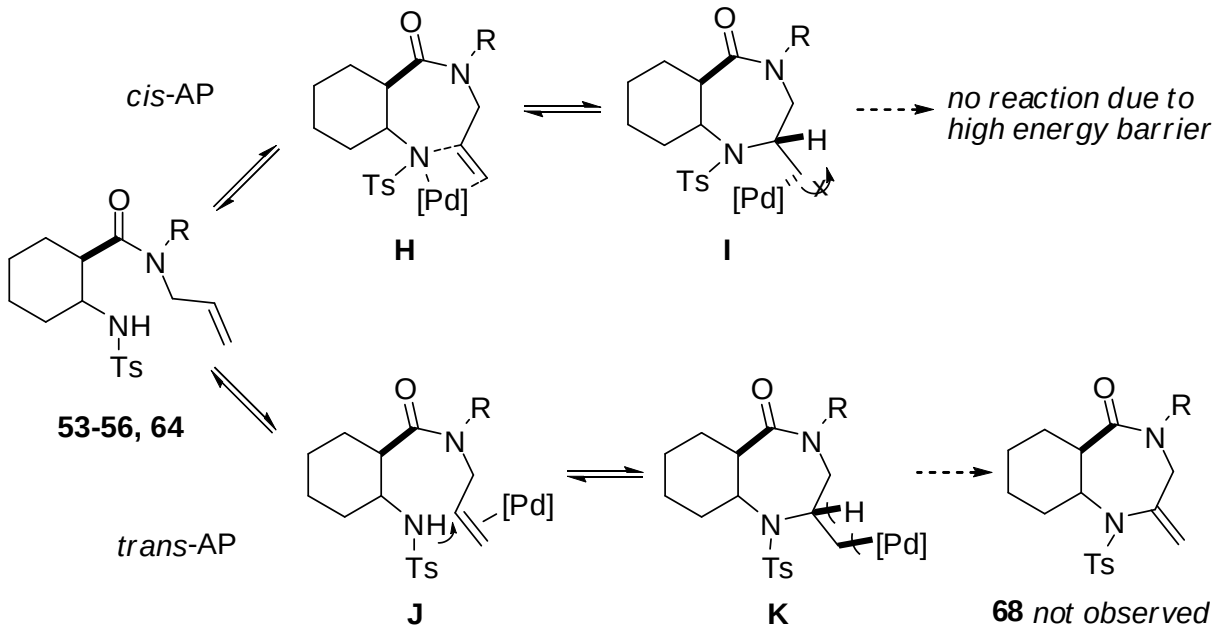
cis	$E_{(Me)}$/a.u.	$E_{(allyl)}$/a.u.	$\Delta E_{(Me)}$/kcal/mol	$\Delta E_{(allyl)}$/kcal/mol
53A, **54A**	-1164.8546	-1241.6629	0.00	0.00
53C, **54C**	-1164.8456	-1241.6601	5.66	1.75
53E, **54E**	-1164.8279	-1241.6389	16.74	15.05

trans	$E_{(Me)}$/a.u.	$E_{(allyl)}$/a.u.	$\Delta E_{(Me)}$/kcal/mol	$\Delta E_{(allyl)}$/kcal/mol
55A, **56A**	-1164.8562	-1241.7100	0.00	0.00
55C, **56C**	-1164.8440	-1241.6949	7.67	9.44
55E, **56E**	-1164.8563	-1241.7128	-0.02	-1.76

Table 5

The calculations demonstrated that, for carboxamides **53** and **54**, *cis*-aminopalladation is less favoured by 15 and 16.7 kcal/mol, respectively, in the formation of **53E** and **54E**, these intermediates yielding diazocinone-type products. Additionally, the calculations confirmed that an "upper-face" attack is preferred to a "lower-face" attack in the formation of quinazolinones **58, 60, 61** and **65**. However, for **53**, the calculations suggested an almost equal chance (<2 kcal/mol difference) for the "upper" and "lower-face" attacks, which would result in a diastereomeric mixture in parallel to the reaction in the non-coordinating toluene. The fact that **57** is the only diastereomer formed in DMSO reveals the explicit effect of the solvent molecules on the transition state, the transformation being shifted to proceed via an "upper-face" pathway.

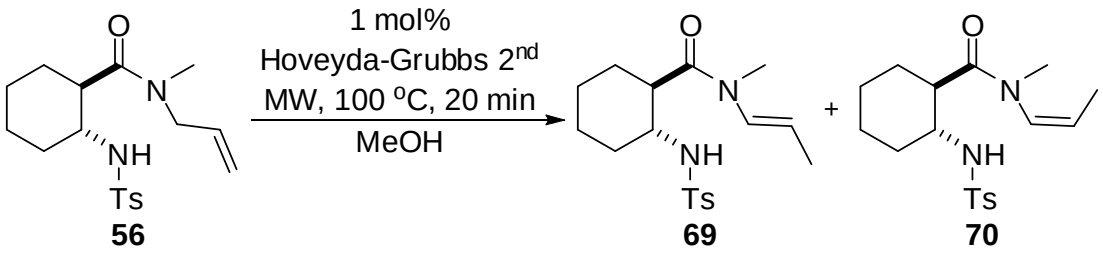
We assumed that the absence of diazepine-type products could serve as further evidence of *cis*-aminopalladation. The suggested mechanism is depicted in Scheme 39.



Scheme 39

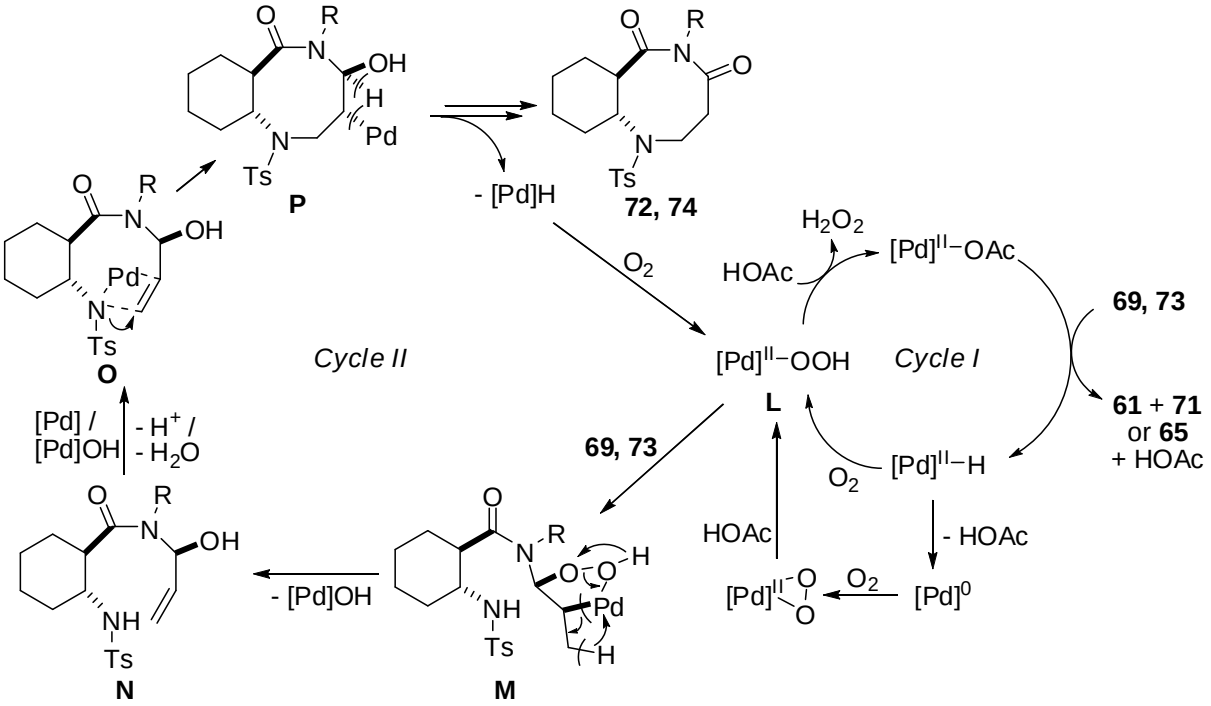
According to the previously established mechanism, the formation of diazepine-type compounds via *cis*-aminopalladation would proceed via intermediate **H**, albeit *syn*-β-hydride elimination would require an energy-demanding 120º rotation of the Pd moiety around the C-C bond in intermediate **I**. Moreover, coordination of the oxygen atom in the tosyl group would stabilize **I**, increasing the total energy demand of the transformation. On the other hand, *trans*-aminopalladation would favour *syn*-β-hydride elimination from **K**, but **68** was not detected.

Eventually, we performed an experiment to support that no π-allyl-palladium mechanism is involved in these transformations. Compound **69** was synthetized (Scheme 40) and subjected to the conditions shown in Table 4 Entry 3 in order to obtain **61** exclusively.



Scheme 40

Interestingly, a three-component mixture was obtained, from which **61** and its ($2S^*$) diastereomer **71** were isolated in 10% yield, besides a new cyclic imide **72** in 64% yield. For this outcome, we propose a novel domino oxidation/oxidative amination cascade reaction (Scheme 41).



65, 73, 74: R = PMB; **61, 69, 71, 72**: R = Me

Scheme 41

We suggest that the first cycle, in which quinazolinones are formed, produces the key palladium hydroperoxo intermediate **L**[108-112] for the second catalytic cycle. This species then undergoes 1,3-dipolar cycloaddition to generate **M**, which transforms into **N** via *syn*-β-

hydride elimination. Next, **N** undergoes a cyclization similar to that shown in Scheme 38, to provide **72** finally. To investigate the possibility of water incorporation[113] instead of oxygen incorporation, water was added in a control experiment, though it did not improve the yield or the ratio of **72**. On the other hand, when the reaction was run under argon and with one equivalent of catalyst, quinazolinones **61** and **71** were formed exclusively, thereby supporting our mechanistic proposal excluding a μ^3-allyl-palladium intermediate.

In order to broaden the substrate scope of this novel transformation, **73**, the PMB-substituted analogue of **69** was prepared and successfully cyclized to give **74** in 63% yield.

4. Summary

Novel enantiopure γ-amino alcohols **4, 5, 7** and **9** and diamine **6** were synthetized from (+)- and (-)-α-pinene, respectively, and were used as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes, as test reactions resulting in optically active secondary alcohols. Diamine **6** showed no enantioinduction, while amino alcohol **7** provided the product 1-aryl-1-propanols with moderate enantioselectivities and with *R* selectivity. Catalyst **9** gave both the highest yields and enantioselectivities up to 72% ee with *S* selectivity. To the best of our knowledge, this is the first report on an *N*-substituent-dependent enantioswitch in the field of 1,3-amino alcohol-catalysed asymmetric reactions. Results of the molecular modelling studies performed were in good accordance with our experimental findings.

Alicyclic condensed 1,3-oxazines **17-20** were transformed into the corresponding *N*-substituted 1,3-amino alcohols **22-27** in the presence of a ketone **21a-d** in a simple one-pot, reductive process.

We found that the reaction can proceed via two different pathways: classical reductive debenzylation followed by Schiff base formation, or transimination of the chain form of the ring-chain tautomeric mixture obtained by partial reduction of the starting oxazine. We successfully provided experimental evidence for the alternative transimination pathway via the application of 2-methyl-substituted oxazine, where debenzylation cannot occur.

An efficient MW-assisted method was developed for the cyclization of Cbz-protected *cis*- and *trans*-cyclohexane- and *cis*-cyclopentane-formylmethyl carboxamides to furnish the corresponding 5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-one derivatives **40-42** and **45**. The developed method gives a high yield in general and was also applied for non-alicyclic β-amino acid derivatives.

Efficient cyclizations of tosyl-protected *cis*- and *trans*-*N*-allyl-2-aminocyclohexane-carboxamides (**53-56** and **64**) were carried out in the Pd(II)-catalysed oxidative amination reaction, resulting in cyclohexane-fused 2-vinylpyrimidin-4-ones **57-61** and **65** and 1,5-diazocin-6-ones **62, 63** and **66**.

We found that *cis* starting materials cyclize into 2-vinylpyrimidin-4-ones diastereo-selectively, whereas *trans* compounds cyclize regioselectively into a mixture of 1,5-diazocin-6-ones as major and 2-vinylpyrimidin-4-ones as minor products.

A marked solvent effect on the regioselectivity was observed, and acetonitrile was identified as the best solvent for the selective preparation of 1,5-diazocin-6-ones.

The mechanistic studies performed clearly indicated that an aminopalladation/β-hydride elimination pathway is feasible in these transformations.

A novel MW-assisted allyl to propenyl isomerization was developed in order to obtain a model compound to provide experimental support for our mechanistic theory.

As a result of this experimental study, a new 1,5-diazocine-4,6-dione-type compound was obtained, formation of which was explained by a novel Pd(II)-catalysed domino oxidation/oxidative amination cascade reaction.

In the course of the experimental work, 50 novel, structurally diverse alicyclic compounds were synthetized and characterized.

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