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Salient features of the *aza*-Wacker cyclization reaction

Annu Anna Thomas, Someshwar Nagamalla and Shyam Sathyamoorthi *

The intramolecular *aza*-Wacker reaction has unparalleled potential for the site-selective amination of olefins, but it is perhaps underappreciated relative to other alkene oxidations. The first part of this review makes the distinction between classical and tethered *aza*-Wacker cyclization reactions and summarizes examples of the latter. The second portion focuses on developments in asymmetric *aza*-Wacker cyclization technology. The final part of the review summarizes applications of all classes of *aza*-Wacker cyclization reactions to natural product assembly.

1. Introduction

The oxidative functionalization of alkenes remains a central area of focus within the synthetic community.^{1–3} Within this extensive field, Wacker oxidations of alkenes into ketones⁴ and Wacker-type cyclizations of alkenyl alcohols into furans have been extensively investigated. In sharp contrast, the corresponding oxidative cyclization of alkenyl amines, generally termed *aza*-Wacker reactions, has received less attention.^{5–7} This is unfortunate, as intramolecular *aza*-Wacker reactions offer unparalleled opportunity for the site-selective amination of alkenyl moieties.

Aspects of *aza*-Wacker chemistry have been summarized in other elegant reviews, often within the context of larger accounts of palladium-catalyzed reactions.^{1,3,5} The purpose of this review is to highlight past progress and future

opportunities within the field of *aza*-Wacker cyclization reactions. Specifically, we will focus on three categories of the intramolecular *aza*-Wacker reaction:

(1) *Tethered aza-Wacker cyclizations*: it is generally believed that intramolecular *aza*-Wacker cyclizations generally proceed by Pd(II)-assisted attack of an amine onto an alkene moiety followed by β -hydride abstraction, reductive elimination, and re-oxidation of Pd(0) to Pd(II). It is important to note however that Pd(II) assisted C–H cleavage forming a π -allyl Pd complex followed by attack of an amine nucleophile often furnishes identical products; distinguishing between these two competing mechanisms has been the foundation of many elegant physical organometallic experiments. Within the *aza*-Wacker reaction class, there are two fundamental subsets: (A) *Classical aza-Wacker chemistry*, which utilizes native amines and amides for the oxidative cyclization event and (B) *Tethered aza-Wacker chemistry*, which makes use of nitrogen-containing auxiliaries that can be easily appended to other functional

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groups in the molecule followed by oxidative cyclization and then removal. This distinction has not previously been made in the literature, but we find this essential in order to organize future efforts in this exciting field (Fig. 1). The importance of a tethered reaction is that it frees the synthetic practitioner from the constraint of needing a pre-existing C–N bond in order to forge a new one. This greatly expands the contexts in which the *aza*-Wacker cyclization can be employed.

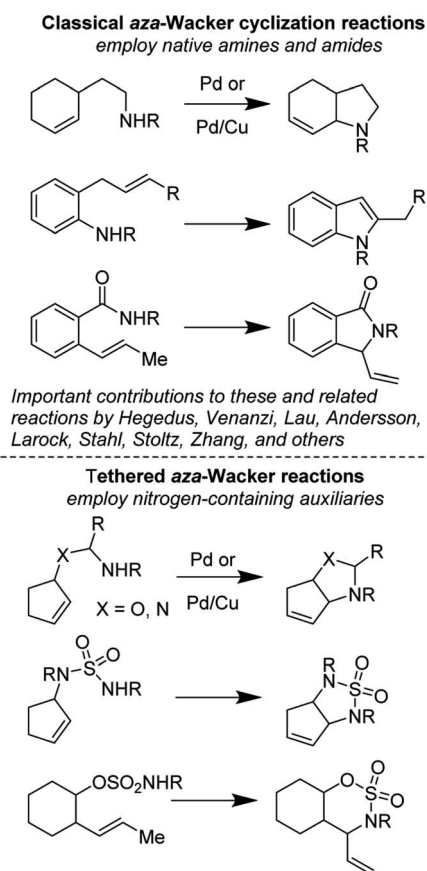


Fig. 1 Classical and tethered *aza*-Wacker cyclization reactions.



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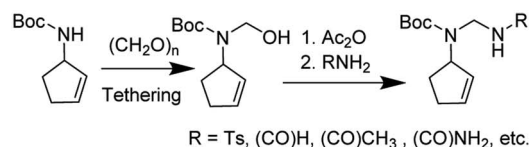
(2) *Enantioselective aza-Wacker reactions*: the development of enantioselective *aza*-Wacker chemistry is an exciting, burgeoning field. Currently, few examples of this challenging transformation exist. The reasons for this are numerous and stem from the inherent reversibility of amino-palladation, competing *cis/trans* nucleopalladation, and a general lack of asymmetric ligands for Pd(II)–Pd(0) redox manifolds. We will describe existing enantioselective *aza*-Wacker processes.

(3) *aza-Wacker chemistry in natural product synthesis*: there are currently only a handful of examples of *aza*-Wacker chemistry utilized in the assembly of natural products. This is in sharp contrast to other alkene and alkane oxidation reactions, especially C–H amination technology.⁸ We will summarize existing examples, which we believe illustrate the great precision with which *aza*-Wacker chemistry allows for the installation of nitrogen functionality. The wider adoption of *aza*-Wacker reactions, especially tethered *aza*-Wacker cyclizations, by the synthetic community would represent an important shift in the logic of nitrogen insertion during complex molecule assembly.

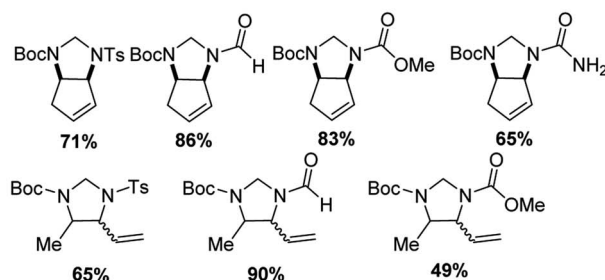
We hope that calling attention to these facets of the *aza*-Wacker cyclization reaction will inspire creative developments in synthetic methodology and elegant applications in total synthesis.

Aminal Tethered *aza*-Wacker Cyclization

1. Installation of the Tether



2. *Aza*-Wacker Cyclization Reaction



3. Tether Removal

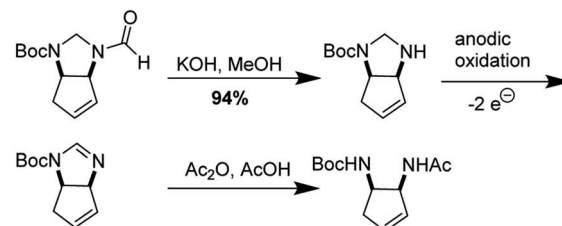


Fig. 2 Hiemstra's aminal tethered *aza*-Wacker cyclization.



2. Tethered *aza*-Wacker cyclization reactions

2.1 Amino tethered *aza*-Wacker cyclization (1994)

One of the first examples of a tethered *aza*-Wacker cyclization reaction was disclosed by Hiemstra and co-workers in 1994,⁹ who showed that an amino tether was competent for the formation of vicinal diamines (Fig. 2). The tether was appended in three steps from an allylic monoamine, involving synthesis of an *N,O*-acetal followed by nucleophilic displacement of the O-

group by a nitrogen containing functional handle, such as formamide, acetamide, methyl carbamate, and *p*-toluenesulfonamide. Aminoals were prepared from either *N*-Boc-2-cyclopentenyl amine and *N*-Boc-3-pent-2-(*E*)-enylamine. *aza*-Wacker cyclization then proceeded upon treatment with 5 mol% Pd(OAc)₂ in DMSO under 1 atm O₂. Of the various nucleophiles tested, it was found that aminoals derived from formamide were the most competent. Tether removal proved to be surprisingly difficult and required KOH hydrolytic removal of the formamide group, electrocatalytic conversion into the amidine, and transformation into the protected diamine by reaction with acetic anhydride in 1 : 1 acetic acid/water.

Amide Tethered *aza*-Wacker Cyclization

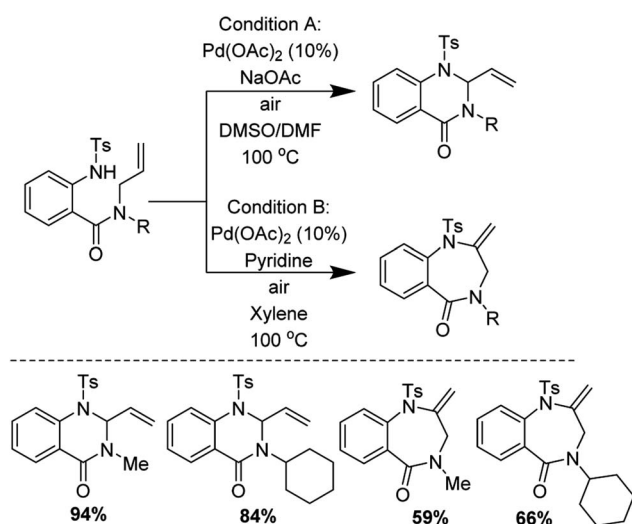


Fig. 3 Divergent reaction conditions for the formation of quinazolin-4-ones and 1,4-benzodiazepin-5-ones.

2.2 Amide tethered *aza*-Wacker cyclization (2004)

Broggini and coworkers reported an amide tethered *aza*-Wacker cyclization for the synthesis of 1,4-benzodiazepin-5-ones from tosylated *N*-allyl-anthranilamides (Fig. 3); importantly, they found that conditions could be tuned to also furnish quinazolin-4-one products.¹⁰ They found that choice of solvent had a critical effect in biasing the formation of one of these heterocycles relative to the other. In the presence of 10 mol% Pd(OAc)₂, with a polar, aprotic solvent like DMSO or DMF, quinazolin-4-ones were formed in good yield; conversely, when xylene/pyridine was used, 1,4-benzodiazepin-5-ones were furnished preferentially. The authors found that the presence of base, exposure to air, and choice of protecting group on the amine were essential for product formation.

Under standard conditions, for the formation of 6-membered quinazolin-4-one products, the authors hypothesized that the first step in the reaction pathway is palladium-mediated allylic C-H cleavage to form an η -3-allyl-palladium

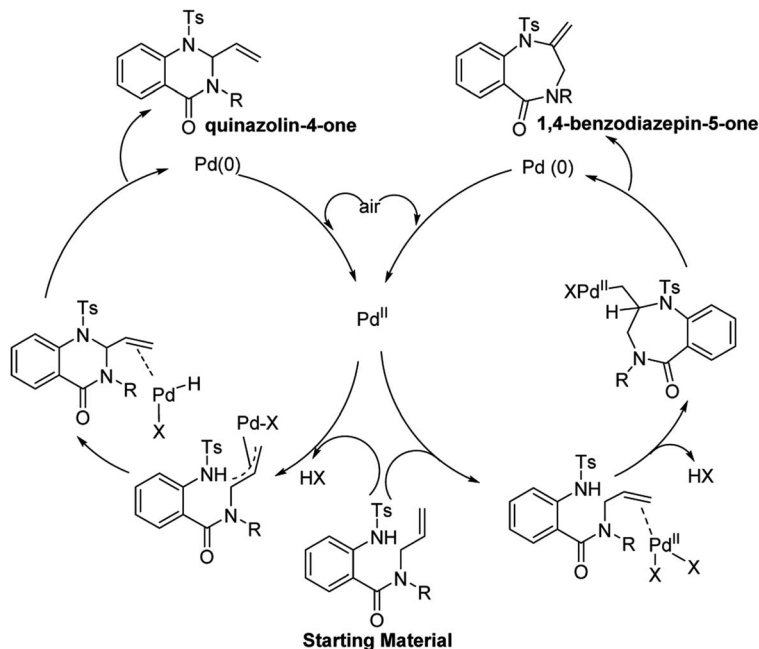


Fig. 4 Proposed reaction mechanism.



complex (Fig. 4). Subsequent nucleophilic attack by the pendant protected amine would furnish the 6-membered heterocyclic ring. This hypothesis was further bolstered by using probe substrate **1** (Fig. 5). Here, synthesis of products **2** and **3** would *necessitate* prior formation of an η -3-allyl-palladium complex. For the formation of 7-membered 1,4-benzodiazepin-5-one products, the authors proposed that the first step in the reaction pathway was a nucleopalladation reaction followed by β -hydride elimination and reductive elimination (Fig. 4).

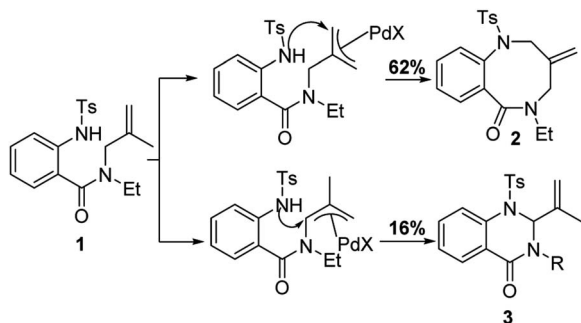


Fig. 5 Mechanistic studies using probe substrate **1**.

2.3 Sulfamide tethered *aza*-Wacker cyclization (2010)

In 2010, Stahl and co-workers reported an elegant synthesis of 1,2-diamines using a sulfamide tether (Fig. 6).¹¹ Starting materials were synthesized in a two-step sequence from mono-amine precursors. Oxidative cyclization occurred in good yields and with excellent diastereoselectivity (often >30 : 1) using the reagent combination of 5 mol% Pd(TFA)₂, 10 mol% DMSO, 20 mol% NaOBz in THF under 1 atmosphere of O₂. The reaction was tolerant of a range of substituents on the nucleophilic nitrogen and worked on diverse alkenyl amines, both open-chain and cyclic. The sulfonyl group could be removed by treatment with LiAlH₄ to furnish highly valuable diamine products.

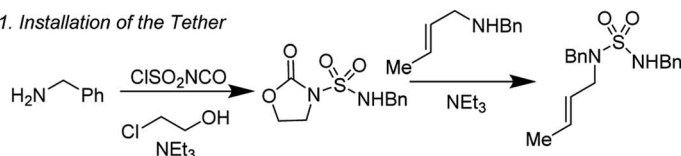
Stahl and co-workers studied the mechanism of this reaction thoroughly (Fig. 7). Using variable temperature ¹H NMR studies, they showed that DMSO can coordinate to Pd(II) *via* both sulfur and oxygen and is kinetically labile. They noted that two reaction pathways are possible but were able to rule out an allylic C–H activation mechanism by employing probe substrate **4**.

2.4 Carbamate tethered *aza*-Wacker cyclization (2012)

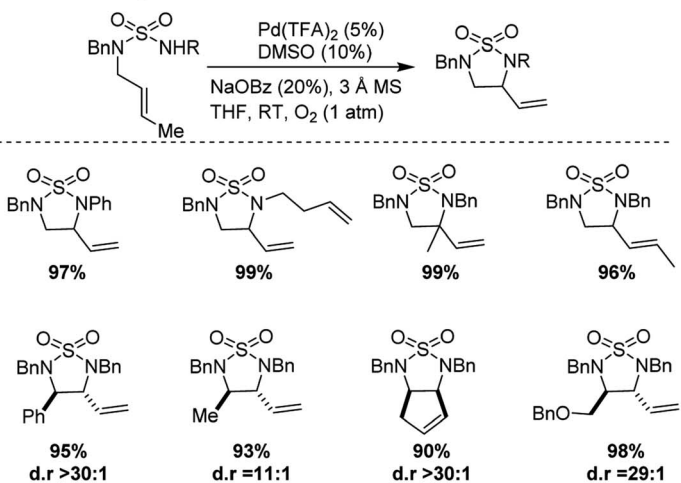
Bäckvall and co-workers showed that carbamate tethers were competent for *aza*-Wacker cyclization reactions (Fig. 8).¹²

Sulfamide Tethered *aza*-Wacker Cyclization

1. Installation of the Tether



2. *Aza*-Wacker Cyclization



3. Removal of the tether

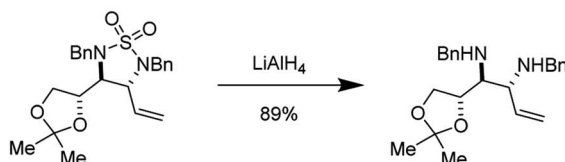


Fig. 6 Stahl's sulfamide tethered *aza*-Wacker cyclization.



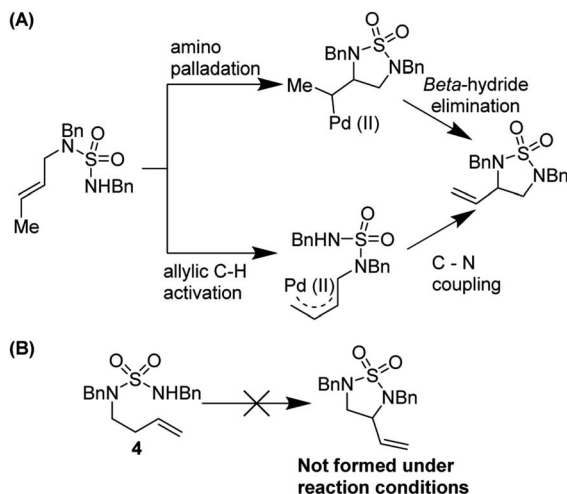
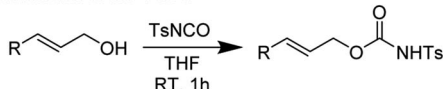


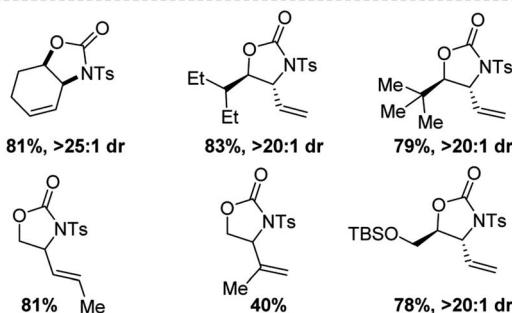
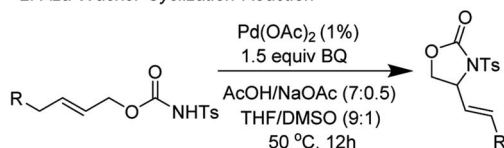
Fig. 7 (A) Two possible reaction pathways (B) substrate probe experiment shows that nucleopalladation is more likely.

Carbamate Tethered aza-Wacker Cyclization

1. Installation of the Tether



2. Aza-Wacker Cyclization Reaction



3. Tether Removal

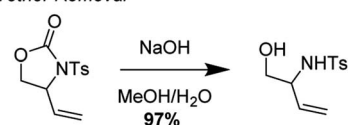


Fig. 8 Backvall's carbamate tethered aza-Wacker cyclization.

Despite using very low palladium loadings (1 mol%), the reactions proceeded in good yield and with excellent diastereoselectivity. Interestingly, they found that the starting olefin geometry had a profound effect on reaction progress; carbamates derived from (*Z*)-allylic alcohols cyclized much more reliably than those from the corresponding (*E*) isomer. The reaction worked best for carbamates derived from disubstituted

allylic alcohols; reaction times were markedly extended for those derived from trisubstituted allylic alcohols.

They conducted an elegant series of experiments in order to elucidate the reaction pathway (Fig. 9). As no reaction was observed with probe substrate 5, they concluded that amidopalladation was more likely as a first step compared to allylic C-H cleavage to form a π -allyl complex. Further, using deuterated substrate 6, they were able to determine that the reaction likely proceeds *via trans*-amidopalladation followed by *syn*- β -hydrogen-elimination.

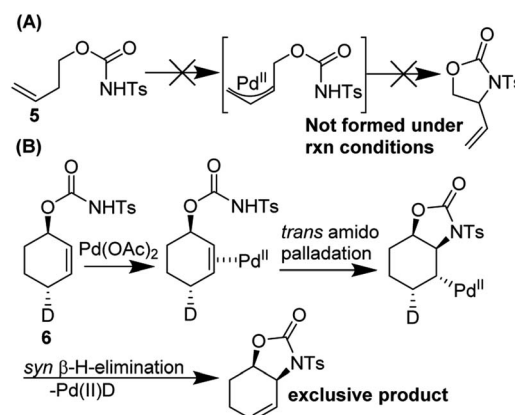
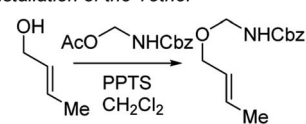


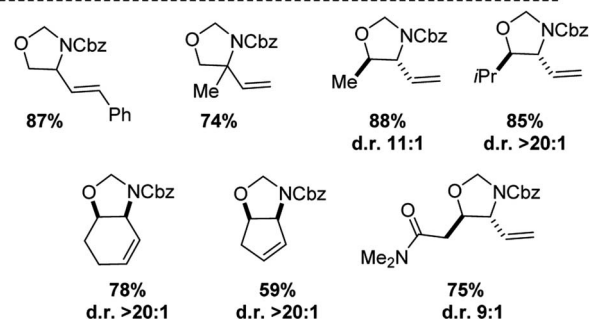
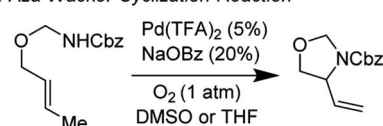
Fig. 9 Backvall's experiments suggest (A) a nucleopalladation mechanism and (B) *trans*-amidopalladation.

N,O-Acetal Tethered aza-Wacker Cyclization

1. Installation of the Tether



2. Aza-Wacker Cyclization Reaction



3. Tether Removal

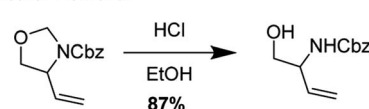


Fig. 10 Stahl's *N,O*-acetal tethered aza-Wacker cyclization.

2.5 *N,O*-Acetal tethered *aza*-Wacker cyclization (2013)

Stahl and co-workers developed an elegant approach for the synthesis of masked 1,2-aminoalcohols using an *N,O*-acetal tethered *aza*-Wacker cyclization reaction (Fig. 10).¹³ The cyclization reaction was highly selective for the formation of 5-membered rings and exhibited excellent diastereoselectivity. The tether was appended in a single step reaction by reacting various allylic alcohols with Cbz-amino-methyl acetate and could be facily removed using HCl in MeOH. They were able to apply this reaction successfully in a redox-relay synthesis (Fig. 11) of the 2-deoxy-3-aminosugar-(−)-acosamine (see Section 4 of this review for full details of the synthesis).

2.6 *N*-Sulfonyl-amide tethered *aza*-Wacker cyclization (2017)

In 2017, Poli, Broggini, and co-workers reported an interesting *N*-sulfonyl-amide tethered *aza*-Wacker cyclization reaction for the synthesis of imidazolidine-4-one and piperazin-2-one heterocycles (Fig. 12).¹⁴ They found that by tuning the reaction conditions, namely the nature of the hypervalent iodine oxidant used, they could bias the formation of one heterocyclic product relative to the other.

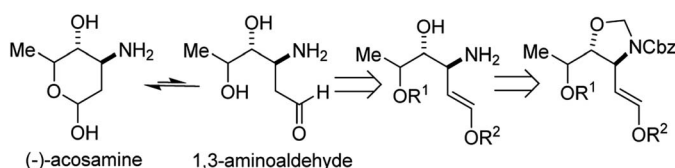


Fig. 11 Redox-relay approach to (−)-acosamine.

N-Sulfonyl-Amide Tethered *Aza*-Wacker Cyclization

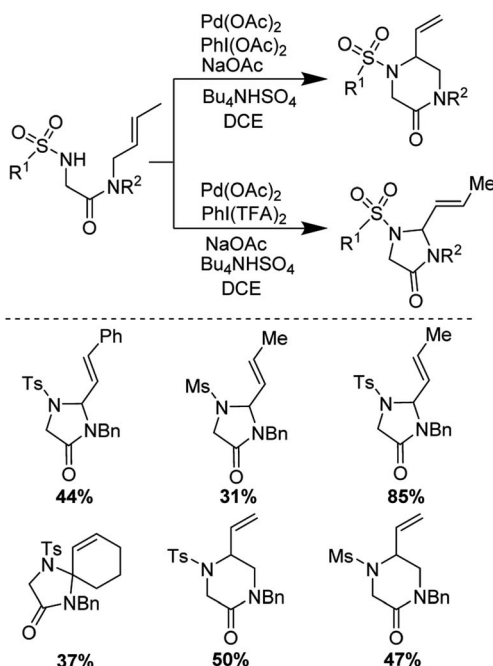


Fig. 12 Poli and Broggini's *N*-sulfonyl-amide tethered *aza*-Wacker cyclization.

They hypothesized that for the formation of 6-membered piperazinone products, initial aminopalladation lead to the formation of an alkyl-Pd species which was followed by β -hydrogen abstraction and reductive elimination (Fig. 13). $\text{PhI}(\text{OAc})_2$ promoted oxidation of $\text{Pd}(0)$ to $\text{Pd}(\text{II})$. $\text{PhI}(\text{TFA})_2$, however, promoted allylic C–H bond cleavage allowing for a pathway favoring 5-membered imidazolidinone formation.

2.7 *N*-Ts hydrazine tethered enantioselective *aza*-Wacker cyclization (2018)

In 2018, Yang, Zhang, and co-workers developed an elegant asymmetric *aza*-Wacker cyclization using *N*-tosyl hydrazine as a tether which could be attached to ketone moieties (Fig. 14).¹⁵ The reaction was tolerant of a variety of olefin substrates; the authors found that with the combination of $\text{Pd}(\text{OAc})_2$ and the chiral ligand *t*Bu-Pyrox, enantiomeric excesses as high as 98% could be obtained. In the majority of substrates, quaternary stereocenters could be formed in good yield and excellent enantioselectivity. In certain substrates, products with two vicinal stereocenters could be generated in one step as a single diastereomer, a highly challenging transformation within the realm of *aza*-Wacker chemistry.

The authors carefully examined the mechanism of the reaction using a combination of substrate probe studies and isotope labelling experiments (Fig. 15). Based on this, they hypothesized that this *aza*-Wacker cyclization proceeds *via syn*-amino-palladation.

2.8 Sulfamate tethered *aza*-Wacker cyclization (2020)

Sathyamoorthi and Shinde recently disclosed a sulfamate tethered *aza*-Wacker cyclization reaction that reliably forms six-membered oxathiazinane heterocyclic rings in good yields and with reasonable (3 : 1) to excellent (>20 : 1) diastereoselectivities (Fig. 16).¹⁶ The sulfamate auxiliary could be conveniently appended to a variety of alcohols and cyclized onto diverse pendant alkenes. The reaction utilizes the unusual reagent combination of $\text{Pd}_2(\text{dba})_3$ along with $\text{Cu}(\text{OAc})_2$ under 1 atm of

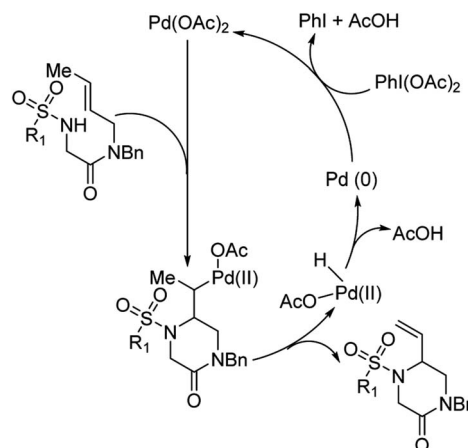


Fig. 13 Proposed catalytic cycle for the formation of piperazinone products.



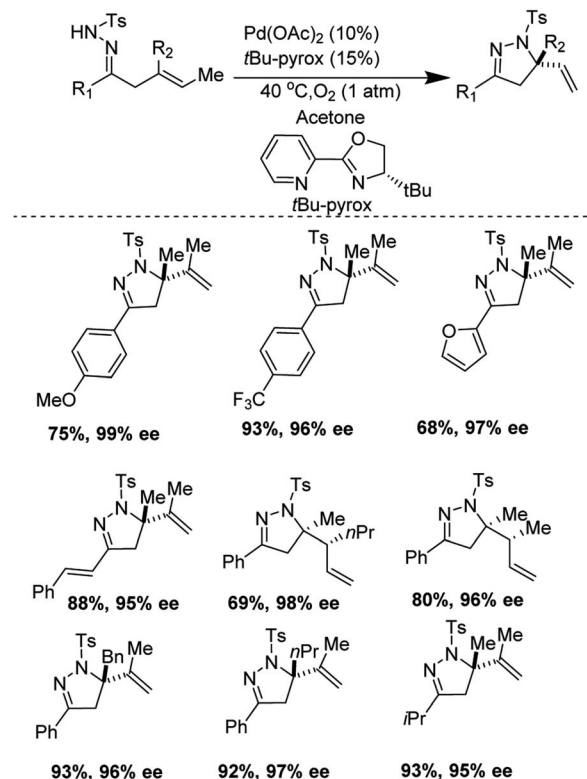
Hydrazine Tethered *aza*-Wacker Cyclization

Fig. 14 Zhang and Yang's hydrazine tethered asymmetric *aza*-Wacker cyclization.

O_2 . Diverse aryl and alkyl groups attached to the nitrogen of the sulfamate were tolerated. In addition, even when the scale was increased from 0.2 mmol of substrate (~ 50 mg) to 10 mmol

(~ 2.8 g), the yield did not suffer.¹⁷ The oxathiazinane ring is a masked 1,3-amino alcohol and served as a convenient synthon for ring-opening reactions with a variety of nucleophiles, including phenoxides, alkoxides, and thiols.¹⁸

3. Enantioselective *aza*-Wacker cyclization reactions

Examples of enantioselective *aza*-Wacker cyclization reactions remain sparse in the literature. This is a highly challenging transformation to design for multiple factors, including the possibility of both *cis* and *trans* nucleopalladation as well as a general lack of asymmetric ligands for the $\text{Pd}(\text{II})$ - $\text{Pd}(0)$ redox manifold.¹⁹ The purpose of this section is to summarize what exists of the intramolecular asymmetric *aza*-Wacker reaction.

3.1 Enantioselective synthesis of indolines through tandem C-N and C-C bond formation (2006)

A pioneering example of an asymmetric *aza*-Wacker type cyclization reaction was reported by Yang and co-workers in 2006. Using the reagent combination of $\text{Pd}(\text{TFA})_2/(-)$ -sparteine, tricycles were rapidly synthesized with enantiomeric excesses ranging from 75–86% (Fig. 17).²⁰ In one step, a new C-N bond is forged with reasonable enantioselectivity followed by formation of a new C-C bond through a carbopalladation mechanism. The Yang laboratory has worked to significantly expand the scope of this transformation through ligand design; in subsequent reports, they demonstrated that $\text{Pd}(\text{TFA})_2/(S,S)$ -diPh-pyridine-oxazoline and $\text{Pd}(\text{OAc})_2/t$ -Bu-quinoline-oxazoline allowed for cascade cyclizations of a diverse array of diene substrates in good yields and high enantioselectivities.^{21,22}

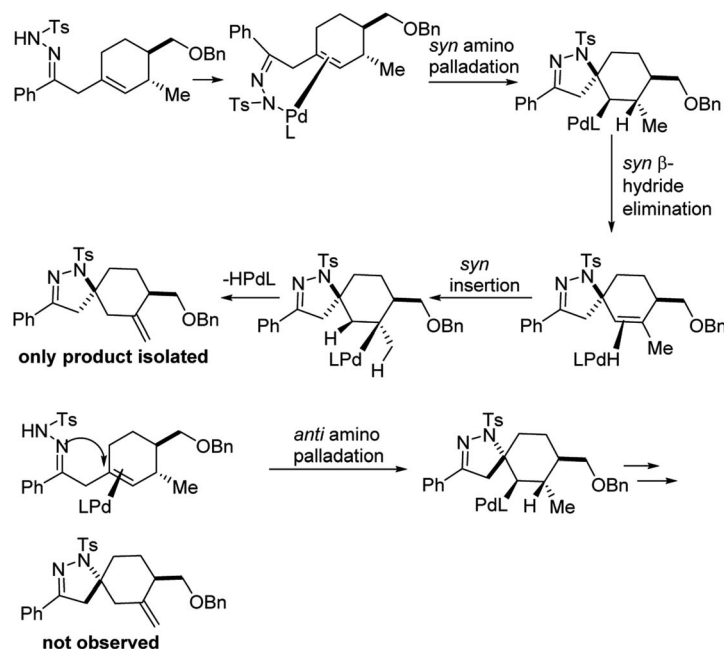
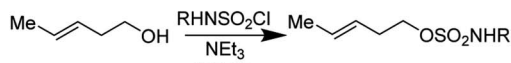
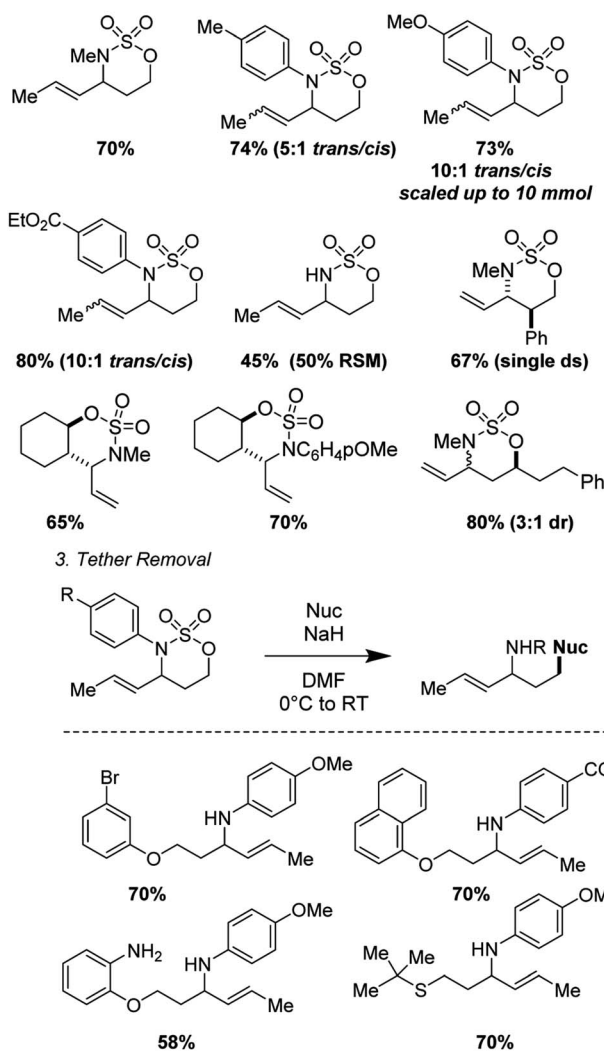
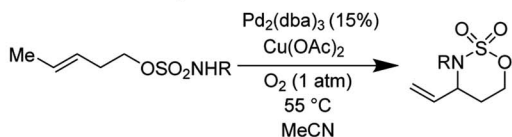


Fig. 15 Mechanistic studies suggest a *syn*-amino-palladation pathway.



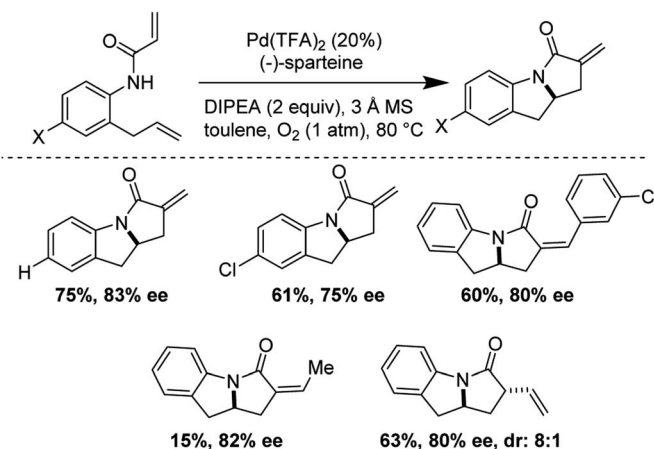
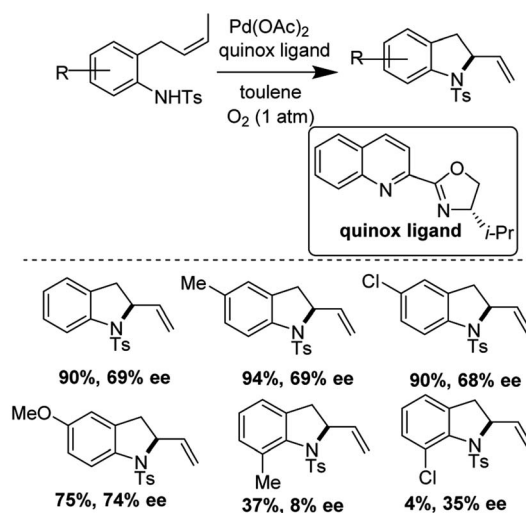
Sulfamate Tethered *aza*-Wacker Cyclization

1. Installation of the Tether

2. *Aza*-Wacker Cyclization ReactionFig. 16 Sathyamoorthi's tethered *aza*-Wacker cyclization.3.2 Enantioselective *aza*-Wacker cyclization reaction of tosylated aryl amines (2010)

Zhang and co-workers reported a pioneering example of an asymmetric *aza*-Wacker cyclization reaction of olefinic tosylamides using the reagent combination of $\text{Pd}(\text{OAc})_2$ /quinox ligand under 1 atm O_2 in toluene (Fig. 18).²³ They found that the best enantioselectivities (74% ee) were achieved with *para*-substituted substrates; enantioselectivity markedly worsened with substrates with *ortho*-substituents.

Asymmetric Synthesis of Indolines

Fig. 17 Asymmetric synthesis of indolines via a tandem *aza*-Wacker cyclization/carbopalladation sequence.Asymmetric *aza*-Wacker Cyclization of Olefinic TosylamidesFig. 18 Asymmetric cyclization of olefinic tosylamides using $\text{Pd}(\text{OAc})_2$ /quinox.3.3 Enantioselective *aza*-Wacker cyclization reaction of tosylated alkyl amines (2011)

In 2011, Stahl and co-workers disclosed a highly enantioselective cyclization reaction of tosylated alkyl amines using a $\text{Pd}(\text{TFA})_2$ /pyrox manifold (Fig. 19).^{24,25} The reactions proceeded at room temperature and furnished cyclized alkenyl pyrrolidine products in good yields (~60–98%) and excellent enantioselectivities (ee = 92–98%). By examining cyclization reactions with racemic pyrox ligand as well as with the (*R*) and (*S*) antipodes individually, they discovered that the nature of the ligand could override diastereomeric bias conferred by the inherent steric and electronic properties of the substrate. Extensive DFT computations revealed that the transition state leading to the major enantiomer is approximately



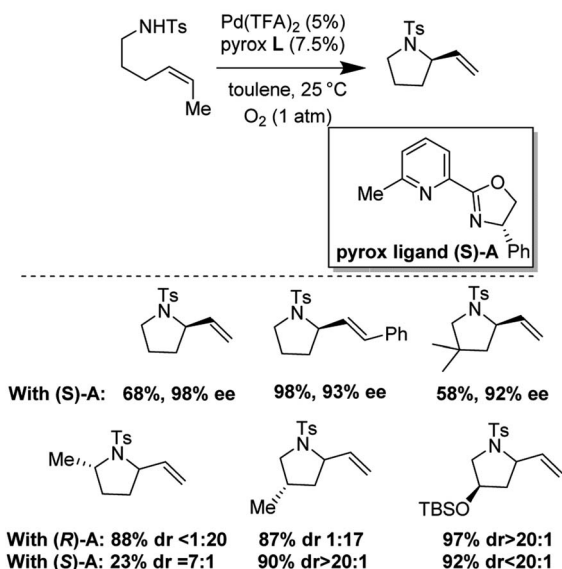
Enantioselective *aza*-Wacker Cyclization of Alkenyl Amines

Fig. 19 Stahl's enantioselective cyclization of alkenyl amines.

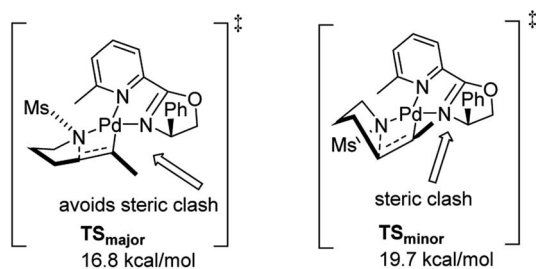


Fig. 20 Calculated transition state for major and minor enantiomers.

3 kcal mol⁻¹ lower than that leading to the minor one (Fig. 20).

3.4 Enantioselective *aza*-Wacker cyclization for the synthesis of isoindolinones (2012)

In 2012, Zhang and co-workers disclosed a highly enantioselective *aza*-Wacker cyclization which furnishes isoindolinones bearing quaternary stereocenters (Fig. 21).²⁶ After testing a variety of quinox and pyrox ligands in combination with Pd(II) salts, they discovered that the reagent manifold of Pd(TFA)₂/tBu-pyrox under 1 atm of O₂ in CH₃CN furnished products with excellent yields and enantioselectivities (ee up to 99%). Importantly, they found that the *N*-OMe is cleaved facilely using SmI₂ yielding *N*-unfunctionalized amide products. They hypothesized that the *N*-atom of the methoxyamine auxiliary is bound to the Pd center, *cis* to the pyridine moiety of the pyrox ligand; the substrate olefin is thus bound *trans* to the pyridine moiety (Fig. 22). If this olefin has *Z* geometry, the terminal methyl group is oriented up and away from the pyrox *tert*-butyl group, allowing for strong asymmetric induction. Finally, *syn*-amino-palladation and β-hydrogen elimination furnishes product.

Enantioselective Synthesis of Isoindolinones

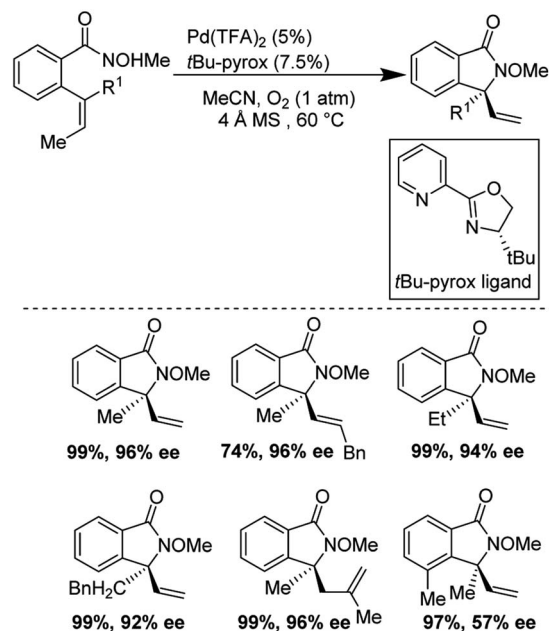


Fig. 21 Zhang's enantioselective synthesis of isoindolinones.

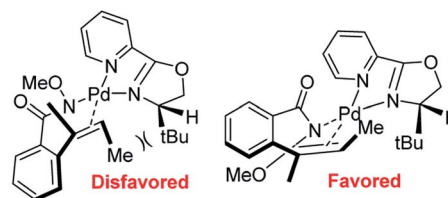


Fig. 22 Zhang's model for asymmetric induction.

3.5 Enantioselective *aza*-Wacker cyclization for the synthesis of 6-membered heterocycles (2018)

In 2018, Sen, Takenaka, and Sasai disclosed an enantioselective synthesis of 6-membered heterocycles using an *aza*-Wacker cyclization reaction, patterned on Stahl's previous racemic disclosure in 2012 (Fig. 23).²⁷ For this reaction, they used catalytic Pd(OAc)₂ in conjunction with (*P,R,R*)-iPr-SPRIX ligand and oxone as the terminal oxidant; they had previously used the combination of Pd(II) and SPRIX ligands for Yang-type cascade cyclizations, but the enantioselectivities of these reactions did not cross 61%.²⁸ They hypothesized that the low σ-donor ability of the SPRIX ligand allows for preservation of the Lewis acidity of the Pd(OAc)₂ and efficient alkene activation. Survey of a variety of alkenyl substrates revealed that the presence of a bulky substituent at the olefin terminus was critical for efficient enantio-induction. Sasai and co-workers conjectured that avoidance of unfavorable steric clashing between bulky groups on the olefin and the isopropyl groups of the SPRIX ligand allowed for olefin facial discrimination during the critical *syn*-amino-palladation event (Fig. 24). Under optimal conditions,



Enantioselective Synthesis of 6-membered Heterocycles

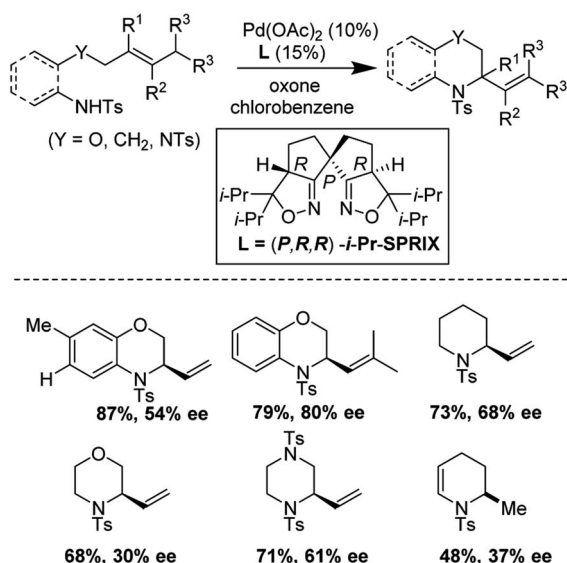


Fig. 23 Asymmetric synthesis of diverse six-membered heterocycles using $\text{Pd}(\text{OAc})_2$ /i-Pr-SPRIX.

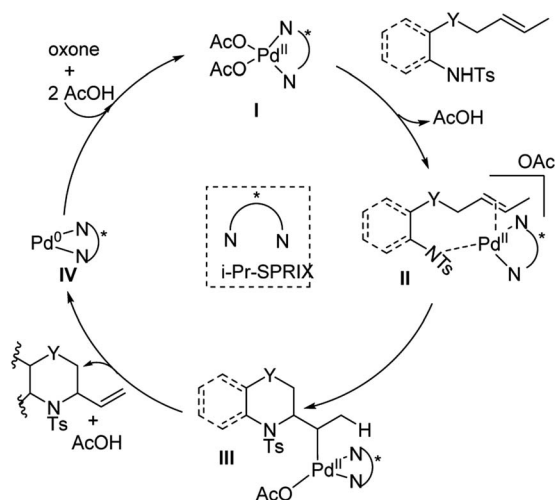


Fig. 24 Proposed catalytic cycle.

they were able to achieve yields as high as 87% with enantioselective excesses as large as 80%.

3.6 Enantioselective synthesis of 6,5-bicyclic *aza*-heterocycles (2014)

Building upon foundational work by the Yang laboratory (*vide supra*), in 2014, Gong and co-workers disclosed a highly enantioselective oxidative tandem cyclization reaction which furnished 6,5-bicyclic *aza*-heterocycles in good yields and enantioselectivities up to 92%.²⁹ They found that the unusual combination of $\text{Pd}(\text{TFA})_2$, *t*Bu-quinolineoxazoline, and a chiral phosphoric acid additive were essential for reaction optimization (Fig. 25).

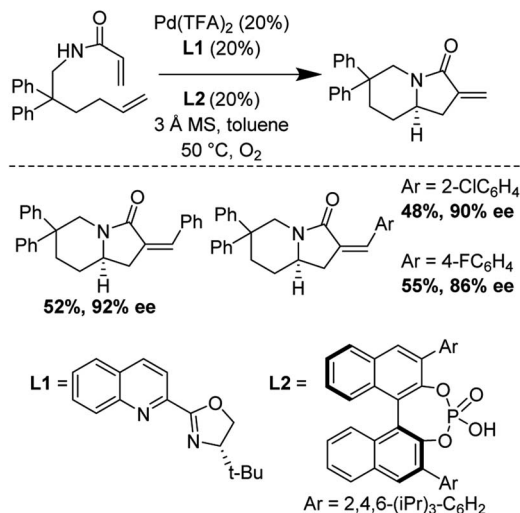
Enantioselective Synthesis of 6,5-*aza*-Heterocycles

Fig. 25 Gong's enantioselective synthesis of 6,5-heterocycles through tandem cyclization reactions.

3.7 Enantioselective synthesis of indolines (2019)

He and co-workers recently improved upon the tandem *aza*-Wacker carbopalladation sequence first reported by Yang and co-workers in 2006.³⁰ In this report, they developed a new class of chiral ligand, the quinidine oxazoline, and applied it in an asymmetric tandem *aza*-Wacker carbopalladation cascade (Fig. 26). Using this exciting new ligand framework, they were

Enantioselective Synthesis of Indolines

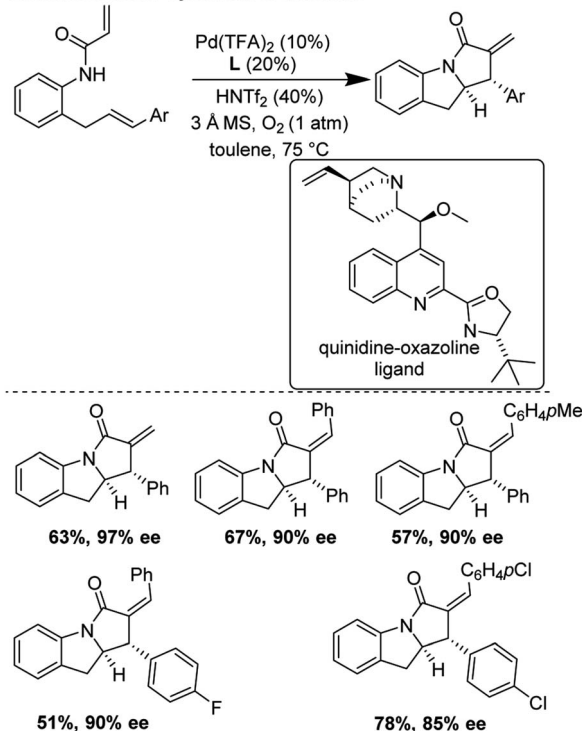


Fig. 26 He's improved asymmetric synthesis of indolines.

able to obtain enantioselective excesses up to 97%, with diastereomeric ratios generally greater than 20 : 1. For select substrates, the reaction scaled well, with little loss in yield and enantioselectivity.

4. *aza*-Wacker cyclization reactions applied to natural products synthesis

There are very few examples of *aza*-Wacker cyclization reactions applied as key steps in the synthesis of complex natural products. This is in sharp contrast to other alkene and alkane oxidation reactions, especially C–H amination.³¹ We find this to be a missed opportunity because intramolecular *aza*-Wacker reactions offer great precision in the site-selective functionalization of alkene moieties. Not only is a new C–N bond formed but also the alkenyl moiety is transposed into a new location, essentially serving as a blank slate for a variety of subsequent mono- and di-functionalization reactions.

In this portion, we summarize existing examples of *aza*-Wacker cyclization reactions utilized in the pursuit of complex natural products. Most of these examples are *aza*-Wacker reactions employing native amines or amides; the lone exception is Stahl's elegant assembly of (–)-acosamine, which highlights the use of a tethered *aza*-Wacker reaction. The wider adoption of *aza*-Wacker reactions by the synthetic community would represent an important shift in the logic of nitrogen insertion during complex molecule assembly.

4.1 Total synthesis of (±)-bukittinggine

Bukittinggine is a *Daphniphyllum* alkaloid with potent anti-inflammatory activity that was first isolated from the leaves and branches of *Sapium baccatum* collected near the town of Bukittinggi, West Sumatra, Indonesia.³² Of this large family of alkaloids, bukittinggine is one of the only members with a heptacyclic framework, providing a challenging target for synthetic chemistry efforts.

Clayton H. Heathcock and co-workers achieved the first total synthesis (±)-bukittinggine. Highlights of their synthesis include a marvelous intramolecular Diels–Alder reaction followed by an acid-mediated cationic cyclization to furnish the secodaphnane nucleus (Fig. 27). The pyrrolidine ring was constructed using an *aza*-Wacker oxidative cyclization reaction, one of the first applications of this reaction in natural product synthesis (Fig. 28).

During significant optimization of this reaction, the authors observed a marked improvement when using palladium(II) trifluoroacetate relative to palladium(II) acetate. Further, they found that the quality of benzoquinone was critical and that the reaction proceeded best when it was recrystallized prior to use. Following the *aza*-Wacker cyclization reaction, the final stereocenter was set using a diastereoselective hydroboration–oxidation reaction followed by removal of the resulting alcohol. The final lactone ring was formed through oxidation with Ag₂CO₃ adsorbed onto Celite.

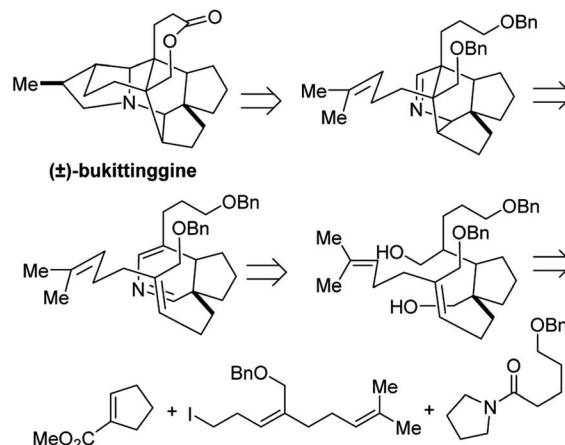


Fig. 27 Bukittinggine is a complex heptacyclic alkaloid.

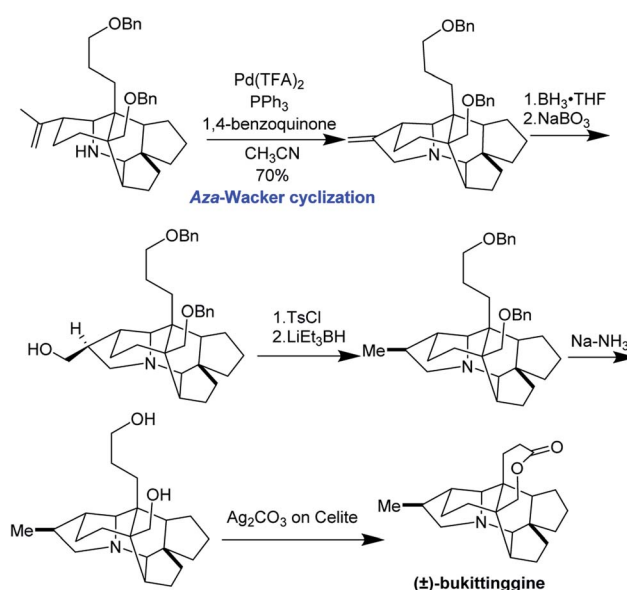


Fig. 28 The *aza*-Wacker cyclization is a key step in Heathcock's synthesis.

4.2 Enantioselective syntheses of (–)-melinonine-E and (+)-strychnoxanthine

β-Carbolinium alkaloids are a large family of structurally interesting, biologically active natural products (Fig. 29). Melinonine-E was first isolated in 1957 from the bark of *Strychnos melinoniana* Baillon (Loganiaceae), a plant used in

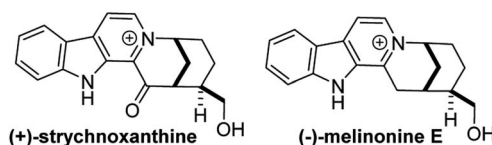


Fig. 29 β-Carbolinium alkaloids with a fused 2-azabicyclo[3.3.1]nonane skeleton.



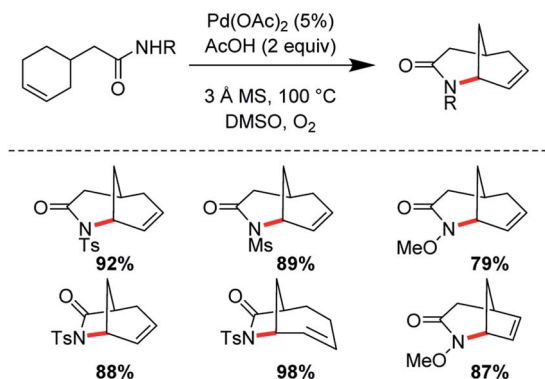


Fig. 30 Hong's aza-Wacker cyclization constructs bicyclic rings.

African folk medicine for malarial therapy.³³ A related natural product, strychnoxanthine, was isolated by Angenot and co-workers from *Strychnos gossweileri* Exell (Loganiaceae);³⁴ importantly, strychnoxanthine was found to inhibit *Plasmodium falciparum* ($IC_{50} = 8.4 \mu\text{m}$).³⁵ Both melinonine-E and strychnoxanthine are pentacycles with a β -carboline motif fused to a 2-azabicyclo[3.3.1]nonane skeleton.

Ran Hong and co-workers furnished the first asymmetric syntheses of (–)-melinonine-E and (+)-strychnoxanthine; a key step in both syntheses was an elegant aza-Wacker cyclization to construct the bicycle (Fig. 30).^{36,37} Cyclization precursor **8** was constructed from chiral lactone **7** in 2 steps; this lactone had previously been synthesized by Hong and co-workers as a key intermediate in the construction of other alkaloid natural products.³⁸ Interestingly, the *N*-substituent had a marked effect on the success of the aza-Wacker cyclization. When the OMe group was replaced by a tosyl substituent, the yield dropped significantly (Fig. 31). The resulting bicycle was expeditiously converted into (–)-melinonine E in a series of five steps, with a powerful $\text{TiF}_2\text{O}/2,6\text{-DTBP}$ cyclodehydration reaction as a highlight (Fig. 32). Intermediate **10** was converted into (+)-strychnoxanthine after acylation and SeO_2 oxidation (Fig. 32).

4.3 Enantioselective synthesis of (–)-arcutinine

(–)-Arcutinine is a C_{20} diterpenoid alkaloid molecule, a member of a much larger family of C_{18} , C_{19} , and C_{20} natural products

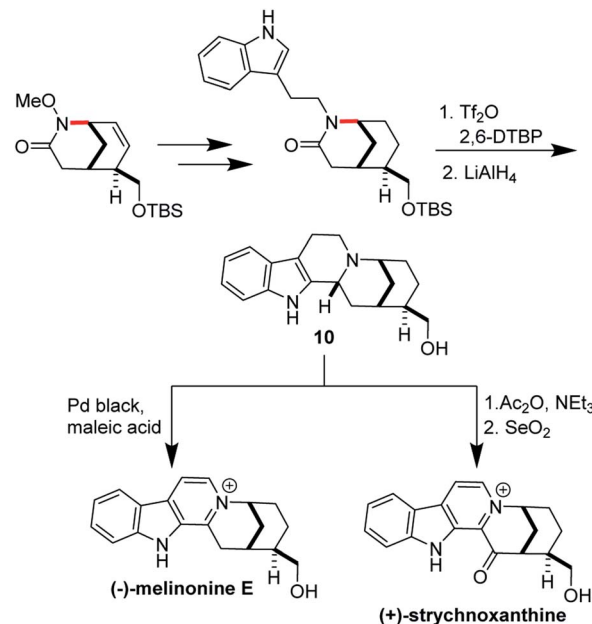


Fig. 32 Endgame of the melinonine and strychnoxanthine synthesis.

isolated from the *Acontium*, *Delphinium*, and *Spiraea* genera of plants.³⁹ Arcutinine-type alkaloids are characterized by a challenging, functional group adorned hexacyclic framework with three all-carbon quaternary centers. (–)-Arcutinine was first isolated by Saidkhodzhaeva and co-workers from *Aconitum arcuatum*.⁴⁰

Yong Qin and co-workers realized the first asymmetric synthesis of (–)-arcutinine using the Stahl aza-Wacker cyclization⁴¹ as a key step (Fig. 33). The cyclization precursor was assembled in several steps from 1,3-cyclohexanedione; highlights of this sequence include an asymmetric conjugate addition of TMS cyanide, a diastereoselective palladium-catalyzed decarboxylative allylation, and a palladium-catalyzed olefin isomerization (Fig. 34).

The aza-Wacker cyclization proceeded with a reasonable diastereoselectivity of 2.5 : 1 in a total yield of 76%. The resulting product was elaborated into (–)-arcutinine in a dramatic sequence of reactions, of which an oxidative

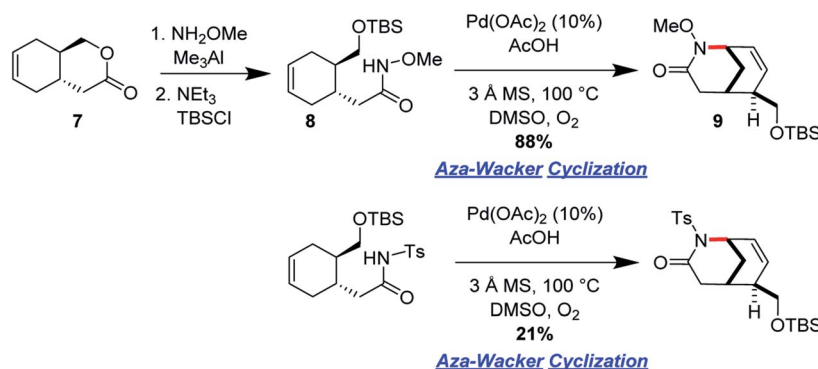


Fig. 31 Hong's aza-Wacker cyclization reaction is exquisitely sensitive to steric and electronic factors.

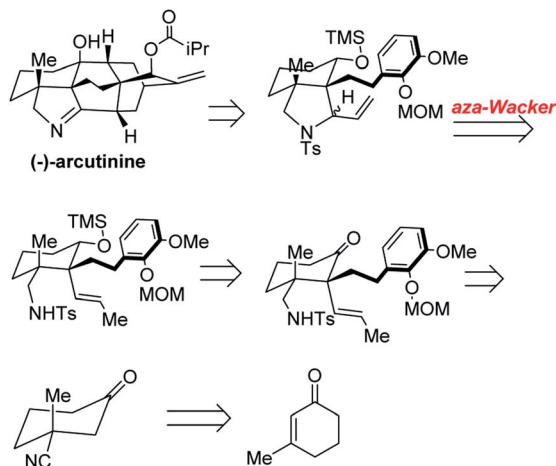
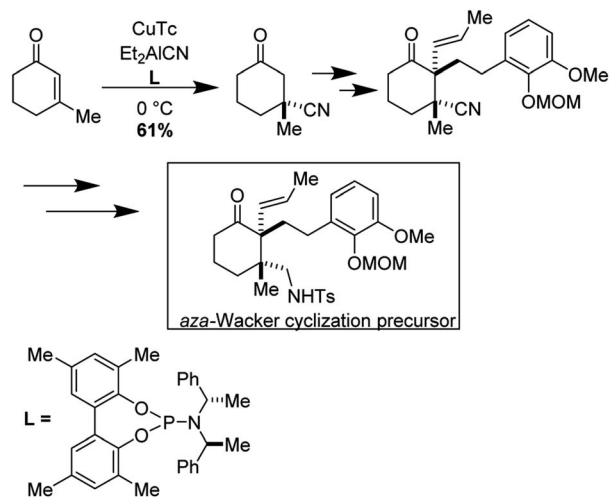


Fig. 33 Yong Qin's retrosynthesis of (-)-arcutinine.

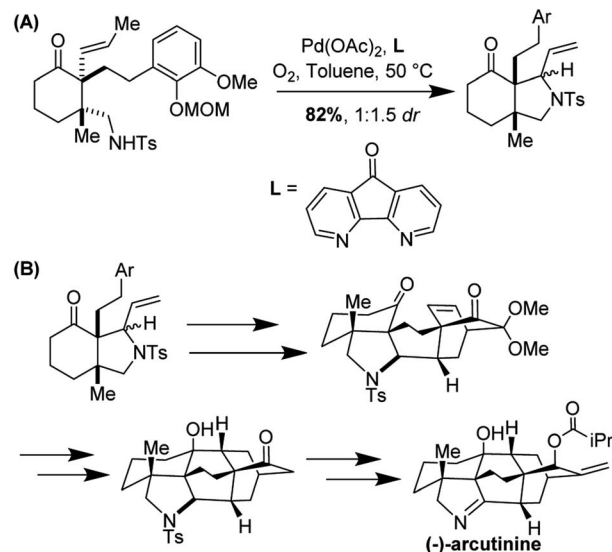
Fig. 34 Opening sequence of reactions sets up the *aza*-Wacker cyclization.

dearomatization/intramolecular Diels–Alder cascade and a ketyl–olefin cyclization are highlights (Fig. 35).

4.4 Enantioselective synthesis of (-)-acosamine

(-)-Acosamine is a member of the 3-amino-2,3,6-trideoxyhexose sugars, important elements of antibacterial and antitumor antibiotics.⁴² Shannon Stahl and co-workers have reported an elegant synthesis of (-)-acosamine, applying their hemiaminal tethered *aza*-Wacker cyclization reaction (Fig. 36).¹³ This synthesis is also notable as it remains the lone example of a tethered *aza*-Wacker cyclization applied to the assembly of a natural product.

Stahl's synthesis commences from TBS-protected (-)-lactaldehyde and furnishes the hemiaminal precursor for the key *aza*-Wacker cyclization reaction in two steps. The hemiaminal tethered *aza*-Wacker cyclization reaction proceeds in good yield and excellent diastereoselectivity

Fig. 35 (A) *aza*-Wacker cyclization using Stahl conditions (B) elaboration into (-)-arcutinine.

to furnish a cyclic 5-membered *N,O*-acetal. Silyl deprotection followed by acid mediated ring closure furnishes (-)-*N*-Cbz-*O*-methyl-acosamine, a convenient surrogate of (-)-acosamine.

4.5 Enantioselective synthesis of (-)-mesembrane and (+)-crinane

(-)-Mesembrane and (+)-crinane are alkaloid natural products which are present in the *Amaryllidaceae* plant family. Their *cis*-3a-aryloctahydroindole framework, decorated with a variety of quaternary and tertiary stereocenters, has attracted much attention from the synthetic community.^{43,44} Jieping Zhu and co-workers have recently realized enantioselective syntheses of (-)-mesembrane and (+)-crinane by applying an elegant catalytic, enantioselective, desymmetrizing *aza*-Wacker cyclization reaction (Fig. 37).⁴⁵ It should be noted that the authors discovered that for the best enantioselectivity, *two* chiral ligands were necessary, one pre-complexed to the palladium catalyst and the other added into the reaction mixture.

Cyclization precursor 12 was synthesized in three steps from biaryl 11. Zhu's desymmetrizing *aza*-Wacker cyclization proceeded in reasonable yield and enantioselectivity. From this common intermediate, the synthesis of (-)-mesembrane proceeded by removal of the tosyl group and subsequent reductive amination. BBr₃ di-demethylation, methylenation of the resulting catechol, tosyl removal, and final Pictet–Spengler cyclization afforded (+)-crinane (Fig. 38).

4.6 Enantioselective synthesis of (-)-mitomycin K

Mitomycins are a family of aziridine-containing antitumor and antibacterial natural products isolated from culture broths of *Streptomyces caespitosus* and *Streptomyces lavendulae*.⁴⁶ One



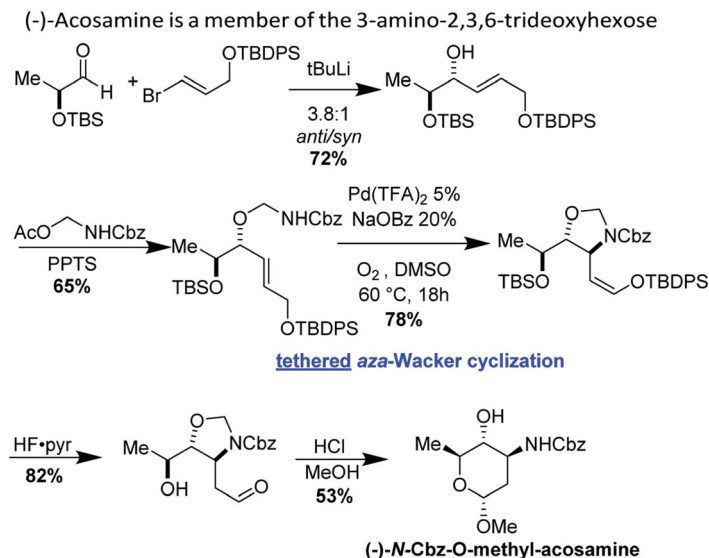


Fig. 36 Stahl's synthesis of protected (-)-acosamine.

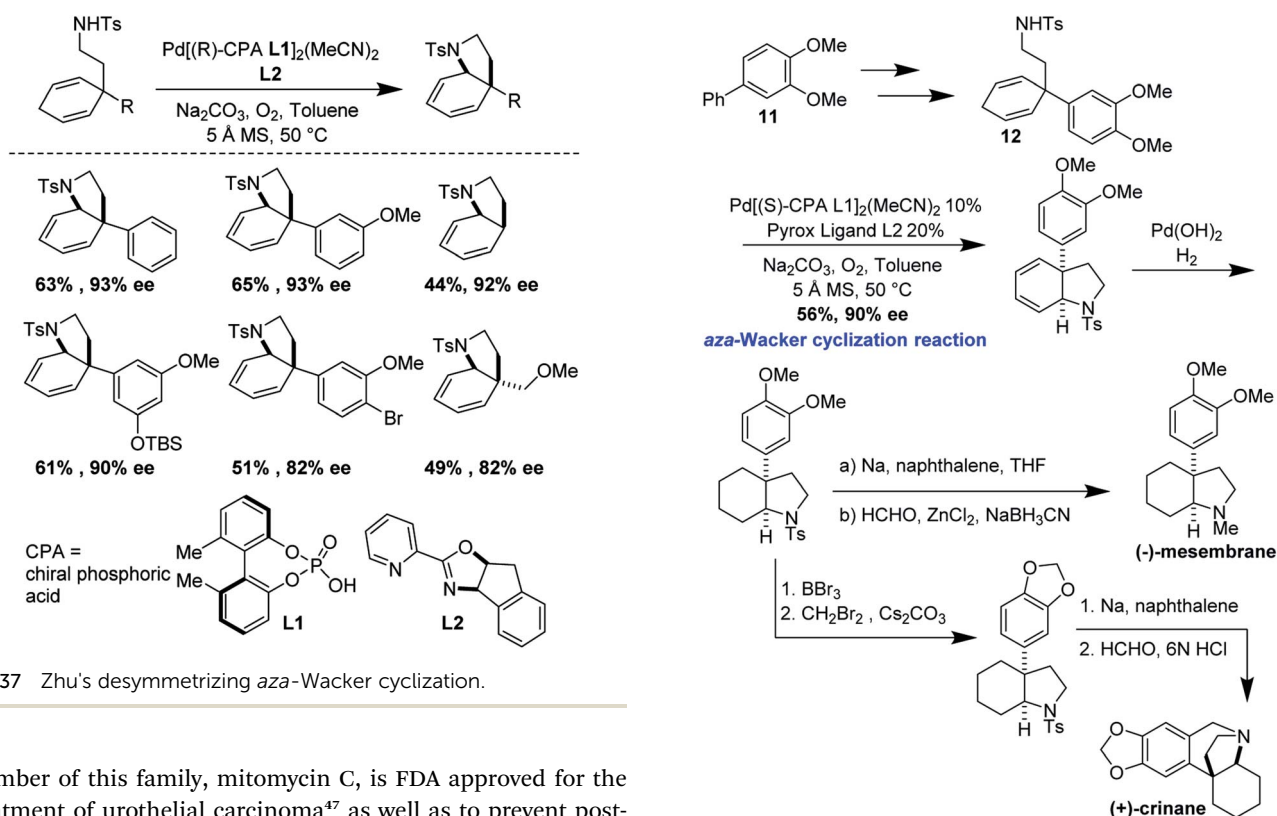


Fig. 37 Zhu's desymmetrizing aza-Wacker cyclization.

Fig. 38 Zhu's synthesis of (-)-mesembrane and (+)-crinane.

member of this family, mitomycin C, is FDA approved for the treatment of urothelial carcinoma⁴⁷ as well as to prevent post-operative scarring following trabeculectomy to relieve intraocular pressure in glaucoma.⁴⁸ Dan Yang and co-workers recently succeeded in the first enantioselective synthesis of another member of this remarkable family, mitomycin K, using an elegant aza-Wacker type amination carbopalladation cascade.⁴⁹ In one step, this reaction forms a new C–N bond with high enantioselectivity followed by a new C–C bond with high diastereoselectivity (Fig. 39).

Cyclization precursor **13** was assembled in several steps from commercially available 3-methylcatechol (Fig. 40). After

significant optimization, the authors found that the combination of Pd(TFA)₂/(+)-sparteine afforded the desired tricycle in 78% yield, 83% ee; this was increased to 94% after recrystallization in the next step. This tricycle served as a key intermediate for elaboration into (-)-mitomycin K.



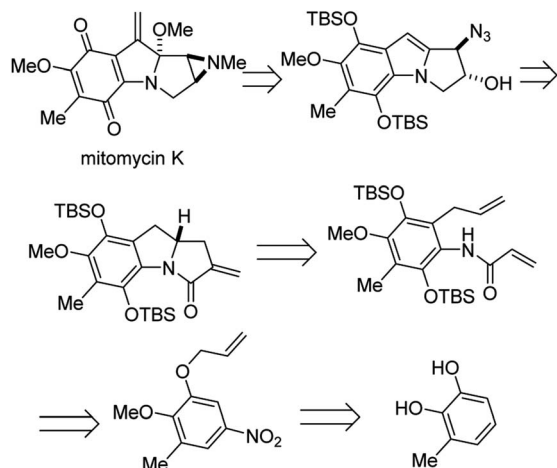


Fig. 39 Mitomycin K is a potent antitumor antibiotic Yang's retrosynthesis is shown here.

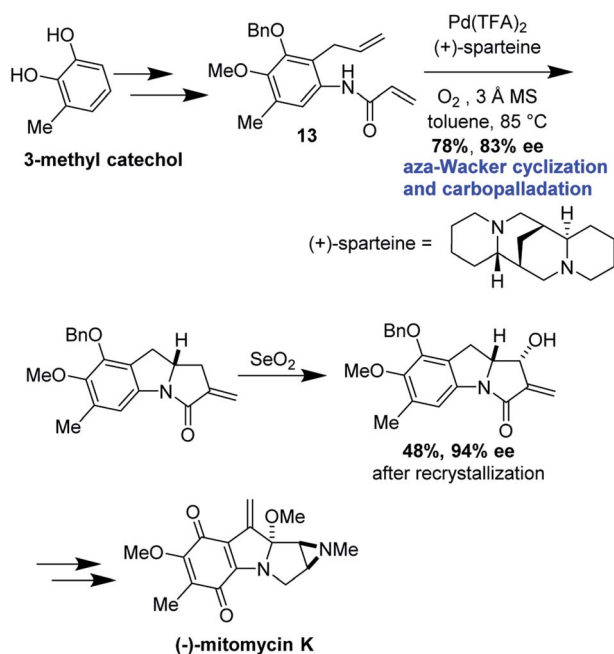


Fig. 40 Mitomycin K forward synthetic route.

5. Conclusion and outlook

Several aspects of the intramolecular *aza*-Wacker alkene functionalization reaction are highlighted herein. We first drew the distinction between traditional *aza*-Wacker cyclizations and tethered *aza*-Wacker reactions and summarized existing examples of the latter. We next focused on the development of asymmetric *aza*-Wacker cyclizations, an emerging and exciting subfield. Finally, we summarized applications of *aza*-Wacker reactions in the synthesis of natural products. Where applicable, mechanistic details of each reaction were discussed. While *aza*-Wacker cyclizations have been elegantly developed by efforts world-wide, much work remains before they join the

pantheon of the most prized organic transformations, such as asymmetric hydrogenation, cross-coupling, and olefin metathesis. In particular, there are few examples of tethered *aza*-Wacker cyclization methods, and their applications to total synthesis are also limited. Collectively, we hope that this review will serve to inspire the development of new *aza*-Wacker reactions for creative applications in complex molecule assembly.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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