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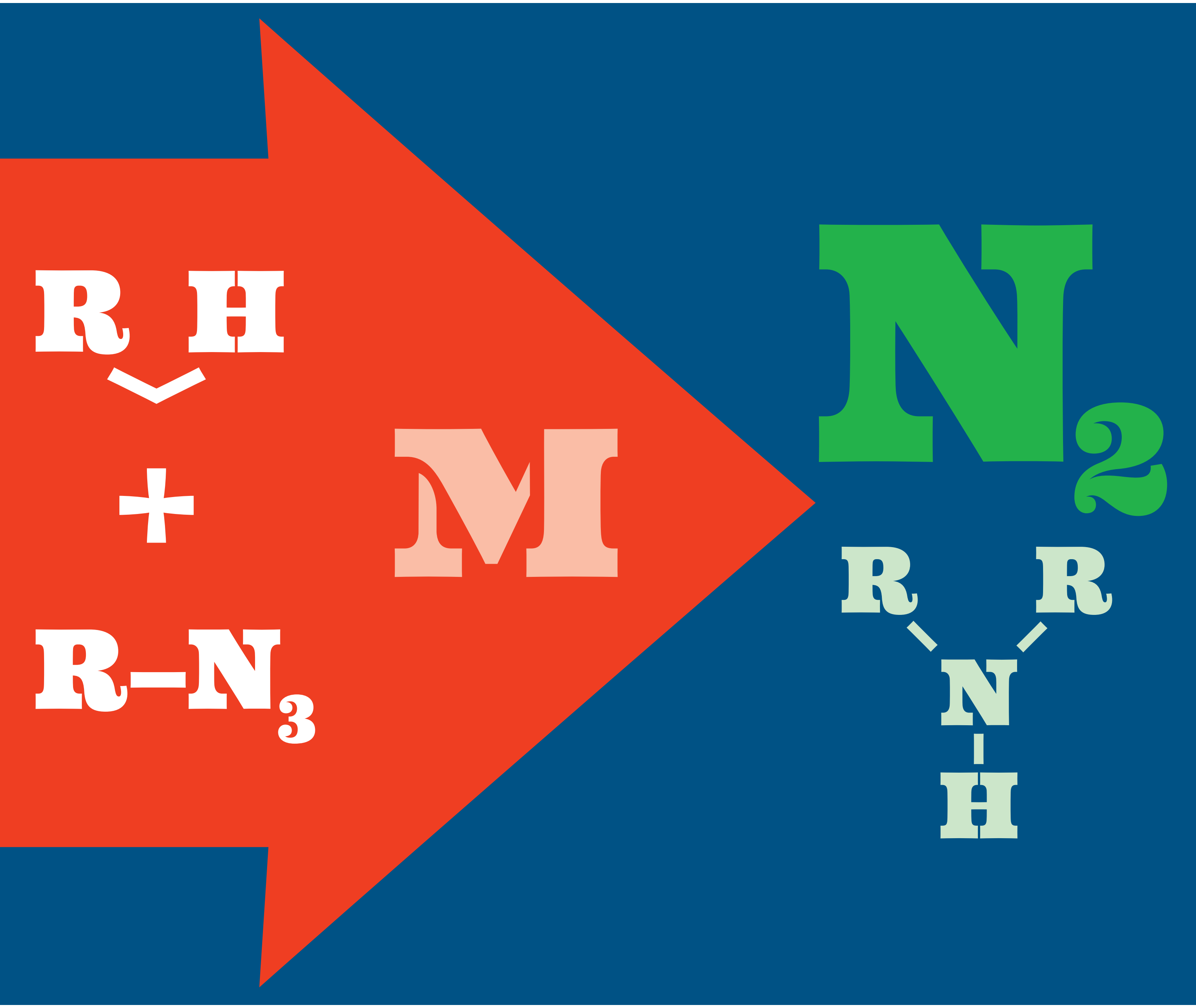

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Recent advances in transition metal-catalyzed *N*-atom transfer reactions of azides

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Transition metal-catalyzed *N*-atom transfer reactions of azides provide efficient ways to construct new carbon–nitrogen and sulfur–nitrogen bonds. These reactions are inherently green: no additive besides catalyst is needed to form the nitrenoid reactive intermediate, and the by-product of the reaction is environmentally benign N_2 gas. As such, azides can be useful precursors for transition metal-catalyzed *N*-atom transfer to sulfides, olefins and C–H bonds. These methods offer competitive selectivities and comparable substrate scope as alternative processes to generate metal nitrenoids.

Introduction

Azides participate in a wide range of reactions that construct new carbon–nitrogen or nitrogen–heteroatom bonds.[1] Their reactivity has motivated considerable research interest since the discovery of phenyl azide in 1864.[2] Azides have enjoyed a renaissance in recent years since their potential was recognized for use in "click" reactions, which rapidly increase molecular complexity by bringing together two molecules together in a reliable and stereoselective fashion.[3,4] Their use in transition metal-catalyzed *N*-atom transfer reactions, however, has garnered considerably less attention than other nitrenoid precursors despite the attractiveness of azides.[5–7] Their appeal stems from (1) their ready availability from sodium azide;[8,9] (2) they require no additive besides catalyst to form the nitrenoid reactive intermediate; and (3) the by-product of the *N*-atom transfer reaction is N_2 gas. These positive attributes provide motivation to develop high yielding and stereoselective *N*-atom transfer reactions, and this perspective describes the recent progress to achieve these atom-economical and environmentally benign processes.

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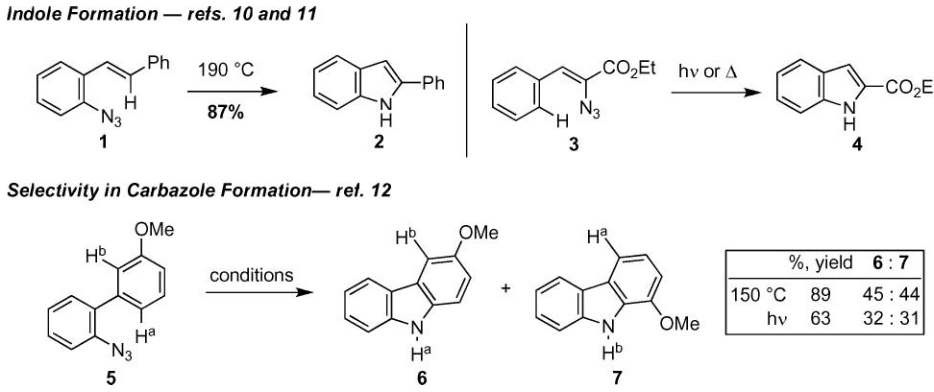
Azides were recognized early as nitrene precursors.[1,10,11] Thermolysis or photolysis of biaryl azides was reported by Smith and co-workers in 1951 to afford substituted carbazoles.[11d] This result was extended to styryl azides (*e.g.* **1**) by Sundberg and co-workers and to vinyl azides (*e.g.* **3**) by Hemetsberger and co-workers. While good to excellent yields can be achieved with aryl- or vinyl substituents, carbazole formation is not generally selective: thermolysis or photolysis of biaryl azide **5** produced a 1 : 1 mixture of the two possible carbazole products (Scheme 1).[12]

The reactivity of the aryl azide depends on the identity of the *ortho*-substituent. When a methylene spacer was placed in between the two π-systems, the temperature controlled the amount of electrophilic cyclization *versus* C–H bond amination: at 190 °C, azepine **9** was formed; whereas, flash vacuum pyrolysis (350 °C) produced **10** and acridine **11** (Scheme 2).[13] Extending the spacer length by an additional methylene eliminates azepine formation to produce indoline **13** or indole **2**, albeit with reduced yields.[14b,15,16] In contrast to aryl azides, few selective intramolecular cyclizations of nitrenes derived from sulfonyl-,[17] acyl-,[18] or phosphoryl[19] azides exist. Even fewer synthetically useful examples of intermolecular thermal or photochemical *N*-atom transfer have been reported.[18,20–22]

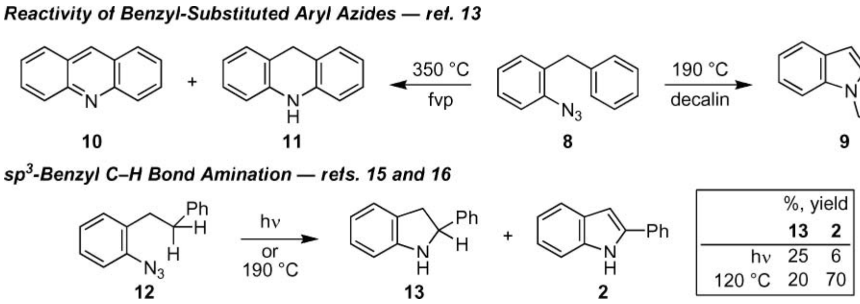
Thermal- and photochemical reactions of azides demonstrated their potential as precursors for nitrenes. While these reactions do provide access to a variety of *N*-heterocycles, they are limited by the hyper reactivity of the nitrene, which can lead to poor selectivity and extensive decomposition. Attenuating the reactivity of the nitrene by developing transition metal-catalyzed decomposition reactions of azides to provide nitrenoids would address these limitations. The development of mild, low temperature reactions would enable azides to realize their potential in *N*-atom transfer reactions.

Transition-metal catalyzed *N*-atom transfer to sulfides

The thermal or photochemical transfer of nitrene from an azide to the sulfur-atom in a sulfide or sulfoxide produces sulfoximides and sulfimides.[23] Due to the harsh conditions required to liberate

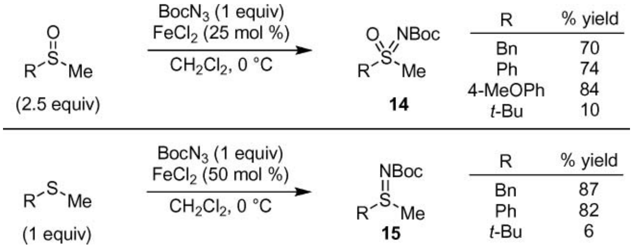


Scheme 1 Representative examples of intramolecular C–H bond amination to afford indoles or carbazoles.



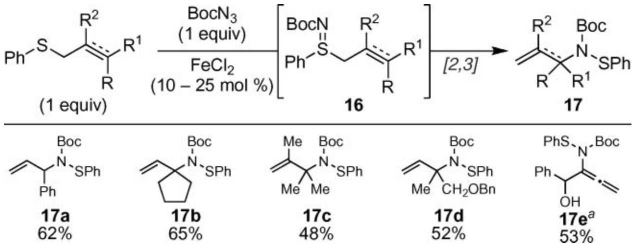
Scheme 2 Examples of intramolecular sp^3-C–H bond amination processes.

nitrene, however, the yield of these processes is low. These unproductive side reactions and the hazards associated with the thermolysis of azides make this reaction a good target for catalysis. Iron(II) chloride was reported by Bach and co-workers to dramatically improve the synthetic efficiency of this process by reducing the reaction temperature from 90 °C to 0 °C (Scheme 3).[24,25] These mild conditions allowed *tert*-butoxycarbonyl azide (Boc–N_3) to be used as the source of the nitrogen-atom. In addition to sulfides and sulfoxides, other nucleophiles could be used in this reaction including silyl enol ethers, although the yield was modest.



Scheme 3 Examples of intermolecular C–H Bond amination reactions.

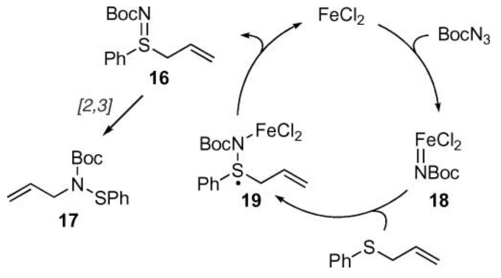
The synthetic potential of this transformation was realized when allylic sulfides were used as substrates (Scheme 4).[26] Bach and co-workers reported that $FeCl_2$-catalyzed *N*-atom transfer to the allylic sulfide was followed by a facile [2,3] sigmatropic rearrangement to efficiently produce α-substituted allylic amines **17** in a stereochemically defined manner. While the functional group tolerance of this reaction was broad, the synthetic utility of this transformation was diminished by the low reactivity of chiral α-substituted allylic sulfides. Van Vranken and co-workers extended this reaction to include propargylic substrates to enable access to *N*-allenylsulfenamides (*e.g.* **17e**).[27]



Scheme 4 Bach reaction: tandem sulfimination–[2,3] sigmatropic rearrangement. [a]dppeFeCl$_2$ (10 mol%) used; see ref. 27.

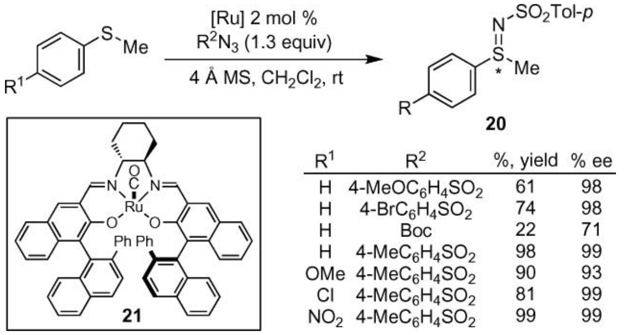
The observed reactivity trends led the authors to report that the mechanism of this transformation involved a redox process (Scheme 5).[26] Iron-mediated decomposition of Boc-azide produces iron nitrenoid **18**, which is followed by a stepwise *N*-atom transfer to form **16** *via* the iron(III) intermediate **19**. A subsequent [2,3] rearrangement furnishes the allylic amine. This stepwise mechanism accounts for the formation of the sulfonamide and sulfenamide by-products, which are commonly observed.

Since the initial report of this transfer reaction by Bach in 1998, synthetic efforts have been aimed at achieving the asymmetric *N*-atom transfer to sulfides. If allylic sulfides could be used, this reaction would enable the synthesis of chiral, non-racemic allylic amines from achiral sulfides. In 2001, Katsuki and co-workers reported that ruthenium salen complexes effectively catalyzed the sulfimidation of alkyl aryl sulfides with excellent enantioselectivity



Scheme 5 Proposed mechanism of the Bach reaction.

(eqn (1)).[28,29] While several different arylsulfonyl azides exhibited excellent enantioselectivities, Boc-azide afforded the iminosulfide in reduced yield. This reaction tolerated a variety of functional groups including nitro- and methoxy groups, but was limited to aryl alkyl sulfides: benzyl methyl sulfide reacted slowly and with reduced selectivity.



R^1	R^2	%, yield	% ee
H	4-MeOC$_6$H$_4$SO$_2$	61	98
H	4-BrC$_6$H$_4$SO$_2$	74	98
H	Boc	22	71
H	4-MeC$_6$H$_4$SO$_2$	98	99
OMe	4-MeC$_6$H$_4$SO$_2$	90	93
Cl	4-MeC$_6$H$_4$SO$_2$	81	99
NO$_2$	4-MeC$_6$H$_4$SO$_2$	99	99

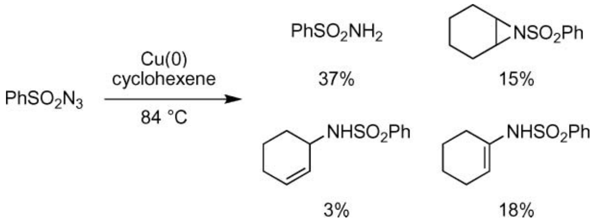
(1)

The enantioselective imidation of allylic sulfides using ruthenium salen complexes triggered a [2,3] sigmatropic rearrangement to produce allylic amines with enantioselectivities greater than 80% ee (Scheme 6).[30] While the initial *N*-atom transfer to the sulfide occurred with % ee greater than 90%, some loss of optical activity occurred in the sigmatropic rearrangement. The resulting *N*-arylthioarylsulfonamides were hydrolyzed to allylic amines upon exposure to KOH in methanol without loss of optical activity. The reaction tolerated a broad range of aryl sulfide substituents as well as either *E*- or *Z*-olefin substituents. Importantly, the reaction was stereospecific: the chirality of **23c** and **23d** depended on the identity of the olefin isomer. Since nitrenoid transfer to the starting allylic sulfide was identical for either the *E*- or *Z*-isomer, the authors interpreted these results to indicate that the transition state of the subsequent [2,3] rearrangement is unique to the starting olefin isomer. While trisubstituted olefins did participate in the reaction, no chiral induction of the [2,3] rearrangement was observed. The lack of stereoselectivity led the authors to conclude that multiple reaction mechanisms are possible in the rearrangement.

Transition metal-catalyzed *N*-atom transfer to olefins

Aziridination

In 1967, Kwart and Khan reported the first metal-catalyzed nitrogen-atom transfer from an azide to an olefin (eqn (2)).[31] They reported that copper powder promoted the decomposition of benzenesulfonyl azide in cyclohexene. In addition to cyclohexene aziridine, they also obtained C–H amination products as well as benzenesulfonamide. The product distribution is consistent with a nitrene or metal nitrenoid reactive intermediate.[32] A radical mechanism could also account for the observed products.[33] After these reports, Migita and co-workers reported palladium-catalyzed *N*-atom transfer reactions to olefins,[34] and Groves and co-workers reported a stoichiometric *N*-atom transfer from a nitridomanganese(V) porphyrin to cycloalkenes.[35]

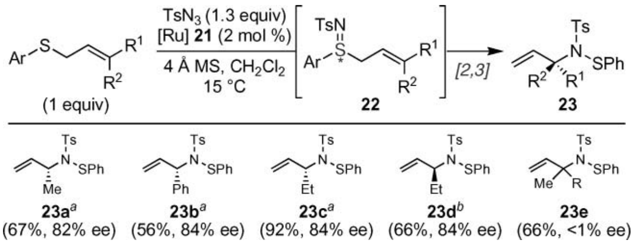


(2)

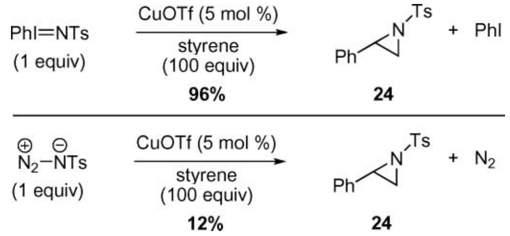
After these seminal reports, the use of iminoiodinanes supplanted azides as nitrene precursors in metal-mediated *N*-atom transfer reactions to olefins.[36] Evans and Faul and co-workers found that tosyl azide was not as effective of a nitrene precursor as Ph=NTs—use of the iminoiodinane produced phenyl aziridine **24** in 96% yield whereas, using tosyl azide as the nitrene precursor produced only a 12% yield of **24** (Scheme 7).[36b36d] These observations were subsequently echoed by Jacobsen and co-workers in their report of copper diimine-catalyzed aziridination of olefins.[36c] While these iodine(III) reagents dramatically improved the efficiency of *N*-atom transfer to olefins, they were not as atom economical or green as azides because a stoichiometric quantity of iodobenzene was also produced.

Inspired by the aforementioned reports of stoichiometric *N*-atom transfer from azides to olefins using transition metal porphyrins, Cenini and co-workers investigated the possibility of a catalytic reaction of aryl azides with olefins in the presence of metal porphyrin catalysts.[37] An examination of a wide range of metal porphyrins revealed that nitrene transfer from *p*-nitrophenyl azide to cycloalkenes was catalyzed only by ruthenium- and cobalt complexes. The best results were obtained with ruthenium tetraphenylporphyrin (RuTPPCO) and cobalt octaethylporphyrin (CoOEP).[38] The electronic nature of the aryl azide influenced the product distribution: when the nitro-group was substituted with a methoxy group, the only product observed was the corresponding aniline. Reduction of the aryl azide to the aniline is a common by-product observed in the thermal- or photochemical decomposition of azides.[14] Formation of this product has been attributed to the intermediacy of a divalent nitrogen reactive intermediate.[14,39]

Using the most active ruthenium tetraphenylporphyrin complex, *N*-atom transfer to a variety of olefins was attempted (Scheme 8).[37] Similar to the results of Kwart and Khan,[31,32] a

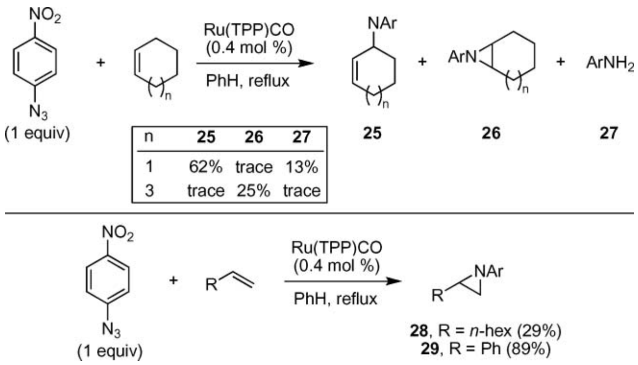


Scheme 6 Asymmetric tandem sulfimination–[2,3] sigmatropic rearrangement. [a]Allyl sulfide approximately a 90 : 10 mixture of *E* : *Z*. [b]Allyl sulfide approximately a 10 : 90 *E* : *Z*.



Scheme 7 Comparison of the efficiency of copper-catalyzed nitrenoid transfer to styrene.

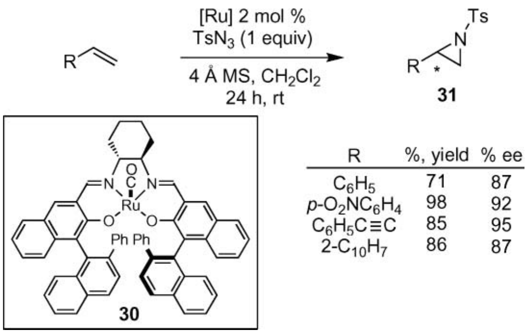
range of products were observed for cyclohexene. Switching the olefin to cyclooctene resulted in the formation of aziridine **26** as the major product in 25% yield. The major by-products were *p*-nitroaniline and the azo compound. Monosubstituted olefins also produced aziridines as the major product: 1-hexene formed aziridine **28** in 29% yield. Substrates lacking α-protons provided more promising results: styrene afforded **29** as the only product in 89% yield. *trans*-Stilbene, on the other hand, did not produce any amination products.



n	25	26	27
1	62%	trace	13%
3	trace	25%	trace

Scheme 8 Ruthenium porphyrin-catalyzed aziridine formation from aryl azides.

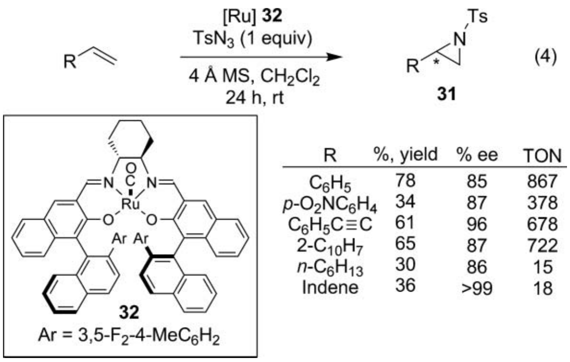
Substantial research effort by the Katsuki and Zhang groups has resulted in the development of methods that achieve the asymmetric formation of aziridines from monosubstituted styrenes with excellent yields and very good enantioselectivities. Prior to their work, two seminal reports by Jacobsen and Mueller,[36c,40] established that asymmetric *N*-atom transfer from azides to olefins could be achieved with modest enantioselectivities. Katsuki and co-workers reported that the asymmetric formation of aziridines from sulfonyl azides could be achieved using a chiral ruthenium(II) salen complex (eqn (3)).[41] This complex was previously shown to catalyze the formation of iminosulfides with excellent enantioselectivities and large turnover numbers. Because iminosulfide formation was believed to occur *via* *N*-atom transfer, the authors anticipated that aziridines could be formed from nucleophilic olefins. *N*-Tosyl aziridines were formed from terminal conjugated olefins with good yields and high enantioselectivity. Non-conjugated olefins (*e.g.* 1-octene) or trisubstituted olefins did not produce aziridines.



R	%, yield	% ee
C_6H_5	71	87
p-$O_2NC_6H_4$	98	92
$C_6H_5C{\equiv}C$	85	95
2-$C_{10}H_7$	86	87

(3)

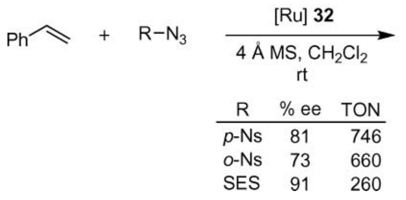
After examining crystal structures of **30**, Katsuki and co-workers designed a new ruthenium(II) salen complex, **32**, which they anticipated would be a more reactive aziridination catalyst that would suppress the undesired allylic C–H bond amination reaction.[42] A crystal structure of **30** showed that the *meta*-hydrogens on the phenyl group were close (3.59 Å) to the *N*-atom of a bound acetonitrile ligand. Since acetonitrile would be replaced with the nitrene group when exposed to an azide, the *meta*-hydrogens might react with the nitrene to decompose the catalyst. Replacing these *meta*-hydrogens with fluorine atoms would render the catalyst more robust by eliminating this potential decomposition pathway. In line with this hypothesis, higher turnover numbers (TON) without attenuation of enantioselectivity was observed when ruthenium salen **32** was used to catalyze the aziridination of terminal olefins (eqn (4)). For the aziridination of *para*-nitrostyrene, a turnover number of 5 was observed using **30**, whereas, a TON of 34 was observed using the fluorinated **32**.



R	%, yield	% ee	TON
C_6H_5	78	85	867
p-$O_2NC_6H_4$	34	87	378
$C_6H_5C{\equiv}C$	61	96	678
2-$C_{10}H_7$	65	87	722
n-C_6H_{13}	30	86	15
Indene	36	>99	18

(4)

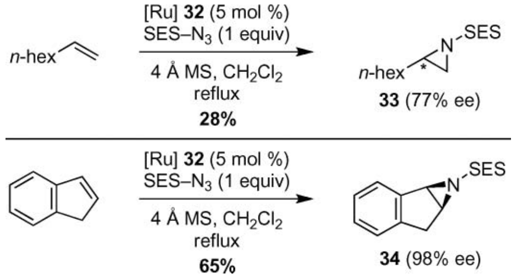
One weakness these aziridination reactions share is that efficient reaction rates occurred only when *para*-tolylsulfonyl azide was used. Relatively harsh conditions (*e.g.* NaNp, DME)[43] are required to remove this group from the aziridine product. The discovery of a more active and robust catalyst enabled the Katsuki group to examine other azides bearing more easily removable groups on nitrogen (eqn (5)).[44,45] They examined nitrobenzenesulfonyl azide (NsN_3) and 2-(trimethylsilyl)ethanesulfonyl azide ($SESN_3$) as a potential sources for the nitrenoid because both the *p*-Ns-group[46,47] and SES-group[48,49] can be removed under mild conditions. While both azides were shown to be competent sources of nitrene, higher enantioselectivities were observed when SES–N_3 was used. Significantly higher turnover numbers, however, were obtained using *p*-NsN_3—up to 746 as compared to 260 for $SESN_3$.



R	% ee	TON
p-Ns	81	746
o-Ns	73	660
SES	91	260

(5)

With this more reactive catalyst, aziridination of non-conjugated olefins could be achieved (Scheme 9).[42,45] The fluorinated ruthenium salen complex (**32**) successfully catalyzed the formation of aziridines **33** and **34** from alkyl substituted alkenes although higher temperatures were required (eqn (4)). No competing allylic C–H bond amination was reported under these conditions. Even disubstituted alkenes, such as indene, were competent substrates.



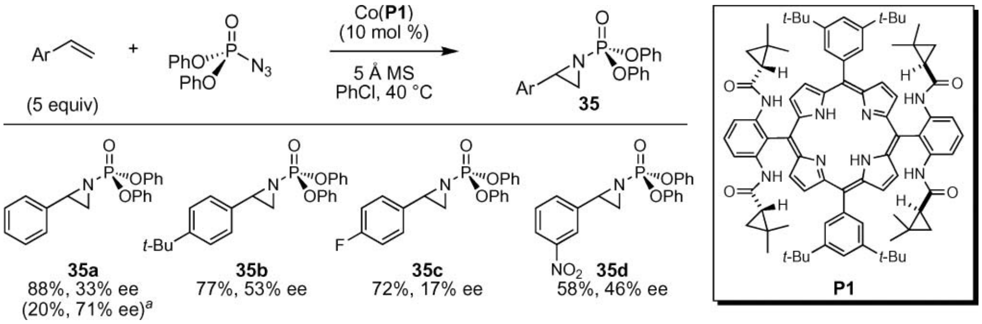
Scheme 9 Increased substrate scope with perfluorinated ruthenium–salen **32** catalyst.

The Zhang group has pursued complementary approaches to the synthesis of chiral aziridines from azides. Like the Katsuki group, Zhang and co-workers have been motivated to develop a reaction wherein the product aziridine contains an easily removable group on nitrogen. Towards this end, they have developed several aziridination methods that employ diphenylphophoryl- or nosyl azide.

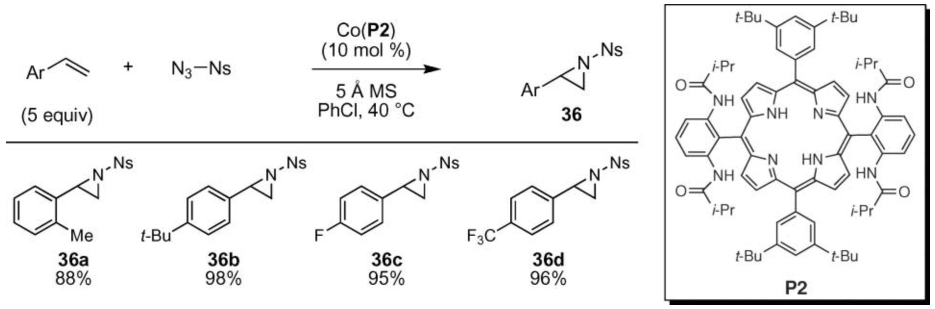
The Zhang group chose diphenylphosphoryl azide as their nitrogen-atom source because the nitrogen–phosphorous bond in the product aziridine is readily hydrolyzed.[50–52] Low catalyst loads and high chemical yields were realized when a D2-symmetric chiral porphyrin was used as a ligand for cobalt (Scheme 10).[52] This ligand contains chiral, non-racemic cyclopropyl-substituted amide side chains, which prevent the cobalt amido complex from decomposing in the reaction. It is easily synthesized from a tetrabromo-substituted porphyrin through a palladium-catalyzed quadruple amidation.[53] While the asymmetric induction for diphenylphosphoryl *N*-atom transfer was moderate, it does represent a launching point for future method development.

Increased yields and broader substrate scope was observed when the azide substituent was changed from diphenylphosphoryl to sulfonyl.[54] For this transformation, a non-chiral tetraamide porphyrin **P2** was used as the ligand on cobalt. While cobalt tetraphenylporphyrin did not react with the sulfonyl azide, efficient *N*-atom transfer was obtained with the cobalt **P2** porphyrin complex. A variety of substituted styrenes were reported to demonstrate the broad scope of their method (Scheme 11). They found that changing the electronic- or steric nature of the styrene did not lead to attenuated yields. Their optimized conditions tolerated substrates with *ortho*-substituents as well as strongly electron-withdrawing groups. *N*-Atom transfer from *para*-nosylazide was possible to a broader range of substrates than using diphosphoryl azide. One weakness of this system, however, was that aliphatic and disubstituted styrenes were not tolerated as substrates.

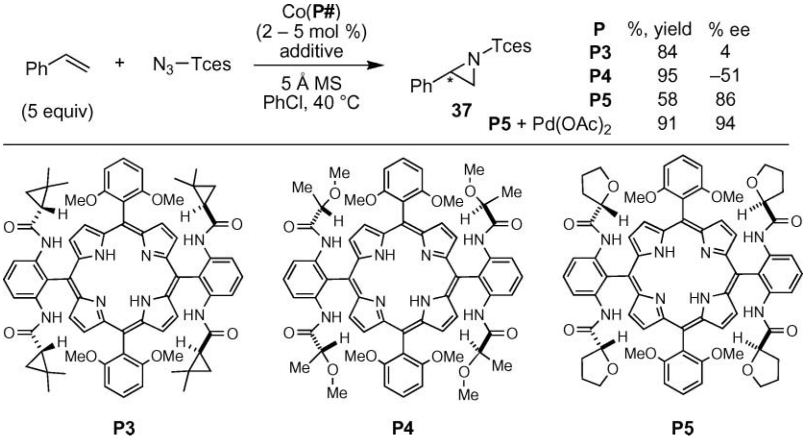
A model was suggested to account for the enhanced reactivity of the cobalt **P2** complex.[54] The cobalt porphyrin complex was designed to place the amide N–H bond close to the SO$_2$ group



Scheme 10 Asymmetric cobalt-catalyzed aziridination of styrenes using phosphoryl azide. ^{a}20 mol% DMAP added.



Scheme 11 Scope of cobalt-catalyzed aziridination of styrenes using *para*-nosyl azide.



Scheme 12 Optimization of cobalt-catalyzed aziridination of styrene using Tces–azide.

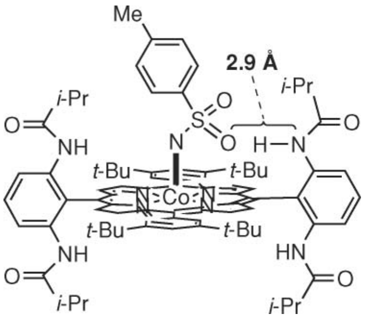
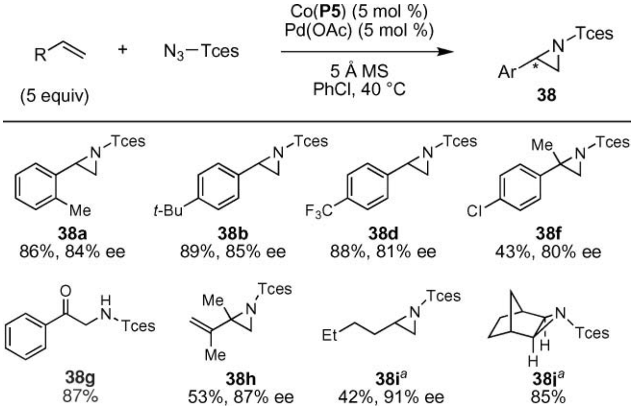


Fig. 1 H-Bonding explanation for increased catalyst efficiency and lifetime.

present on the nitrene (Fig. 1). The subsequent hydrogen bond formation was anticipated to stabilize the formation of the postulated metal nitrenoid intermediate and enhance its electrophilicity. While no experimental evidence was provided to back up these assertions, computational modeling produced a minimal geometry of the cobalt nitrenoid that had an N–H–O bond distance of 2.9 Å. This short distance indicates that significant hydrogen bonding could occur between the nitrenoid and the amide. This hydrogen-bonding model may account for the increased reactivity of the cobalt **P1** complex for the aziridination of styrenes with phosphoryl azide.

An important advance was realized by the Zhang group when they used their D2 symmetric cobalt porphyrin complex to catalyze the formation of aziridines from trichloroethoxysulfonyl (TCES) azide and an alkene (Scheme 12).[55] In pursuit of discovering conditions that provided chiral aziridines with easily removable groups on nitrogen, the Zhang group found that trichloroethoxysulfonyl azide was a promising nitrene source. Optimization of the porphyrin ligand revealed that the highest yields and enantioselectivity could be achieved using porphyrin **P5**. While higher yields were observed using other D2-symmetric porphyrins, this porphyrin afforded the highest enantioselectivities. Examination of additives revealed that the addition of palladium acetate led to improved yields without loss of enantioselectivity.

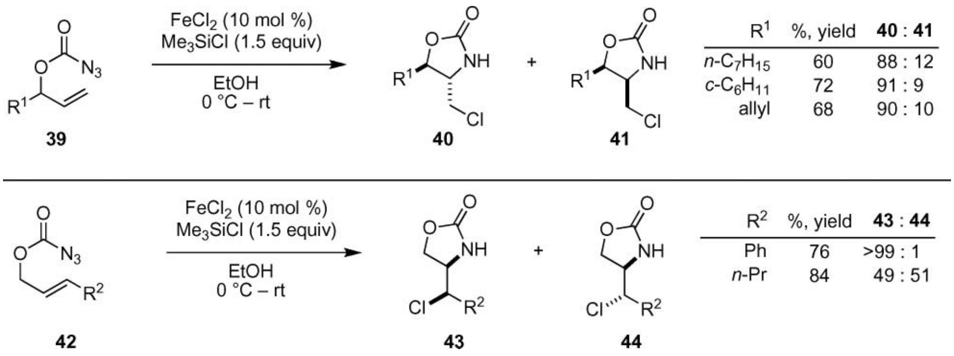
These optimized conditions enabled a large range of alkenes to be transformed into aziridines with high yields and good enantioselectivities (Scheme 13). A screen of styrenes revealed that the electronic nature of the styrene did not affect the yield or selectivity of the process. The nitrenoid could be transferred to styrenes with *ortho*-substitution as well as *gem*-disubstituted styrenes to give **38e** and **38f**. For the latter substrates, attenuated yields were obtained without much diminishment of enantioselectivity. Even aryl-substituted silyl enol ethers could be used as substrates, as in **38g**, although no enantioselectivity was observed. Even dienes and alkyl-substituted olefins were tolerated as substrates.[55] This report by Zhang is the first to show that these substrates could be converted to aziridines without competing side reactions, such as dimerization of the nitrenoid and allylic C–H bond amination of the olefin.



Scheme 13 Scope of cobalt-catalyzed aziridination of styrenes using Tces–Azide. [a]$PdOAc_2$ (5 mol%) used.

Aminochlorination/aminoalkoxylation

The intramolecular aminochlorination of an olefin can be achieved using substoichiometric amounts of iron(II) chloride to decompose azidoformates (Scheme 14).[56,57] Bach and co-workers reported that monosubstituted alkenes **39** could be transformed to oxazolidinones diastereoselectively using 10–30 mol% of $FeCl_2$ in the presence of a slight excess of trimethylsilylchloride (1.5 equiv). Irrespective of the R-group, the diastereoselectivity of the reaction was consistently about 9 : 1. Propargyl substrates are also tolerated as substrates. Insight into the mechanism of this transformation was gained from the reactivity of disubsituted alkenes **42**. While nearly perfect stereochemical fidelity was obtained with a phenyl



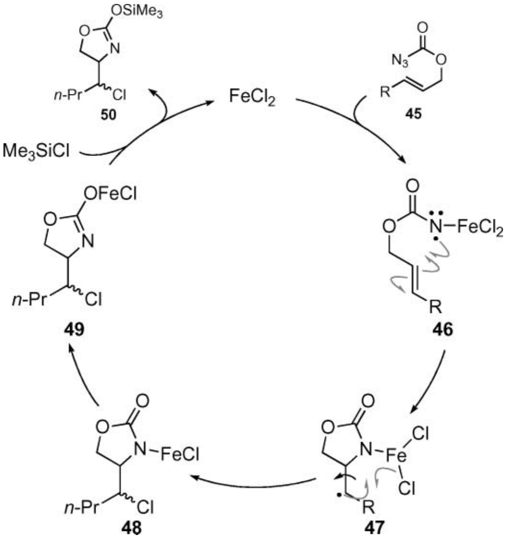
R^1	%, yield	**40 : 41**
n-C_7H_{15}	60	88 : 12
c-C_6H_{11}	72	91 : 9
allyl	68	90 : 10

R^2	%, yield	**43 : 44**
Ph	76	>99 : 1
n-Pr	84	49 : 51

Scheme 14 Fe(II)-catalyed intramolecular aminochlorination of olefins.

substituent, the n-propyl substrate afforded a 1 : 1 mixture of products.

To account for the lack of stereospecificity, Bach and co-workers proposed a mechanism involving the intermediacy of radical intermediates (Scheme 15).[56,57] Iron-mediated decomposition of the azidoformate produced Fe(III) nitrene **46**, which underwent a 5-*exo*-trig cyclization to give **47**. Even though chlorination was proposed to occur intramolecularly, this atom-transfer process occurred more slowly than bond rotation. Experiments to determine the lifetime of radical **47**, were not successful.



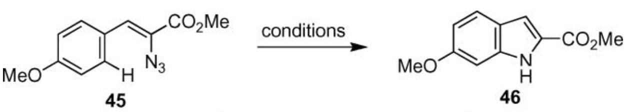
Scheme 15 Proposed mechanism of Fe(II)-catalyzed intramolecular aminochlorination.

C–H bond amination

Achieving the selective transformation of an unactivated C–H bond to a C–N bond would enable the rapid functionalization of readily available hydrocarbons. The use of azides as the nitrogen source in C–H bond amination reactions has motivated several research groups because the only by-product of C–N bond formation is N_2. Azides also do not require additives to access divalent nitrogen, or to neutralize by-products of the activation. Together, these attributes simplify purification of the reaction mixture as well as ensure that the pH of the reaction remains constant to eliminate the need of base. Consequently, the resulting process has the potential to be quite environmentally benign if the appropriate solvent/catalyst pairing is discovered. Towards the goal of achieving selective C–H bond amination significant progress has been made in the functionalization of both sp^2- and sp^3-C–H bonds.

Functionalization of sp^2-C–H bonds

The Hemetsberger–Knittel–Moody indole reaction represents a rapid synthesis of 2-carboxylate-substituted indoles in two-steps from commercially available aryl aldehydes.[10] Thermolysis of the vinyl azide substrate produces the indole in good yields. The Driver group reported that the rate of reaction could be accelerated by rhodium(II) perfluorobutyrate to form indoles at ambient temperature (eqn (6)).[58] Other rhodium(II) tetracarboxylate complexes, such as $Rh_2(OAc)_4$ and other transition metal salts (*e.g.* FeX_2, ZnX_2, CuX_2, AgX, AuX) were found to be ineffective as catalysts.



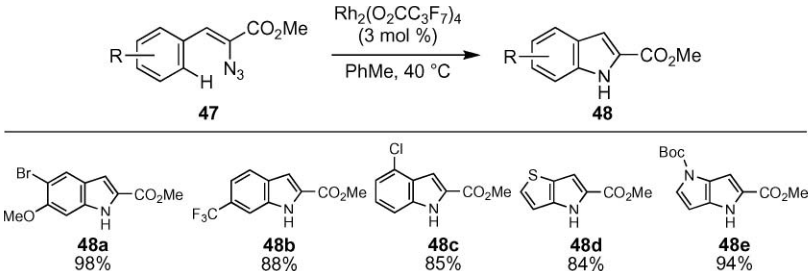
conditions	%, yield
150 °C	80
$Rh_2(O_2CC_3F_7)_4$ (5 mol %), rt	>95

(6)

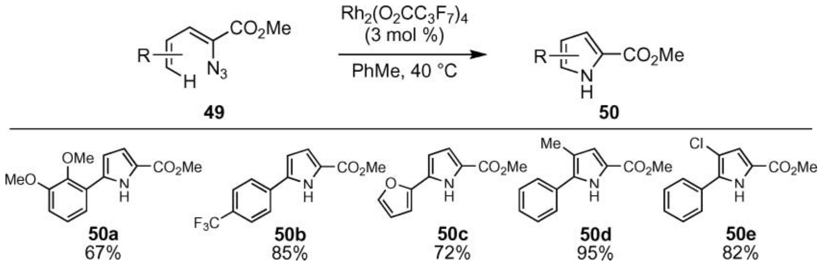
Rhodium(II) perfluorobutyrate proved to be an effective catalyst to enable the synthesis of a range of indoles **48** from vinyl azides **47** (Scheme 16). The reaction tolerated a variety of functional groups, including halogen-, trifluoromethyl-, and methoxy substituents as well thiophenes, furans, and pyrroles. The Lewis acidity of the rhodium(II) carboxylate limited the substrate scope to those that contained non-Lewis basic functional groups: azides bearing cyano-, and dimethylamino groups did not produce indoles.

Rhodium(II)-catalyzed *N*-heterocycle formation was extended to include pyrroles (Scheme 17).[59] The functional group tolerance of this reaction mirrored the indole reaction and a variety of di- and trisubstituted pyrroles could be produced in good yield.

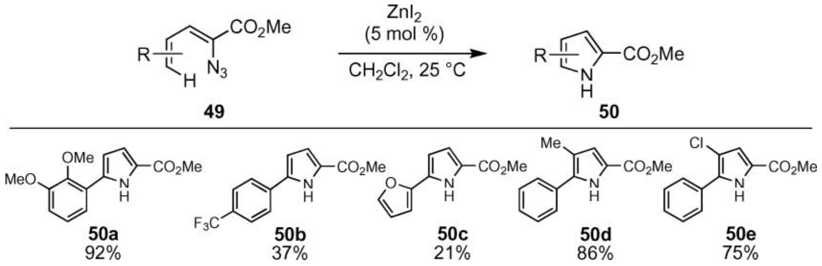
In contrast to indole synthesis, a variety of transition metal salts were able to catalyze pyrrole formation (Scheme 18).[59] In addition to rhodium(II) carboxylates, copper(II) triflate and zinc iodide were found to be competent catalysts. In the presence of 5 mol% of zinc iodide, the pyrrole formation occurred readily at room temperature. Comparison of reaction conversions revealed different substrate preferences: higher yields were obtained with



Scheme 16 Representative examples of rhodium(II)-catalyzed indole formation.



Scheme 17 Representative examples of rhodium(II)-catalyzed pyrrole formation.

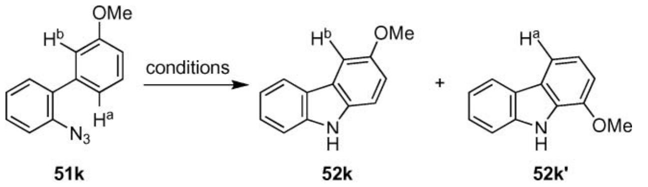


Scheme 18 Representative examples of zinc-catalyzed pyrrole formation.

dienylazides bearing electron-deficient aryl groups using rhodium perfluorobutyrate (**50b**, **50c**), while zinc iodide was preferred for substrates with electron-donating dienyl azide substituents (*e.g.* **50a**).

The Driver group also developed a complementary synthesis of *N*-heterocycles with C2-aryl or alkyl substituents from aryl azides **51** through the construction of the C2 C–N bond (Scheme 19).[60] While the analogous thermal and photochemical reactions are known,[11] they are rarely used to make *N*-heterocycles because the rate of decomposition of the aryl nitrene competes[61] with the desired C–H amination reaction. Using rhodium(II) perfluorobutyrate or octanoate as catalyst, a range of indoles (**52**) were formed at 60 °C from aryl azides (**51**). In addition to indoles, a variety of carbazoles could be formed from the corresponding biaryl azides.[62]

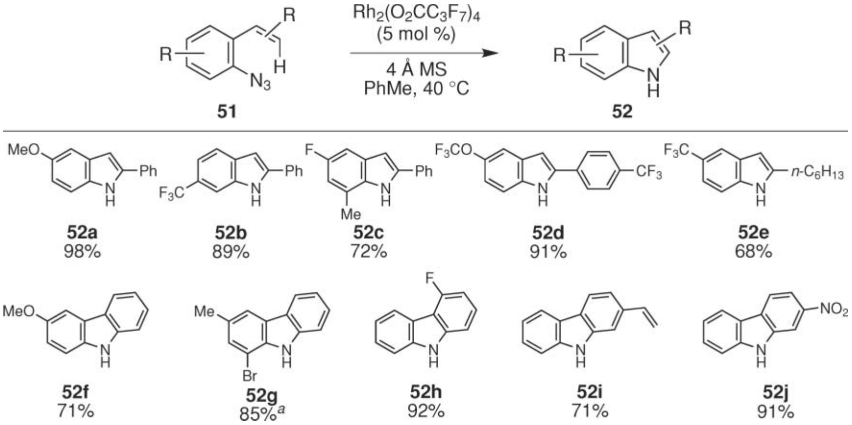
Examination of the reactivity of biaryl azides revealed a significant advantage to using rhodium(II) carboxylates as catalysts to form *N*-heterocycles (eqn (7)).[62] Thermolysis or photolysis of biaryl azide **51k** produced a nearly 50 : 50 mixture of the two possible carbazoles.[12] In contrast, rhodium(II) octanoate significantly improved the selectively to form carbazole **52k** as the major product. The Driver group interpreted this selectivity as evidence that the metal complex was involved in the C–N bond forming step of the mechanism.



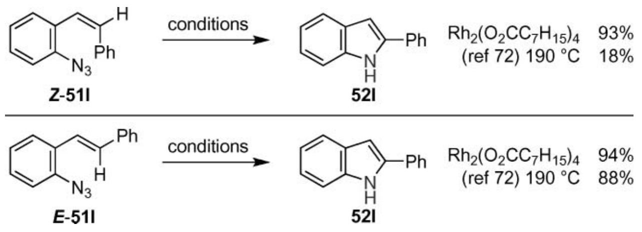
conditions	%, yield	**52k : 52k'**
150 °C or hν	40 – 70	50 : 50
$Rh_2(O_2CC_7H_{15})_4$ (5 mol %), 60 °C	71	94 : 6

(7)

Further insight into the mechanism was obtained from the observed reactivity of both the *E*- and *Z*-styryl azide isomers **51l** (Scheme 20). While the *E*-isomer was found to readily produce 2-phenylindole, Smith and co-workers reported that thermolysis of the *Z*-isomer resulted in the formation of a tarry substance in addition to a significantly lower yield of indole.[63] In contrast, exposure of either the *E*- or the *Z*-isomer to 5 mol% of rhodium(II) carboxylate produced 2-phenylindole cleanly. The Driver group interpreted this result as evidence that indole formation occurred through a stepwise process where C–N bond formation preceded C–H bond cleavage.

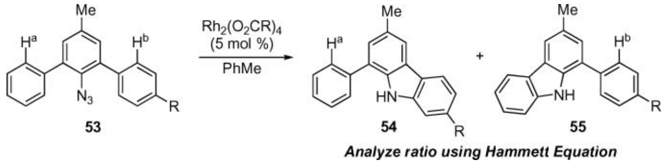


Scheme 19 Representative examples of rhodium(II)-catalyzed indole and carbazole formation from aryl azides. [a]Reaction performed on multi-gram scale.



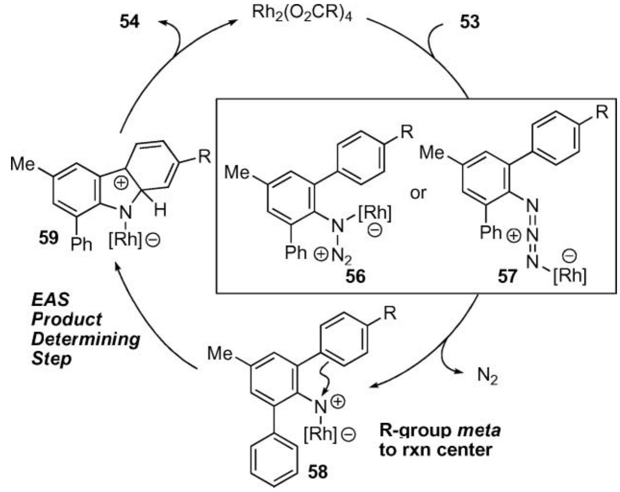
Scheme 20 Stereospecificity of rhodium(II)-catalyzed indole formation from aryl azides.

Further insight into the mechanism came from a study on the reactivity of triaryl azides **53** (eqn (8)).[64] The ratio of products would be analyzed using the Hammett equation, and the results were anticipated to provide insight into the nature of C–N bond formation. The original hypothesis was that C–N bond formation occurred through electrophilic aromatic substitution and a linear correlation to σ_{meta}-constants was expected. Because the methoxy-group is at the *meta*-position to the reaction center, it would act as an inductive electron-withdrawing group if an electrophilic aromatic substitution (EAS) mechanism was occurring (Scheme 21).



(8)

In contrast to these expectations, no correlation with σ_{meta}-constants was observed. On the basis of this data, electrophilic aromatic substitution was eliminated as the mechanism for C–N bond formation. Instead, bisecting straight lines were observed when the product ratios were plotted against Hammett σ^+-constants (Fig. 2).[65] Related V-shaped graphs have been interpreted as evidence for a change in the identity of the rate-determining step, or as evidence that a change in the mechanism is occurring.[66]



Scheme 21 Disproven electrophilic aromatic substitution mechanism for carbazole formation.

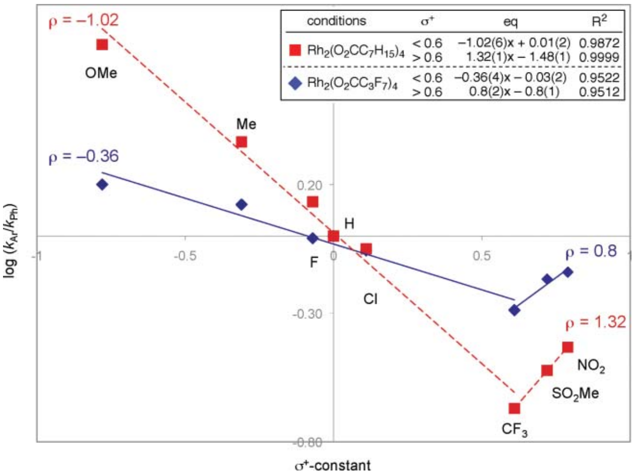
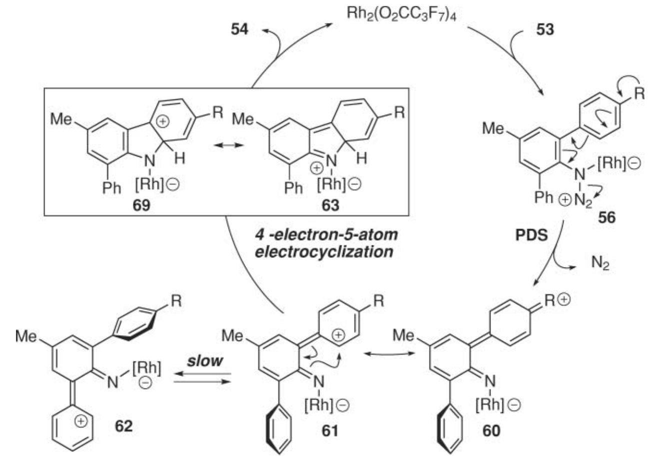


Fig. 2 Relationship of carbazole product ratio with Hammett equation.

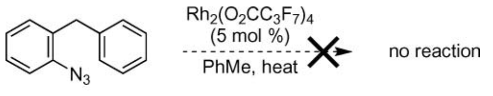
The Driver group interpreted the correlation with σ^+-constants as evidence that the product-determining step occurred before C–N bond formation (Scheme 22). Linear correlation with σ^+-constants would be expected if the more electron-rich aryl group assists in the formation of the rhodium nitrenoid (**56** to **60**). Considering the rhodium nitrenoid as *ortho*-azaquinoid



Scheme 22 4π-Electron-5-atom-electrocyclization mechanism for carbazole formation.

60 provides an explanation for the selectivity in C–N bond formation. A resonance structure of the resulting *ortho*-azaquinoid (**61**) places the positive charge on the *ortho*-carbon to trigger a four-π-electron-five-atom electrocyclization[67] to form the C–N bond in **69**. This electrocyclization must occur faster than tautomerization of the metalloimine (**61** to **62**),[68] which would abolish selectivity in C–N bond formation. A 1,5-hydride shift from **63** then affords the carbazole product.

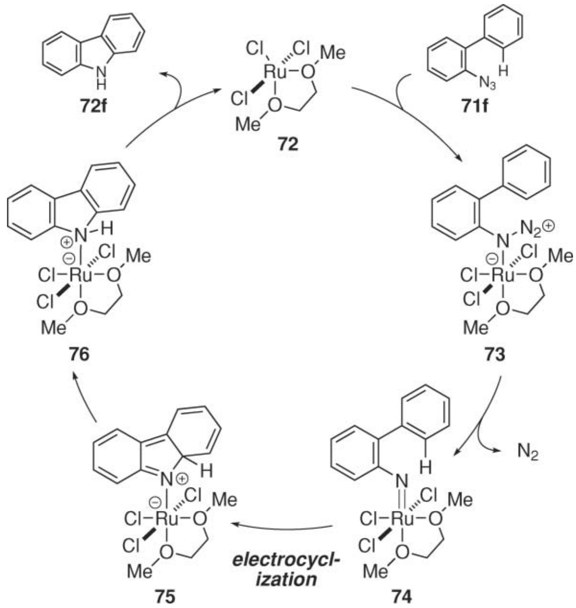
The requirement of a contiguous π-system was examined with **70** (eqn (9)). If electron assistance was required for rhodium nitrenoid formation, azide **70** was expected not to react. As anticipated, exposure **70** to reaction conditions resulted in no reaction.



70 (9)

The Jia group recently reported that ruthenium trichloride could be used as a catalyst to promote *N*-heterocycle formation from aryl- and vinyl azides (Scheme 23).[69] While carbazole and pyrrole formation occurred at 85 °C, slightly higher temperatures (105 °C) were required to form indoles from vinyl azides **71**. In comparison to the use of rhodium(II) carboxylate complexes, slightly elevated temperatures were required to form the desired *N*-heterocycle. This limitation is mitigated by the significantly reduced cost of the catalyst and increased functional group tolerance of the reaction—Lewis basic groups such as dimethylamine (**71b**) were allowed. The stereoselectivity of this Ru-catalyzed *N*-heterocycle formation has not yet been reported.

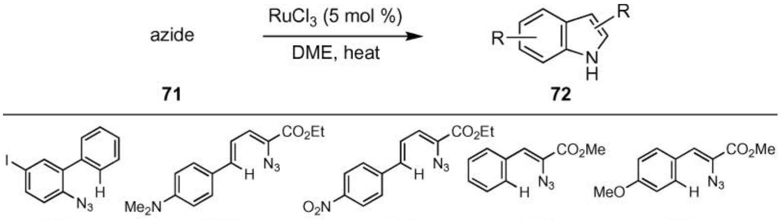
To provide insight into the mechanism of this process, density functional theory calculations were performed on a variety of possible reactive intermediates.[69] The Jia group interpreted these calculations to suggest that a Ru(III)/Ru(V) catalytic cycle occurs and that the C–N bond is formed through a similar electrocyclization mechanism as reported by Driver and co-workers (Scheme 24). In support of this mechanism, aryl azide **70** did not react when exposed to ruthenium trichloride.



Scheme 24 Potential electrocyclization mechanism for ruthenium(III)-catalyzed carbazole formation.

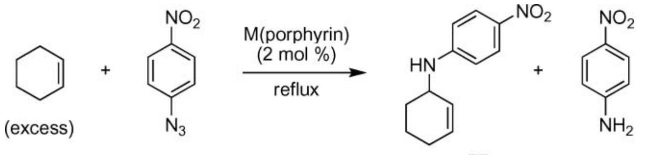
Towards a general aliphatic C–H bond amination method

In 1999, ruthenium- and cobalt porphyrin complexes were reported by Cenini and co-workers to catalyze sp^3-C–H bond amination reactions using *para*-nitrophenylazide as the source of the nitrogen-atom.[37,38] While cycloheptene and cyclooctene were effectively converted to the corresponding aziridine, exposure of cyclohexene to either catalyst formed allyl amine **77** (eqn (10)). The major by-product was reduction of the azide to form *para*-nitroaniline. The product distribution was affected by the electronic nature of the aryl azide: when an electron-rich azide was used (*e.g.* *p*-methoxyphenylazide), the yield of allylic C–H bond amination was reduced.



71a 93% **71b** 74% **71c** 87% **71d** 35% **71e** 88%

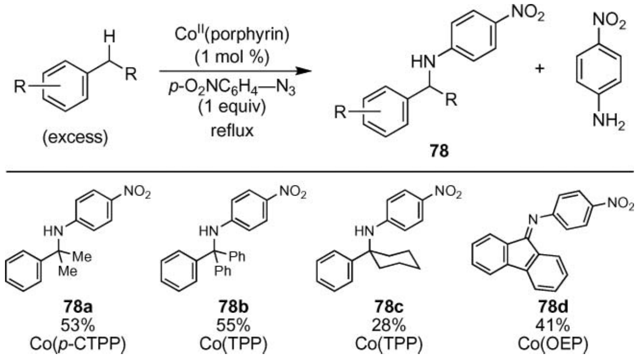
Scheme 23 Representative examples of ruthenium(III)-catalyzed *N*-heterocycle formation.



M(porphyrin)	%, yield 77	 aniline
Co(TPP)	53	17
Co(OEP)	61	10
Ru(TPP)(CO)	62	16
Ru(OEP)(CO)	45	9

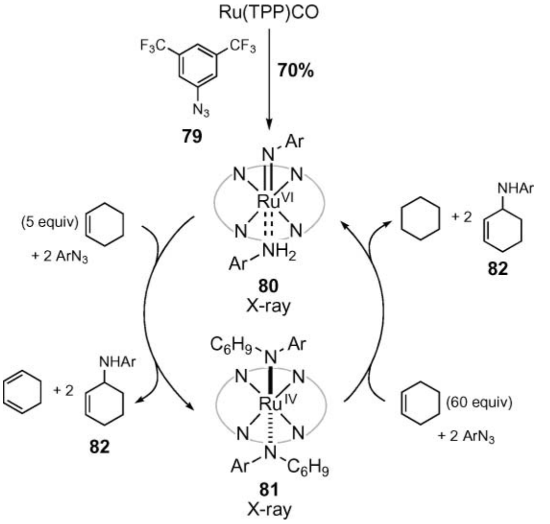
(10)

Cobalt(II)-catalyzed benzylic C–H bond amination was also investigated using *para*-nitrophenylazide (Scheme 25).[70,71] While a variety of cobalt(II) porphyrins catalyzed the formation of amine **78**, empirical evidence revealed that changing the hydrocarbon substrate required a screen of different porphyrin ligands to achieve the highest yield.



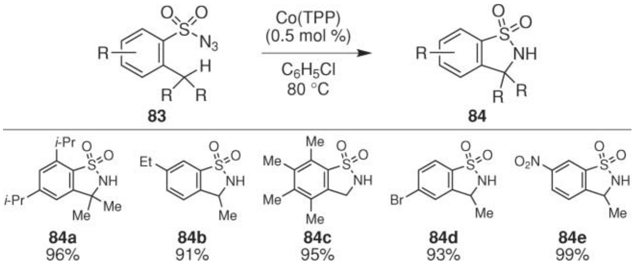
Scheme 25 Cobalt-catalyzed sp^3-C–H bond amination.

Further insight into the mechanism of allylic C–H bond amination came from the isolation of a ruthenium diimido complex **80** (Scheme 26).[72] Exposure of ruthenium tetraphenyl porphyrin to aryl azide **79** resulted in the formation of diimido complex **80**, whose structure was determined by X-ray crystallography.[73] This complex catalyzed *N*-atom transfer from aryl azide to cyclohexene. Exposure of an excess of cyclohexene to **80** resulted in the formation of allylic amine **82** and 1,3-cyclohexadiene. X-Ray crystallography revealed that the ruthenium product was diamide complex **81**. This complex was also a competent amination catalyst. Reaction of **81** and cyclohexene produced allylic amine and cyclohexane. The ruthenium was then oxidized to produce the diimide complex to complete the catalytic cycle. This data contrasts with the kinetic and mechanistic data obtained from Cenini's previous study of cobalt porphyrin-catalyzed *N*-atom transfer to alkenes.[38,71]



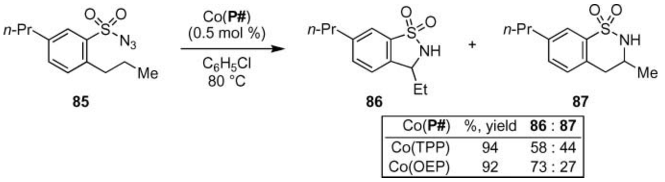
Scheme 26 Characterization and reactivity of ruthenium porphyrin reactive intermediates.

Significant advances in this field have been achieved by the Zhang group.[74–76] They reported both intra- and intermolecular sp^3-C–H bond amination using cobalt(II) porphyrin complexes. In 2007, they reported that cobalt tetraphenylporphyrin catalyzed the intramolecular amination of benzylic C–H bonds (Scheme 27).[74] Cobalt tetraphenylporphyrin emerged as the best catalyst from a series of transition metal porphyrin complexes. No reaction, or inefficient reaction rates were observed using vanadium(IV), iron(III), copper(II), chromium(III), zinc(II), manganese(III), nickel(II), or ruthenium(II) porphyrin complexes. The optimal reaction conditions were determined to only require 0.5 mol% of Co(TPP) to decompose the aryl sulfonyl azide. The scope of benzyl C–H bond amination was found to be broad. Tertiary-, secondary-, and primary C–H bonds could be functionalized to produce *N*-heterocycle **84**. In addition to alkyl groups, the reaction also tolerated bromo- and nitro-substituents.



Scheme 27 Cobalt-catalyzed intramolecular sp^3-C–H bond amination of arylsulfonyl azides.

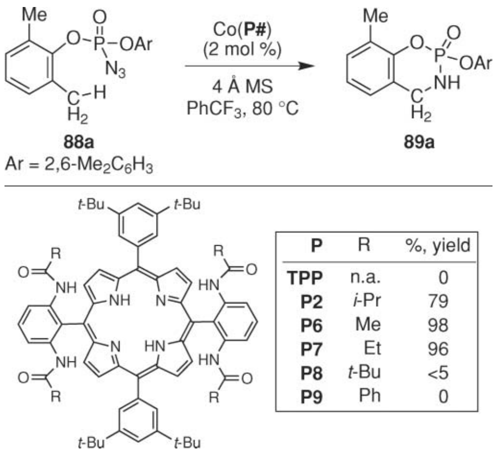
The Zhang group investigated the selectivity of their C–H bond amination by screening aryl sulfonyl azide **85** (eqn (11)).[74] The Du Bois group has reported that the related sulfonamide nitrenoid rhodium complexes prefer reaction with C–H bonds to form six-membered *N*-heterocycles.[77] To compare the selectivity of their cobalt-catalyzed process, the Zhang group investigated **85**, which contains two reaction centers. Amination of the weaker benzylic C–H bond would produce a five-membered ring, whereas reaction with the β-C–H bond would produce a six-membered ring. The Zhang group reported that the ratio of **86** to **87** depended on the identity of the porphyrin ligand, with Co(OEP) promoting a more selective reaction. Control of the product ratio indicates that the metal complex is involved in the C–N bond-forming step of the mechanism.



Co(**P#**)	%, yield	**86 : 87**
Co(TPP)	94	58 : 44
Co(OEP)	92	73 : 27

(11)

The Zhang group also reported that intramolecular benzylic C–H bond amination could be accomplished from aryl phosphoryl azides (Scheme 28).[75] The optimal reaction conditions were determined using azide **88a**. The Zhang group found that the reaction efficiency strongly depended on the identity of the porphyrin ligand. In contrast to their sulfonyl azide study, cobalt tetraphenylporphyrin was found to be inactive. Instead, effective conversion to phosphoramidite **89a** was accomplished using the catalyst formed from porphyrins **P2**, **P6**, or **P7**. The higher activity of these complexes was attributed to their participation in hydrogen bonding of the amide N–H with the oxide of the phosphoryl group on the nitrenoid.[54] The yield of the process depended on the steric nature of the R group on the amide. The highest yields were observed with a methyl- or ethyl substituent. Increasing the size of the amide (R = *i*-Pr) resulted in a diminished yield. Further increasing the size to a *t*-Bu group completely inhibited the reaction. No product formation was also observed with an *N*-phenylamide (**P9**) ligand.



P	R	%, yield
TPP	n.a.	0
P2	*i*-Pr	79
P6	Me	98
P7	Et	96
P8	*t*-Bu	<5
P9	Ph	0

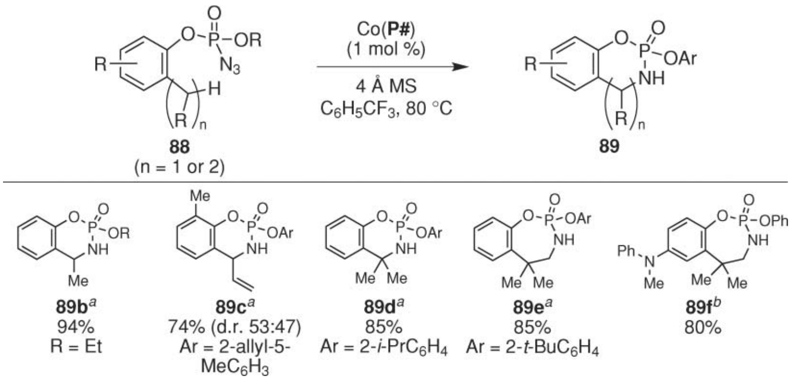
Scheme 28 Cobalt-catalyzed intramolecular sp^3 C–H bond amination of arylphosphoryl azides.

The scope of this reaction was quite broad (Scheme 29).[75] The reaction could form either a six- or a seven-membered ring, the latter ring size being particularly noteworthy for C–H bond amination because it is rarely observed. Six-membered phosphoramidites could be formed in high yield from primary-, secondary-, or tertiary benzylic C–H bonds. The successful conversion of **88c** revealed that aziridination was not a competitive reaction. Even phosphoryl azides containing Lewis basic groups such as a tertiary amine (**88f**) were competent substrates. If the benzylic position was fully substituted, seven-membered ring formation readily occurred without increasing the catalyst loading or reaction temperature. The cyclic phophoramidite amination products can be reduced with $LiAlH_4$ or methanolyzed to produce value added amine-containing products.[75]

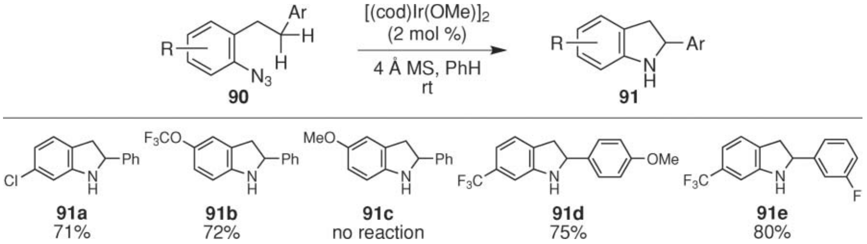
In addition to phosphoryl- and sulfinylazides, intramolecular benzylic C–H bond amination of aryl azides is also possible. The Driver group found that iridium(I) catalyzed the formation of indolines **91** from electron-deficient aryl azides **90** at room temperature (Scheme 30).[16] Cyclooctadiene iridium methoxide dimer was identified empirically from a screen of nearly 200 different transition metal salts and complexes known to catalyze the functionalization of C–H bonds. Indoline formation was sensitive to the electronic nature of the starting azide. While electron-deficient aryl azides were efficiently converted, no reaction was observed with electron-rich substrates. In contrast, the reaction was not affected by the electronic nature of the β-aryl substituent: good conversions were observed with both electron-rich and electron-poor substituents. One weakness of this method was the strict requirement for Schlenk experimental techniques: in the absence of rigorous air and water exclusion, the major product of the reaction was aniline.

A primary kinetic effect was observed in the intramolecular competition experiment of **91f**-d_2 (Scheme 31).[16] Driver and co-workers interpreted this result as evidence that C–H bond amination occurred stepwise through either an *H*-atom abstraction–radical recombination through diradical **93f**-d_2 or a concerted mechanism *via* **TS-94**. Unfortunately, the lack of reactivity of the cyclopropyl-substituted **90g** prevented further mechanistic conclusions to be drawn.

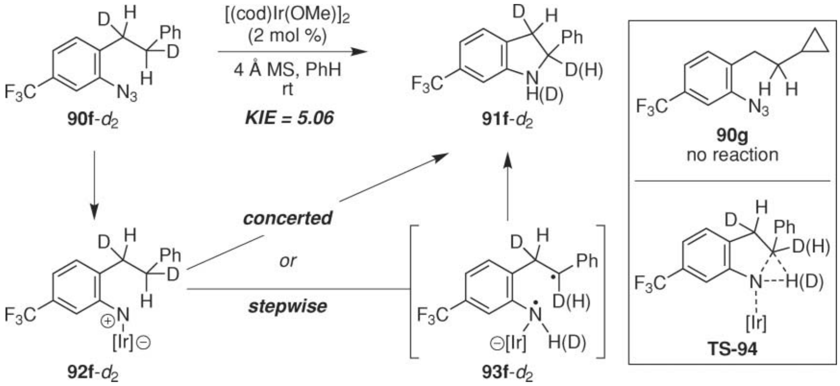
An important advance was realized by the Zhang group when they reported that intermolecular C–H bond functionalization could be achieved using Troc-azide as the *N*-atom source and the commercially available cobalt tetraphenylporphyrin complex



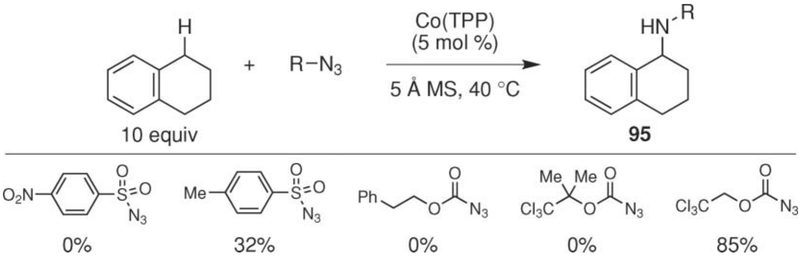
Scheme 29 Cobalt-catalyzed intramolecular sp^3 C–H bond amination of arylphosphoryl azides. ^{a}2 mol% Co(**P6**) used. ^{b}2 mol% Co(**P2**) used.



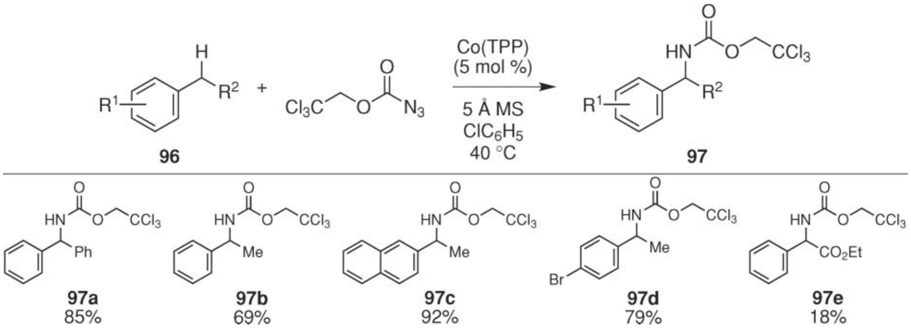
Scheme 30 Iridium(I)-catalyzed indoline formation from aryl azides.



Scheme 31 Potential mechanisms for Ir(I)-catalyzed indoline formation.



Scheme 32 Cobalt-catalyzed intermolecular benzylic C–H bond amination.

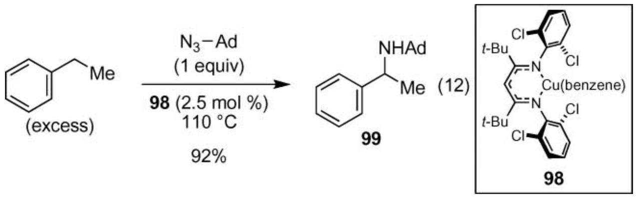


Scheme 33 Scope of cobalt-catalyzed intermolecular benzylic C–H bond amination using Troc-N_3.

as the catalyst (Scheme 32).[76] To achieve this intermolecular reaction, a range of azides were screened as potential nitrogen-atom sources. Only tosyl-azide and Troc-azide were found to be competent starting materials and significantly higher yields were observed with Troc-azide. The facile removal of the Troc-protecting group from the product amine is another significant advantage offered by this process.[78] This *N*-atom transfer reaction was sensitive to the electronic- and steric nature of the azide. Replacing the methyl group on the sulfonyl azide with a nitro group inhibited the reaction. Increasing the steric nature of the Troc-azide by adding two methyl substituents also resulted in no reaction.

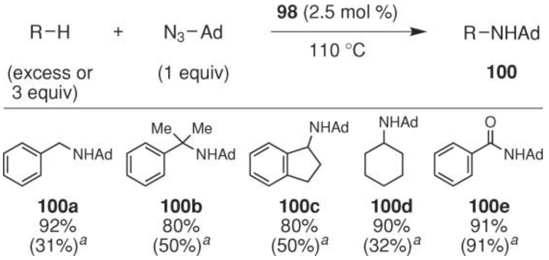
The scope of the reaction was examined using Troc-azide as the *N*-atom source (Scheme 33).[76] The reaction worked best for the functionalization of secondary benzylic C–H bonds. Attenuating the electron density of the aryl substituent led to a slightly reduced yield (**97d**), whereas adding an ester group to the benzylic carbon (**97e**) led to a significantly lower yield. No reaction was observed with substrates containing primary benzylic C–H bonds (*e.g.* toluene) or non-benzylic C–H bonds (*e.g.* cyclohexane).

Intermolecular nitrene transfer was also recently reported by the Warren laboratory using a copper ketiminate complex **98** (eqn (12)).[79] While this complex is not commercially available, it can be synthesized from $Cu(Ot\text{-}Bu)_2$ using inert experimental techniques from copper *tert*-butoxide.[80,81] The catalyst was quite selective: the reaction of ethylbenzene with adamantyl azide produced only benzyl amine **99**.



(12)

A variety of hydrocarbons were screened to investigate the scope of this reaction (Scheme 34).[79] While higher yields were observed with secondary benzyl C–H bonds than primary or tertiary C–H bonds. For primary C–H bonds, the product amine reacted to afford adamantyl aldimine **100e**. In addition to benzyl C–H bonds, cyclohexane could be converted to cyclohexyl amine. For this substrate, slightly longer reaction times were required. While excellent yields were observed if the reaction was performed neat in hydrocarbon, lowering the amount of the substrate to one equivalent resulted in diminished yields for toluene and cyclohexane. For more reactive C–H bonds (such as secondary benzylic C–H bonds) the yield was not as attenuated.

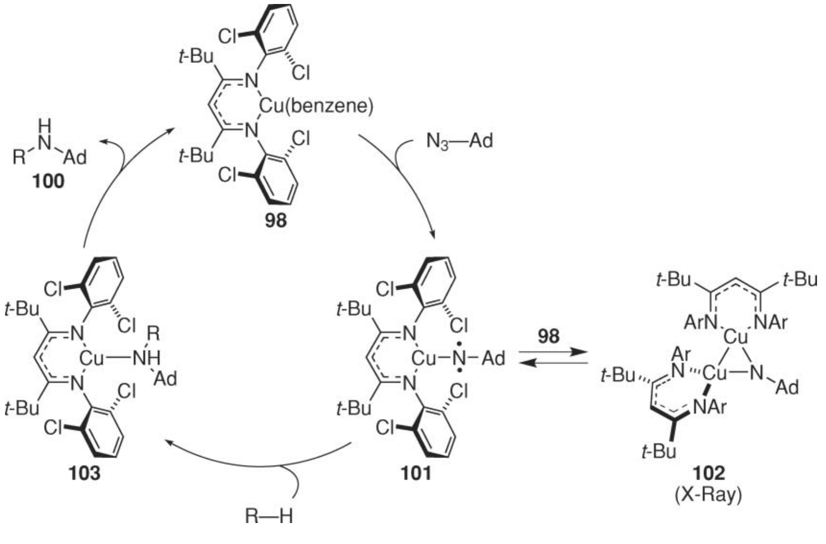


Scheme 34 Scope of copper-catalyzed intermolecular sp^3 C–H bond amination using adamantyl azide. [a]3 equiv of the alkane used.

A catalytic cycle for this process was postulated on the basis of several isolated copper species (Scheme 35).[79] Reaction of copper ketiminate with adamantyl azide forms copper nitrenoid **101**. This species can react with an additional copper ketiminate to produce the isolable **102**, or with a C–H bond to produce the copper amine **103**. Dissociation of the amine regenerates the copper ketiminate complex. Density functional theory calculations were performed to investigate the nature of copper nitrenoid **101**. The ground state of **101** was determined to be a singlet biradical and to exist 18 kcal mol^{-1} below the triplet state.

Conclusions and future outlook

Substantial progress has been made in the development of transition metal-catalyzed *N*-atom transfer reactions using azides as the nitrogen-atom precursor. The attractiveness of azides in these processes stems from their ready accessibility, controllable reactivity, and environmentally benign by-products. High yields, good selectivities, and broad substrate scope prove that azides are excellent choices for the nitrenoid precursor in aziridination and sulfimination reactions. Because these reactions can be catalyzed by a range of different transition metal complexes, the reaction conditions can be tailored to match the demands of the process. Considerable strides have also been made using azides in C–H bond amination processes. Intramolecular processes that form new C–N bonds are appealing, alternative methods for the construction of *N*-heterocycles. Selective intermolecular C–H amination processes are just emerging and represent future targets for the development of new chemistry, which use azides with easily removable groups on nitrogen. Achieving transition metal-catalyzed intra- and intermolecular asymmetric C–H bond amination reactions also remains a future goal in this area. Tandem processes triggered by an initial *N*-atom transfer from azides to create multiple bonds also remain underdeveloped. The positive attributes of using azides will insure continued research interest for their use in *N*-atom transfer reactions.



Scheme 35 Potential mechanism for copper-catalyzed C–H bond amination of hydrocarbons.

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