**Topic: Saturated N-heterocycle synthesis**

1. **Introduction**

Aromatic and heteroaromatic rings are prevalent in pharmaceutical compounds as a large variety of building blocks and general, well-developed methods for their functionalization are available.

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| As a structural feature, aromatic rings possess fewer degrees of freedom than their saturated counterparts or the open chain form. This often increases the ligand–receptor binding (by reducing the entropy term), therefore leading to increased potency.  [*Drug Discov. Today* **2009**, *14*, 1011.](http://dx.doi.org/10.1016/j.drudis.2009.07.014) |

* 1. Trend towards saturated heterocycles – “Escape from Flatland”

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| Saturation allows the preparation of more complex molecules resulting in the exploration of more diverse chemical space, without increasing molecular weight and lipophilicity significantly - increased opportunity to introduce out-of-plane substituents. Saturated heterocycles unlike their aromatic counterparts contain the chiral information in the molecule, thus can potentially provide more selective binding in the body. |
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| “The fewer the number of (hetero)aromatic rings contained in an oral drug candidate, the more developable that candidate is likely to be.” |
| [*J. Med. Chem.* **2009***, 52,* 6752.](http://dx.doi.org/10.1021/jm901241e) |
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* 1. Top selling drugs

Many of the top selling and top prescribed drugs contain a chiral nitrogen heterocycle motif. In general, the nonaromatic nitrogen heterocycles are highly represented in drugs approved by the FDA as four out of the top five nitrogen heterocycles used are saturated (e.g. Rank 1 = Piperidine, Rank 3 = Piperazine). A few examples are depicted in the scheme and more structures can be viewed following the links below.



[Top 200 Brand Name Drugs by US Prescriptions](http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster)

[J. Med. Chem. 2014, (DOI: 10.1021/jm501100b)](http://dx.doi.org/10.1021/jm501100b)

* 1. Most popular classes of N heterocycles

Some of the most common representatives of N-heterocycles are shown in the scheme. These literature highlights are mainly focused on the synthesis of the corresponding classes of molecules.



1. **-Functionalization of unsubstituted N-heterocycles**

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| Functionalized, nitrogen heterocycles constitute a widespread structural motif in biologically active compounds and are an invaluable template for chiral auxiliaries in asymmetric synthesis. Several methods exist for the synthesis of N-heterocycles possessing functionalization adjacent to nitrogen. This strategy is extremely appealing for a rapid access of compound libraries as the synthesis is started from an inexpensive common building block. |
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| (Review) [*Chem. Eur. J.* **2012**, *18*, 10092.](http://dx.doi.org/10.1002/chem.201201539)  (Review) [*Chem. Soc. Rev.* **2007**, *36*, 1069.](http://dx.doi.org/10.1039/b607547a) |

* + 1. Functionalization via -aminoorganolithiums

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| The oldest reported method for the functionalization of nitrogen-containing heterocycles is directed -lithiation with alkyllithium/diamine complexes, producing a dipole-stabilized carbanion, followed by electrophilic substitution. Several dipole-stabilizing groups, including amide, phosphoramide, formadine, oxazoline, nitroso, and carbamate functionalities, have proven to be effective for directed metallation adjacent to nitrogen in heterocycles. Of these, the *tert*-butyl carbamate (Boc) directing group is the most common due to the availability, practicality, and ease of installation and removal.  Lithiation of seven-membered ring compounds followed by trapping with electrophiles is known but less efficient than that of smaller rings analogs. |
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| Stereoselective reactions at –78 °C are often limited to very reactive electrophiles such as aldehydes, TMSCl, Me2SO4, epoxides, and other activated electrophiles as chiral lithiated-aminocarbanions generated with chiral amine ligands are configurationally not as stable at temperatures above –50 °C and unactivated electrophiles hardly react at such temperatures.      [*J. Am. Chem. Soc.* **2000**, *122*, 3344.](http://dx.doi.org/10.1021/ja9923235) & [*Org. Biomol. Chem.* **2006**, *4*, 4285.](http://dx.doi.org/10.1039/b608013h)  For highly stereoselective reactions with less reactive electrophiles transmetallation to other metals is necessary. Many organozinc or organocuprate reagents for example are configurationally stable up to room temperature.    Stereoselective-lithiation of piperidine and piperazine derivatives has proven to be more difficult. The alkyllithium/diamine complex with (*–*)-sparteine **L1** as ligand shows poor reactivity towards these substrates. To overcome this limitation, O’Brien and co-workers prepared a synthetic pseudo-enantiomer of sparteine **L2**. The alkyllithium-sparteine surrogate (**L2**) complex is capable of fully deprotonate the six membered heterocycles at low temperatures, and they can be subsequently trapped with various electrophiles.  Stereoselective reactions with piperidines and piperazines are sometimes carried out with ligand exchange catalysis to reduce the amount of chiral ligand. This is carried out by the addition of a catalytic quantity of a chiral ligand (**L**\*) to the system in conjunction with a stoichiometric quantity of a sacrificial achiral ligand (**L**). While both ligands form configurationally stable BuLi/diamine complexes at low temperatures that undergo rapid ligand exchange, the BuLi/**L**\* complex, being more reactive, causes rapid stereoselective -deprotonation. Subsequent ligand exchange with the BuLi/**L** complex allows the active chiral ligand (**L**\*) to re-enter the catalytic cycle.  In addition to the above-mentioned ligand-exchange catalysis, one of the most significant recent developments in asymmetric -deprotonation and functionalization of nitrogen-protected pyrrolidines and piperidines is the use of dynamic resolution to obtain enantioenriched heterocycles. The dynamic resolution can be performed either kinetically or thermodynamically. The resolution process is based on the principle  that the generated diastereomeric organolithium/diamine complexes undergo inversion. When the interconversion of these diastereomeric complexes is rapid relative to the trapping rate by the electrophile, a dynamic kinetic resolution (DKR) is at work, with the product having the lowest G≠ for the reaction with the electrophile being favored (Curtin-Hammett principle).  However, if the interconversion between the diastereomeric complexes is slow relative to subsequent trapping by electrophile, control of the equilibrium population of the diastereomeric complexes by means of temperature variation can favor product formation with the complex that is thermodynamically most stable, allowing for dynamic thermodynamic resolution (DTR). This is often applied to *N*-alkyl-2-lithiopyrrolidines or piperidines produced by transmetallation from the corresponding racemic stannane with an organolithium and a chiral ligand.    - Catalytic enantioconvergent asymmetric Negishi -alkylation of racemic -zincated *N*-Boc-pyrrolidine with unactivated secondary alkyl electrophiles. Fu and co-workers demonstrated derivatization of pyrrolidines, by use of a chiral nickel catalyst instead of a chiral base in the deprotonation step. The product stereochemistry is controlled predominantly by the stereochemistry of the chiral Ni complex. |
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| [*J. Am. Chem. Soc.* **2013**, *135*, 10946.](http://dx.doi.org/10.1021/ja4054114) |

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| - Ligand-controlled -selective C(sp3)–H (hetero)arylation of *N*-Boc-piperidines whereas the /-arylation selectivity was controlled by a “flexible” biarylphosphine ligand providing mainly the -arylated products with the enecarbamate as a byproduct. Arylation of saturated nitrogen heterocycles of different ring size (5, 7, 8) occurred predominately adjacent to the nitrogen atom in the -position with low overall yield. |
| [*Chem. Sci*. **2013**, *4*, 2241.](http://dx.doi.org/10.1039/c3sc50428j) |
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* + 1. Functionalization of pre-functionalized, bench-stable building blocks

Hesp and co-workers developed a two-step procedure for the synthesis of -heteroaryl piperidines. Initial Pd-catalyzed Suzuki cross-coupling of pharmaceutically relevant heteroaryl bromides with a bench-stable boronate ester followed by subsequent transfer hydrogenation affords the desired nitrogen heterocycles in moderate to good yield obviating the need to prepare highly reactive organolithium compounds.



[*Org. Lett. 2014, 16, 413.*](http://dx.doi.org/10.1021/ol403367b)

* 1. Functionalization via cyclic imines (Cross-Dehydrogenative couplings – CDC)

Seidels group recently reported a one-pot redox-neutral -arylation/alkynylation to prepare cyclic -substituted amines viatrapping a cyclic iminium with a nucleophile. Choice of the aldehyde and source of copper catalyst proved to be important in order to suppress a side reaction – direct nucleophile addition to iminium **1**. Requirements for the aldehyde are steric bulk to decrease the rate of the nucleophile addition to **1** and electron withdrawing substituents which render the iminium intermediate more acidic. This favors the isomerization to iminium **3**, which gets intercepted with the nucleophile. The carboxylate ligands from the copper source promote isomerization via proton transfer.

Five, six and seven membered N-heterocycles can be used and subsequently deprotected to afford alpha monosubstitued parent N-heterocyclic compounds.

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| [*Angew. Chem. Int. Ed.* **2013**, *52*, 3765.](http://dx.doi.org/10.1002/anie.201300021) & [*Org. Lett*. **2013**, *16*, 730.](http://dx.doi.org/10.1021/ol403431u) |

* 1. Radical based C–H activation

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| The generation of a carbon-centered radical at a remote position, in this case on a benzyl protecting group, and translocating it via 1,5-hydrogen atom transfer prior to the desired reaction constitutes straightforward method to access -amino radicals in nitrogen-containing heterocycles. |
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| - Early report by Snieckus and Curran of heteroannulation and -nitrogen functionalization by radical translocation and trapping with an intra- or intermolecular radicophile. |
| [*J. Am. Chem. Soc.* **1990**, *112*, 896.](http://dx.doi.org/10.1021/ja00158a075) |

* 1. Alpha-functionalization via C-H activation

The group of Sames reported a C–H activation method to -functionalize pyrrolidines using a cleavable directing group and a ruthenium carbonyl trimer complex. Various aryl and heteroaryl substituents can be introduced in a single step. The mechanism can be cut down into four key steps – 1) directed metal insertion; 2) ketone insertion – in order to generate a low oxidation state metal alkoxide complex which can readily transmetallate with a boronic ester; 3) transmetallation; 4) reductive elimination. After the reaction the directing group can be removed by treatment with a hydrazine-TFA mixture.



[*J. Am. Chem. Soc.* **2006**, *128,* 14220.](http://dx.doi.org/10.1021/ja064481j)

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| * 1. Alpha-functionalization via photoredox   The group of MacMillan reported a photoredox method to directly functionalize *N*-protected pyrrolidines, piperidines, azapanes, morpholines, piperazines and various acyclic amines in the -position. Various electron deficient cyano arenes can be used as reagents to introduce the substituent on the heterocycle. In the mechanism it is proposed, that photon from the 26W light source promotes the iridium complex to its excited state, which serves as a powerful reductant and donates an electron into the aromatic system (note that electron poor substrates have to be used, to stabilize the radical anion). The resulting Ir (IV) complex then oxidizes the amine to a cation radical, which after alpha deprotonation forms a neutral radical species. The final product is obtained after both radicals combine and eliminate cyanide to regenerate the aromaticity. Unfortunately the protecting group on the nitrogen cannot be removed after the reaction!    [*Science* **2011***, 334,* 1114*.*](http://dx.doi.org/10.1126/science.1213920) |
| Recently, a decarboxylative photoredox nickel catalysis was developed in the MacMillan labs. This method has the advantage that electron rich and electron poor as well as heteroaryls can be used to functionalize various heterocycles including pyrrolidines, piperidines, morpholines, and many more. In addition, the nitrogen protecting group was switched to an easy removable Boc-group.    [*Science* **2014**, *345*, 437.](http://dx.doi.org/10.1126/science.1255525) |

1. **Dearomatization**

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| A widely used approach to prepare unsaturated nitrogen heterocycles is based on dearomatization of their aromatic counterparts either by full hydrogenation or partial desaturation. This approach can be used to synthesize piperidine and tetrahydroquinolines resp. isoquinolines. It is less common for pyrrolidine synthesis and cannot be used to obtain morpholines, azepanes and other structures, which simply do not posses the corresponding aromatic starting material.   * 1. Hydrogenation   Hydrogenation usually is a very clean transformation leading to little or no byproducts, therefore often it is done on an industrial scale using various metals (Pd/C, PtO2, Rh/Al2O3 and others) to yield the product with usually all *cis* stereochemistry. Such reactions are normally carried out in acidic media. Not only does the protonation render the substrate more prone to hydrogenation, it also suppresses the catalyst poisoning by the resulting unsaturated N-heterocycle. Note that N-heterocycles can be selectively hydrogenated over benzene derivatives and the reaction often can be carried out under atmospheric pressure of H2. |
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| [*Org. Process Res. Dev.* **2005***, 9,* 51*.*](http://dx.doi.org/10.1021/op049808k) |
| * 1. Asymmetric hydrogenation of various heteroaromatics   In the past few decades a lot of effort have been devoted to render hydrogenation of aromatic heterocycles asymmetric. A few selected examples are covered in this chapter.  (Review) [*Chem. Rev.* **2012***,**112*, 2557.](http://dx.doi.org/10.1021/cr200328h)  (Review) [*Acc. Chem. Res.* **2007**, *40*, 1357.](http://dx.doi.org/10.1021/ar700094b) |

* + 1. Asymmetric hydrogenation of pyrroles

Pyrroles are more electron rich than isoquinolines or pyridines (which can be regarded as electron sinks) and as a consequence are more difficult to hydrogenate. Normally, high H2 pressure has to be used. One of the few examples has recently been disclosed by groups of Zhou and Fan where partial asymmetric hydrogenation of pyrroles was achieved using palladium and a bisphosphine ligand system in a combination with a strong acid under elevated H2 pressure (600 psi). The corresponding enantioenriched 1-pyrrolines can be reduced further to *cis-*pyrrolidines without loss of enantiopurity.

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| [*J. Am. Chem. Soc.* **2011***,133,* 8866*.*](http://dx.doi.org/10.1021/ja203190t) |
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* + 1. Asymmetric hydrogenation of pyridines

While pyridines are relatively easy to hydrogenate under acidic conditions it is much harder to render this process asymmetric. Zhou and his co-workers reported a method based on different type of pyridine activations – namely pyridinium salt formation. Pyridines reacted with benzylbromide form stable *N*-benzyl pyridinium bromides, which are good electrophiles and do not coordinate to the catalyst as good as pyridines, thus the overall reactivity can be enhanced (increased catalyst turnover number). Still elevated hydrogen pressures are required, but in combination with iridium and a bisphosphine ligand system, products with good optical purity in excellent yields were obtained. Both, yields and optical purity decreases once the substrate posses an aliphatic substituent alpha to the nitrogen

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| [*Angew. Chem. Int. Ed.* **2012**,*51*, 10181.](http://dx.doi.org/10.1002/anie.201205187) |

* + 1. Asymmetric hydrogenation of quinolines and isoquinolines

Numerous efficient catalytic systems have been found for asymmetric hydrogenation of quinolines. They are mainly based on iridium systems with bisphosphine ligands. As the nitrogen atom in the product is in conjugation with the aromatic system it doesn’t inhibit the catalyst activity as much as other saturated N-heterocycles.



However structurally related compounds like isoquinolines and as already mentioned pyridines have proven to be much more problematic. Recently, the group of Mashima reported a system based on a halogen bridged iridium (III) complex with a chiral ligand, which could hydrogenate isquinoline derivatives with good to excellent selectivities. As seen before, the N-heterocycle has to be used in its salt form due to the high basicity of the tetrahydroisoquinoline, which poisons the catalyst.

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| [*Angew. Chem. Int. Ed.* **2013**,*52*, 2046.](http://dx.doi.org/10.1002/anie.201207748) |

* 1. Nucleophilic addition to acylpyridiniums

In 1980’s group of Comins reported nucleophile addition to acylpyridiniums affording partially saturated pyridine derivatives, which are easy to modify further. Diverse and structurally complicated systems can be readily prepared using various nucleophiles (enolates, cuprates, Grignards and others).

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| [*J. Org. Chem.* **1982**, *47,* 4315.](http://dx.doi.org/10.1021/jo00143a028) |

The Comins group and numerous other groups have used this strategy to prepare various natural products. A fraction of them are depicted below:

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Based on the work by Comins, Doyles group recently reported an asymmetric piperidinone synthesis using nickel catalyst in combination with phosphoramidite ligands and arylzinc nucleophiles. While this method works with excellent selctivities for electron deficient aryl nucleophiles, electron rich aromatics such as para-methoxyphenyl zinc bromides afforded racemic products (0% ee).

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| [*Angew. Chem. Int. Ed.* **2013**,*52*, 9153.](http://dx.doi.org/10.1002/anie.201303994) |

1. **Cyclization methods to assemble substituted saturated nitrogen heterocycles**

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| Cyclization methods to assemble saturated nitrogen heterocycles are also commonly used. However, depending on the method chosen, the starting material needs to be prepared in several steps and the introduction of further functionality can be laborious. Shown are some of the most often used methods: |
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* 1. Cyclization of primary amines

Enantiopure primary amines can be prepared via reduction of sulfonamides, derived from Ellman’s chiral auxiliary followed by cyclization. Guijarro’s group reported a practical and concise cyclization procedure to prepare three, five, six and seven membered ring N-heterocycles. Various length haloketones were transformed into corresponding sulfonamides via imine formation and subsequent transfer hydrogenation. The cyclization was achieved using bases such as KO*t*Bu or KHMDS. In the cases of five membered cycles, the ease of protecting group cleavage with HCl was demonstrated, however this is much more difficult for the aziridines as they are prone for ring opening under acidic conditions.

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| [*J. Org. Chem.* **2013**, *78*, 9181.](http://dx.doi.org/10.1021/jo4014386) |

* 1. C–H Bond amination

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| Intramolecular iron catalyzed direct C(sp3)–H bond amination via iron bound imido radical generated from aliphatic azides with extrusion of nitrogen as sole byproduct was recently reported by Betley’s group. Boc anhydride to protect the secondary amine of the product was needed for the catalyst turnover due to the product inhibition, in which a tight Lewis acid/base pair between the dipyrrinato iron and the heterocyclic nitrogen atom was formed. A drawback of this method is that the synthesis of piperidines is always accompanied by the formation of pyrrolidines as the cyclization rate to form 5-membered rings are higher.    A pathway via H-atom abstraction by the Fe(III) radical imido intermadiate was excluded in submitting radical clock substrate (2-(4-azidobutyl)cyclopropyl) to the reaction conditions and pyrrolidine product 1-Boc-2-(2-phenylcyclopropyl)pyrrolidine was formed exclusively with the cyclopropyl unit intact. |
| [*Science* **2013**, *340*, 591.](http://dx.doi.org/10.1126/science.1233701) |
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* 1. Hydroamination

The hydroamination reaction deals with the direct formation of a new carbon–nitrogen bond by addition of an amine to an unsaturated carbon–carbon bond. This transformation is thermodynamically feasible but it suffers from a high activation barrier due to electrostatic repulsions between the lone pair of the nucleophilic nitrogen atom and the -orbital of the electron-rich double bond (electron rich double bonds react slower). The [2+2] cycloaddition of N–H across the C–C bond, is orbital-forbidden under thermal conditions, but can be promoted with light or by the use of a catalyst opening other reaction pathways. The hydroamination of alkenes is more difficult compared with that of alkynes because of the electron density of C–C bonds.



(Review) [*Chem. Rev.* **2008**, *108*, 3795.](http://dx.doi.org/10.1021/cr0306788)

(Review) [*Chem. Eur. J.* **2013**, *19*, 4972.](http://dx.doi.org/10.1002/chem.201203956)

* + 1. Metal catalyzed hydroaminations

Huge efforts have been devoted in the past 60 years to develop this transformation and numerous catalysts have been discovered belonging to alkali bases, but also to the class of alkaline earth metals, rare-earth (actinides), Group 4 (and 5) elements, late transition metals. As a general trend, group 1–5 metal-based catalysts have been proposed to proceed by activation of the amine through a rapid protonolysis reaction thanks to the presence of a strongly Brønsted basic moieties on the metal (X = alkyl or amido) and the ionic character of the M–X bond. The activation of the amine functionality by this deprotonation pathway leads to the formation of a metal amido (or imido) complex that will further react through a -insertive, non-insertive, or [2+ 2] mechanism to subsequently deliver the hydroamination product.

- One-pot catalytic asymmetric synthesis morpholines/piperazines and a modular diastereoselective synthesis of 2,5-substituted piperazines.



[*Angew. Chem. Int. Ed.* **2012**, *51*, 12219.](http://dx.doi.org/10.1002/anie.201206826)

* + 1. Metal free hydroaminations

Shenvi’s group reported an elegant method based on directed hydroboration to prepare polysubstituted indolizidines in a two-step, one-pot manipulation. The relative stereochemistry of the product is dependent on the configuration of the double bond, which gets hydroborated first. In order to proceed with the second hydroboration a screen of oxidants was performed and revealed the need for excess of I2 and NaOMe. The second ring is formed via an intramolecular Mitsunobu reaction.

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| [*J. Am. Chem. Soc.* **2012**, *134*, 2012.](http://dx.doi.org/10.1021/ja211090n) |

* + - 1. Cope-type hydroaminations

The group of Beauchemin has demonstrated applications of Cope-type hydroaminations, in the synthesis of various alkaloid natural products. Synthesis of 6-membered heterocycles via Cope-type hydroamination is very challenging. The subtle changes of substituents in the molecules play a dramatic effect in this transformation. In this study the authors describe methods to enhance the cyclization (aid of Thorpe-Ingold effect; use of *N*-allyl hydroxylamines which cyclize much faster and subsequently undergo a Meisenheimer rearrangement) rendering this methodology more general.

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| [*J. Org. Chem.* **2013**, *78*, 12735.](http://dx.doi.org/10.1021/jo4023149) |

* 1. SnAP (Tin (Sn) Amine Protocol)

Air- and moisture stable SnAP reagents for the copper(II) mediated mild transformation of widely available (hetero)aromatic and aliphatic aldehydes into 6, 7, 8 and 9-membered substituted unprotected saturated N-heterocycles were developed to provide an alternative to cross-coupling reactions. This process offers an easily recognized retrosynthetic disconnection and has an outstanding substrate scope.



Preliminary mechanistic studies suggest oxidative generation of a heteroatom stabilized primary carbon centered radical. Although radical cyclizations onto alkenyls typically proceed via *exo*-bond formation, the SnAP reagents as aza analogues always prefer formation of the *endo* products. This is presumably due to the formation of a stable nitrogen radical, which is reduced by a copper (I) species and the thermodynamic preference of forming a stronger C–C bond over a C–N bond. Additional, kinetic factors as orbital overlap of the SOMO with the LUMO (\*) of the imine that has the higher coefficient on the carbon or polarization effects – the nucleophilic radical adds to the electrophilic imine carbon - may also contribute to this high regioselectivity.



[*Angew. Chem. Int. Ed.* **2013**, *52*, 1705.](http://dx.doi.org/10.1002/anie.201208064)

[*Org. Lett.* **2014***, 16,* 1236.](http://dx.doi.org/10.1021/ol500210z)

[*Nat. Chem.* **2014**, *6*, 310.](http://dx.doi.org/10.1038/nchem.1878)

* 1. Annulation strategies

Reaction of bromoethylsulfonium salt with 1,2-/1,3-aminoalcohols affords six- and seven-membered rings in good-to-excellent yields. The reactions proceed through generation of a vinyl sulfonium salt followed by annulation to yield 1,4-heterocyclic compounds such as morpholines and benzoxazepines in a single step. The method accommodates a range of nitrogen substituents and the amino alcohol can be substituted by amino thiols and diamines. The cascade of events is initiated by nucleophilic attack of the amide on the electrophilic sulfonium salt, which forms an intermediate sulfur ylide. A proton transfer unmasks a second electrophilic center and creates a potent nucleophile, leading to the heteroatom displacing the sulfide forming the desired heterocyclic product. The need for a protected nitrogen limits this method as does the use of the large excess of the strong base sodium hydride.



[*Angew. Chem. Int. Ed.* **2008**, *47*, 3784.](http://dx.doi.org/10.1002/anie.200800373)

[*Org. Lett.* ***2009****, 11,* 257*.*](http://dx.doi.org/10.1021/ol8023727)

(Analysis of protecting groups) [*Eur. J. Org. Chem.* **2012**, 160.](http://dx.doi.org/10.1002/ejoc.201101272)

* 1. Carboamination

Over the past several years, palladium-catalyzed alkene aminoarylation reactions have emerged as powerful tools for the synthesis of 2-(arylmethyl)pyrrolidines and related nitrogen heterocycles. These transformations effect the cross-coupling of simple aminoalkene substrates with aryl or alkenyl halides to generate the heterocyclic ring with formation of a C–N bond, a C–C bond, and one or more stereocenters, with good to excellent stereocontrol. Moreover, these methods are quite useful for generating analogues of a particular scaffold, as a wide variety of aryl electrophiles are readily available.

(Review) [*Synthesis* **2012**, 351.](http://dx.doi.org/10.1055/s-0031-1289668)

- Recently, Wolfe reported a mild diastereoselective Pd-catalyzed carboamination of *N*-protected hex-4-enylamines and 1-, 3-, and 4-substituted pent-4-enylamines. This method shows a broad substrate scope and alkenes do not need to be pre-activated, however, trisubstituted alkenes are not tolerated. Electron-rich and electron-poor aryl bromides are tolerated and the nitrogen protecting group can easily be removed. Carboamination reactions of *ortho*-substituted aryl bromides with hex-4-enyl-amine derivatives were generally not effective and efforts to couple alkenyl bromide electrophiles were also unsuccessful, although alkenyl bromides can be used in carboamination reactions of terminal alkene substrates when NaOtBu is employed as base.



The transformations are presumably initiated by oxidative addition of the aryl bromide to a Pd(0) catalyst. The resulting LnPd(Ar)(Br) intermediate is likely converted to palladium(aryl)(amido) complex through reaction with the amine substrate and base. Intramolecular *syn*-aminopalladation followed by reductive elimination affords the desired product and regenerates the catalyst.



[*J. Org. Chem.* **2008*,*** *73*, 8851.](http://dx.doi.org/10.1021/jo801631v)

(Piperazine synthesis)[*Org. Lett.* ***2007****, 9, 3279.*](http://dx.doi.org/10.1021/ol071241f)

(Morpholine synthesis)[*J. Org. Chem.* **2009**, *74*, 5107.](http://dx.doi.org/10.1021/jo9007223)

* 1. Ring closing metathesis (RCM)

RCM is commonly used in synthetic chemistry to form rings of various sizes. It is a reliable strategy and very often can be found as the key transformation for ring formation in natural product synthesis. Mainly due to the lengthy synthesis of the necessary bis-vinyl starting materials, this methodology is more often found in synthesis of complicated alkaloids rather than preparation of substituted medium size nitrogen heterocycles.

(Review)[*Chem. Rev.* **2004**, *104*, 2199.](http://dx.doi.org/10.1021/cr0200872)

* + 1. RCM for synthesis of small ring heterocycles

In beginning of 1990’s Grubbs group reported RCM of protected bis allyl amines. Commonly used, commercially available Grubbs 1st and 2nd generation catalysts, which tolerate many functional groups, do not work in the presence of a free amine. However RCM was achieved with amides, carbamates or with HCl salts of the corresponding amine.

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| [*J. Am. Chem. Soc.* **1993***, 115,* 9856*.*](http://dx.doi.org/10.1021/ja00074a085) |

* + 1. Asymmetric ring closing metathesis

A decade later groups of Hoveyda and Schrock reported an asymmetric variant of the RCM. By using a molybdenum carbene catalyst, six-, seven-, and even eight-member rings were prepared via desymmetrization of an achiral starting material.

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| [*J. Am. Chem. Soc.* **2002**,*124*, 6991.](http://dx.doi.org/10.1021/ja051330s) |

4.8 Pictet-Spengler reaction

A practical and general route to prepare tetrahydroisoquinolines was reported already in the beginning of the 20th century using -arylenylamine in the combination with the corresponding ketone or aldehyde. This reaction consists of several elementary steps: imine formation, Friedel-Crafts type ring closure and rearomatization.

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[*Ber. Dtsch Chem. Ges.* **1911***, 44,* 2030*.*](http://dx.doi.org/10.1002/cber.19110440309)

While the imine formation is relatively fast, the ring closure is dependent on the electronic nature of the aromatic system and is much faster for electron rich aromatics.

Jacobsen’s group reported an enantioselective variant of this transformation using chiral thioureas as catalysts. In order to achieve the ring closure additional activation is needed, thus the imine is acylated *in situ* to form a *N*-acyliminium, which then readily undergoes cyclization.



[*J. Am. Chem. Soc.* **2004***, 126,* 10558*.*](http://dx.doi.org/10.1021/ja046259p)

Alternatively tetrahydroisoqinolines can be prepared from the same amine component but using acylchlorides in a Bischler-Napieralski reaction. This strategy requires additional activation of the amide with a dehydrating agent like P2O5 and a hydrogenation step to reduce the formed imine (or dihydroisoquinoline).



While the extra steps might not make this strategy so appealing, the final intermediate (dihydroisoquinoline) is set up for asymmetric hydrogenation which is often used as an industrial approach for the synthesis of optically pure tetrahydroisoquinolines.





[*Org. Process. Res. Dev.* **2013***, 17,* 1531*.*](http://dx.doi.org/10.1021/op400268f)

1. Ring expansion reactions

The Carreira lab’s recently reported the use of 3-oxetanone as a common building block for synthesis of various substituted morpholines, thiomorpholines and piperazines. The ketone is transformed into the corresponding aminal, hemiaminal or thioaminal, by treatment with the corresponding amine, aminoalcohol or thioamine. Subsequently cyanide is added under Lewis acidic conditions, followed by expansion of the four membered cycle to yield the product in excellent yields. In this study further manipulations of the products are also demonstrated.

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| [*Angew. Chem. Int. Ed.* **2013**, *52*, 11908.](http://dx.doi.org/10.1002/anie.201306563) |
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* 1. Beckmann rearrangement

A classical method to prepare 2-substituted nitrogen heterocycles is based on the ring expansion of corresponding ketoximes via Beckmann rearrangement. It is also a key transformation for the synthesis of caprolactam, which is used for the production of Nylon-6 (multi-ton scale). While this method can deliver 2-substituted pyrrolidines, piperidines, azapanes and even bigger cycles, one always needs to prepare the corresponding ketone starting material and reduce the lactam product to afford the final compound.

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| While this method might not be appealing for medicinal chemists to prepare a library of compounds, it serves as a valuable tool to prepare complicated substrates from parent ketones which most of the time are much easier to derivatize.  This approach was used by Shenvi’s group to prepare a key intermediate for the synthesis of (–)-Neothiobinupharidine.    [*J. Am. Chem. Soc.* **2013***, 135,* 1209*.*](http://dx.doi.org/10.1021/ja310778t) |