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Philippe Dauban, Romain Rey-Rodriguez, Ali Nasrallah. Stereoselective C-N Bond Forming Reactions Through C(sp³)-H Bond Insertion of Metal Nitrenoids. Prof. Françoise COLOBERT and Dr. Joanna WENCEL-DELORD. C-H Activation for Asymmetric Synthesis, 2019, 10.1002/9783527810857.ch2 . hal-03033713

HAL Id: hal-03033713

<https://hal.science/hal-03033713v1>

Submitted on 8 Dec 2020

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Stereoselective C-N Bond Forming Reactions Through C(sp³)-H Bond Insertion of Metal Nitrenoids

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Abstract:

Direct catalytic C(sp³)-H fonctionnalization with metal nitrenoid species as key intermediates is a straightforward strategy for the formation of C(sp³)-N bonds. Over the past decade significant progress has been made in asymmetric nitrene C(sp³)-H insertions. Inter- and intramolecular processes starting either from iminoiodinanes, azides, and *N*-sulfonyloxycarbamates as nitrene precursors have been reported using mainly chiral rhodium but also ruthenium and manganese catalysts. These asymmetric C-H amination reactions proceed with good to high stereoselectivities thereby providing access to benzylic and allylic amines as key building blocks for the synthesis of relevant molecules for biological studies.

Keywords:

Catalysis – nitrene – hypervalent iodine – azide – rhodium – ruthenium - manganese

1. Introduction

The grafting of a nitrogen group onto a molecular backbone is a chemical operation that finds application in several scientific domains. The presence of a nitrogenous function indeed confers to the product the ability to interact with other surrounding molecules or macromolecules through a network of hydrogen bonds and/or electrostatic interactions. It also modulates its physicochemical properties by changing its polarity and solubility. There are myriad examples of amine derivatives that highlight the key value of nitrogen in science. The figure 1 displays some of them and showcases that chiral amines can be found in natural products (the neurotoxic natural amino acid (-)-*Dysiherbaine* of marine origin), pharmaceuticals (the antidiabetic drug *Sitagliptin*), agrochemicals (the herbicide *Indaziflam*), ligands (the privileged chiral *BOX ligands*), or organometallic species (*Ugi's amine*). The ubiquity of nitrogen, thus, has been a source of inspiration for the organic chemists to design efficient synthetic methods for the formation of C—N bonds.[1-3]

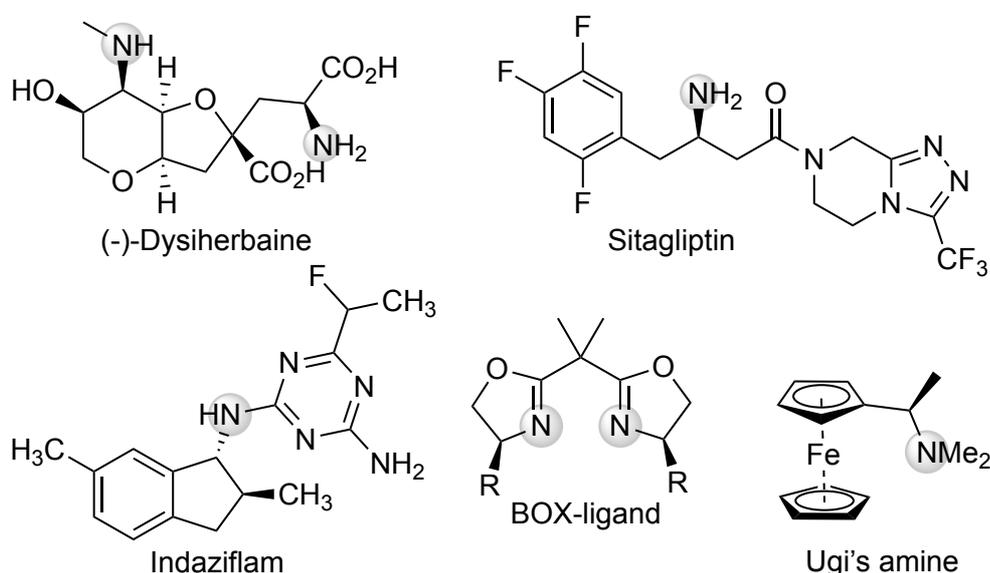


Figure 1. Chiral amines in chemical and life sciences.

Catalytic C—H amination reaction has recently emerged as a new synthetic tool for the synthesis of amines.[4-12] By comparison with other modern amination methods such as reductive amination or cross-coupling reactions, the direct conversion of a C—H to a C—N bond is a step- and atom-economical process. Given the high number of C—H bonds in organic products, it can lead to the formation of several regioisomeric amines providing that suitable conditions should be found for the chemo- and stereoselective functionalization of specific sites. The scope of catalytic C—H amination reaction, in addition, is complementary to that provided by other C—N bond forming processes. It, thus, provides an access to a new molecular space of utmost interest in the context of late-stage C—H functionalization.[13-15]

Significant achievements in catalytic C—H amination have been reported through the application of nitrene transfers as highlighted in numerous reviews and book chapters.[16-35] Nitrenes are neutral monovalent nitrogen species that behave as two-electron oxidants with a high capacity to undergo insertion reactions into C—H or C=C bonds, allowing the introduction of nitrogen groups

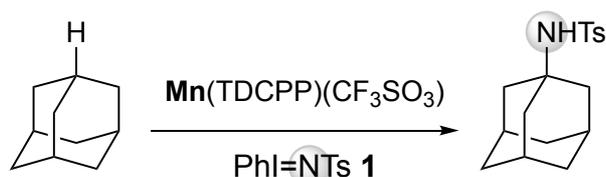
according to click-type reactions. To this end, the ability of transition metal complexes to promote these nitrene additions was crucial to optimize their efficiency and selectivity. Various catalytic inter- and intramolecular C—H amination reactions, thus, have been described since the first example of metal-catalysed nitrene transfers reported fifty years ago. These almost lead to the functionalization of C(sp³)—H bonds, thereby paving the way to the design of catalytic stereoselective processes. The last twenty years witnessed significant progress in asymmetric nitrene C(sp³)—H insertions that mainly rely on the use of iminoiodinanes, azides, and *N*-sulfonyloxycarbamates as nitrene precursors.[36-39] This chapter will give an overview of the main results obtained in this area according to the nature of the nitrene source, with an emphasis on the reactions for which an asymmetric version has been further successfully developed.

2. Historical background

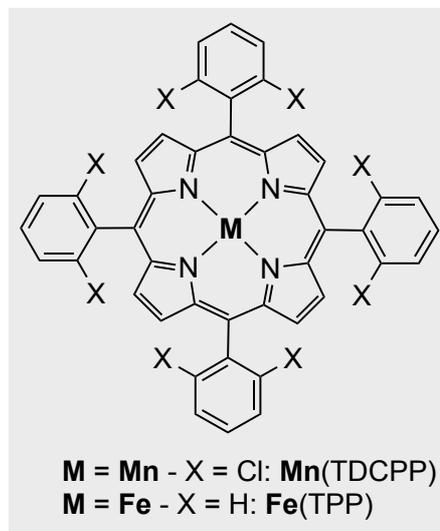
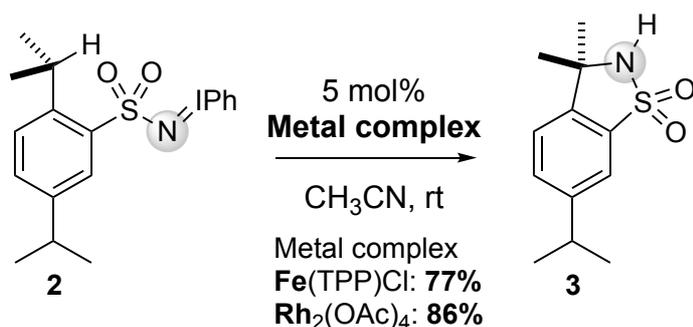
2.1. Seminal studies in catalytic C(sp³)—H amination

The ability of transition metals to mediate the insertion of nitrenes into C(sp³)—H bonds was first demonstrated fifty years ago. A couple of articles revealed the capacity of copper and zinc to react with azides or haloamines, and, then, promote the amination of simple alkanes, though with very limited synthetic application.[40-42] Much more relevant were the seminal results published by the groups of Breslow[43,44] and Mansuy[45,46] in the 80s. They both showcased the capacity of iron- and manganese-porphyrins to catalyse the amidation of hydrocarbons such as cyclohexane, heptane, or adamantane, the latter being converted to a single regioisomer (Scheme 1a). Importantly, these C(sp³)—H amination reactions rely on the use of the hypervalent iodine reagent PhI=NTs **1**. The latter belongs to the family of iminoiodinanes of general formula PhI=NR that can be prepared from various sulfonamides by reaction with PhI(OAc)₂ under basic conditions.[47] According to this protocol, Breslow and Gellman were able to prepare the iminoiodinane **2** that could be converted to the corresponding cyclic sulfonamides **3** in 77% yield in the presence of the iron-porphyrin Fe(TPP)Cl (Scheme 1b). This result, notably, could be further improved by using the commercially available Rh₂(OAc)₄

1a. Mn-Porphyrin catalyzed intermolecular amination of adamantane



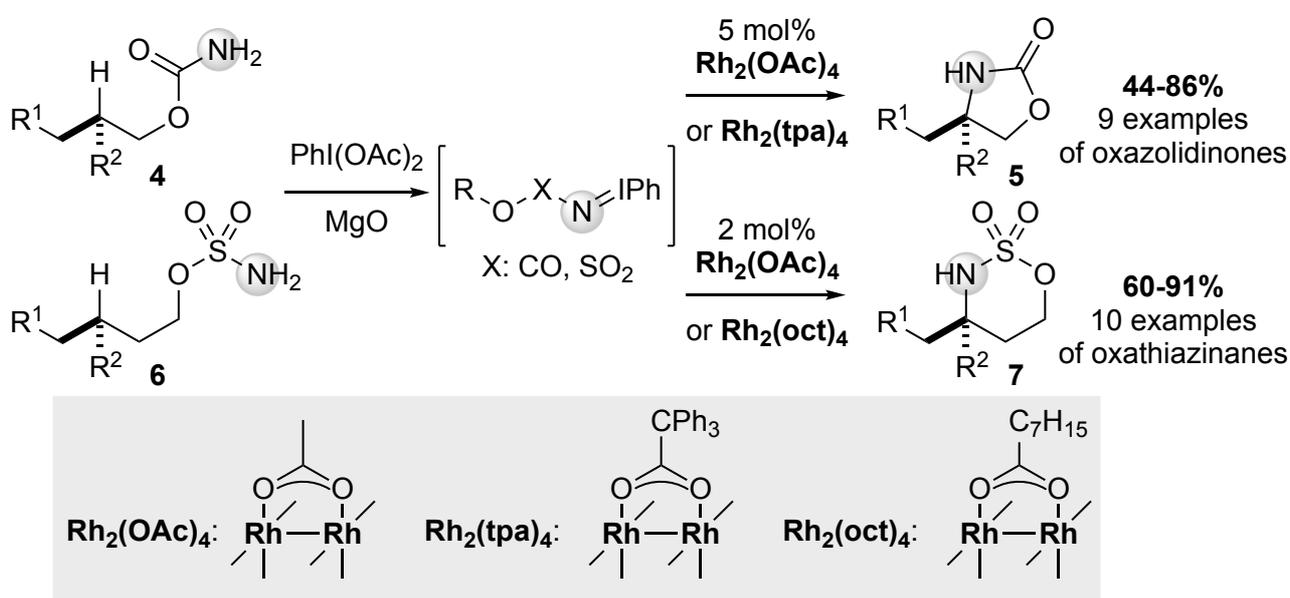
1b. Catalytic intramolecular benzylic C(sp³)—H amination



Scheme 1. Seminal studies in catalytic C(sp³)—H amination with iminoiodinanes.

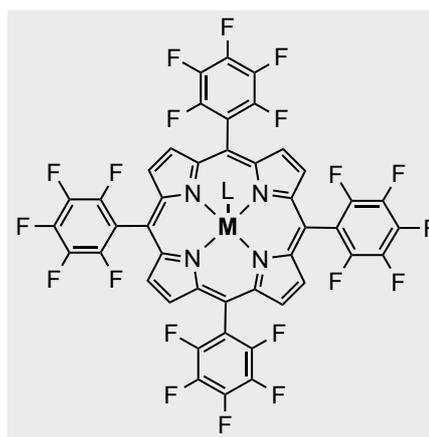
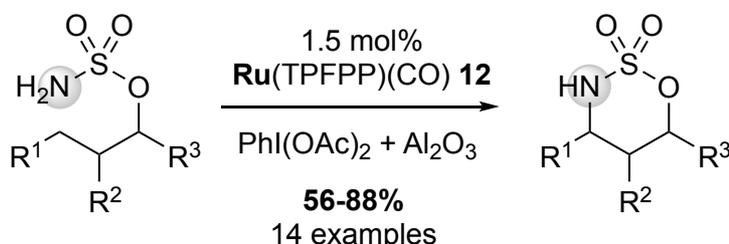
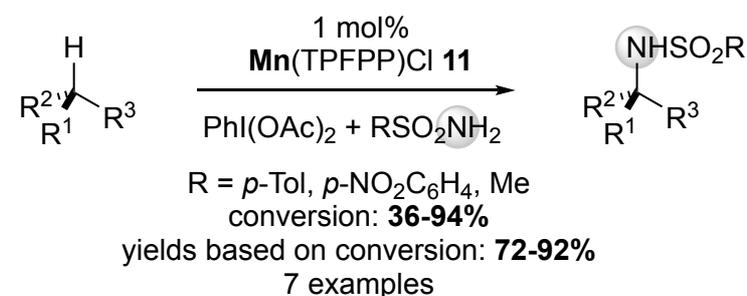
These seminal studies were an invaluable source of inspiration to design efficient protocols for catalytic nitrene addition reactions. Thus, the use of the preformed iminoiodinane PhI=NTs and its nitro analog PhI=NNs as nitrene precursors was further explored by the groups of Evans[48] and Müller[49] for the development of, respectively, copper- and rhodium-catalysed alkene aziridination. The work from the Müller's group, particularly, highlighted again the unique ability of dirhodium(II) tetracarboxylates complexes to catalyse nitrene C(sp³)—H insertion, a general transformation that was studied more in details by the same group in a subsequent article (*vide infra*).[50]

However, more significant progress with the aim to develop synthetically useful C(sp³)—H amination reactions was made by the group of Du Bois who managed to design a practical expedient procedure for the formation of metallanitrenes. The latter involves the *in situ* generation of iminoiodinanes from various nitrogen functions, such as carbamates **4** [51] or sulfamates **6**, [52] by simple reaction with the commercially available PhI(OAc)₂ in the presence of MgO. This protocol that avoids the troublesome preparation of iminoiodinanes, has led to the discovery of highly efficient intramolecular C(sp³)—H amination reactions catalysed by readily available Rh₂(OCOR)₄ complexes. These transformations afford the oxazolidinones **5** and oxathiazinanes **7**, that can be considered as precursors of 1,2- and 1,3-amino alcohols, respectively (Scheme 2). However, the ability of cyclic sulfamates to undergo regiocontrolled nucleophilic additions should be pointed out as it provides many other versatile opportunities in synthesis. [53,54]



Scheme 2. Rhodium-catalysed intramolecular C(sp³)—H amination of carbamates and sulfamates. The scope as well as the efficiency of these catalytic intramolecular processes were greatly improved by the design of the highly robust and active dirhodium(II) complex Rh₂(esp)₂ **8** the ligands of which derive from an $\alpha,\alpha,\alpha',\alpha'$ -tetrasubstituted dicarboxylic acid. [55] The bidentate nature of the ligand combined with the *m*-xylene tether provides an optimal geometry to the complex that proves to be kinetically stable under the oxidizing reaction conditions. Complex **8**, thus, has enabled to extend the scope of the intramolecular C(sp³)—H amination reaction that can be performed with catalyst loading as low as 1 mol% starting from ureas and guanidines, [56] sulfamides, [57] and *O*-(sulfamoyl)-hydroxylamines. [58]

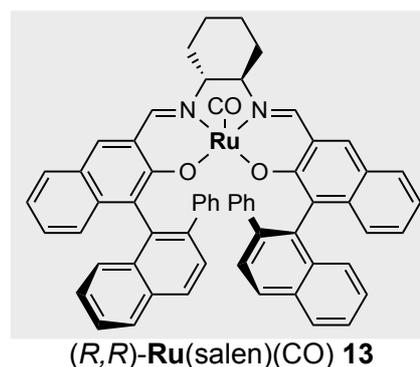
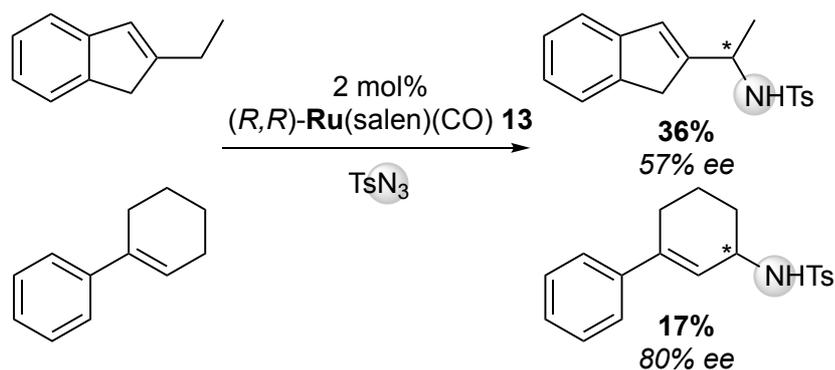
More importantly, the Rh₂(esp)₂ complex **8** has led to the development of efficient conditions for the intermolecular C(sp³)—H amination reaction. Good conversions were often achieved only in the presence of an excess of substrate because of the high reactivity of the metallanitrene species. This limitation was overcome by using complex **8** in the presence of the more soluble iodine(III) oxidant PhI(OCO*t*-Bu)₂ or by using the carboxylic acid PhMe₂CCOOH as an additive. Importantly, the chemoselectivity of the reaction that can often be tuned by the ligands of the dirhodium(II)



M = Mn - L = Cl: Mn(TPFPP)Cl 11
M = Ru - L = CO: Ru(TPFPP)(CO) 12

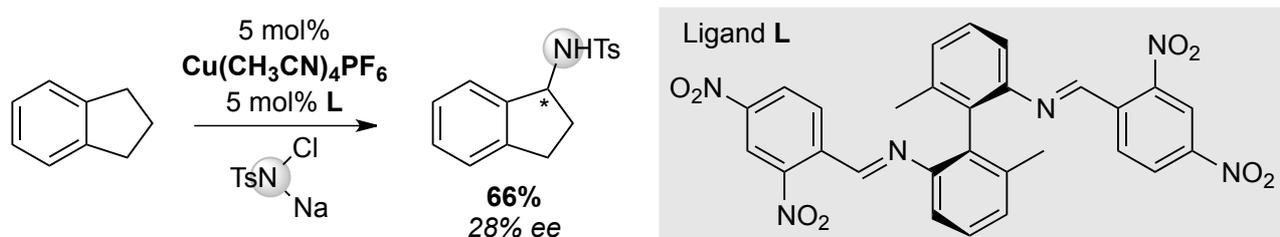
Scheme 4. Mn- and Ru-porphyrin-catalysed C(sp³)—H amination.

Most of the progress in catalytic C(sp³)—H amination has been made with the use of iodine(III) oxidants, as highlighted by many beautiful synthetic applications.[73] However, remarkable achievements have also been reported with other nitrene precursors. Thus, the capacity to uncover synthetically useful nitrene insertions from azides was demonstrated more than thirty years after the seminal study of Kwart and Kahn.[40] The group of Katsuki, to this end, has contributed significantly with the design of the Lewis acidic ruthenium(Salen) complex **13** that has proved to catalyse intermolecular nitrene C(sp³)—H insertions with tosylazide, though with moderate efficiency (Scheme 5).[74] Nevertheless, such results have paved the way to develop a catalytic asymmetric process of broad scope (*vide infra*). Cobalt porphyrins[75-78] and iron complexes[79] have also been shown to catalyse the intramolecular C(sp³)—H amination starting from alkyl-, sulfonyl-, and sulfamoylazides, although non-enantioselectively.



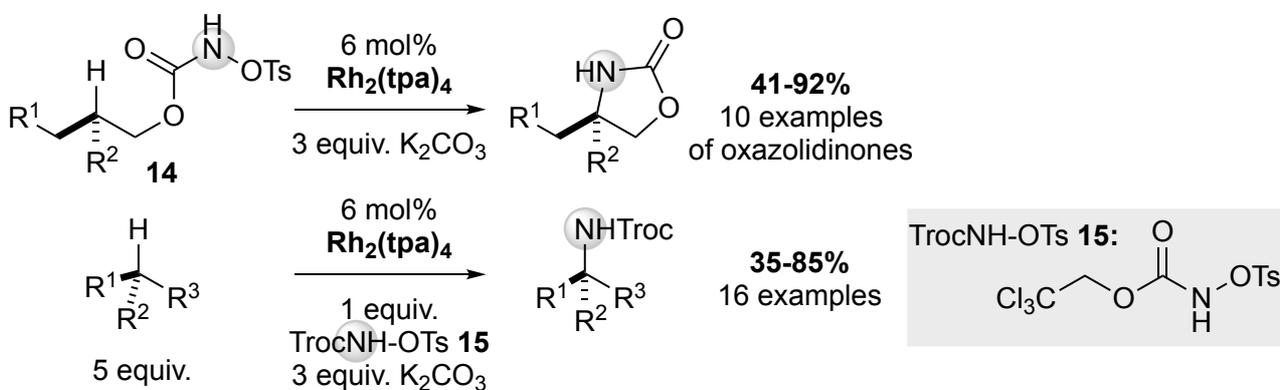
Scheme 5. Ru(salen)-catalysed C(sp³)—H amination with azides.

Azides are atom-efficient nitrene precursors because the only by-product released in the process is dinitrogen that is more acceptable than the iodobenzene moiety generated with iminoiodinanes. In such a context of sustainable chemistry, the use of haloamines offers relevant opportunities. However, these nitrene sources have received moderate attention so far, probably because of the poor stereoselectivity observed in the reactions involving these reagents (Scheme 6).[80-82]



Scheme 6. Copper-catalyzed C(sp³)—H amination with chloramine-T.

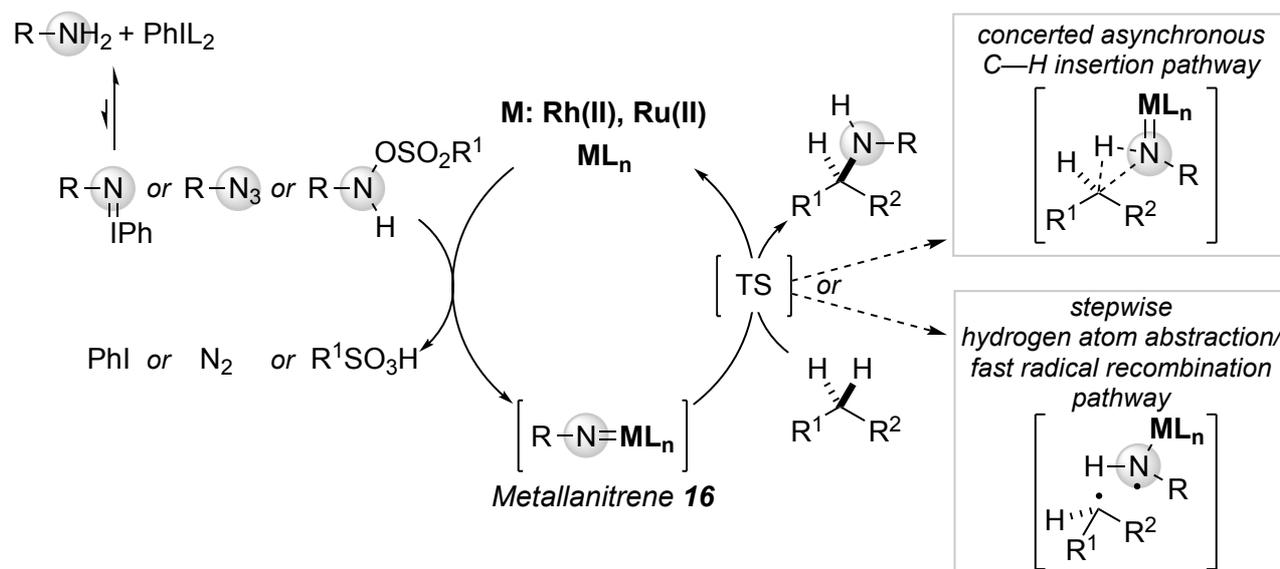
By comparison, *N*-(sulfonyloxy)carbamates have been found to be efficient sources of metallanitrenes following their reaction with dirhodium(II) tetracarboxylates complex in the presence of K₂CO₃.^[83] Intra- and intermolecular C(sp³)—H amination reactions have been described by the group of Lebel, respectively from carbamates **14** and **15**. It is noteworthy that the scope of these transformations is complementary to that of the reactions based on iodine(III) oxidants (Scheme 7).



Scheme 7. Rhodium(II)-catalysed C(sp³)—H amination with *N*-(sulfonyloxy)carbamates.

2.2. Mechanistic and stereochemical issues

The mechanism of catalytic C(sp³)—H amination reactions has been extensively investigated since the seminal work of Müller on the dirhodium(II)-catalysed process.[50] The transformations depicted in the previous schemes, particularly, have been the purpose of detailed studies performed, respectively, by the groups of Du Bois,[59,84-86] Che,[87,88] Katsuki,[89] and Lebel.[83] The results described in these articles allow for drawing a general mechanism for the C(sp³)—H insertion of nitrenes (scheme 8).



Scheme 8. General mechanism for the catalytic C(sp³)—H amination reactions.

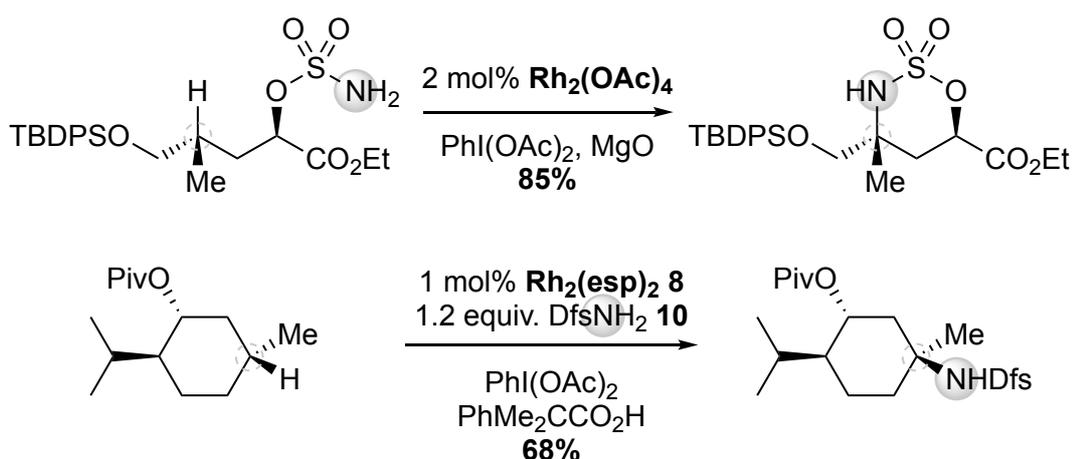
Catalytic C(sp³)—H amination reactions all involve the metallanitrene species **16** (also referred to “metal-nitrenoid species” or “imido metal complex”) as the key intermediate. The latter has been characterized by the group of Che with a ruthenium porphyrin either as a mono- or bis-imido complex,[87] or detected by desorption electrospray ionization mass spectrometry with a rhodium complex.[86] These metallanitrene species are formed by reaction of the metal complex with iminoiodinanes, azides or *N*-(sulfonyloxy)carbamates that generates iodobenzene, dinitrogen, or a sulfonic acid, respectively, as a by-product. It should be mentioned that, in the case of the rhodium catalysis, the *in situ* generation of the iminoiodinane would be the rate-limiting step,[84] and the subsequent generation of **16** might also proceed through two consecutive proton-coupled electron transfer.[90]

Several physical organic experiments including Hammett studies, the reactions with cyclopropyl radical clocks or stereochemical probes, and the measurement of kinetic isotope effects have enabled the elucidation of the nature of the nitrene C(sp³)—H insertion step. These experimental data led to the conclusion that the direct amination of the C—H bond can proceed via either a concerted asynchronous pathway or a stepwise radical process. The latter involves a first step of hydrogen atom abstraction followed by the sometimes extremely fast recombination of the radical intermediates. Whereas the concerted pathway is now generally accepted to describe the

intramolecular C(sp³)—H amination, as corroborated by DFT calculations,[91-93] recent studies suggest that the intermolecular process would be best described by the stepwise mechanism.[60,94] With respect to their scope, catalytic C(sp³)—H amination reactions often take place at electron rich positions such as secondary benzylic and allylic sites, and methylene groups in α -position to ethers, because the electron-deficient metallanitrene species is sensitive to steric effects. However, secondary unactivated sites can also be functionalized by application of intramolecular additions. Such a regioselectivity in favour of a CH₂ group is appropriate to design catalytic stereoselective processes. To this end, the scheme 8 clearly indicates that the chirality must be included in the metallanitrene species to discriminate two stereotopic C—H bonds in the nitrene insertion step. The next chapters will demonstrate that this issue has been addressed by introducing a chiral auxiliary either on the metal catalyst or the nitrene precursor. Although the latter option implies the use of chiral amides in stoichiometric amounts, this solution has led to remarkable achievements in catalytic stereoselective C—N bond forming reactions.

It is worth pointing out that the selectivity in nitrene C(sp³)—H insertions can also be controlled by the stereochemistry of the substrate. Several reviews have already summarized the main results in this domain,[18,33,35] and the following paragraphs will give a summary of the most important contributions.

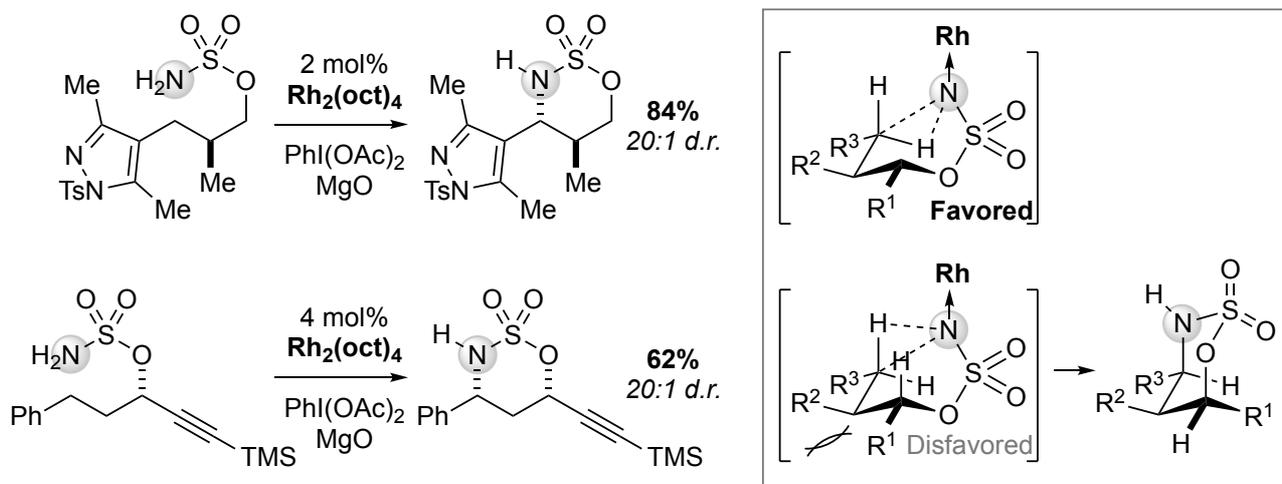
The studies of Müller[50] and Du Bois[51,52,60] have clearly highlighted that inter- and intramolecular C(sp³)—H amination reactions also enable the functionalization of tertiary centres. Importantly, in the course of their mechanistic investigations, both groups have demonstrated the stereospecificity of the reaction starting from stereodefined tertiary site-containing substrates, an observation that is in line with a concerted asynchronous C—H insertion pathway. Accordingly, the catalytic amination of enantiopure tertiary C(sp³)—H bonds occurs stereospecifically with retention of configuration thereby giving access to optically pure tertiary amines in a single step (Scheme 9).



Scheme 9. Stereospecific C(sp³)—H amination of tertiary centres.

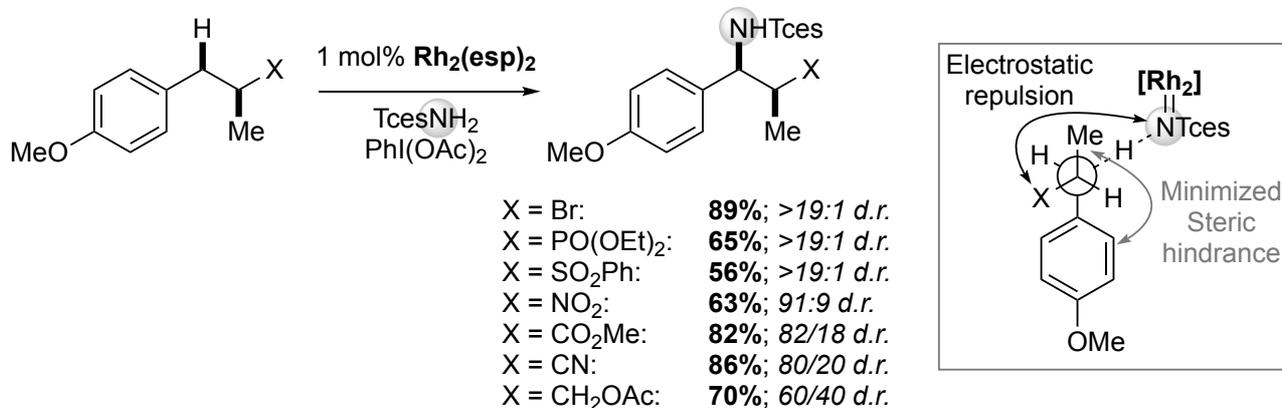
Conformational factors allow to perform intramolecular C(sp³)—H amination reactions with high levels of diastereocontrol. Particularly, sulfamates can be converted to substituted 6-membered rings with excellent 1,2-*trans* and 1,3-*cis* selectivities (Scheme 10).[95] These results have been rationalized by the preferred nitrene insertion into the equatorial C(sp³)—H bond because

unfavorable torsional effects would develop in the resulting oxathiazinane following reaction at the axial C(sp³)—H bond. In addition, the reaction would proceed through a chairlike transition state in which the substituents would be in a pseudo-equatorial layout to minimize *gauche* interactions.



Scheme 10. Diastereoselective intramolecular C(sp³)—H amination of sulfamates.

Moderate to excellent acyclic stereocontrol has been also reported for the intermolecular functionalization of secondary benzylic positions, providing that the latter is substituted at the α -position by a stereogenic centre.[94] *Syn* products, thus, are preferentially obtained as a result of a favoured conformation where the reacting C(sp³)—H bond and the electron-withdrawing substituent are antiperiplanar because of steric repulsions, as are the aromatic and methyl groups for steric reasons (Scheme 11).

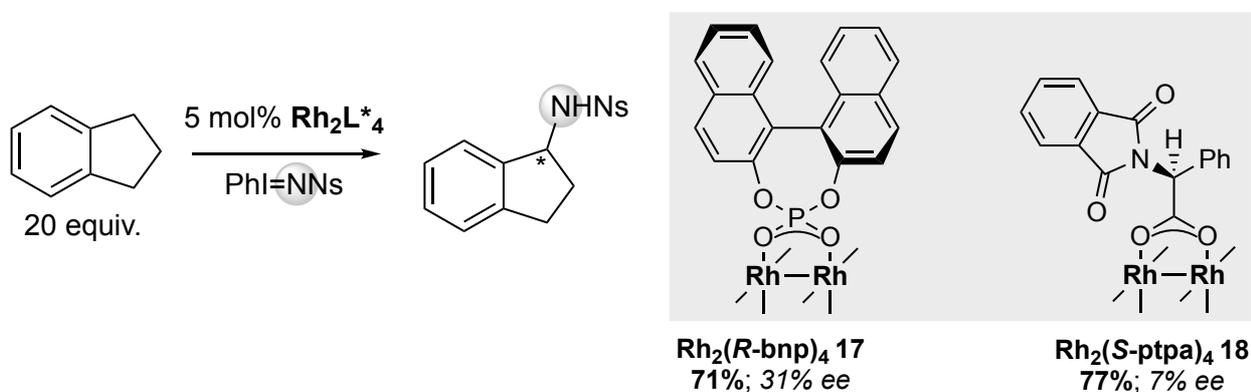


Scheme 11. Diastereoselective intermolecular C(sp³)—H amination of benzylic methylene groups.

3. Catalytic stereoselective C(sp³)—H amination reactions with iminoiodinanes

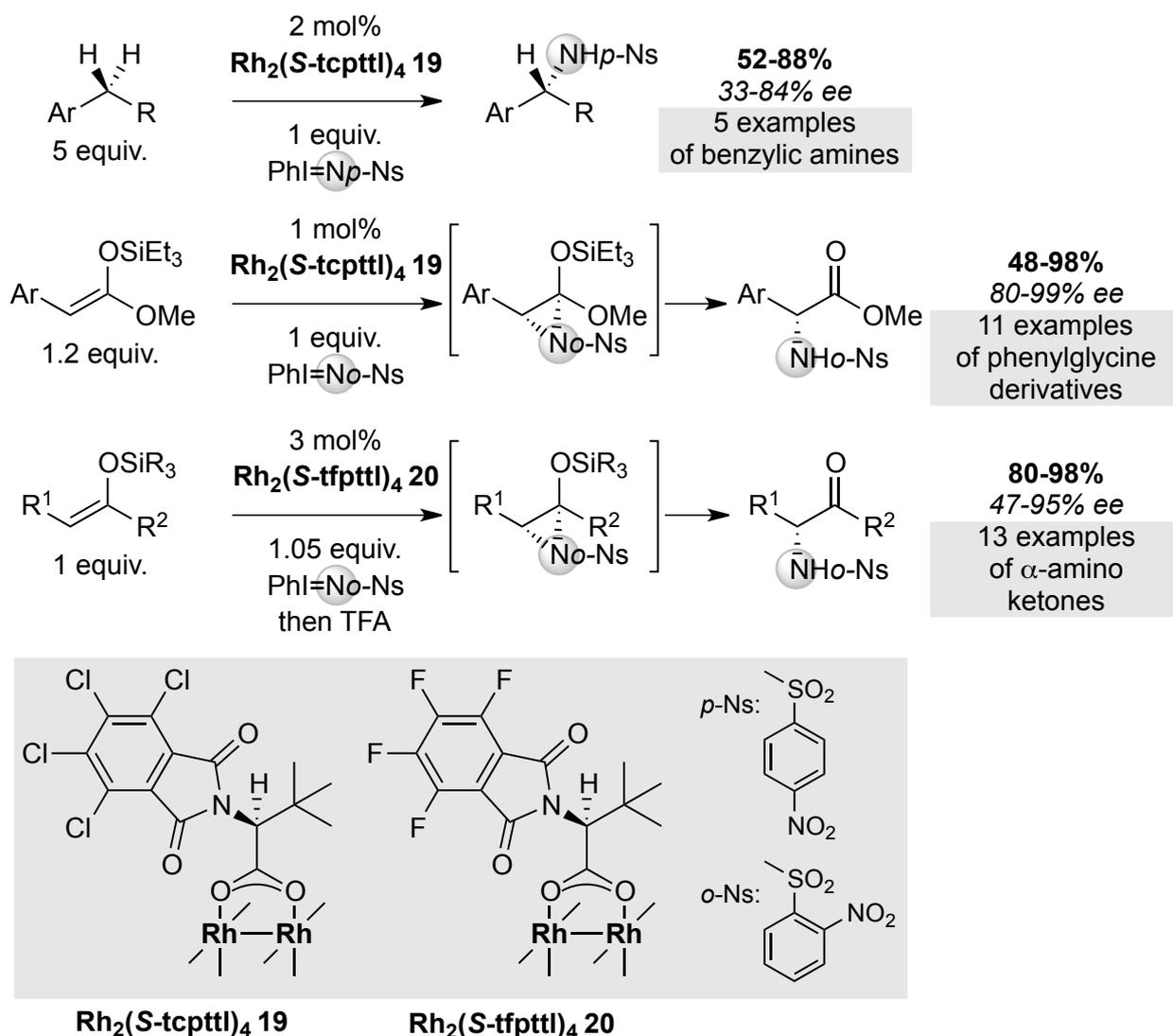
3.1. Catalytic intermolecular enantioselective reactions (chirality only on the metal complex)

The first examples of asymmetric induction in catalytic C(sp³)—H amination reactions were reported in the seminal study of Müller.[50] The reaction of indan in the presence of the chiral dirhodium(II) complexes Rh₂(*R*-bnp)₄ **17** or Rh₂(*S*-ptpa)₄ **18** led to the expected enantioenriched benzylic amines albeit with low to moderate enantiocontrol (Scheme 12). With the aim to improve the enantiomeric excess of 31% obtained with Rh₂(*R*-bnp)₄, substitution of the 3-3' position of the BINOL backbone could be envisaged according to the excellent results recorded with the corresponding phosphoric acids in asymmetric catalysis.[96] However, such substituted BINOL derivatives are too sterically hindered to be installed on the dirhodium core. By contrast, the amino acid of complex **18** could offer the possibility to modify either the side chain or the nitrogen protecting group to increase the ees, an opportunity that has been investigated successfully by several groups (*vide infra*).

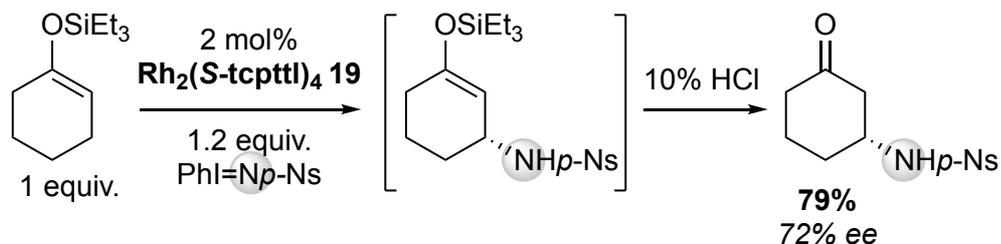


Scheme 12. Seminal study in rhodium(II)-catalyzed asymmetric C(sp³)—H amination reaction.

Based on their long expertise in the design of chiral dirhodium(II) complexes derived from protected amino acids,[97,98] Hashimoto and coworkers have screened various *N*-phthaloyl and *N*-benzene-fused-phthaloyl-(*S*)-amino acids, thus, demonstrating that the *per*-halogenated ligands confer the capacity to induce good to excellent enantiocontrol to the resulting rhodium complex. The *per*-chlorinated complex Rh₂(*S*-tcpttl)₄ **19** that derives from *tert*-leucine, proved to be the most efficient catalyst for the amination of secondary benzylic sites[99] and silylketene acetals[100] while the *per*-fluorinated analog Rh₂(*S*-tfpttl)₄ **20** was optimal in the reaction with silyl enol ethers (Scheme 13).[101] It is worth mentioning that the last two sets of reactions should only be considered as formal nitrene C—H insertions as they rather involve a catalytic alkene aziridination of the enol moiety followed by a ring opening. However, they proceed efficiently from substrates used in stoichiometric amounts or so, giving access to enantiopure phenylglycine derivatives, likely to be converted to chiral oxazolidinones, and α -amino ketones that are useful intermediates in synthesis. In the context of sustainable chemistry, it should be pointed out that the Rh₂(*S*-tfpttl)₄ catalyst can be immobilized on a polymer, thereby allowing its recycling in the asymmetric amination of silyl enol ethers.[102]

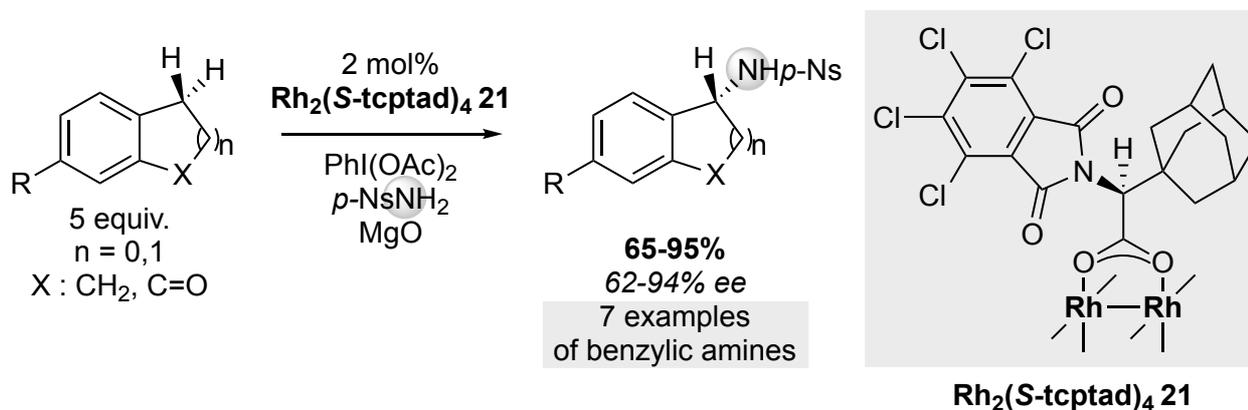


Scheme 13. Catalytic asymmetric nitrene additions with *per*-halogenated rhodium(II) complexes. The amination of silyl enol ethers is specific to the (*Z*)-isomers. Acyclic (*E*)-derivatives did not react under these conditions, whereas a cyclic (*E*)-enol ether underwent a catalytic allylic C(sp³)—H amination. Use of the Rh₂(S-tcpttl)₄ **19** complex, thus, led to the formation of the enantioenriched allylic amine which, after hydrolysis, afforded a β-amino ketone in good yield and ee (Scheme 14).[103] This rare example of catalytic asymmetric intermolecular allylic C(sp³)—H amination is a relevant example of a switch in chemoselectivity controlled by the substrate.



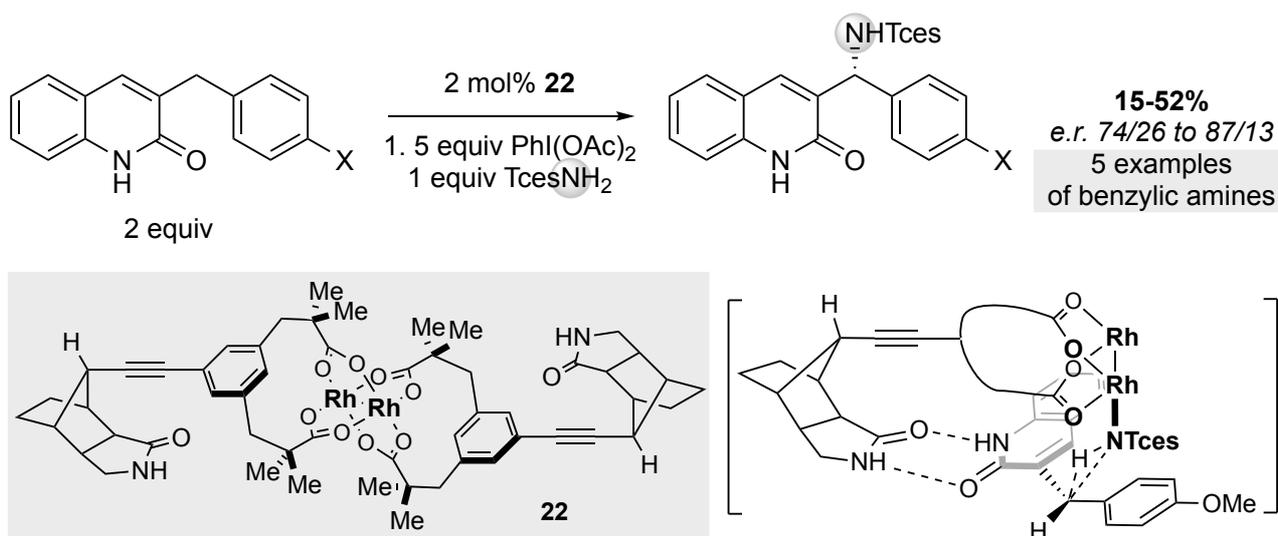
Scheme 14. Catalytic asymmetric intermolecular allylic amination of a cyclic enol ether. The scope of the catalytic benzylic C(sp³)—H amination reaction has been extended with the design of the bulkier complex Rh₂(S-tcptad)₄ **21** that results from the replacement of the *tert*-butyl side chain of the Rh₂(S-tcpttl)₄ complex **19** by an adamantyl group.[104] Higher yields in the 62-

94% range and enantioselectivities of up to 94%, were obtained from various indans, indanones, and their higher cyclic homologs in the presence of **21** (Scheme 15). However, as a major limitation, the reaction requires an excess of substrate to secure good conversion.



Scheme 15. Catalytic asymmetric intermolecular benzylic amination with Rh₂(S-tcptad)₄ **21**.

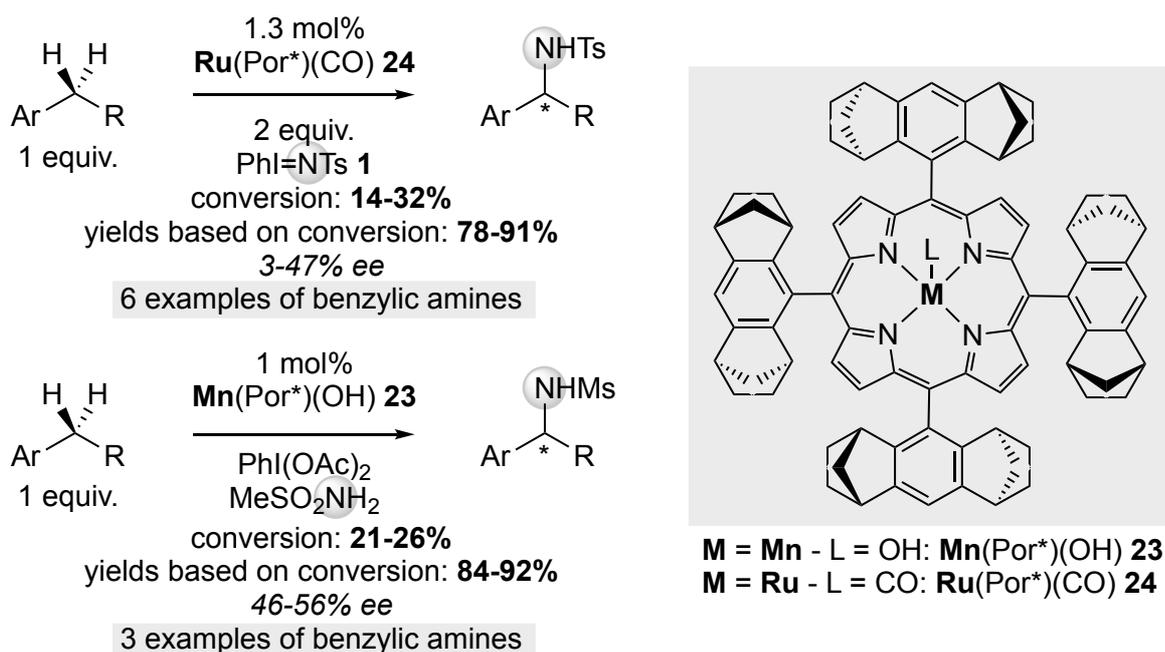
The design of an efficient catalytic enantioselective intermolecular amination reaction of broad scope is still an issue to address. A possible solution could arise from the design of chiral analogs of the highly active Rh₂(esp)₂ complex **8**, but this approach has not proved conclusive so far. The best results reported up to now have been obtained through the design of the elegant supramolecular rhodium(II) complex **22** (Scheme 16).[105] The latter includes two lactam binding sites that can interact with substrates bearing two complementary hydrogen bond donor and acceptor, such as 3-benzylquinolones. The coordination through the two expected hydrogen bonds allows for discriminating the two enantiotopic benzylic C(sp³)—H bonds. The enantiomeric ratios, that were found to increase with lower concentrations, are moderate to good, however, such a supramolecular approach remains specific in scope.



Scheme 16. Catalytic asymmetric intermolecular amination with the supramolecular complex **22**.

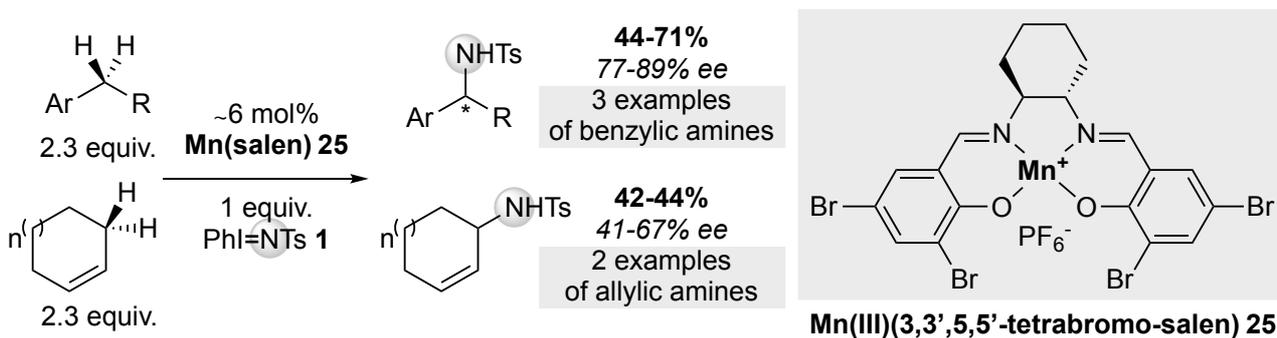
Chiral Mn- and Ru-porphyrins derived from complexes **11** and **12** have been tailored by the group of Che to induce enantiocontrol in intermolecular C(sp³)—H amination reaction in the presence of the preformed PhI=NTs **1** or using the one pot procedure for the *in situ* generation of the iminoiodinane.[106] Starting from a stoichiometric amount of various benzylic substrates, the

yields are in the 78-91% range, however these are based on conversion that remains low, while the enantiomeric excesses do not exceed 56% (Scheme 17).



Scheme 17. Catalytic asymmetric intermolecular amination with chiral porphyrins **23** and **24**.

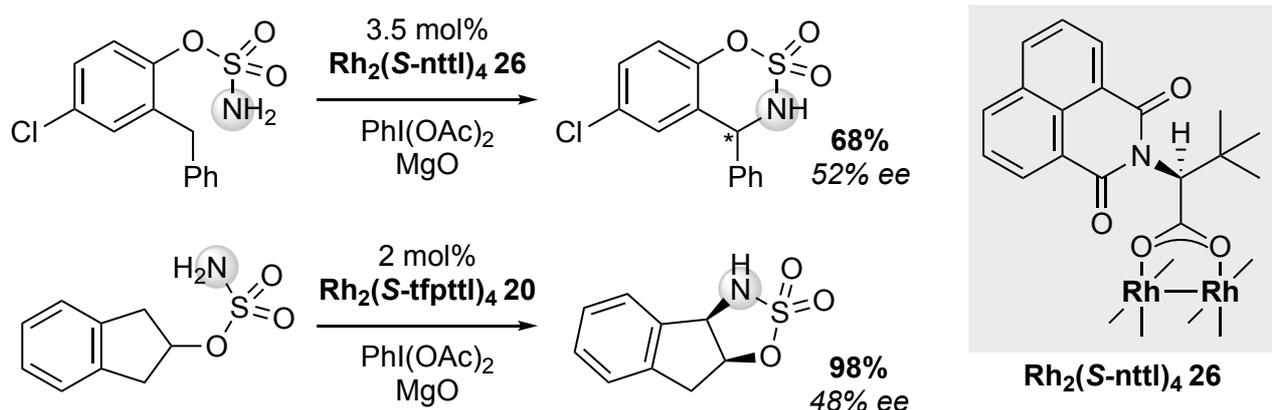
Porphyrin ligands are somewhat sophisticated and, therefore, costly to prepare. By comparison, the salen ligands appear more flexible and versatile with the aim to search for an efficient asymmetric nitrene C(sp³)—H insertion. Surprisingly, this approach has been rarely investigated in combination with iodine(III) oxidants so far. The group of Katsuki, nevertheless, has documented the use of the tetrabromo-Mn(Salen) complex **25** in the enantioselective intermolecular C(sp³)—H amination with the preformed PhI=NTs **1**.^[107] In addition to benzylic sites, this catalyst enables the functionalization of secondary allylic positions with acceptable enantiocontrol but, remarkably, with complete chemoselectivity (Scheme 18).



Scheme 18. Catalytic asymmetric intermolecular amination with Mn(Salen) **25**.

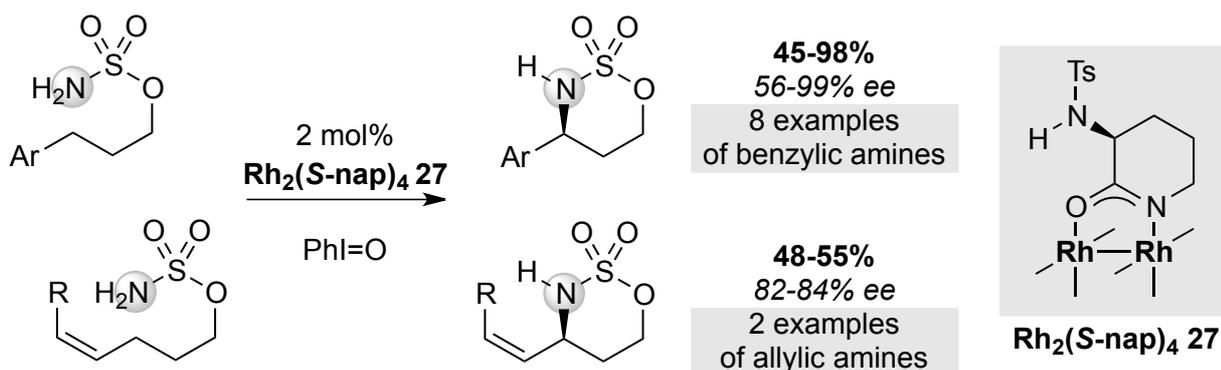
3.2. Catalytic intramolecular enantioselective reactions

The catalytic intramolecular C(sp³)—H amination reaction mediated by iodine(III) oxidants has been reported from various nitrogen functions. However, the related enantioselective processes have been successfully developed mostly from sulfamates so far, because these are more efficient nitrene precursors than sulfonamides, carbamates, ureas, or guanidines. Surprisingly, the use of chiral dirhodium(II) tetracarboxylates such as Rh₂(S-nttl)₄ **26** or Rh₂(S-tfpttl)₄ **20** has met a limited success in this context as the enantiomeric ratios are at best in the 3:1 range (Scheme 19).[108-110]



Scheme 19. Rhodium-catalyzed asymmetric intramolecular amination of sulfamates.

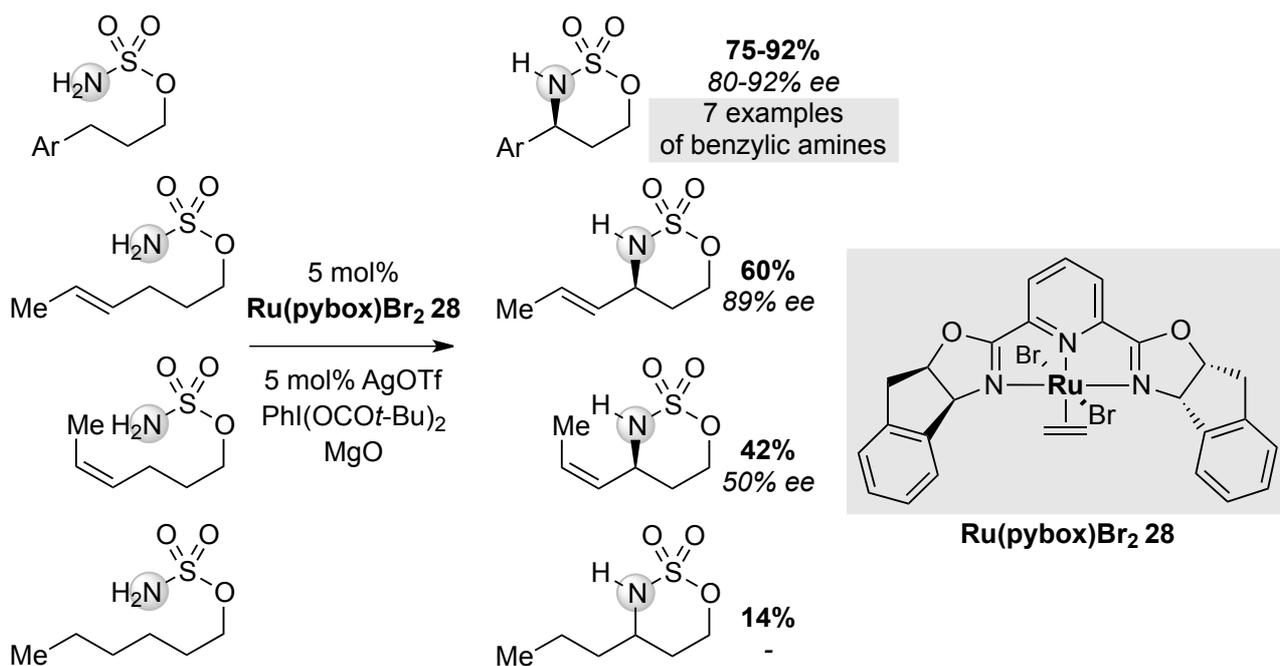
More significant achievements have been made with the cleverly designed rhodium(II) carboxamidate Rh₂(S-nap)₄ **27** that allows for performing the catalytic asymmetric intramolecular C(sp³)—H amination of sulfamates with high levels of efficiency and enantiocontrol.[111] A relevant feature of **27** is its finely adjusted electrophilic character that makes Rh₂(S-nap)₄ a rare example of a dirhodium(II) tetracarboxamidate complex able to mediate catalytic nitrene transfer under oxidizing conditions. The reaction proceeds at secondary benzylic sites of various aromatic and heterocyclic compounds with yields of up to 98% and enantiomeric excesses of up to 99% (Scheme 20). More importantly, this new catalyst mediates the chemoselective functionalization of allylic substrates leading to enantioenriched allylic amines but only starting from (Z)-alkenes. The comparison of the results obtained with the classical Rh₂(OAc)₄ clearly showcases the influence of the ligands on the chemoselectivity of allylic nitrene C(sp³)—H insertions. Moreover, the nitrogen-protecting group strongly but inexplicably influences the catalytic performance.[33]



Scheme 20. Asymmetric intramolecular benzylic and allylic amination with Rh₂(S-nap)₄ **27**.

Concomitant with the study on chiral dirhodium(II) complexes, the chiral Ru-porphyrin **24** as well as a neutral Mn(Cl) analog of the Mn(salen) **25** were shown to catalyze the intramolecular benzylic C(sp³)—H amination with sulfamates, though with lower efficiency and enantioselectivity (ees of up to 88% and 79%, respectively).[62,112,113] But it is worth mentioning that 5-membered rings can be easily obtained from various aryethanol-derived sulfamates using these two catalysts.

More significant results, however, have been reported by the group of Blakey with the neutral Ru(II)(pybox)Br complex **28** in the presence of AgOTf.[114] This additive is indeed crucial to generate a cationic ruthenium(II) complex that proved to be more reactive than the parent complex **28**. In parallel to the study of Du Bois with the Rh₂(S-nap)₄ complex **27**, Blakey and coworkers have developed efficient conditions for the intramolecular benzylic and allylic amination that afford the expected products in good to excellent yields of up to 92% and with high levels of enantiocontrol (Scheme 21). The scope of the chemoselective allylic C(sp³)—H amination, in addition, is complementary to that described by Du Bois as an (*E*)-alkene is more reactive under these conditions than the corresponding (*Z*)-isomer. However, the low yield of 14% obtained from *n*-hexylsulfamate clearly demonstrates the limitation of catalytic asymmetric intramolecular amination reactions that, still, poorly apply to unactivated C(sp³)—H bonds.

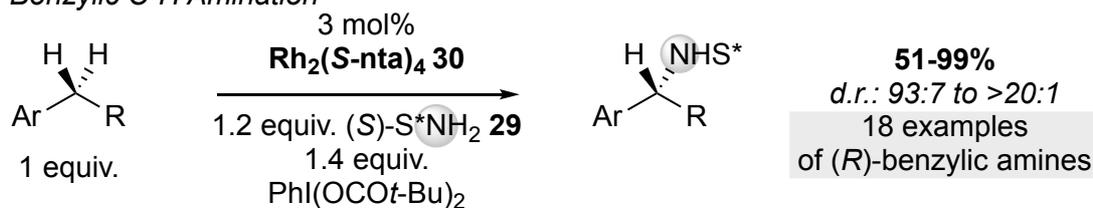


Scheme 21. Asymmetric intramolecular benzylic and allylic amination with Ru(II)(pybox)Br **28**.

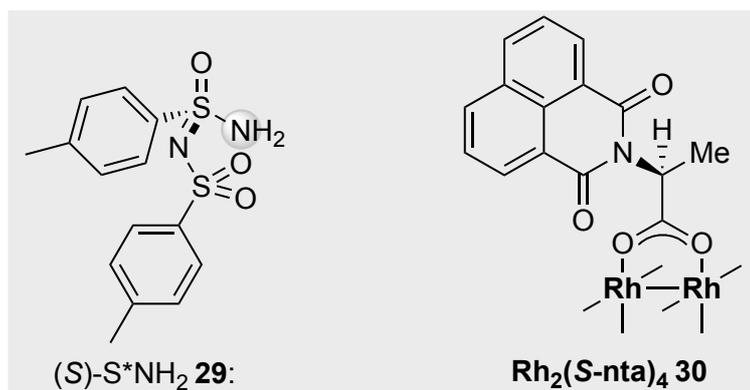
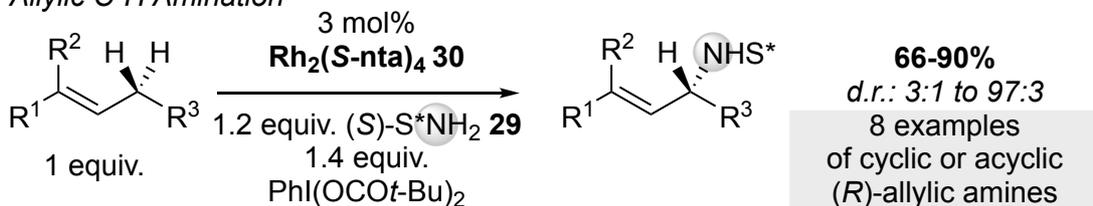
3.3. Catalytic intermolecular diastereoselective reactions (chirality on the metal complex and the nitrene precursor)

The catalytic asymmetric intermolecular C(sp³)—H amination reactions are generally of limited scope, and often suffer from low conversion that compels to work with an excess of substrate to obtain good yields. Nevertheless, these limitations have been overcome with the discovery of sulfonimidamides **29** as highly efficient chiral nitrene sources. These reagents are the aza-analogues of sulfonamides in which one of the S=O bond has been replaced by an S=NTs function, thereby making the sulfur center chiral. Excellent diastereocontrol in catalytic nitrenoid C(sp³)—H insertion reactions was then reported by combining the optically pure sulfonimidamide (S)-**29** with the chiral rhodium complex Rh₂(S-nta)₄ **30**. This matched pair of reagents has led to uncover a rhodium-catalyzed stereoselective C(sp³)—H amination of benzylic and allylic substrates used as the limiting component.[115-117] The corresponding (R)-benzylic and allylic amines were isolated with yields of up to 99% and diastereomeric ratios of up to >20:1 (Scheme 22), the other (S)-enantiomer being also efficiently obtained using the other matched pair of reagents. *Phrase supprimée*

Benzylic C-H Amination



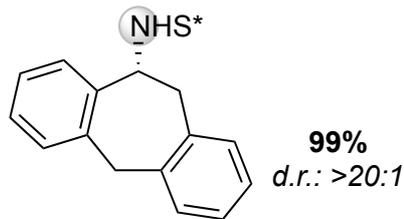
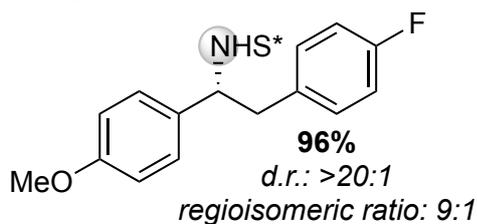
Allylic C-H Amination



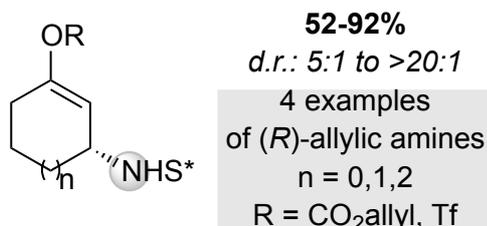
Scheme 22. Stereoselective intermolecular benzylic and allylic amination with sulfonimidamides.

The reaction can be applied with equal levels of efficiency and selectivity to more complex substrates such as diphenyl derivatives, enol ethers or terpenes.[117,118] In each case, a single compound was isolated and the course of the C(sp³)—H functionalization was rationalized by a combination of steric, conformational and electronic factors (Figure 2).

Benzylic C-H Amination of diphenyl derivatives



Allylic C-H Amination of enol ethers



Allylic C-H Amination of terpenes

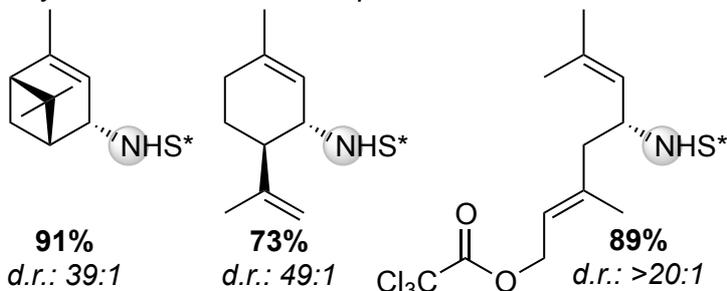
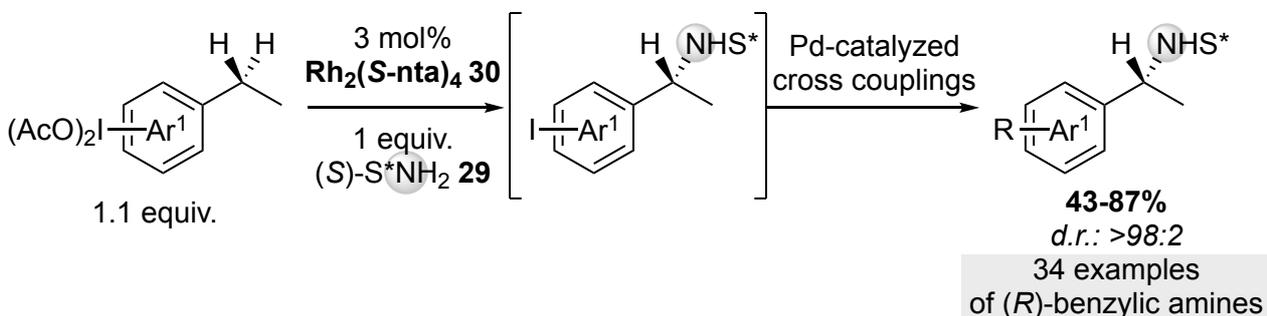


Figure 2. Stereoselective intermolecular amination of complex substrates with sulfonimidamides.

The matched combination of the (S)-reagent **29** with the (S)-rhodium catalyst **30** has been recently applied to the catalytic stereoselective C(sp³)—H amination of benzylic iodine(III) oxidants. The reaction delivers a functionalized iodo compound that can be subsequently engaged in one-pot palladium-catalysed cross couplings. This tandem process, therefore, has led to produce a library of more than thirty complex enantiopure benzylic amines (Scheme 23).[119]



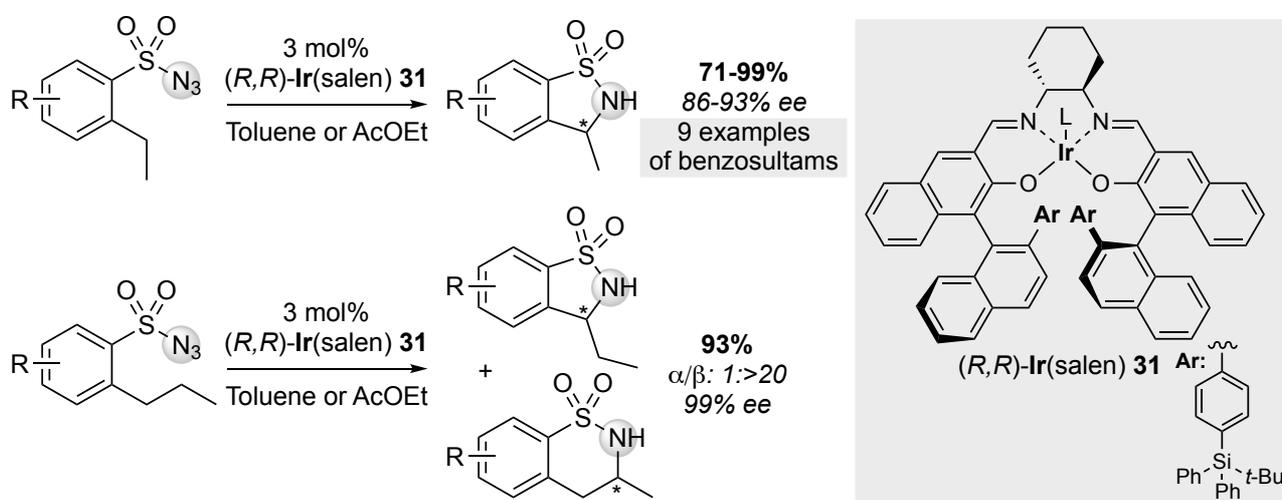
Scheme 23. Tandem catalytic intermolecular benzylic C—H amination-cross coupling reactions.

4. Catalytic stereoselective C(sp³)—H amination reactions with azides

4.1. Transition metal-catalyzed C(sp³)—H amination reactions

Mechanistic investigations of the ruthenium(salen)-catalyzed nitrene C(sp³)—H insertion reactions depicted in scheme 5 has enabled the design of an efficient catalytic asymmetric C(sp³)—H amination with azides. The low turnover number observed with complex **13** was supposed to arise from its inactivation following an intramolecular C(sp²)—H amination promoted by the Ru(salen)-azide complex. This undesirable reaction was supposed to proceed at a *meta* C—H bond of one of the aromatic rings located at the C2'' position of the BINOL moiety. Accordingly, the group of Katsuki has conceived two strategies to avoid this side reaction and improve the catalytic activity of Ru(salen) complexes.

First, the introduction of a bulky *tert*-butyldiphenylsilyl group at the *para* position of the C2''-phenyl rings has allowed the preparation of the iridium(III)(salen) complex **31** that has proved to be the best catalyst for the intramolecular C(sp³)—H amination of sulfonyl azides.[120] A variety of 2-ethylbenzenesulfonyl azides, thus, was efficiently converted to the corresponding 5-membered benzosultams in excellent yields of up to 96% and high enantiomeric excesses of up to 93% (Scheme 24). Interestingly, the length of the 2-alkyl side chain strongly influences the regiochemical course of the reaction. The latter, for example, occurs exclusively at the homobenzylic position starting from the *n*-propyl analog. This switch in regioselectivity would be the consequence of the subtle combination of steric and stereoelectronic effects.

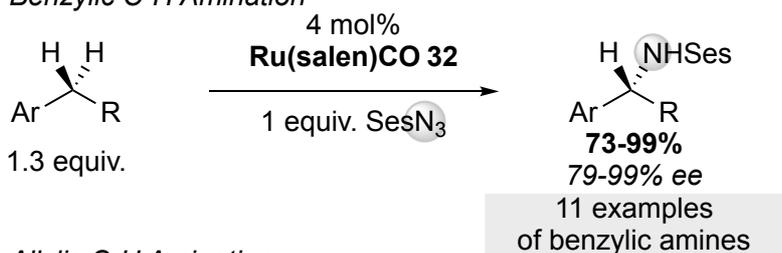


Scheme 24. Ir(salen)-catalysed intramolecular C(sp³)—H amination of benzenesulfonyl azides.

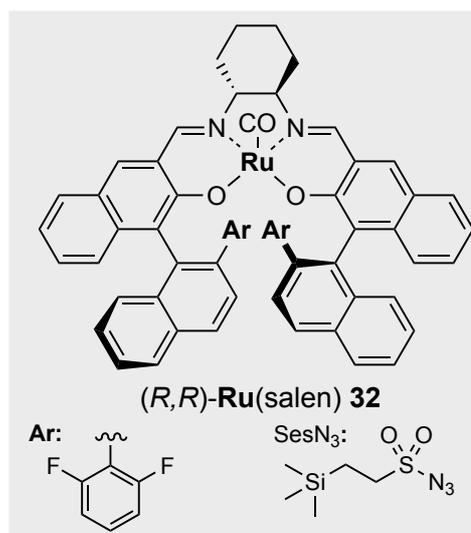
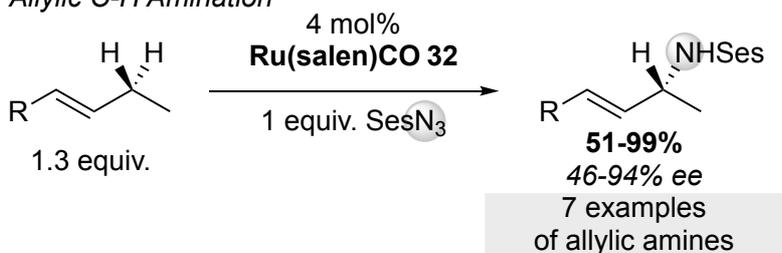
The second strategy envisaged by the group of Katsuki was to introduce halogen substituents on the C2''-phenyl rings. Accordingly, a 2,6-difluorophenyl group was optimal to design a Ru(salen)-catalysed enantio- and regioselective intermolecular C(sp³)—H amination of large scope using 2-trimethylsilylethanesulfonyl azide as the nitrene source.[121] Several *N*-(Ses)-benzylic and -allylic amines, thus, were isolated in good to excellent yields, and enantiomeric excesses generally greater than 90% (Scheme 25). Importantly, the reaction mostly takes place at ethyl substituents, thereby allowing the discrimination of a benzylic or allylic ethyl group against a propyl group or a longer chain, probably because of hyperconjugative effects. Another relevant feature of the

reaction is the use of the easily cleavable Ses protecting group, which gives the opportunity to isolate the free amines by simple reaction with a fluoride anion source.

Benzylic C-H Amination



Allylic C-H Amination



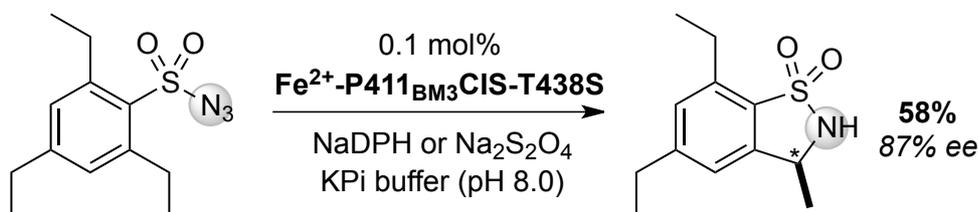
Scheme 25. Ru(salen)-catalysed asymmetric intermolecular C(sp³)—H amination with SesN₃.

4.2. Enzymatic C(sp³)—H amination reactions

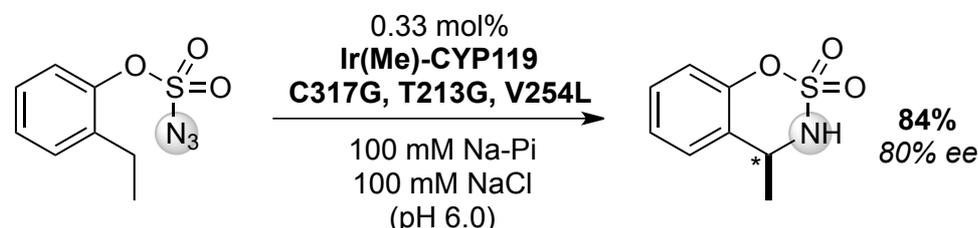
Catalytic C—H amination is a truly synthetic method that has been discovered thanks to the creativity of chemists. Many oxidases are indeed known in nature to catalyse the regio- and stereoselective C—H hydroxylation of alkanes. By contrast, no natural enzyme able to mediate the direction amination of C—H bonds has been described so far. Nevertheless, several groups have recently managed to engineer cytochrome P450 to produce modified enzymes that are able to catalyse C(sp³)—H amination reactions. These studies have taken inspiration from the seminal work of Breslow on the intramolecular amination of *N*-(arenesulfonyl)iminoiodinanes catalysed by a Fe(III)-containing P450 enzyme.[122] The groups of Arnold[123] and Fasan,[124] thus, have demonstrated that intramolecular benzylic amination of arenesulfonyl azides can be performed with turnover numbers in the 390 range using carefully mutated P450 enzymes. Strikingly, this chemistry can be carried out *in cellulo* on a 50 mg scale, the resulting benzosultam being isolated in 69% yield and 87% ee (Scheme 26a). However, the scope of these asymmetric reactions remains limited to a couple of examples.

Key to the success of the enzymatic intramolecular amination of sulfonyl azides was the introduction of a reduced Fe(II) center into the porphyrin. Significant progress was then made by designing a new CYP119 mutant containing an iridium porphyrin cofactor Ir(Me)-PIX. The asymmetric intramolecular C(sp³)—H amination of azides proceeds with yields of up 98% in the presence of Ir(Me)-PIX CYP 119 mutant, and with a broader substrate scope that was extended to sulfamates (Scheme 26b).[125]

26a. Fe(II)-containing P411 variant-catalysed intramolecular C—H amination



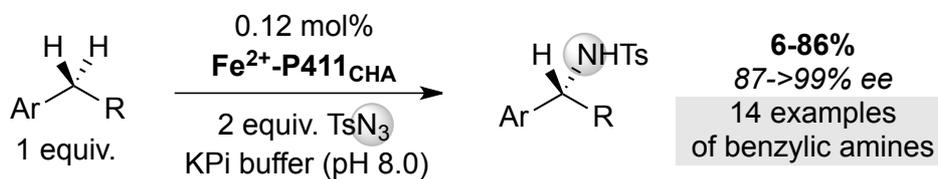
26b. Ir-containing CYP119 variant-catalysed intramolecular C—H amination



Scheme 26. Enzymatic asymmetric intramolecular C(sp³)—H amination of azides.

In a recent and more impressive study, directed mutagenesis of selected residues located in the haem domain of an evolved variant has led to discover a highly active biocatalyst that has allowed to perform asymmetric intermolecular benzylic C(sp³)—H amination reactions with high turnover numbers of up to 1,300 in the presence of tosylazide. Various benzylic amines can thus be isolated with high levels of enantioselectivity in the presence of the cytochrome P411_{CHA} (Scheme 27).[126]

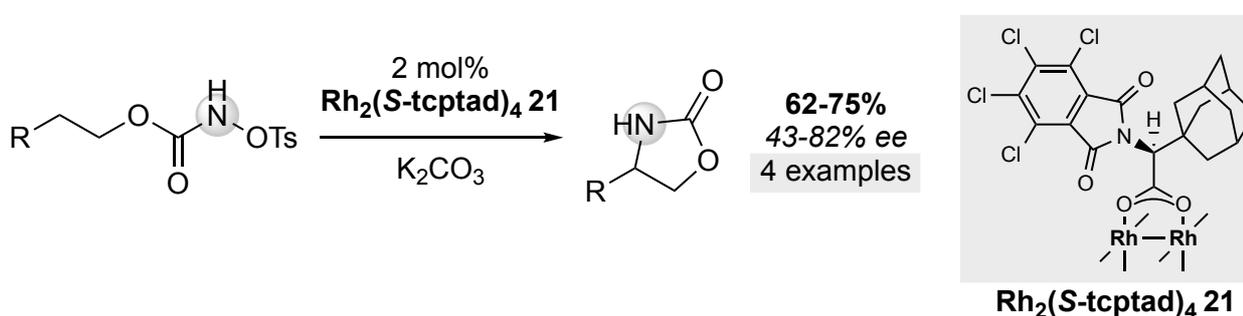
Importantly, the protein not only provides the appropriate chiral environment for achieving excellent enantiocontrol, it also promotes the reactivity of the iron cofactor that was found inactive when tested alone. Though the scope of the reaction is limited to secondary electron-rich benzylic sites, this study should definitely be a source of inspiration for the design of more efficient biocatalysts complementary to chemical catalysts in terms of scope.



Scheme 27. Enzymatic asymmetric intermolecular C(sp³)-H amination with tosylazide.

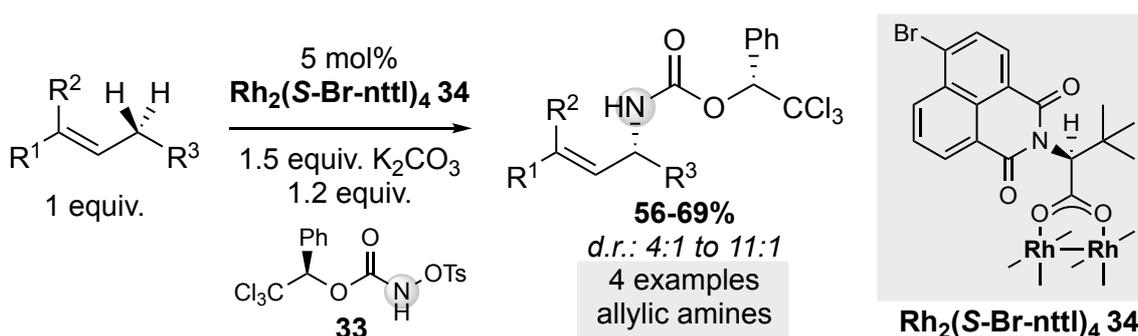
5. Catalytic stereoselective C(sp³)—H amination reactions with *N*-(sulfonyloxy)-carbamates

The bulky complex Rh₂(*S*-tcptad)₄ **21**, that was designed by the group of Davies for the catalytic intermolecular benzylic nitrene C(sp³)—H insertion (Scheme 14), was also shown to catalyse the intramolecular C(sp³)—H amination of *N*-(sulfonyloxy)carbamates.[104] The reaction proceeds with enantiomeric excesses in the 43-82% range for benzylic, allylic and unactivated methylene groups, but the scope remains limited to 4 examples (Scheme 28). It is noteworthy that the intramolecular C(sp³)—H amination provides enantioenriched oxazolidinones, which are not accessible using the iodine(III) oxidant chemistry. However, the rhodium complex **21** as well as others such as Rh₂(*S*-nttl)₄ **26** did not prove relevant to mediate the intermolecular addition of *N*-(sulfonyloxy)carbamate-derived nitrenes as the enantiomeric ratio is at best of 2.57:1.[127]



Scheme 28. Enantioselective intramolecular C(sp³)—H amination with *N*-(tosyloxy)carbamates.

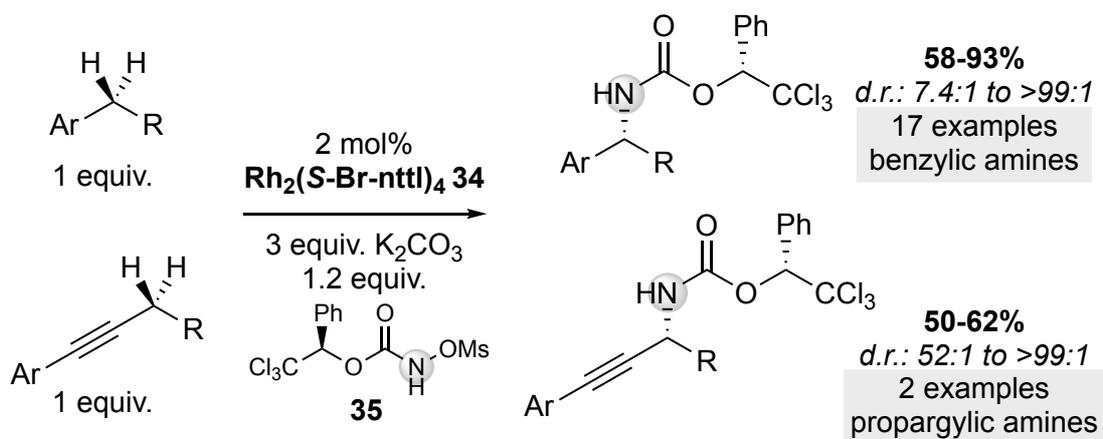
Using the matched-pairs approach previously described with iodine(III) oxidants, diastereoselective intermolecular C(sp³)—H amination reactions have been reported in the presence of chiral *N*-(sulfonyloxy)carbamates derived from the Troc-reagent **15**. The tosyloxy derivative **33**, thus, reacts with substituted (*E*)-alkenes in the presence of the Rh₂(*S*-Br-nttl)₄ complex **34** to afford allylic amines with very good diastereocontrol (Scheme 29).[128]



Scheme 29. Stereoselective intermolecular allylic C(sp³)—H amination with tosyloxy reagent **33**.

It should be mentioned that application of these reaction conditions to terminal alkenes or (*Z*)-alkenes exclusively afford the corresponding aziridines. The diastereoselective intermolecular C(sp³)—H amination reaction was then extended to benzylic and propargylic substrates following the development of the more sustainable mesyloxy reagent **35** that releases the biodegradable potassium methanesulfonate as the only by-product. After purification by flash chromatography or recrystallisation, benzylic and propargylic amines were isolated with very high levels of

diastereocontrol (Scheme 30).[129] This chemistry can be performed on a gram scale using a catalyst loading as low as 0.3 mol%, then the chiral auxiliary can be recovered following simple methanolysis.



Scheme 30. Stereoselective intermolecular allylic C(sp³)-H amination with mesyloxy reagent **35**.

6. Conclusion

Significant progress has been made since the pioneering studies reported by Müller in 1997, in the stereoselective C—N bond forming reactions through C—H amination of metal-bound nitrenes generated from iodine(III) oxidants, azides or *N*-(sulfonyloxy)carbamates. These transformations involve the direct C(sp³)—H insertion of a metallic nitrene that proceeds via either a concerted asynchronous pathway or a stepwise radical process. Inter- and intramolecular enantioselective reactions have been reported following the design of chiral transition metal complexes. Mainly rhodium but also ruthenium and manganese complexes, have proved to be the metals of choice to this end. Catalytic intermolecular diastereoselective processes have been also described by combining a chiral dirhodium complex with a chiral nitrene source. These have significantly extended the scope and efficiency of C(sp³)—H amination reactions as they enable the functionalization of substrates used as the limiting component. All these synthetic methods now are reliable tools for the organic chemists that provide a rapid access to a large variety of enantiopure benzylic and allylic amines.

Challenging issues in catalytic asymmetric C(sp³)—H amination, nevertheless, still need to be addressed. While electron-rich benzylic and allylic C(sp³)—H bonds can be converted to C—N bonds, the asymmetric intramolecular amination of unactivated C(sp³)—H bonds has not been reported so far. More fundamentally, the search for an efficient transition metal-catalysed asymmetric intermolecular process remains a great challenge for the synthetic chemists. In the context of sustainable chemistry, the development of such protocols that will be based on the use of the more abundant hence less expensive first row transition metals, is highly desirable.

Acknowledgements:

We wish to thank the French National Research Agency (program n° ANR-15-CE29-0014-01; fellowships to R. R.-R. and A. N.) for the financial support.

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