Nitrene transfer catalysts for enantioselective C–N bond formation

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Abstract | Transition-metal-catalysed, non-enzymatic transformations of C–H and C=C bonds to C–N bonds through nitrene transfer (NT) are powerful synthetic tools to prepare valuable amine building blocks. Although the first examples of racemic NT were reported more than 50 years ago, catalysts that mediate enantioselective NT with a broad substrate scope have been slow to emerge. However, the past ten years have seen the discovery of several first-row, second-row and third-row transition metal catalysts for asymmetric NT. This Review covers recent developments in asymmetric aziridination and C–H bond amination reactions. We describe catalyst design principles, re-evaluate traditional catalyst architectures, show how the scope of nitrene precursors has expanded and present new mechanistic insights. Following this, we highlight remaining opportunities and challenges to developing more practical and general synthetic methodologies. Realizing chemoselective, site-selective and enantioselective intermolecular NT will streamline amine synthesis and allow us to explore new chemical space.

Nitrogen atoms are found in a multitude of biologically important molecules and play a crucial role in modulating the structure and function of DNA, proteins and metal coordination compounds[1,2]. Countless biologically active natural products and pharmaceuticals contain N atoms, such that general methods for the predictable and efficient formation of C–N bonds are highly desirable. A common and effective way to transform C=C or C–H bonds into new C–N bonds is through a transition-metal-catalysed nitrene transfer (NT) reaction. The first evidence for such a reaction came from Kwart and Khan, who, in 1967, observed Cu-catalysed decomposition of a sulfonyl azide[3,4]. Since this initial report, catalytic functionalization of organic molecules via metal–nitrene intermediates $RNML_n$ has become a topic of intense interest in organic synthesis[5–17].

There are two major ways to introduce C–N bonds into organic molecules through NT: the NR can add to a C=C bond (aziridination; FIG. 1a) or insert into a C–H bond (amination). Although numerous examples of racemic NT promoted by a variety of transition metals are known[8–10,13,14,16], the development of general enantioselective reactions has been substantially more challenging. Nonetheless, rapid progress continues to be made beyond the chiral metal complexes of ligands that include bis(oxazoline) (BOX) derivatives, bis(Schiff base)s, chiral tetracarboxylates, salens and porphyrinato ligands, which were all reported primarily in the 1990s. Excitingly, over the past 5 years, the synthetic community has witnessed a renaissance in asymmetric NT chemistry, largely owing to new catalyst designs that mediate unprecedented enantioselective C–N bond formations (FIG. 1b).

This Review focuses on catalyst design strategies for selective, efficient asymmetric C–N bond formation through NT, involving both C=C aziridination and C–H amination pathways. Reviews that have appeared over the past decade only partially cover the topic of catalytic, enantioselective NT[18–21], and are largely limited to a specific transformation, such as either alkene aziridination or C–H bond amination. A comprehensive review of asymmetric NT methods covering alkene aziridination and C–H amination has not appeared since 2003 (REF.[22]). Herein, we cover asymmetric NT reactions and give representative examples of the products that can be prepared using these methodologies. We offer insights into catalyst design strategies and new opportunities to access unexplored chemical space.

General NT mechanism

A simplified mechanism of transition-metal-mediated NT[23–29] (FIG. 1a) involves initial reaction of a metal catalyst ML_n with a nitrene precursor RN=LG (where LG denotes a leaving group such as PhI, N_2 or CO_2) to give a metal–nitrene $RNML_n$. This reactive intermediate can engage a C=C bond to form an aziridine or insert into a C–H bond to generate an amine product. Depending on the electronic structure of the nitrene species, the reaction can occur through either a concerted or a stepwise pathway[25–28,30–32]. The metal–nitrene intermediate typically exists in either a singlet or a triplet electronic ground state. Singlet metal nitrenes generally perform

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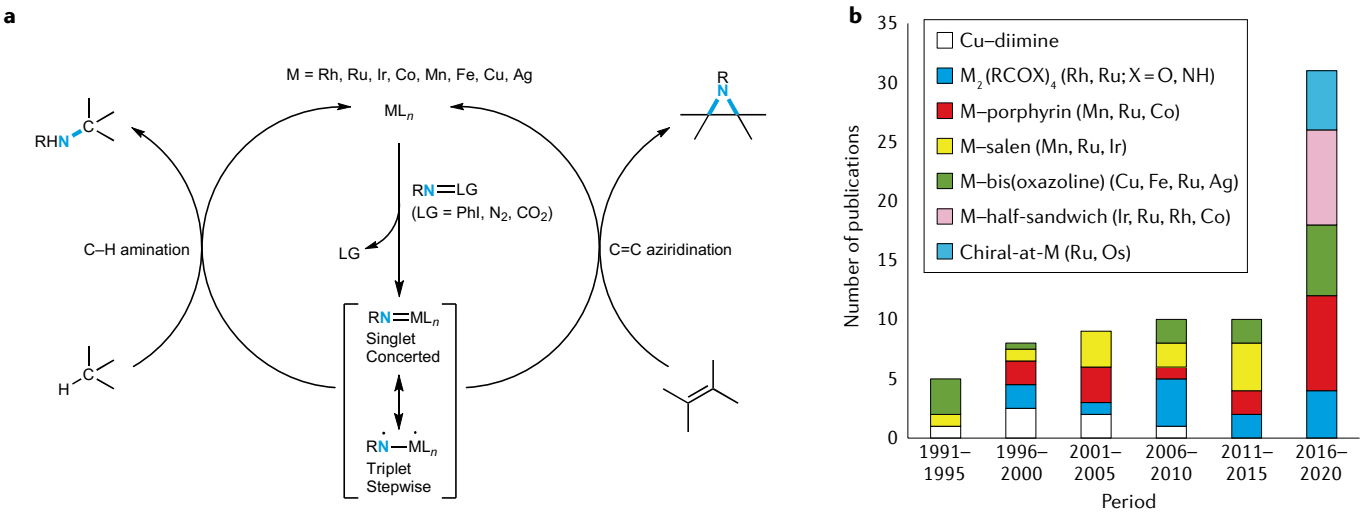


Fig. 1 | **Classical reactions of metal–nitrenes and some catalysts with which they are realized. a** | A simplified mechanism of transition-metal-mediated C=C aziridination or C–H amination or through nitrene transfer. A metal catalyst ML_n reacts with a nitrene precursor RN=LG to release the LG leaving group and form the key metal–nitrene intermediate $RNML_n$, which can typically exist in singlet or triplet electronic ground states. **b** | The renaissance of asymmetric nitrene transfer chemistry in recent years has seen the development of new catalyst archetypes (SciFinder search, February 2021).

NT through concerted pathways involving asynchronous transition states. Concerted NT has been reported for $[Rh_2(O_2CR)_4]$ catalysts[27], as well as Ru-based and Ir-based half-sandwich[33,34] and chiral-at-Ru complexes[35]. In contrast, triplet nitrene complexes afford radical intermediates by H-atom transfer or radical addition to the alkene, followed by radical recombination. Metals that participate in stepwise NT include Fe, Ru, Cu, Co and Ag, among others[17,25,26,28,32,36–38]. Ru–nitrene complexes can exhibit reactivity characteristic of both singlet and triplet complexes, indicating that the nature of a metal catalyst can influence the electronic structure of the resulting metal–nitrene and affect the reaction outcome. In many cases, particularly in intramolecular NT, radical recombination is sufficiently rapid that the amination may appear to be concerted and cannot be distinguished experimentally from a stepwise pathway. These two mechanisms have different transition state (TS) geometries and can lead to different stereochemical outcomes. It is crucial to understand the interplay between metal–nitrene electronic structure and the mechanism to rationally design asymmetric NT catalysts.

D_2-symmetric Co porphyrinates

Metal–porphyrinato complexes are arguably the most frequently used asymmetric NT catalysts. Early work by Che and colleagues focused on the development of chiral Mn^{III} and Ru^{II} porphyrinato complexes for C–H amination of sulfamate-derived iminoiodinane nitrene precursors in up to 88% enantiomeric excess (*ee*) (REFS[29,39–42]). Inspired by these initial reports, Zhang and colleagues prepared [Co(**P2**)], a Co^{II} catalyst supported by a D_2-symmetric porphyrinato $\mathbf{P2}^{2-}$ (FIG. 2a) that proved capable of transforming monosubstituted and 1,1′-disubstituted alkenes into aziridines with good asymmetric induction (80–99% *ee*)[43] (FIG. 2b). Another key factor to the success of this asymmetric NT Co^{II} catalyst system is the use of azide nitrene precursors. Phosphoryl[44,45], sulfonyl[43] and aryl azides[46] lose N_2 in the presence of chiral amidoporphyrinato complexes, affording radical Co^{III}–nitrene intermediates that add to alkenes as part of asymmetric aziridination. Computational and experimental studies suggest that these Co^{III}–nitrene radicals engage alkenes in a stepwise radical addition–substitution pathway[32,47,48]. 2,4,6-Trifluorophenyl azide afforded particularly high yields and enantioselectivities in the aziridination of styrene with Co^{II} catalyst [Co(**P1**)], while not requiring excess olefin[46]. Other *ortho*-fluoroaryl azide substrates gave similar results, with *ee* values up to 96% in enantioselective aziridinations of styrenes. Good yields were also observed using [Co(**P4**)] at lower loadings (5 → 1 mol%; FIG. 2c). Zhang and colleagues hypothesized that a non-covalent N–H···F interaction between the amide N–H of the porphyrinato and the F atoms of the fluoroaryl groups of a nitrene precursor stabilized the TS and accelerated the reaction. This unique nitrene precursor has recently also enabled enantioselective benzylic C–H amination of arylacetate, arylcrotonate and aryltetrolate esters[49].

In 2017, Zhang and colleagues reported that another chiral Co^{II} complex [Co(**P3**)] (FIG. 2a) promotes intramolecular aziridination of allyl azidoformates to afford fused aziridine/oxazolidinone bicycles[50]. Although the majority of the [3.1.0]-bicyclic aziridine products were not isolable owing to their low stability, in situ ring-opening reactions afforded enantioenriched oxazolidinones with high diastereoselectivity and enantioselectivity. A pair of disubstituted allyl azidoformates with opposite alkene stereochemistry ((*E*)-**1** and (*Z*)-**1**) afford the same *trans*-aziridine product (*E*)-**2** as a single diastereomer under the same conditions, supporting a stepwise radical mechanism (FIG. 2d).

The present Co^{II} catalysts have been used to synthesize 6-membered cyclic sulfamides[51] and 5-membered cyclic sulfonamides[52], as the Co^{III}–nitrene intermediates

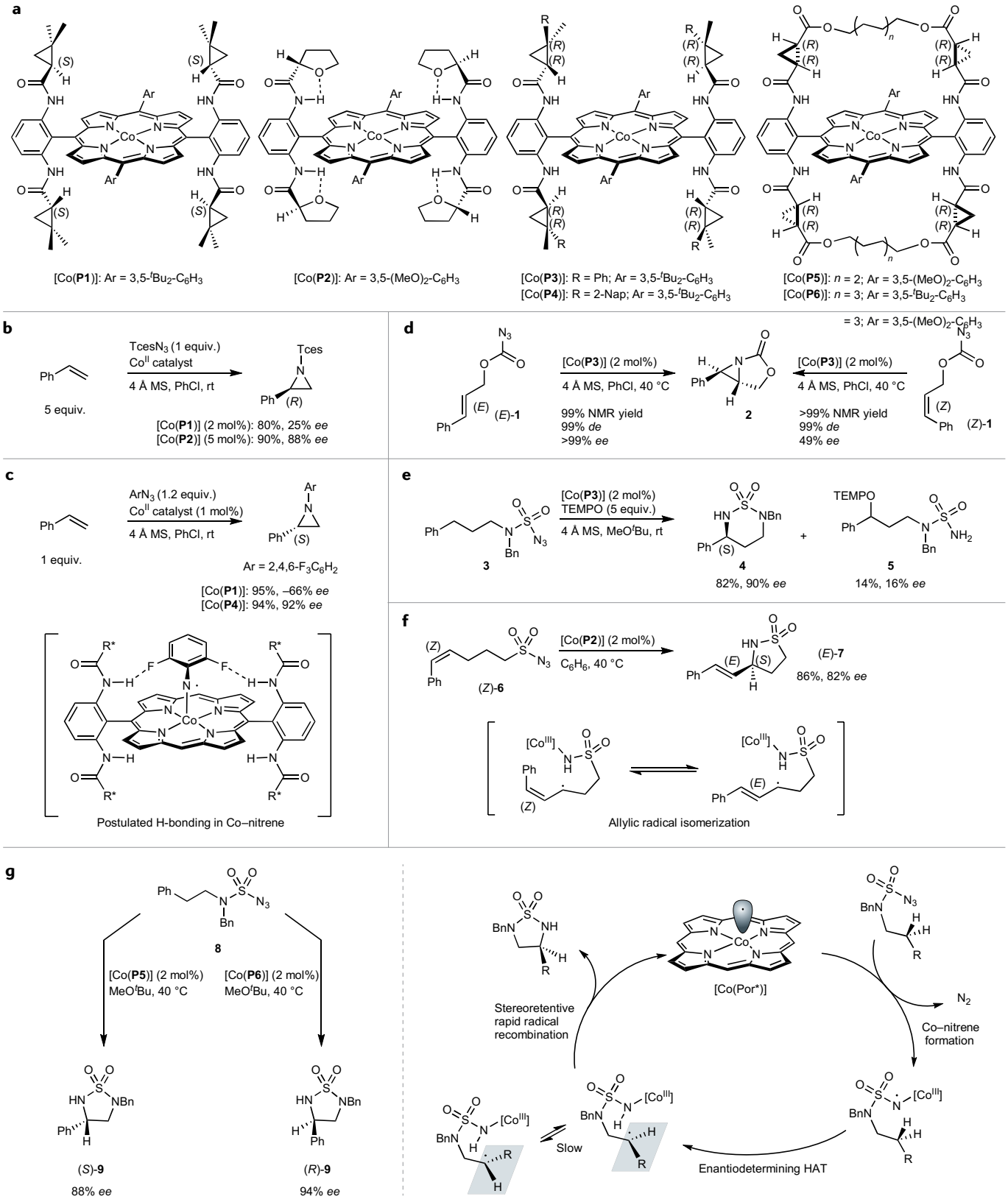
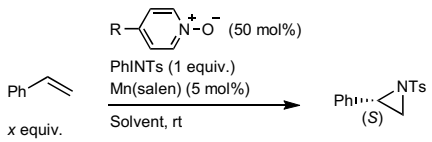


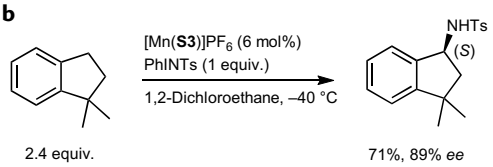
Fig. 2 | **Asymmetric nitrene transfer reactions catalysed by Co complexes of D_2-symmetric porphyrins. a** | Porphyrinatocobalt(II) catalysts with amide substituents offer coordination sites near chiral H-bond donors[43–46,49–55]. **b** | [Co(**P2**)] outperforms [Co(**P1**)] in asymmetric styrene aziridination with trichloroethoxysulfonyl azide ($TcesN_3$)[43]. **c** | Asymmetric styrene aziridination works even better when using 2,4,6-trifluorophenyl azide as the nitrene precursor[46]. **d–f** | Spectroscopic evidence suggests that the Co catalysts participate in stepwise nitrene transfer involving radical intermediates[50–52]. **g** | Co-catalysed aminations of reactive benzylic C–H bonds can be enantiodivergent in that a prochiral substrate can afford either enantiomer, depending on the catalyst used[54]. *de*, diastereomeric excess; *ee*, enantiomeric excess; HAT, H-atom transfer; rt, room temperature.

a



Mn(salen)	Solvent	R	*x*	yield	*ee*
[Mn(**S1**)]OAc	CH_3CN	H	10	9%	–61%
[Mn(**S2**)]OAc	CH_2Cl_2	Ph	39	76%	94%

b



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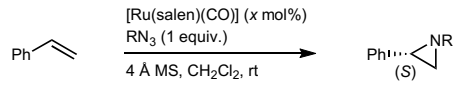
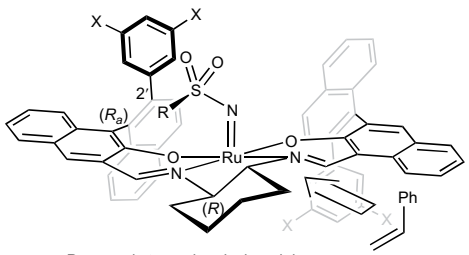


[Ru(salen)(CO)]	*x*	*y*	R	Yield	*ee*	TON
[Ru(**S4**)(CO)]	2	1.0	Ts	71%	87%	36
[Ru(**S5**)(CO)]	0.09	1.0	Ts	76%	94%	867
[Ru(**S5**)(CO)]	1	1.0	Ns	34%	84%	34
[Ru(**S6**)(CO)]	0.1	1.0	Ns	70%	81%	746*
[Ru(**S6**)(CO)]	0.1	1.0	SES	26%	91%	260*
[Ru(**S7**)(CO)]	0.1	1.2	SES	57%	90%	570

*Calculated according to ^{1}H NMR analysis.



Proposed stereochemical model for asymmetric induction

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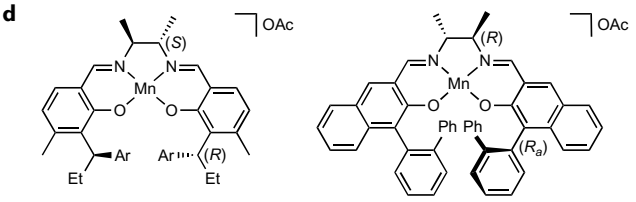

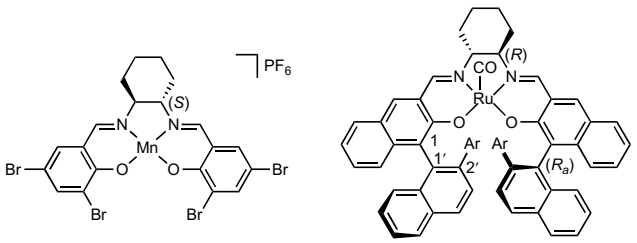

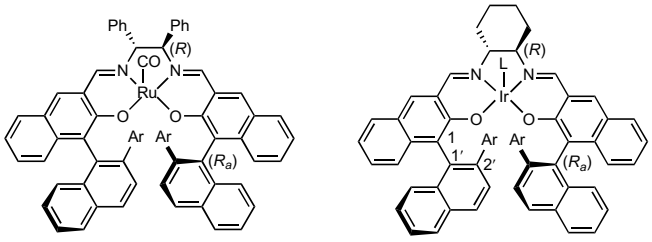

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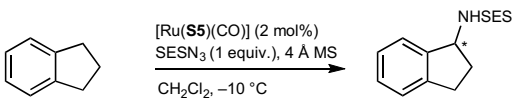

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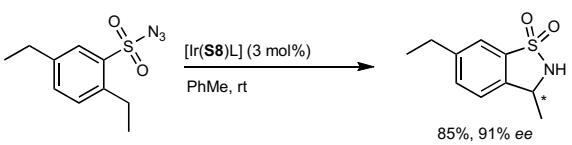

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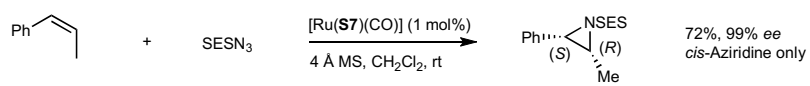

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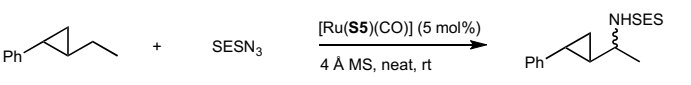

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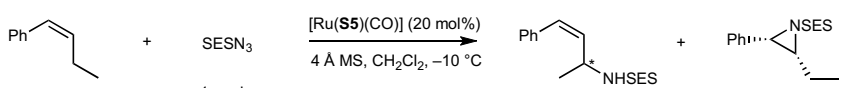


are also active for C–H amination. In the case of the cyclic sulfamides, [Co(**P3**)] again proved the most effective catalyst for the intramolecular C–H amination of sulfamoyl azides, leading to high yields and enantioselectivities with benzylic, allylic, propargylic and α/β-carbonyl C(sp^3)–H bonds[51]. Conducting the reaction in the presence of TEMPO (2,2,6,6-tetramethylpiperidinyloxy) also affords the adduct **5** (FIG. 2e), providing evidence that the amination involves radical intermediates. Taking advantage of these prochiral intermediates, this work

◀ Fig. 3 | **Metal–salen complexes catalyse asymmetric nitrene transfer. a** | Early Mn^{III} catalysts could mediate asymmetric styrene aziridination but required large excesses of styrene and a pyridine *N*-oxide additive[56,57]. **b** | Asymmetric Mn^{III}-catalysed allylic and benzylic C–H aminations with iminoiodinanes can proceed with up to 89% *ee* (REF.[58]). **c** | Ru^{II} catalysts improve on the early Mn^{III} systems to effect asymmetric aziridination with efficient stereochemical induction and without the need for excess styrene or additives[59–63]. **d** | A variety of salen^{2-} ligands can support Mn, Ru and Ir for asymmetric nitrene transfer (NT)[56–66]. **e** | Improved Ru^{II}-catalysed intermolecular asymmetric C–H amination[66]. **f** | An Ir catalyst mediates intramolecular benzylic C–H amination[65]. **g–i** | Mechanistic studies of asymmetric NT suggest that chiral [Ru(salen)CO] derivatives perform NT through a concerted pathway[63,66]. *ee*, enantiomeric excess; rt, room temperature; TON, turnover number.

was extended to enantioconvergent amination of racemic tertiary C–H bonds[53]. Arylsulfonyl and alkylsulfonyl azides are activated by the catalyst [Co(**P2**)] in benzylic, allylic and alkyl C–H bond aminations that give cyclic sulfonamides[52]. This catalyst has a more rigid conformation than earlier catalysts, and this is proposed to induce a high degree of asymmetric induction owing to intramolecular N–H···O H-bonding in the (*S*)-(−)-2-tetrahydrofurancarboxamide units. The presence of radical intermediates was further supported by an olefin isomerization study in which the allylic C–H bond amination of azide (*Z*)-**6** resulted in diastereoconvergent formation of sulfonamide (*E*)-**7** (FIG. 2f).

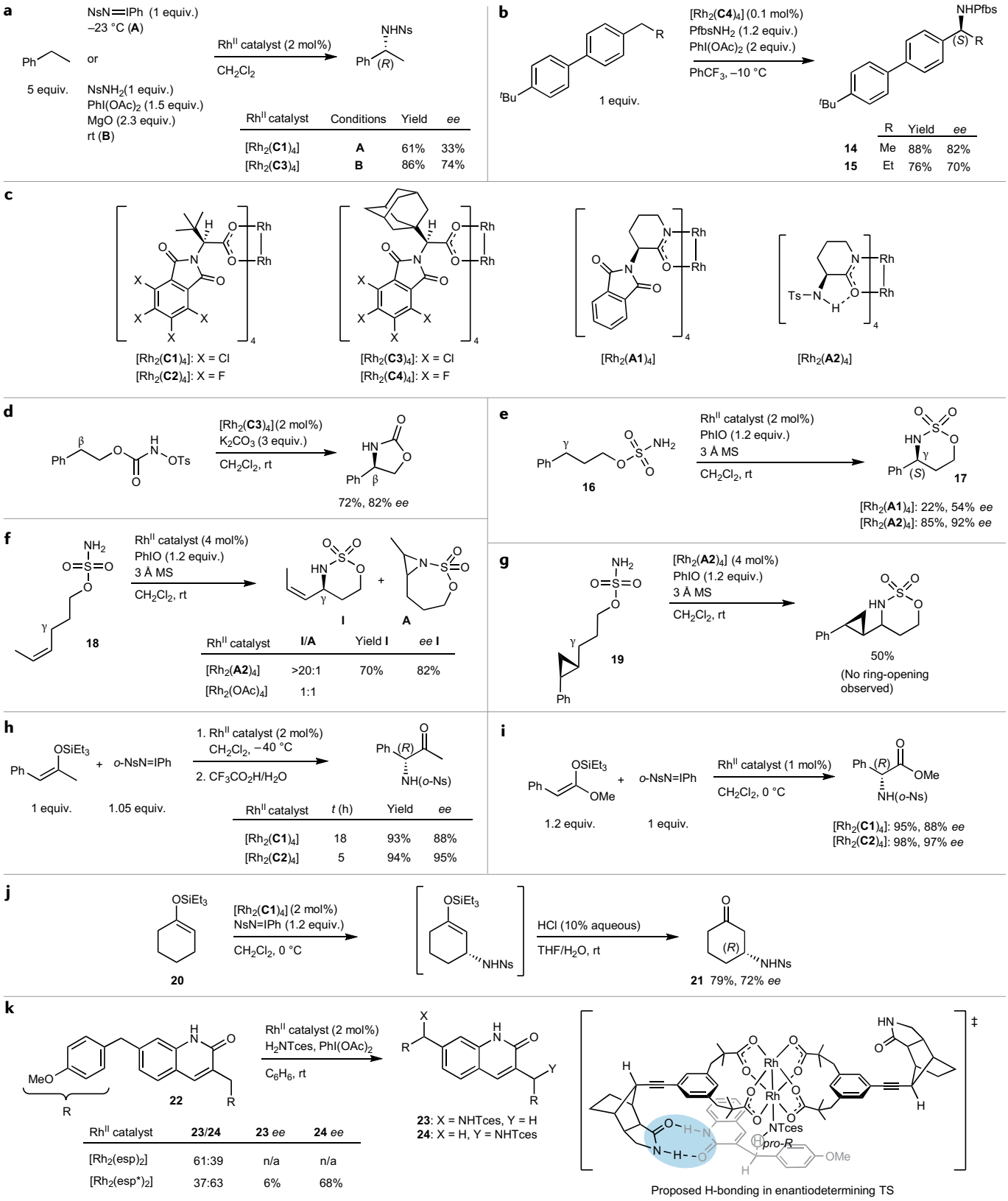
In 2019, the Zhang group further expanded the scope of intramolecular C–H amination to sulfamoyl azides containing β-C(sp^3)–H bonds using a new class of chiral Co^{II} complexes[54]. The 1,2-diamine motifs were synthesized with high enantioselectivity by employing D_2-symmetric chiral amidoporphyrins that contain alkyl bridges across two chiral amide units on both sides of the porphyrin plane (H_2**P5** and H_2**P6**)[55]. The two catalysts [Co(**P5**)] and [Co(**P6**)], which differ largely by two ethylene groups, convert prochiral precursor **8** into the two enantiomers (*S*)-**9** and (*R*)-**9**, respectively (FIG. 2g, left). This cavity effect was further exaggerated by using either 3,5-di(*tert*-butyl)phenyl or 2,6-dimethoxyphenyl groups as the 5,15-aryl substituents on the porphyrinato ligand. The observed enantiodivergence is remarkable given that only the distal alkyl bridges and the remote achiral substituents were changed, without altering the point chirality of the ligand. Density functional theory (DFT) calculations provided evidence for a sequence of enantiodetermining H-atom transfer and stereoretentive, radical recombination steps (FIG. 2g, right), as well as stereochemical models for the bridge-length-dependent H-atom transfer.

Point and axially chiral metal–salen complexes

Chiral ligands derived from H_2salen (2,2′-ethylenebis (nitrilomethylidene)diphenol) have been staples in asymmetric catalysis. In 1993, Katsuki and colleagues demonstrated that asymmetric induction in the intermolecular aziridination of styrene is possible using [Mn(**S1**)]OAc (FIG. 3d), which features a salen derivative (**S1**$^{2-}$) that is chiral on account of the 1,2-diamine backbone and a salicylaldehyde substituent[56]. In styrene aziridination with [*N*-(*p*-toluenesulfonyl) imino]-phenyliodinane (PhI=NTs) as the nitrene precursor, [Mn(**S1**)]OAc gave only a moderate 61% *ee*. The point chirality of the salicylaldehyde substituent can be replaced with planar chirality to give [Mn(**S2**)]OAc, a catalyst that affords 94% *ee* (REF.[57]) (FIG. 3a). Matching the planar and axial chiralities was crucial for efficient asymmetric induction — the *ee* dropped to 13% when the diastereomer of [Mn(**S2**)]OAc was used. Despite the impressive improvement in enantioselectivity, the further development of Mn^{III}(salen) catalysts for asymmetric aziridination was hindered by the requirement for a large excess of styrene substrate, narrow substrate scope and a lack of understanding of the role of pyridine *N*-oxide additives. Asymmetric allylic and benzylic C–H aminations of cyclic substrates proceed with up to 89% *ee* using a [Mn(**S3**)]PF_6 catalyst derived from (1*S*,2*S*)-*trans*-1,2-cyclohexanediamine and brominated salicylaldehyde[58] (FIG. 3b).

The catalytic efficiency and enantioselectivity of intermolecular olefin aziridination can be improved dramatically by using azides and a Ru^{II} catalyst to readily form Ru–nitrene intermediates[59–63] (FIG. 3c). Thus, one can minimize the olefin loading by moving from a Mn^{III}/iminoiodinane to a Ru^{II}/azide system. Zhang and colleagues also used azide precursors in their Co-catalysed NT methods development (mentioned in the previous section). Although *p*-toluenesulfonyl azide (TsN_3) resulted in good enantioselectivity, it gave only moderate catalytic turnover number (TON) when using the chiral catalyst [Ru(**S4**)(CO)], which bears a *trans*-1,2-diaminocyclohexane backbone with point chirality and two 2′-phenyl-1,1′-binaphthyl units with axial chirality[59]. Replacing the *meta*-H atoms of the Ph substituent with F atoms (and adding *para*-Me group for ease of synthesis) furnishes [Ru(**S5**)(CO)], a catalyst that improves the TON by 24×, while maintaining a similar *ee* (REF.[60]). The greater activity was thought to result from the F atoms protecting the ligand from the competing amination of *meta*-C–H bonds.

To increase the utility of asymmetric aziridination, Katsuki and Uchida studied the advantages of different types of azide precursors, including *p*-nitrophenylsulfonyl azide (NsN_3) and 2-(trimethylsilyl)ethanesulfonyl azide ($SESN_3$)[61], whose respective Ns-*N*-protecting and SES-*N*-protecting groups can be removed under mild or orthogonal conditions. However, these precursors are not interchangeable and must be paired with the appropriate Ru^{II} catalyst, limiting generalizability. For example, a [Ru(**S6**)(CO)] catalyst bearing 2′-Ar rings containing two *meta*-Cl groups and a *para*-$SiMe_3$ group is efficient for styrene aziridination with NsN_3 but gave a lower TON with $SESN_3$. The [Ru(**S6**)(CO)]/$SESN_3$ combination was later found to also be highly compatible with vinyl ketones[64]. By 2012, further catalyst tuning afforded [Ru(**S7**)(CO)], which features *meta*-CF_3 groups and converted a variety of monosubstituted and 1,2-disubstituted olefins into *N*-SES-protected aziridines with high TONs and synthetically useful *ee* values (generally ≥90%)[63]. A model based on the absolute stereochemistry of an aziridine product and the structure of prototypical catalyst [Ru(**S4**)(CO)], as determined by X-ray crystallography, was proposed[62] (FIG. 3c, bottom). According to the model, the olefin substrate approaches from the side of the imino group adjacent to the bottom naphthalene



ring of the **S4**$^{2-}$ ligand. The bulkiest substituent of the incoming alkene points up and away from the *N*-sulfonyl group to minimize steric repulsion, as the *N*-sulfonyl group is pushed to the front by the 2′-aryl substituent on the rear left side (drawn in bold). As a result, the (*S*)-aziridine product forms when Ru is supported by a (R,R_a)-salen^{2-} ligand.

The [Ru(**S5**)(CO)] catalyst described above, which was developed for olefin aziridination[65], can also effect intermolecular amination of benzylic and *cis*-allylic

Fig. 4 | **Dirhodium tetracarboxylates and tetracarboxamidates catalyse asymmetric nitrene transfer. a** | $Rh^{II}Rh^{II}$ tetracarboxylates mediate asymmetric C–H amination of acyclic benzylic C–H bonds[69,70]. **b** | An improved catalyst bearing more electron-poor ligands performs C–H amination even at very low loadings[72,73]. **c** | Aside from $Rh^{II}Rh^{II}$ complexes of chiral carboxylato ligands, those of carboxamidato ligands can also catalyse asymmetric nitrene transfer[65–72,74]. **d** | As with the intermolecular benzylic C–H aminations, $Rh^{II}Rh^{II}$ species can mediate intramolecular asymmetric reactions[71]. **e**,**f** | The carboxamidates are useful for asymmetric intramolecular C–H bond amination[79]. **g** | The cyclopropyl ring in a radical clock substrate would open were radical intermediates involved in the $Rh^{II}Rh^{II}$-catalysed C–H bond amination. The intact ring suggests that the reaction is concerted[79]. **h** | Asymmetric aziridination of silyl enol ethers affords ketones with chiral α-C centres in high *ee* (REF.[74,75]). **i** | The same reaction with silyl ketene acetals affords intact esters with chiral α-C centres[76]. **j** | Asymmetric allylic C–H bond amination of cyclic silyl enol ethers instead gives ketones with chiral β-C centres[77]. **k** | Intermolecular asymmetric benzylic C–H bond amination relies on H-bonding for enantioselectivity[83]. *ee*, enantiomeric excess; rt, room temperature; TS, transition state.

C–H bonds with high enantioselectivity using $SESN_3$. For example, indane is converted into a chiral derivative with high selectivity[66] (FIG. 3e). If, instead, intramolecular C–H amination of arylsulfonyl azides is desired, one can use the Ir^{III} complex [Ir(**S8**)(*p*-tolyl)] to accomplish efficient synthesis of benzosultams through regioselective and enantioselective benzylic C–H amination[64] (FIG. 3f).

Katsuki and Uchida have carried out several experiments to elucidate the behaviour of Ru(salen)–nitrene intermediates (FIG. 3g–i). Combining *cis*-β-methylstyrene and $SESN_3$ with catalyst [Ru(**S7**)(CO)] affords a *cis*-aziridine as a single diastereomer[63] (FIG. 3g). Examining the C–H amination of the radical clock **10** with [Ru(**S5**)(CO)] gave two diastereomeric amination products **11** in low yields with no ring-opened product detected[66] (FIG. 3h). Finally, a *cis*-β-ethylstyrene substrate affords both the C–H amination product **12** and the aziridination product **13**, with no experimental evidence of radical intermediates[66] (FIG. 3i). These results suggest that Ru(salen) catalysts perform NT through a concerted mechanism, although the existence of short-lived radical species cannot be completely ruled out.

Dirhodium catalysts

In the late 1990s, Müller and colleagues reported the first examples of asymmetric induction in intermolecular aziridination[67] and C–H amination[68] using an iminoiodinane precursor and a $Rh^{II}Rh^{II}$ catalyst featuring an axially chiral binaphthyl phosphate ligand. This ligand type was soon replaced by optically active carboxylato and carboxamidato ligands (FIG. 4c), which are more modular[69–79]. In 2003, Hashimoto and colleagues described the dirhodium tetracarboxylate $[Rh_2(\mathbf{C1})_4]$ as part of a general protocol for the intermolecular amination of cyclic benzylic C–H bonds with NsN=IPh in moderate *ee* (70–84%)[69]. The $[Rh_2(\mathbf{C1})_4]$ catalyst performed substantially better than its unchlorinated analogue and was later used in desymmetrization of adamantane derivatives[70]. Reddy and Davies improved this catalyst by replacing each ^{t}Bu group with a 1-adamantyl to give $[Rh_2(\mathbf{C3})_4]$, a more general catalyst that tolerates acyclic benzylic C–H bonds[71] (FIG. 4a). More recently, Dauban's group further optimized the chemistry by developing $[Rh_2(\mathbf{C4})_4]$, the fluorinated analogue of $[Rh_2(\mathbf{C3})_4]$, which operates on in situ-generated PfbsN=IPh (Pfbs = pentafluorobenzylsulfonyl) as a nitrene precursor[72,73] (FIG. 4b). This practical Rh-catalysed C–H amination reaction needs only low catalyst loadings, obviates the need for excess substrate, can be carried out on a gram scale and has great potential in process chemistry. The benzylic C–H amination tolerates a wide variety of both electron-withdrawing and electron-donating aryl substituents on ethyl arenes, although the *ee* erodes when the aryl side chain is longer than Et. The benzylic amination product **14** was obtained in 88% yield and 82% *ee* on a multi-gram scale, while **15** was obtained in 70% *ee*. In addition, the Pfbs protecting group can be readily removed by treating the products with pyridine in $MeCN/H_2O$ to afford the free amines in quantitative yield.

In a series of intramolecular C–H aminations, Reddy and Davies demonstrated that optically active oxazolidinones (β-amino alcohol motifs) can be generated in moderate *ee* (43–82%) using $[Rh_2(\mathbf{C3})_4]$ as the catalyst[71] (FIG. 4d). Lebel et al.'s method to generate Rh–nitrene intermediates from *N*-tosyloxycarbamates[80] was used to selectively activate one of the two prochiral benzylic, aliphatic and allylic β-C(sp^3)–H bonds, albeit with limited substrate scope. In contrast, the synthesis of enantioenriched γ-amino alcohol motifs by Rh-catalysed NT required a new valerolactam-derived dinuclear Rh catalyst to achieve a high level of asymmetric control in the cyclization of sulfamate esters[79]. Zalatan and Du Bois showed that the previously used dirhodium tetracarboxylates derived from α-amino acids gave poor asymmetric induction (0–20% *ee*). A decrease in *ee* over the course of the reaction indicated that catalyst degradation may be the major reason for low enantioselectivity. Thus, more electron-donating carboxamidato ligands were evaluated to enhance backbonding of the Rh centres to the π-acidic nitrene ligand, thereby stabilizing the Rh–nitrene intermediate. Indeed, a valerolactam-derived $[Rh_2(\mathbf{A1})_4]$ catalyst showed a promising *ee* of 54% when tested with sulfamate ester **16**, which has benzylic γ-C(sp^3)–H bonds (FIG. 4e). Replacing the phthalimidyl group in the catalyst with a secondary sulfonamide enables intramolecular H-bonding between the N–H group and the carbonyl oxygen in $[Rh_2(\mathbf{A2})_4]$, further enhancing catalyst stability and giving oxathiazinane **17** in 85% yield and 92% *ee*. The catalyst could induce good-to-excellent enantioselectivity (>80% *ee*) on 3-aryl-substituted propyl and *cis*-homoallyl sulfamate esters. The improved oxidative stability of $[Rh_2(\mathbf{A2})_4]$ relative to $[Rh_2(\mathbf{A1})_4]$ is evidenced by the respective $Rh^{II}Rh^{III/II}$ redox potentials (330 and 120 mV versus saturated calomel electrode).

There is often more than one reactive site in a substrate, so chemoselectivity and regioselectivity are important considerations in the development of asymmetric NT methodologies. For example, a $[Rh_2(\mathbf{A2})_4]$ catalyst heavily favours C–H insertion over aziridination when both a reactive C–H bond and a C=C bond are present in a substrate such as **18** (REF.[79]) (FIG. 4f). Although *trans* and terminal olefins did not perform as well as *cis* olefins in terms of asymmetric induction, the allylic C–H amination versus C=C aziridination (**I**/**A**) ratios were still >20:1. This remarkable chemoselectivity, as compared with a generic $Rh^{II}Rh^{II}$ NT catalyst such as $[Rh_2(OAc)_4]$, raised the question as to whether the

mechanism of NT changes from the concerted asynchronous pathway generally accepted for dirhodium tetracarboxylates to a stepwise pathway. However, subjecting a radical clock substrate **19** to the reaction conditions gave no ring-opened products, suggesting that a stepwise NT pathway is likely not operative (FIG. 4g).

In an extension of their previous work, Hashimoto and colleagues discovered that enantioenriched α-amino ketones can be synthesized from silyl enol ethers by enantioselective aziridination followed by ring-opening[74,75]. The best enantioselectivity and reaction rate came when using *o*-NsN=IPh in combination with $[Rh_2(\mathbf{C2})_4]$, the fluorinated analogue of $[Rh_2(\mathbf{C1})_4]$ (FIG. 4h). The utility of this Rh-catalysed NT protocol was further demonstrated by an asymmetric formal synthesis of (−)-metazocine[74] and a total synthesis of (−)-ritodrine[75] from an easily accessible α,β-unsaturated enone. The chemistry was also applied to silyl ketene acetals derived from methyl phenylacetates to provide phenyl glycine derivatives in high yields and excellent *ee* (REF.[76]) (FIG. 4i). Interestingly, when cyclic silyl enol ether **20** was subjected to the same conditions, desilylation afforded only β-amino ketone **21** — no trace of the expected α-amino ketone was observed[77] (FIG. 4j). This result suggests that cyclic silyl enol ethers prefer to undergo allylic C–H amination instead of C=C aziridination, which is partially due to the low reactivity of (*E*)-silyl enol ethers towards aziridination. The β-amino ketone **21** was then carried forward to achieve an asymmetric formal synthesis of (−)-pancracine.

In 2013, Bach and colleagues showed that introducing a chiral octahydro-1*H*-4,7-methanoisoindol-1-one skeleton into a known $[Rh_2(esp)_2]$ (esp^{2-} = α,α,α′,α′-tetramethyl-1,3-benzenedipropionato) NT catalyst[81,82] can enable regioselectivity and enantioselectivity in intermolecular benzylic C–H bond amination of 3-benzylquinolones[83] (FIG. 4k). The chiral portion of the new $[Rh_2(esp^*)_2]$ catalyst can engage in two-point H-bonding with substrates containing an adjacent H-bond acceptor and donor[84–86]. This substrate binding is consistent with the observed regiocontrol and enantiocontrol in substrate **22**. The C_2-symmetric Rh catalyst was also used for the asymmetric conversion of 3-alkenylquinolones into 2,3-dihydrofuro[2,3-*b*]quinolines through a cascade aziridination and intramolecular ring-opening[87]. This strategy to tether the chiral octahydro-1*H*-4,7-methanoisoindol-1-one unit to a known NT catalyst for asymmetric induction through H-bonding was again demonstrated with the heteroleptic complex $[Ag^{I}LL']^+$, which features one achiral 1,10-phenanthroline derivative and a similar chiral ligand with a H-bonding donor. The complex efficiently catalysed site-selective and enantioselective C–H amination of CH_2 groups in 2-quinolones and 2-pyridones[88]. As with $[Rh_2(esp^*)_2]$, the reaction outcome was rationalized by nitrene C–H insertion occurring within a chiral H-bonded metal complex that targets only one of two prochiral methylene C–H bonds in both a site-selective and an enantioselective manner.

In terms of catalysts for asymmetric NT, the tetracarboxylate paddle-wheel architecture has been predominantly associated with $Rh^{II}Rh^{II}$ species. Although Du Bois and colleagues have shown that achiral $Ru^{II}Ru^{III}$ tetracarboxylates and tetraamidates are highly efficient in NT owing to their high $1e^-$ oxidation potentials[25], chiral analogues have not been realized until very recently. Matsunaga and colleagues showed that mixed-valent paddle-wheel salts $[Ru_2((S\text{-BPTPI})_4)]BAr^F{}_4$ (BPTPI$^-$ is a 3-(benzene-fused-phthalimido)-2-piperidinonate; $BAr^F{}_4{}^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) and $[Ru_2(\mathbf{C1})_4]BAr^F{}_4$ can aminate benzylic and *cis*-allylic C–H bonds in good yields and enantioselectivity (91–95% *ee*)[78], similar to the Rh system that Du Bois and colleagues described previously. Indeed, cyclic voltammetry indicates that the two $Ru^{II}Ru^{III}$ catalysts are more resistant to oxidation than their $Rh^{II}Rh^{II}$ analogues.

Metal BOX complexes in asymmetric NT

C_2-symmetric BOX ligands are among the most widely used chiral ligands in metal-catalysed asymmetric synthesis because of their ease of synthesis, modularity and demonstrated ability to induce high levels of enantioselectivity in diverse transformations[89]. Since the early examples of Cu^{I}(BOX)-catalysed enantioselective aziridinations reported by Evans et al.[90,91] and Lowenthal and Masamune[92], several BOX-supported metal complexes have been developed and used as efficient asymmetric NT catalysts[93–103]. In 2007, Dauban and colleagues reported that $[Cu(CH_3CN)_4]PF_6$ combines with the 2,2′-isopropylidene-bis[(4*S*)-4-*tert*-butyl-2-oxazoline] ((*S*,*S*)-^{t}Bu-BOX) ligand to form an active catalyst for enantioselective intramolecular aziridination of homoallylic sulfamate esters with up to 84% *ee* (REF.[94]). This first example of asymmetric synthesis of bicycloaziridines using intramolecular NT was unfortunately limited to 1,2-disubstituted alkenes for good enantioinduction. In 2017, the scope and efficiency of intramolecular aziridinations was further improved by Schomaker and colleagues by using a $AgClO_4$/(*S*,*S*)-^{t}Bu-BOX catalyst to operate on carbamate ester substrates. The system tolerated both 1,2-disubstituted and 1,2,2-trisubstituted alkenes to generate [3,6]-carbamate-tethered bicyclic aziridine **28** in good yield and with *ee* up to 92%[96] (FIG. 5a). Interestingly, X-ray crystallography showed that the absolute configuration of the asymmetric centres formed using the Ag^{I} catalyst was inverted relative to the product using Dauban and colleagues' Cu^{I} complex, despite both group 10 metals being coordinated to (*S*,*S*)-*t*-Bu-BOX. This result implies a significant geometric difference in the enantiodetermining TS between the two catalysts.

Further development of the Ag^{I}(BOX) system by Schomaker and colleagues enabled intramolecular asymmetric amination of propargylic C–H bonds with up to 99% *ee* (REF.[97]) (FIG. 5b). This was inspired by earlier work demonstrating that Ag^{I} supported by an achiral BOX ligand can effect efficient intramolecular γ-C–H amination of carbamate esters[104]. Taking advantage of the modularity of the BOX scaffold, a new Min-BOX ligand was designed according to a structure–activity relationship analysis of BOX ligand derivatives and the enantioselectivities of the respective Ag^{I} catalysts for carbamate ester substrates bearing γ-alkynyl groups. Although many aryl-substituted BOX ligands are known

for asymmetric catalysis, the Min-BOX ligand uniquely features a fully substituted stereocentre adjacent to the coordinating N atom and bulky *meta*-^{t}Bu groups on the aryl ring. The fully substituted C centre, where H is substituted with a Me group, is particularly interesting, as it might be expected to reduce facial discrimination in the enantiodetermining TS. Schomaker and colleagues also demonstrated that the size of the alkyne substituent

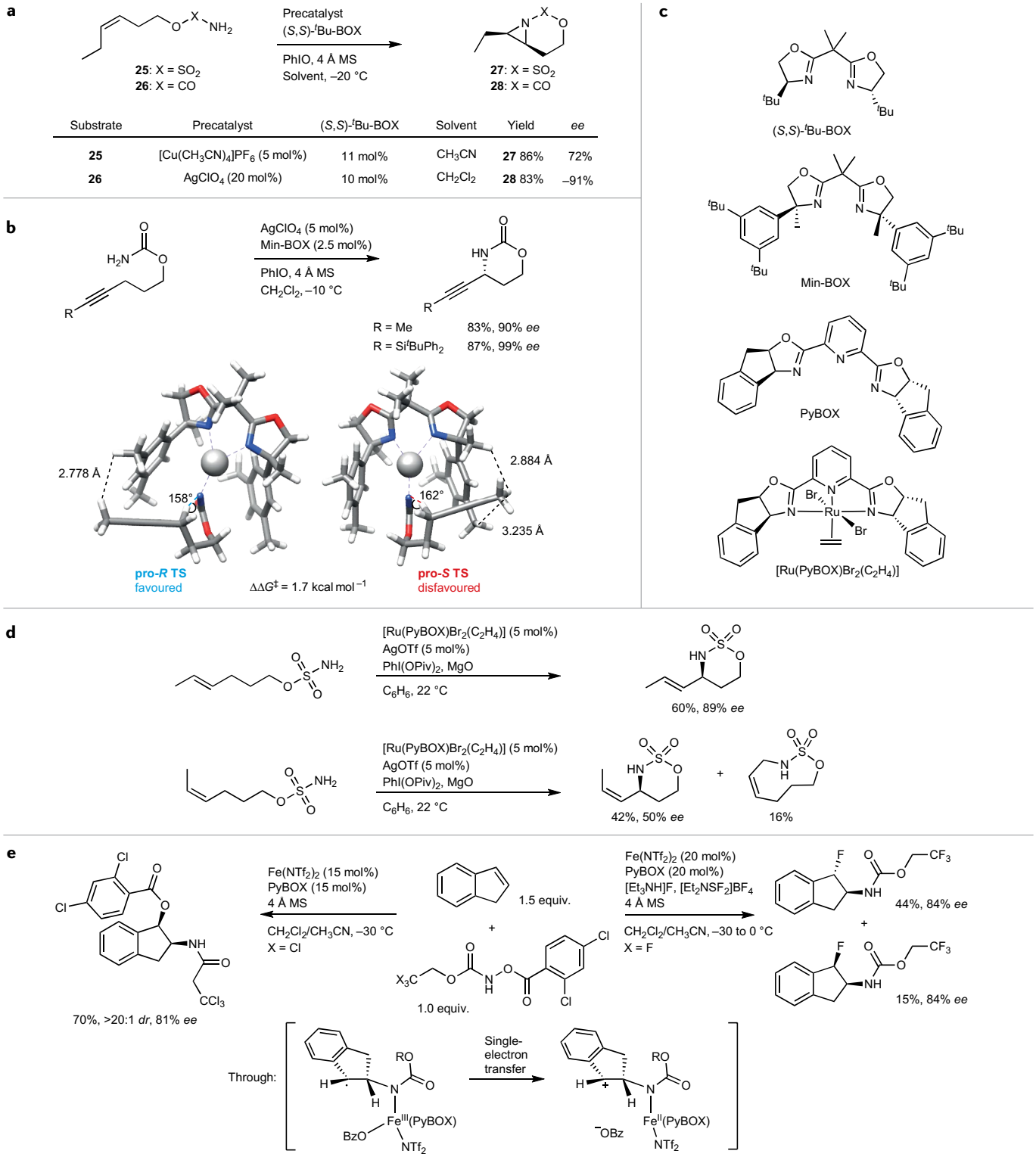


Fig. 5 | **Metal complexes of bis(oxazoline) ligands catalyse asymmetric nitrene transfer. a** | Cu^I and Ag^I derivatives catalyse asymmetric intramolecular aziridination[94,96]. **b** | Ag^I-catalysed propargylic C–H bond amination proceeds with good yields and *ee* (REF.[97]). **c** | Bis(oxazoline) (BOX) and 2,6-bis(oxazolin-2-yl)pyridine (PyBOX) ligands with substituted oxazoline rings can be chiral. **d** | The Ru^{II} precatalyst [Ru(PyBOX)Br$_2$(C$_2$H$_4$)] enables asymmetric intramolecular C–H bond amination[95]. **e** | The PyBOX ligand can also support Fe^{II} to realize alkene aminofunctionalization[100,101]. *dr*, diastereomeric ratio; *ee*, enantiomeric excess; TS, transition state. Part **b** adapted with permission from REF.[97], ACS.

correlates with enantioselectivity by establishing a linear free-energy relationship using the modified Taft equation and Charton's steric parameters[105–109]. As predicted from the relationship, an alkyne substituted with a bulky Si^{t}BuPh$_2$ group resulted in the highest 99% *ee*, while an alkyne with Me afforded lower 90% *ee* (FIG. 5b). DFT calculations were conducted to investigate the effects of Min-BOX's fully substituted C centres located α to the coordinating N atoms and the *meta*-alkyl substitution of the aryl ring on enantiodetermining H-atom transfer[110–113]. The TS leading to the (*R*) configuration of the C–H amination product was favoured by 1.7 kcal mol^{-1} over the structure leading to the (*S*) product. This minimizes steric strain between the alkyne, the fully substituted C centre and the aryl substituents, in accordance with experimental observations.

Derivatives of the 2,6-bis(oxazolin-2-yl)pyridine (PyBOX) ligand have been successfully used in asymmetric NT reactions in combination with Ru and Fe salts. The larger binding site offered by the rigid terdentate PyBOX ligand supports a Ru^{II} centre in the isolable octahedral complex [Ru(PyBOX)Br$_2$(C$_2$H$_4$)][114]. Blakey and colleagues demonstrated that a cationic variant of this complex, generated by abstraction of one Br$^-$ with AgO$_3$SCF$_3$, effectively catalyses intramolecular C–H amination of sulfamate ester substrates containing benzylic or *trans*-allylic C–H bonds[95] (FIG. 5d). Intriguingly, substrates with *cis*-allylic C–H bonds led to decreased enantioselectivity and macrocyclization side products. Although the side reaction explains the diminished yield of the C–H amination product, the observed low enantioselectivity calls for further investigation of the features that control the enantiodetermining step. More recently, Xu and colleagues reported that the same PyBOX ligand effectively supports a Fe^{II} centre to enable enantioselective intermolecular aminooxygenation[101] and aminofluorination[100] of indene (FIG. 5e). Control experiments suggest the presence of a C-centred radical intermediate generated through radical addition of a putative Fe–nitrene. This mechanism differs from the classical aziridination–ring-opening pathway because the radical intermediate is proposed to be oxidized by the resulting high-valent Fe^{III} intermediate through single-electron transfer to generate a carbocation, which subsequently combines with either BzO$^-$ or F$^-$. The same catalytic system was also used to achieve enantioselective intramolecular indole aminooxygenation of indoles in the absence of an additional nucleophile (74–99% *ee*)[98] and intramolecular olefin aminochlorination in the presence of ^{n}Bu$_4$NCl as a Cl$^-$ source (54–91% *ee*)[99].

Emergence of new catalyst scaffolds

As we noted above, recent advances in enantioselective C–N bond formation involve new catalyst scaffolds distinct from the traditional metal complexes discovered during the early development of asymmetric NT. These newer catalysts include half-sandwich complexes bearing a polyhapto ligand bound to a metal centre, chiral-at-metal complexes and a Rh catalyst supported by a chiral diene[115]. Among these paradigms, the half-sandwich and chiral-at-metal complexes are the most promising next-generation catalysts for enantioselective NT because they tolerate a wide variety of substrates and multiple metal centres.

Half-sandwich complexes and dioxazolone precursors. In contrast to previous NT systems that use azides and sulfamate/carbamate-derived iminoiodinanes as nitrene sources, the half-sandwich catalysts (FIG. 6) are exclusively compatible with 3-substituted 1,2,4-dioxazol-5-ones. These precursors lose CO_2 to give acyl nitrene intermediates, which can participate in NT but are also typically prone to undergoing Curtius rearrangement. Thus, one of the challenges with these systems is curbing this rearrangement reaction that produces isocyanate by-products. Chang and colleagues first demonstrated that the Curtius rearrangement is effectively suppressed by using metal complexes of electron-donating monoanionic LX-type ligands for racemic amidations[116]. The same team later found that switching to an enantioenriched amine–amido ligand to give [Ir(**H1**)] (FIG. 6c) still suppressed this side reaction and gave excellent *ee* in intramolecular C–H amidation[34] (FIG. 6a, left). Notably, the generation of a cationic, coordinatively unsaturated Ir centre through Cl$^-$ abstraction (addition of NaBAr$^F_4$ precipitates NaCl) is crucial to enabling formation of the Ir–nitrene intermediate that leads to the desired C–H amidation. Only the isocyanate side product is obtained when NaBAr$^F_4$ is not added. The authors hypothesized that intramolecular H-bonding between substrate and catalyst is crucial in stabilizing the desired diastereomeric adduct in which the Ph group is in an equatorial position in the half-chair TS, with the (*S*)-configuration at the metal centre (FIG. 6a, right). The effect of noncovalent interactions in providing high enantioinduction was supported by DFT calculations, characterization of a structural analogue Ir–amido and examination of catalysts with modified H-bonding strength.

Subsequent to Chang and colleagues' report, the groups of Yu and Chen independently reported analogous transformations using a Ru half-sandwich [Ru(**H2**)][33] or a modified Ir complex [Ir(**H3**)][117] with enhanced catalytic efficiency, respectively. Finally, Yoshino, Matsunaga and colleagues reported the enantioselective C(sp^3)–H amination of thioamides catalysed by a hybrid Co^{III} complex [Co(**H5**)]/chiral carboxylic acid (CCA) system[118] (FIG. 6d). A similar thioamide desymmetrization reaction, albeit with lower enantioselectivity, was realized when CCA was replaced with not a mono-protected α-amino acid but a 2-aryl ferrocene carboxylic acid[119]. Shi and colleagues also constructed a planar-chiral system by enantioselective amidation of ferrocenes using a combination of [Co(**H5**)] and mono-protected α-amino acid[120]. The metal–CCA hybrid system was later applied in (Cp*)Rh-catalysed asymmetric C–H amidation of 8-alkylquinolines[121]. Although the new strategy of combining an achiral half-sandwich metal complex with a CCA promises a general and modular catalyst for asymmetric NT, the CCAs used in the previous methods were structurally quite distinct from each other and the origin of enantioinduction was not always clearly rationalized.

In 2020, Blakey, Baik and colleagues tackled one of the long-standing challenges in asymmetric NT chemistry:

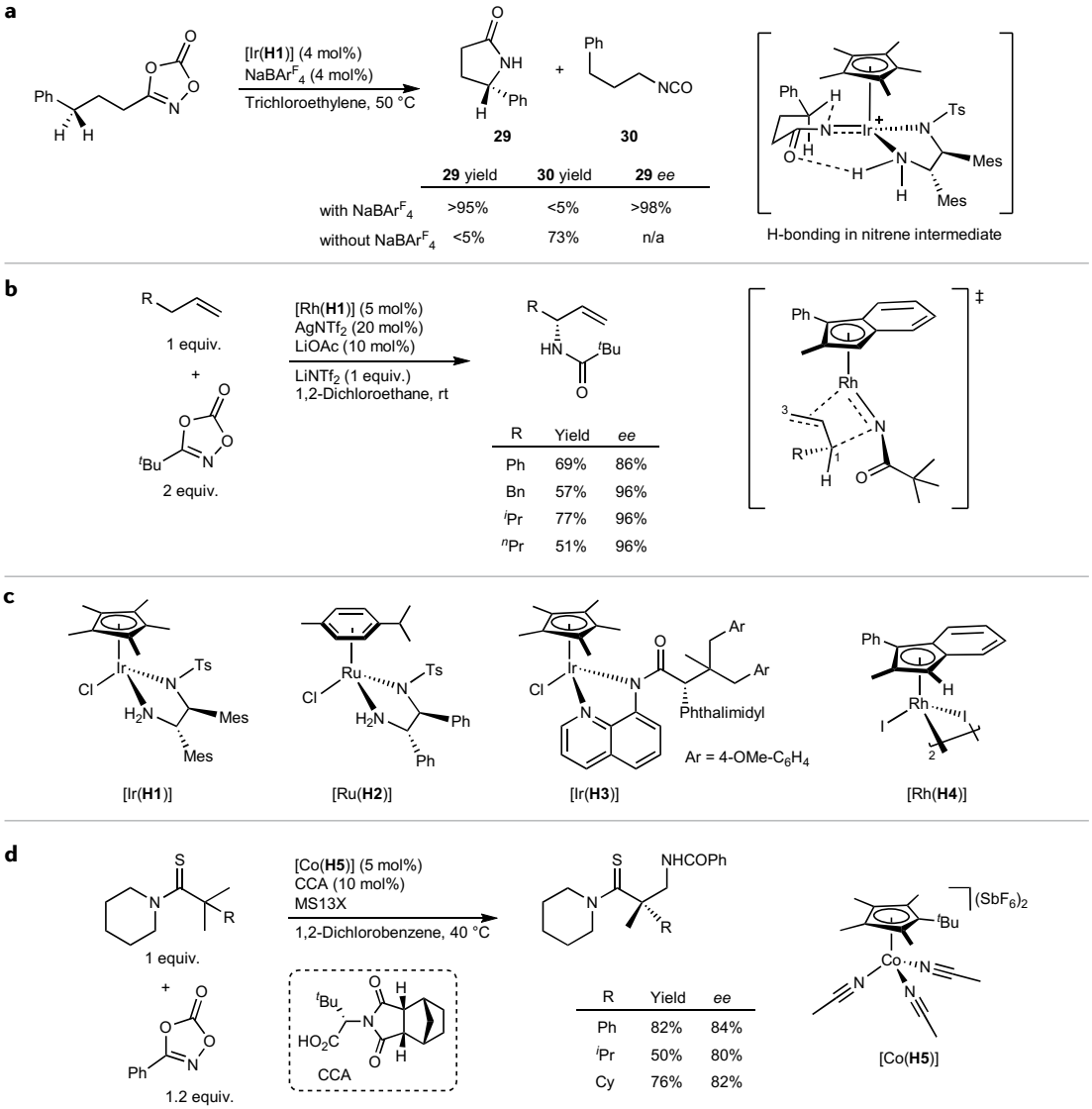


Fig. 6 | **Chiral half-sandwich complexes for asymmetric nitrene transfer. a** | A chiral Ir^{III} half-sandwich complex catalyses asymmetric intramolecular C–H bond aminations[34]. **b** | A related Rh^{III} catalyst effects enantioselective intermolecular allylic C–H bond amination[122]. **c** | Precious metal half-sandwich catalysts for enantioselective C–H bond amination typically feature a hydrocarbon $6e^-$ donor ligand and anionic co-ligands[33,34,117,122]. **d** | A Co^{III} half-sandwich complex can perform enantioselective (albeit intramolecular) amination of an unactivated C–H bond[118]. CCA, chiral carboxylic acid; *ee*, enantiomeric excess; rt, room temperature.

achieving highly chemoselective, regioselective and enantioselective intermolecular allylic C–H amidation[122]. The development of a novel planar-chiral Rh^{III} indenyl complex [Rh(**H4**)] using dioxazolone precursors enabled the selective introduction of an amide group at the allylic C–H bond of a terminal olefin (FIG. 6b). The experimental results, combined with a thorough DFT investigation, suggested that the catalytic cycle forms a (Cp*) Rh^{II}–π-allyl intermediate in the rate-determining and enantiodetermining C–H cleavage step. The dioxazolone then binds at the vacant coordination site, followed by loss of CO_2 to furnish an imido complex, which undergoes the regiodetermining reductive C–N coupling to selectively produce the terminal over the internal olefin. DFT calculations predicted a large kinetic barrier difference (5.0 kcal mol^{-1}) between the two TSs that lead to the two possible C–N coupled products. This energy difference was attributed to the asymmetric character of the indenyl ligand forming a weaker allylic Rh–C bond with C1, which is more easily attacked by the N atom than C3. Owing to the presence of the Rh–π-allyl intermediate, internal olefin substrates that generate a symmetrical π-allyl complex during NT are well tolerated. In contrast, an unsymmetrical 1,2-disubstituted internal styrenyl substrate required a sterically demanding *tert*-butyl dioxazolone nitrene precursor to maintain good regioselectivity to the conjugated amide product, at the expense of yield (23%).

Chiral-at-metal catalysts. The catalysts for enantioselective NT that we have described so far all include chiral ligands coordinated to metal(s). Meggers and colleagues

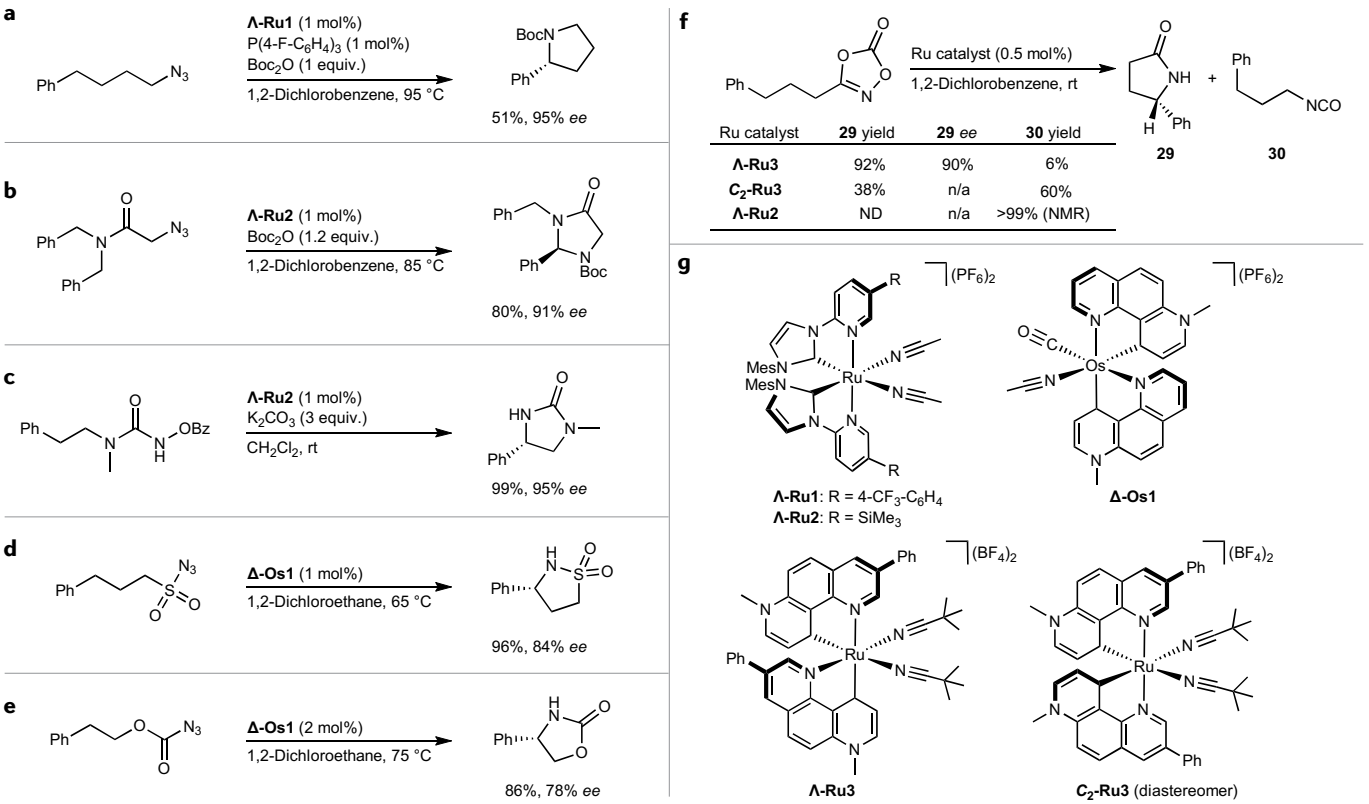


Fig. 7 | **Chiral-at-metal complexes in asymmetric nitrene transfer. a** | Intramolecular Ru^{II}-catalysed asymmetric benzylic C–H aminations furnish pyrrolidines[126]. **b** | A related catalyst performs the reaction to afford 2-imidazolidinones[127]. **c** | Ring-closing can also occur with urea derivatives to give 4-imidazolidinones[128]. **d** | If a sulfonyl azide is the nitrene source, an intramolecular reaction gives γ-sultams. **e** | The analogous reaction with carbonazidic esters gives 2-oxazolidinones[129]. **f** | Dioxazolones are classic nitrene sources that extrude CO_2 and cyclize to give γ-lactams[35]. **g** | Typical chiral-at-metal complexes for enantioselective C–H bond amination feature two bidentate and two monodentate ligands. *ee*, enantiomeric excess; rt, room temperature.

recently introduced a new class of chiral-at-metal catalysts (FIG. 7) that do not feature chiral ligands. These catalysts typically consist of achiral *N*-heterocyclic carbene and pyridine-derived ligands that support a stereogenic metal centre in a Λ or Δ absolute configuration[123–125]. This design is presently limited to catalysts having two non-symmetrical bidentate and two monodentate ligands coordinated to a metal. Despite this lack of structural diversity, the design may provide unique opportunities to develop structurally and electronically distinctive chiral transition metal catalysts.

Applying the chiral-at-metal design strategy, Ru and Os catalysts induce enantioselectivity in a variety of intramolecular benzylic C–H aminations, including the syntheses of pyrrolidines (76–99% *ee*)[126] (FIG. 7a), 2-imidazolidinones (up to 91% *ee*)[127] (FIG. 7b), 4-imidazolidinones (up to 95% *ee*)[128] (FIG. 7c), γ-sultams (76–84% *ee*; FIG. 7d) and 2-oxazolidinones (76–84% *ee*)[129] (FIG. 7e). Furthermore, a highly efficient **Λ-Ru3** catalyst was used to synthesize γ-lactams by mainly targeting benzylic and propargylic C–H bonds (70–99% yields) with high *ee* (80–90%)[35]. 1,4,2-Dioxazol-5-ones were employed as nitrene precursors to afford optically active γ-lactams through intramolecular C–N bond formation (FIG. 7f). Interestingly, the relative stereochemistry at the metal centre is key in suppressing the undesired Curtis rearrangement from the acylnitrene intermediate. A non-C_2-symmetric chiral-at-Ru catalyst **Λ-Ru3** generated the γ-lactam **29** in 92% yield and 90% *ee*. Instead, using the C_2-symmetric diastereomer **C_2-Ru3** gives isocyanate **30** as the major product. The C_2-symmetric catalyst **Λ-Ru2**, used in the enantioselective syntheses of 2-imidazolidinones[127] and 4-imidazolidinones[128], also favoured the Curtius rearrangement pathway exclusively. The authors attributed this to the non-C_2-symmetric arrangement of the strongly electron-donating remote *N*-heterocyclic carbene ligands, which resulted in a more nucleophilic Ru–nitrene intermediate that favours C–H amination over the Curtius rearrangement. This hypothesis was supported by DFT calculations, with Hirshfeld charge analysis showing increased nucleophilicity of the nitrene fragment from the non-C_2-symmetric **Λ-Ru1** catalyst.

Conclusions

Asymmetric NT reactions are a powerful means to generate valuable N-containing products from simple starting materials. Although substantial progress has been made in selected enantioselective NT reactions over the past 30 years, this Review describes both traditional and relatively undeveloped catalyst designs that have emerged. Future directions and challenges to

be addressed for asymmetric NT include: avoiding the use of precious metals (Rh, Ir and Ru), realizing intermolecular aziridination of densely substituted olefins, promoting intermolecular asymmetric amination of allylic, propargylic and aliphatic C–H bonds and developing more robust intramolecular C–H aminations to furnish valuable β-amino and γ-amino alcohols. Moreover, the direct generation of unprotected aziridines and amines through safe and environmentally friendly external oxidants is desirable from a practical point of view. Two other important goals for future catalyst development include obtaining excellent chemoselectivity and regioselectivity when there is more than one reactive site present in the substrate, as well as having a modular and generalizable chiral catalyst to achieve synthetically useful enantioselectivities (>90% *ee*). Steric and electronic modularity of new ligand scaffolds will be particularly important to expand the scope of asymmetric NT chemistry. The examples described in this Review suggest that both the electronic features of the metal–nitrene fragment and a highly ordered enantiodetermining TS are crucial in achieving high reaction efficiency and selectivity. Although there are problems to be solved in the area of asymmetric NT, the recent emergence of new catalyst platforms and the re-evaluation of traditional catalysts will stimulate further developments towards more practical and generally applicable synthetic methodologies.

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1. Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences* (Wiley, 2008).
2. Nugent, T. C. (ed.) *Chiral Amine Synthesis: Methods, Developments and Applications* (Wiley, 2010).
3. Kwart, H. & Kahn, A. A. Copper-catalyzed decomposition of benzenesulfonyl azide in hydroxylic media. *J. Am. Chem. Soc.* **89**, 1950–1951 (1967).
4. Kwart, H. & Khan, A. A. Copper-catalyzed decomposition of benzenesulfonyl azide in cyclohexene solution. *J. Am. Chem. Soc.* **89**, 1951–1953 (1967).
5. Dodd, R. H. & Dauban, P. Iminoiodanes and C–N bond formation in organic synthesis. *Synlett* **11**, 1571–1586 (2003).
6. Díaz-Requejo, M. M. & Pérez, P. J. Coinage metal catalyzed C–H bond functionalization of hydrocarbons. *Chem. Rev.* **108**, 3379–3394 (2008).
7. Collet, F., Dodd, R. H. & Dauban, P. Catalytic C–H amination: recent progress and future directions. *Chem. Commun.* **2009**, 5061–5074 (2009).
8. Fantauzzi, S., Caselli, A. & Gallo, E. Nitrene transfer reactions mediated by metallo-porphyrin complexes. *Dalton Trans.* **2009**, 5434–5443 (2009).
9. Zalatan, D. N. & Du Bois, J. Metal-catalyzed oxidations of C–H to C–N bonds. *Top. Curr. Chem.* **292**, 347–378 (2009).
10. Davies, H. M., Du Bois, J. & Yu, J.-Q. C–H functionalization in organic synthesis. *Chem. Soc. Rev.* **40**, 1855–1856 (2011).
11. Dequirez, G., Pons, V. & Dauban, P. Nitrene chemistry in organic synthesis: still in its infancy? *Angew. Chem. Int. Ed.* **51**, 7384–7395 (2012).
12. Che, C.-M.., Lo., K.-Y.; Zhou, C.-Y. in *Comprehensive Organic Synthesis* 2nd edn Vol. 7 (eds Knochel, P. & Molander, G. A.) 26–85 (Elsevier, 2014).
13. Darses, B., Rodrigues, R., Neuville, L., Mazurais, M. & Dauban, P. Transition metal-catalyzed iodine(III)-mediated nitrene transfer reactions: efficient tools for challenging syntheses. *Chem. Commun.* **53**, 493–508 (2017).
14. Park, Y., Kim, Y. & Chang, S. Transition metal-catalyzed C–H amination: scope, mechanism, and applications. *Chem. Rev.* **117**, 9247–9301 (2017).
This is an excellent introduction to recent developments in transition-metal-catalyzed aminations of diverse C–H bonds that covers common catalysts and nitrene precursors.
15. Hazelard, D., Nocquet, P.-A. & Compain, P. Catalytic C–H amination at its limits: challenges and solutions. *Org. Chem. Front.* **4**, 2500–2521 (2017).
16. Alderson, J. M., Corbin, J. R. & Schomaker, J. M. Tunable, chemo- and site-selective nitrene transfer reactions through the rational design of silver(I) catalysts. *Acc. Chem. Res.* **50**, 2147–2158 (2017).
17. Kuijpers, P. F., van der Vlugt, J. I., Schneider, S. & de Bruin, B. Nitrene radical intermediates in catalytic synthesis. *Chem. Eur. J.* **23**, 13819–13829 (2017).
18. Collet, F., Lescot, C. & Dauban, P. Catalytic C–H amination: the stereoselectivity issue. *Chem. Soc. Rev.* **40**, 1926–1936 (2011).
19. Degennaro, L., Trinchera, P. & Luisi, R. Recent advances in the stereoselective synthesis of aziridines. *Chem. Rev.* **114**, 7881–7929 (2014).
20. Hayashi, H. & Uchida, T. Nitrene transfer reactions for asymmetric C–H amination: recent development. *Eur. J. Org. Chem.* **2020**, 909–916 (2020).
This minireview focuses on recent strategies for asymmetric C–H amination with several nitrogen sources catalysed by molecular catalysts and artificial metalloenzymes.
21. Uchida, T. & Katsuki, T. Asymmetric nitrene transfer reactions: sulfimidation, aziridination and C–H amination using azide compounds as nitrene precursors. *Chem. Rec.* **14**, 117–129 (2014).
22. Müller, P. & Fruit, C. Enantioselective catalytic aziridinations and asymmetric nitrene insertions into CH bonds. *Chem. Rev.* **103**, 2905–2920 (2003).
This review covers early efforts in catalytic asymmetric aziridination using nitrene and carbene transfer strategies.
23. Müller, P., Baud, C. & Naegeli, I. Rhodium(II)-catalyzed nitrene transfer with phenyliodonium ylides. *J. Phys. Org. Chem.* **11**, 597–601 (1998).
24. Fiori, K. W., Espino, C. G., Brodsky, B. H. & Du Bois, J. A mechanistic analysis of the Rh-catalyzed intramolecular C–H amination reaction. *Tetrahedron* **65**, 3042–3051 (2009).
25. Harvey, M. E., Musaev, D. G. & Du Bois, J. A diruthenium catalyst for selective, intramolecular allylic C–H amination: reaction development and mechanistic insight gained through experiment and theory. *J. Am. Chem. Soc.* **133**, 17207–17216 (2011).
26. Maestre, L., Sameera, W. M., Díaz-Requejo, M. M., Maseras, F. & Pérez, P. J. A general mechanism for the copper- and silver-catalyzed olefin aziridination reactions: concomitant involvement of the singlet and triplet pathways. *J. Am. Chem. Soc.* **135**, 1338–1348 (2013).
27. Varela-Álvarez, A. et al. Rh_2(II,III) catalysts with chelating carboxylate and carboxamidate supports: electronic structure and nitrene transfer reactivity. *J. Am. Chem. Soc.* **138**, 2327–2341 (2016).
28. Weatherly, C., Alderson, J. M., Berry, J. F., Hein, J. E. & Schomaker, J. M. Catalyst-controlled nitrene transfer by tuning metal:ligand ratios: insight into the mechanisms of chemoselectivity. *Organometallics* **36**, 1649–1661 (2017).
29. Liang, J.-L., Yuan, S.-X., Huang, J.-S. & Che, C.-M. Intramolecular C–N bond formation reactions catalyzed by ruthenium porphyrins: amidation of sulfamate esters and aziridination of unsaturated sulfonamides. *J. Org. Chem.* **69**, 3610–3619 (2004).
30. Wentrup, C. Carbenes and nitrenes: recent developments in fundamental chemistry. *Angew. Chem. Int. Ed.* **57**, 11508–11521 (2018).
31. Leung, S. K.-Y. et al. Imido transfer from bis(imido) ruthenium(VI) porphyrins to hydrocarbons: effect of imido substituents, C–H bond dissociation energies, and Ru(VI/V) reduction potentials. *J. Am. Chem. Soc.* **127**, 16629–16640 (2005).
32. Lyaskovskyy, V. et al. Mechanism of cobalt(II) porphyrin-catalyzed C–H amination with organic azides: radical nature and H-atom abstraction ability of the key cobalt(III)–nitrene intermediates. *J. Am. Chem. Soc.* **133**, 12264–12273 (2011).
33. Xing, Q., Chan, C.-M., Yeung, Y.-W. & Yu, W.-Y. Ruthenium(II)-catalyzed enantioselective γ-lactams formation by intramolecular C–H amidation of 1,4,2-dioxazol-5-ones. *J. Am. Chem. Soc.* **141**, 3849–3853 (2019).
34. Park, Y. & Chang, S. Asymmetric formation of γ-lactams via C–H amidation enabled by chiral hydrogen-bond-donor catalysts. *Nat. Catal.* **2**, 219–227 (2019).
Iridium catalysts with chiral H-bond-donor ligands use convenient 1,4,2-dioxazol-5-ones to produce γ-lactams in excellent *ee* using non-covalent interactions to control the stereochemical outcome.
35. Zhou, Z. et al. Non-C_2-symmetric chiral-at-ruthenium catalyst for highly efficient enantioselective intramolecular C(sp^3)–H amidation. *J. Am. Chem. Soc.* **141**, 19048–19057 (2019).
36. Aguila, M. J., Badiei, Y. M. & Warren, T. H. Mechanistic insights into C–H amination via dicopper nitrenes. *J. Am. Chem. Soc.* **135**, 9399–9406 (2013).
37. Llaveria, J. et al. Chemo-, regio-, and stereoselective silver-catalyzed aziridination of dienes: scope, mechanistic studies, and ring-opening reactions. *J. Am. Chem. Soc.* **136**, 5342–5350 (2014).
38. Zhang, J. et al. Computational advances aiding mechanistic understanding of silver-catalyzed carbene/nitrene/silylene transfer reactions. *Coord. Chem. Rev.* **382**, 69–84 (2019).
39. Lai, T.-S., Che, C.-M., Kwong, H.-L. & Peng, S.-M. Catalytic and asymmetric aziridination of alkenes catalysed by a chiral manganese porphyrin complex. *Chem. Commun.* **1997**, 2373–2374 (1997).
40. Zhou, X.-G., Yu, X.-Q., Huang, J.-S. & Che, C.-M. Asymmetric amidation of saturated C–H bonds catalysed by chiral ruthenium and manganese porphyrins. *Chem. Commun.* **1999**, 2377–2378 (1999).
41. Liang, J.-L., Yuan, S.-X., Huang, J.-S., Yu, W.-Y. & Che, C.-M. Highly diastereo- and enantioselective intramolecular amidation of saturated C–H bonds catalyzed by ruthenium porphyrins. *Angew. Chem. Int. Ed.* **41**, 3465–3468 (2002).
42. Liang, J.-L., Huang, J.-S., Yu, X.-Q., Zhu, N. & Che, C.-M. Metalloporphyrin-mediated asymmetric nitrogen-atom transfer to hydrocarbons: aziridination of alkenes and amidation of saturated C–H bonds catalyzed by chiral ruthenium and manganese porphyrins. *Chem. Eur. J.* **8**, 1563–1572 (2002).
Early study that showed how chiral metalloporphyrins catalyse asymmetric aziridination of aromatic alkenes and asymmetric amidation of benzylic hydrocarbons.
43. Subbarayan, V., Ruppel, J. V., Zhu, S., Perman, J. A. & Zhang, X. P. Highly asymmetric cobalt-catalyzed aziridination of alkenes with trichloroethoxysulfonyl azide (TcesN$_3$). *Chem. Commun.* **2009**, 4266–4268 (2009).
44. Jones, J. E., Ruppel, J. V., Gao, G. Y., Moore, T. M. & Zhang, X. P. Cobalt-catalyzed asymmetric olefin aziridination with diphenylphosphoryl azide. *J. Org. Chem.* **73**, 7260–7265 (2008).
45. Tao, J., Jin, L.-M. & Zhang, X. P. Synthesis of chiral *N*-phosphoryl aziridines through enantioselective aziridination of alkenes with phosphoryl azide via Co(II)-based metalloradical catalysis. *Beilstein J. Org. Chem.* **10**, 1282–1289 (2014).
46. Jin, L.-M. et al. Effective synthesis of chiral *N*-fluoroaryl aziridines through enantioselective aziridination of alkenes with fluoroaryl azides. *Angew. Chem. Int. Ed.* **52**, 5309–5313 (2013).
47. Hopmann, K. H. & Ghosh, A. Mechanism of cobalt-porphyrin-catalyzed aziridination. *ACS Catal.* **1**, 597–600 (2011).
48. Olivos Suarez, A. I., Jiang, H., Zhang, X. P. & de Bruin, B. The radical mechanism of cobalt(II) porphyrin-catalyzed olefin aziridination and the importance of cooperative H-bonding. *Dalton Trans.* **40**, 5697–5705 (2011).

49. Jin, L.-M., Xu, P., Xie, J. & Zhang, X. P. Enantioselective intermolecular radical C–H amination. *J. Am. Chem. Soc.* **142**, 20828–20836 (2020).
Co(II) supported by D_2-symmetric amidoporphyrinato ligands catalyses challenging asymmetric intermolecular radical C–H amination of esters with organic azides using non-covalent attractive interactions to achieve high *ee*.
50. Jiang, H., Lang, K., Lu, H., Wojtas, L. & Zhang, X. P. Asymmetric radical bicyclization of allyl azidoformates via cobalt(II)-based metalloradical catalysis. *J. Am. Chem. Soc.* **139**, 9164–9167 (2017).
51. Li, C. et al. Catalytic radical process for enantioselective amination of C(sp^3)–H bonds. *Angew. Chem. Int. Ed.* **57**, 16837–16841 (2018).
52. Hu, Y. et al. Enantioselective radical construction of 5-membered cyclic sulfonamides by metalloradical C–H amination. *J. Am. Chem. Soc.* **141**, 18160–18169 (2019).
53. Lang, K., Li, C., Kim, I. & Zhang, X. P. Enantioconvergent amination of racemic tertiary C–H bonds. *J. Am. Chem. Soc.* **142**, 20902–20911 (2020).
This work describes the first Co(II) catalysts for enantioconvergent radical amination of racemic tertiary C(sp^3)-H bonds to create useful quaternary stereocentres.
54. Lang, K., Torker, S., Wojtas, L. & Zhang, X. P. Asymmetric induction and enantiodivergence in catalytic radical C–H amination via enantiodifferentiative H-atom abstraction and stereoretentive radical substitution. *J. Am. Chem. Soc.* **141**, 12388–12396 (2019).
55. Hu, Y. et al. Next-generation D_2-symmetric chiral porphyrins for cobalt(II)-based metalloradical catalysis: catalyst engineering by distal bridging. *Angew. Chem. Int. Ed.* **58**, 2670–2674 (2019).
56. Noda, K., Hosoya, N., Irie, R., Ito, Y. & Katsuki, T. Asymmetric aziridination by using optically active (salen)manganese(III) complexes. *Synlett* **1993**, 469–471 (1993).
57. Nishikori, H. & Katsuki, T. Catalytic and highly enantioselective aziridination of styrene derivatives. *Tetrahedron Lett.* **37**, 9245–9248 (1996).
58. Kohmura, Y. & Katsuki, T. Mn(salen)-catalyzed enantioselective C–H amination. *Tetrahedron Lett.* **42**, 3339–3342 (2001).
59. Omura, K., Murakami, M., Uchida, T., Irie, R. & Katsuki, T. Enantioselective aziridination and amination using *p*-toluenesulfonyl azide in the presence of Ru(salen)(CO) complex. *Chem. Lett.* **32**, 354–355 (2003).
60. Omura, K., Uchida, T., Irie, R. & Katsuki, T. Design of a robust Ru(salen) complex: aziridination with improved turnover number using *N*-arylsulfonyl azides as precursors. *Chem. Commun.* https://doi.org/10.1039/B407693A (2004).
61. Kawabata, H., Omura, K. & Katsuki, T. Asymmetric aziridination: a new entry to optically active non-*N*-protected aziridines. *Tetrahedron Lett.* **47**, 1571–1574 (2006).
62. Kawabata, H., Omura, K., Uchida, T. & Katsuki, T. Construction of robust ruthenium(salen)(CO) complexes and asymmetric aziridination with nitrene precursors in the form of azide compounds that bear easily removable *N*-sulfonyl groups. *Chem. Asian J.* **2**, 248–256 (2007).
63. Kim, C., Uchida, T. & Katsuki, T. Asymmetric olefin aziridination using a newly designed Ru(CO)(salen) complex as the catalyst. *Chem. Commun.* **48**, 7188–7190 (2012).
64. Ichinose, M. et al. Enantioselective intramolecular benzylic C–H bond amination: efficient synthesis of optically active benzosultams. *Angew. Chem. Int. Ed.* **50**, 9884–9887 (2011).
65. Fukunaga, Y., Uchida, T., Ito, Y., Matsumoto, K. & Katsuki, T. Ru(CO)-salen-catalyzed synthesis of enantiopure aziridinyl ketones and formal asymmetric synthesis of (+)-PD 128907. *Org. Lett.* **14**, 4658–4661 (2012).
66. Nishioka, Y., Uchida, T. & Katsuki, T. Enantio- and regioselective intermolecular benzylic and allylic C–H bond amination. *Angew. Chem. Int. Ed.* **52**, 1739–1742 (2013).
67. Müller, P., Baud, C., Jacquier, Y., Moran, M. & Nägeli, I. Rhodium(II)-catalyzed aziridinations and CH insertions with [*N*-(*p*-nitrobenzenesulfonyl)imino]phenyliodinane. *J. Phys. Org. Chem.* **9**, 341–347 (1996).
68. Nägeli, I. et al. Rhodium(II)-catalyzed CH insertions with {[(4-nitrophenyl)sulfonyl]imino}phenyl-λ^3-iodane. *Helv. Chim. Acta* **80**, 1087–1105 (1997).
69. Tsutsui, H. et al. Dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate]: an exceptionally effective Rh(II) catalyst for enantiotopically selective aromatic C–H insertions of diazo ketoesters. *Tetrahedron Asymmetry* **14**, 817–821 (2003).
70. Yasue, R. & Yoshida, K. Enantioselective desymmetrization of 1,3-disubstituted adamantane derivatives via rhodium-catalyzed C–H bond amination: access to optically active amino acids containing adamantane core. *Adv. Synth. Catal.* **363**, 1662–1671 (2021).
71. Reddy, R. P. & Davies, H. M. Dirhodium tetracarboxylates derived from adamantylglycine as chiral catalysts for enantioselective C–H aminations. *Org. Lett.* **8**, 5013–5016 (2006).
72. Nasrallah, A. et al. Catalytic enantioselective intermolecular benzylic C(sp^3)–H amination. *Angew. Chem. Int. Ed.* **58**, 8192–8196 (2019).
73. Nasrallah, A., Lazib, Y., Boquet, V., Darses, B. & Dauban, P. Catalytic intermolecular C(sp^3)–H amination with sulfamates for the asymmetric synthesis of amines. *Org. Process. Res. Dev.* **24**, 724–728 (2019).
74. Anada, M. et al. Catalytic enantioselective amination of silyl enol ethers using chiral dirhodium(II) carboxylates: asymmetric formal synthesis of (–)-metazocine. *Org. Lett.* **9**, 4559–4562 (2007).
75. Hashimoto, S., Tanaka, M., Nakamura, S. & Anada, M. Catalytic asymmetric synthesis of (–)-ritodrine hydrochloride via silyl enol ether amination using dirhodium(II) tetrakis[tetrafluorophthaloyl-(*S*)-*tert*-leucinate]. *Heterocycles* **76**, 1633–1645 (2008).
76. Tanaka, M., Kurosaki, Y., Washio, T., Anada, M. & Hashimoto, S. Enantioselective amination of silylketene acetals with (*N*-arylsulfonylimino) phenyliodinanes catalyzed by chiral dirhodium(II) carboxylates: asymmetric synthesis of phenylglycine derivatives. *Tetrahedron Lett.* **48**, 8799–8802 (2007).
77. Anada, M. et al. Asymmetric formal synthesis of (–)-pancracine via catalytic enantioselective C–H amination process. *Tetrahedron* **65**, 3069–3077 (2009).
78. Miyazawa, T. et al. Chiral paddle-wheel diruthenium complexes for asymmetric catalysis. *Nat. Catal.* **3**, 851–858 (2020).
The first example of chiral paddle-wheel Ru_2 complexes exhibiting reactivity and high *ee* in C–H amination under oxidizing conditions.
79. Zalatan, D. N. & Du Bois, J. A chiral rhodium carboxamidate catalyst for enantioselective C–H amination. *J. Am. Chem. Soc.* **130**, 9220–9221 (2008).
Early examples of Rh_2 complexes supported by chiral lactams enable high site-selective and enantioselective C–H amination using sulfamate esters.
80. Lebel, H., Huard, K. & Lectard, S. *N*-tosyloxycarbamates as a source of metal nitrenes: rhodium-catalyzed C–H insertion and aziridination reactions. *J. Am. Chem. Soc.* **127**, 14198–14199 (2005).
81. Espino, C. G., Fiori, K. W., Kim, M. & Du Bois, J. Expanding the scope of C–H amination through catalyst design. *J. Am. Chem. Soc.* **126**, 15378–15379 (2004).
82. Fiori, K. W. & Du Bois, J. Catalytic intermolecular amination of C–H bonds: method development and mechanistic insights. *J. Am. Chem. Soc.* **129**, 562–568 (2007).
83. Hoke, T., Herdtweck, E. & Bach, T. Hydrogen-bond mediated regio- and enantioselectivity in a C–H amination reaction catalysed by a supramolecular Rh(II) complex. *Chem. Commun.* **49**, 8009–8011 (2013).
84. Lonergan, D. G., Riego, J. & Deslongchamps, G. A convergent hydroxyimide module for molecular recognition. *Tetrahedron Lett.* **37**, 6109–6112 (1996).
85. Lonergan, D. G., Halse, J. & Deslongchamps, G. Comparative probe for stacking interactions in simple A:T base pair mimics. *Tetrahedron Lett.* **39**, 6865–6868 (1998).
86. Lonergan, D. G. & Deslongchamps, G. Tricyclic scaffolds for the rapid assembly of abiotic receptors. *Tetrahedron* **54**, 14041–14052 (1998).
87. Zhong, F. & Bach, T. Enantioselective construction of 2,3-dihydrofuro[2,3-*b*]quinolines through supramolecular hydrogen bonding interactions. *Chem. Eur. J.* **20**, 13522–13526 (2014).
88. Annapureddy, R. R., Jandl, C. & Bach, T. A chiral phenanthroline ligand with a hydrogen-bonding site: application to the enantioselective amination of methylene groups. *J. Am. Chem. Soc.* **142**, 7374–7378 (2020).
89. Desimoni, G., Faita, G. & Jørgensen, K. A. Update 1 of: C_2-symmetric chiral bis(oxazoline) ligands in asymmetric catalysis. *Chem. Rev.* **111**, PR284–PR437 (2011).
90. Evans, D. A., Woerpel, K. A., Hinman, M. M. & Faul, M. M. Bis(oxazolines) as chiral ligands in metal-catalyzed asymmetric reactions. Catalytic, asymmetric cyclopropanation of olefins. *J. Am. Chem. Soc.* **113**, 726–728 (1991).
91. Evans, D. A., Faul, M. M., Bilodeau, M. T., Anderson, B. A. & Barnes, D. M. Bis(oxazoline)–copper complexes as chiral catalysts for the enantioselective aziridination of olefins. *J. Am. Chem. Soc.* **115**, 5328–5329 (1993).
92. Lowenthal, R. E. & Masamune, S. Asymmetric copper-catalyzed cyclopropanation of trisubstituted and unsymmetrical cis-1,2-disubstituted olefins: modified bis-oxazoline ligands. *Tetrahedron Lett.* **32**, 7373–7376 (1991).
93. Adam, W., Roschmann, K. J. & Saha-Möller, C. R. Catalytic asymmetric aziridination of enol derivatives in the presence of chiral copper complexes to give optically active α-amino ketones. *Eur. J. Org. Chem.* **2000**, 557–561 (2000).
94. Dauban, P., Dodd, R., Estéoule, A., Durán, F. & Retailleau, P. Enantioselective intramolecular copper-catalyzed aziridination of sulfamates. *Synthesis* **2007**, 1251–1260 (2007).
95. Milczek, E., Boudet, N. & Blakey, S. Enantioselective C–H amination using cationic ruthenium(II)–pybox catalysts. *Angew. Chem. Int. Ed.* **47**, 6825–6828 (2008).
96. Ju, M., Weatherly, C. D., Guzei, I. A. & Schomaker, J. M. Chemo- and enantioselective intramolecular silver-catalyzed aziridinations. *Angew. Chem. Int. Ed.* **56**, 9944–9948 (2017).
97. Ju, M. et al. Silver-catalyzed enantioselective propargylic C–H bond amination through rational ligand design. *J. Am. Chem. Soc.* **142**, 12930–12936 (2020).
This report showcases the first Ag-catalysed asymmetric nitrene transfer, allowing regioselective and enantioselective amination of propargylic C–H bonds using modular bis(oxazoline) ligands.
98. Zhang, Y.-Q., Yuan, Y.-A., Liu, G.-S. & Xu, H. Iron(II)-catalyzed asymmetric intramolecular aminohydroxylation of indoles. *Org. Lett.* **15**, 3910–3913 (2013).
99. Zhu, C.-L., Tian, J.-S., Gu, Z.-Y., Xing, G.-W. & Xu, H. Iron(II)-catalyzed asymmetric intramolecular olefin aminochlorination using chloride ion. *Chem. Sci.* **6**, 3044–3050 (2015).
100. Lu, D.-F., Zhu, C.-L., Sears, J. D. & Xu, H. Iron(II)-catalyzed intermolecular aminofluorination of unfunctionalized olefins using fluoride ion. *J. Am. Chem. Soc.* **138**, 11360–11367 (2016).
101. Zhu, C.-L., Lu, D.-F., Sears, J. D., Jia, Z.-X. & Xu, H. Practical synthetic procedures for the iron-catalyzed intermolecular olefin aminohydroxylation using functionalized hydroxylamines. *Synthesis* **48**, 3031–3041 (2016).
102. Nie, X., Yan, Z., Ivlev, S. & Meggers, E. Ruthenium pybox-catalyzed enantioselective intramolecular C–H amination of sulfamoyl azides en route to chiral vicinal diamines. *J. Org. Chem.* **86**, 750–761 (2021).
103. Li, L. et al. Complementing pyridine-2,6-bis(oxazoline) with cyclometalated *N*-heterocyclic carbene for asymmetric ruthenium catalysis. *Angew. Chem. Int. Ed.* **59**, 12392–12395 (2020).
104. Ju, M. et al. Tunable catalyst-controlled syntheses of β- and γ-amino alcohols enabled by silver-catalysed nitrene transfer. *Nat. Catal.* **2**, 899–908 (2019).
105. Charton, M. Nature of the ortho effect. II. Composition of the Taft steric parameters. *J. Am. Chem. Soc.* **91**, 615–618 (1969).
106. Charton, M. Steric effects. I. Esterification and acid-catalyzed hydrolysis of esters. *J. Am. Chem. Soc.* **97**, 1552–1556 (1975).
107. Charton, M. Steric effects. II. Base-catalyzed ester hydrolysis. *J. Am. Chem. Soc.* **97**, 3691–3693 (1975).
108. Charton, M. Steric effects. 7. Additional V constants. *J. Org. Chem.* **41**, 2217–2220 (1976).
109. Sigman, M. S. & Miller, J. J. Examination of the role of Taft-type steric parameters in asymmetric catalysis. *J. Org. Chem.* **74**, 7633–7643 (2009).
110. Alderson, J. M., Phelps, A. M., Scamp, R. J., Dolan, N. S. & Schomaker, J. M. Ligand-controlled, tunable silver-catalyzed C–H amination. *J. Am. Chem. Soc.* **136**, 16720–16723 (2014).

111. Dolan, N. S., Scamp, R. J., Yang, T., Berry, J. F. & Schomaker, J. M. Catalyst-controlled and tunable, chemoselective silver-catalyzed intermolecular nitrene transfer: experimental and computational studies. *J. Am. Chem. Soc.* **138**, 14658–14667 (2016).
112. Huang, M., Yang, T., Paretsky, J. D., Berry, J. F. & Schomaker, J. M. Inverting steric effects: using "attractive" noncovalent interactions to direct silver-catalyzed nitrene transfer. *J. Am. Chem. Soc.* **139**, 17376–17386 (2017).
113. Huang, M., Paretsky, J. & Schomaker, J. M. Rigidifying Ag(I) complexes for selective nitrene transfer. *ChemCatChem* **12**, 3076–3081 (2020).
114. Nishiyama, H., Itoh, Y., Matsumoto, H., Park, S.-B. & Itoh, K. New chiral ruthenium bis(oxazolinyl)pyridine catalyst. Efficient asymmetric cyclopropanation of olefins with diazoacetates. *J. Am. Chem. Soc.* **116**, 2223–2224 (1994).
115. Okamoto, K., Nanya, A., Eguchi, A. & Ohe, K. Asymmetric synthesis of 2*H*-azirines with a tetrasubstituted stereocenter by enantioselective ring contraction of isoxazoles. *Angew. Chem. Int. Ed.* **57**, 1039–1043 (2018).
116. Hong, S. Y. et al. Selective formation of γ-lactams via C–H amidation enabled by tailored iridium catalysts. *Science* **359**, 1016–1021 (2018).
117. Wang, H. et al. Iridium-catalyzed enantioselective C(sp^3)–H amidation controlled by attractive noncovalent interactions. *J. Am. Chem. Soc.* **141**, 7194–7201 (2019).
118. Fukagawa, S. et al. Enantioselective C(sp^3)–H amidation of thioamides catalyzed by a cobalt(III)/chiral carboxylic acid hybrid system. *Angew. Chem. Int. Ed.* **58**, 1153–1157 (2019).
119. Sekine, D. et al. Chiral 2-aryl ferrocene carboxylic acids for the catalytic asymmetric C(sp^3)–H activation of thioamides. *Organometallics* **38**, 3921–3926 (2019).
120. Liu, Y.-H. et al. Cp*Co(III)/MPAA-catalyzed enantioselective amidation of ferrocenes directed by thioamides under mild conditions. *Org. Lett.* **21**, 1895–1899 (2019).
121. Fukagawa, S., Kojima, M., Yoshino, T. & Matsunaga, S. Catalytic enantioselective methylene C(sp^3)–H amidation of 8-alkylquinolines using a Cp*Rh(III)/chiral carboxylic acid system. *Angew. Chem. Int. Ed.* **58**, 18154–18158 (2019).
122. Farr, C. M. B. et al. Designing a planar chiral rhodium indenyl catalyst for regio- and enantioselective allylic C–H amidation. *J. Am. Chem. Soc.* **142**, 13996–14004 (2020).
An exciting advance in the chemoselective, regioselective and enantioselective allylic C–H amidation of unactivated olefins using a planar-chiral indenyl Rh complex.
123. Zhang, L. & Meggers, E. Stereogenic-only-at-metal asymmetric catalysts. *Chem. Asian J.* **12**, 2335–2342 (2017).
124. Zheng, Y. et al. Octahedral ruthenium complex with exclusive metal-centered chirality for highly effective asymmetric catalysis. *J. Am. Chem. Soc.* **139**, 4322–4325 (2017).
125. Zhang, L. & Meggers, E. Steering asymmetric Lewis acid catalysis exclusively with octahedral metal-centered chirality. *Acc. Chem. Res.* **50**, 320–330 (2017).
126. Qin, J., Zhou, Z., Cui, T., Hemming, M. & Meggers, E. Enantioselective intramolecular C–H amination of aliphatic azides by dual ruthenium and phosphine catalysis. *Chem. Sci.* **10**, 3202–3207 (2019).
127. Zhou, Z. et al. Enantioselective ring-closing C–H amination of urea derivatives. *Chem* **6**, 1851–1853 (2020).
128. Zhou, Z. et al. Catalytic enantioselective intramolecular C(sp^3)–H amination of 2-azidoacetamides. *Angew. Chem. Int. Ed.* **58**, 1088–1093 (2019).
129. Wang, G., Zhou, Z., Shen, X., Ivlev, S. & Meggers, E. Asymmetric catalysis with a chiral-at-osmium complex. *Chem. Commun.* **56**, 7714–7717 (2020).

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