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Alkene Hydroamination via Earth-Abundant Transition Metal (Fe, Co, Cu and Zn) Catalysis: A Mechanistic Overview

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Abstract. This review gives a mechanistic overview of the the most relevant advances in the area of alkene (formal) hydroamination promoted by earth-abundant transition metal catalysts involving iron, cobalt, copper and zinc. Focus will be on catalytic systems for which deep investigations have been conducted to elucidate the activation pathway and operating mechanism. The relevant literature has been covered from 2012 until early 2019.

Keywords: Earth-abundant 3d transition metal; Hydroamination; Mechanistic studies; Alkenes; Amines.

1 Introduction

The direct addition of N-H amine functionality onto an unsaturated carbon-carbon double bond, the so-called alkene hydroamination reaction, is one of the most appealing route to access valuable nitrogen-containing compounds with 100% atom efficiency from ubiquitous amines and alkenes. The past few decades have witnessed the development of a plethora of catalysts derived from Group 1-5 (mainly, Li, Mg, Ca, Ba, Sc, Y, Zr, Ta) and noble metals (mainly Pd, Rh, Ir) to control the selectivities and extend the scope of this reaction.^[1] The current growing trend for the incorporation of earth-abundant late transition metals in catalysis has recently offered great developments in addressing some of the selectivity issues and widen the reaction applicability.^[1h-k] These developments have been accomplished from the exploitation of established activation strategies^[2a,3a,4a,5,6,7] and also from the exploration of novel strategies^[8,9,10,11] to formally achieve N-H addition on alkenes. This review will outline the most relevant advances in the area of alkene (formal) hydroamination promoted by earth-abundant transition metal catalysts involving iron, cobalt, copper and zinc. Focus will be on catalytic systems for which in-depth mechanistic studies have been conducted to elucidate the activation pathway and the operating mechanism. All relevant asymmetric developments to access chiral amines will also be covered. The diverse activation strategies and mechanistic dissimilarity encountered with these systems will be stressed. The relevant literature has been covered from 2012 until early 2019. For early developments, the reader should refer to previously reported reviews.^[1a,c,d,h,i,j,k] Achievements in the direct addition of electronically biased amines (such as as

sulphonamides, carbamates or amides) on unactivated alkenes are out of the scope of this review as such C-N bond formation reactions are today more appropriately called hydroamidation reactions.^[1g]

Pierre Colonna was born in Dourdan (France) in 1996 and studied physico-chemistry at the Université Paris-Saclay (France). He is currently a Master of science internship's student under the supervision of Dr Jérôme Hannedouche at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO) (Université Paris-Sud/Université Paris-Saclay, France). He is working on cross-dehydrogenating coupling reactions catalyzed by low-coordinate 3d transition metal complexes.



Sophie Bezzenine-Lafollée received her Ph.D. degree from Université Paris VI in 1998. After a postdoctoral stay on asymmetric synthesis with Pr. P. Müller at the University of Geneva, Switzerland, she spent two years in the laboratory of Pr. J. Ardisson at the University of Cergy-Pontoise working on total synthesis. In 2001, she became Maître de Conférence in Orsay University at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO). Actually, she works on enantioselective catalysis with rare earth and first row late transition metal complexes.



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Richard Gil studied chemistry at Université Paris-Sud (Orsay, France) where he received his PhD in 1993. His thesis work was under the supervision of Professor Jean-Claude Fiaud and dealt with enantioselective palladium-catalyzed reactions. He then spent one post-doctoral year (1993–1994) at Imperial College London under the group of Pr. Susan E. Gibson. In 1995, he went to Université de Cergy-Pontoise and became Maître de Conférences in 1996. In 2002, he returned to ICMMO. His research interests include enantioselective reactions catalyzed by rare earth elements.

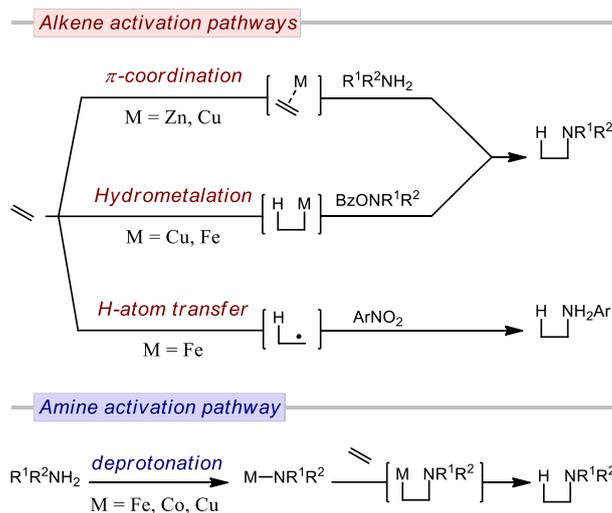


Jérôme Hannedouche received his PhD degree (2004) from the University of Warwick (UK) under the supervision of Prof. Martin Wills. After a 2-year postdoctoral stay at the Université Catholique de Louvain (Belgium) with Prof. Olivier Riant, he was appointed (2006) at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO) (Université Paris-Sud/Université Paris-Saclay, France) as a CNRS fellow researcher. His research interests lie in the development and mechanistic study of novel synthetic methodologies in asymmetric catalysis, mainly for C–N bond formation via hydroamination reaction catalyzed by rare-earth and first-row late transition metal complexes.



2 Mechanism overview

Over the years, different approaches have emerged to tackle the issues related to the hydroamination reaction. These approaches rely on preliminary activation of either the alkene or the amine functionality of the reactants by the earth-abundant transition metal. Depending on the catalytic systems involved, the alkene activation pathways feature either olefin π -coordination to a Lewis acidic metal center,^[2,3,4] hydrometalation^[8,9,10] or hydrogen atom transfer^[11] from in situ generated metal-hydride species (Scheme 1, top). The ensuing C–N bond formation ends from either nucleophilic attack of the amine moiety on the activated olefin,^[2,3,4] umpolung electrophilic amination^[8,9,10] or radical^[11] coupling. Similarly to Group 1–5 element based catalysts, the amine activation pathway is triggered by the formation of a reactive metal-amido complex from deprotonation of the amine by a basic catalyst (Scheme 1, bottom).^[5,6,7] The C–N bond formation arises from olefin insertion into the metal-amido σ -bond of this complex.^[5,6,7]



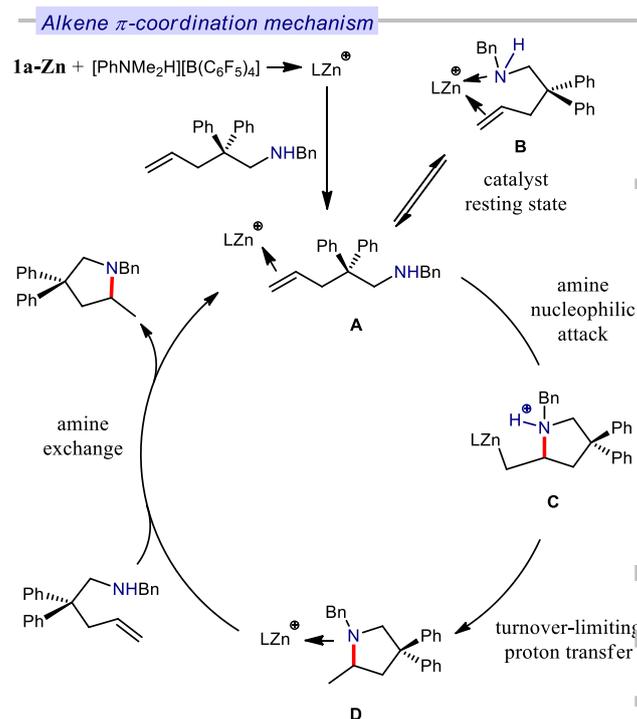
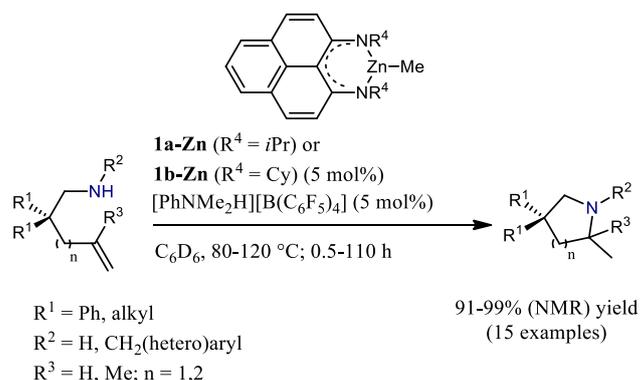
Scheme 1. Mechanism overview of the metal-catalyzed alkene hydroamination processes discussed herein.

3 Alkene activation pathways

3.1 π -coordination

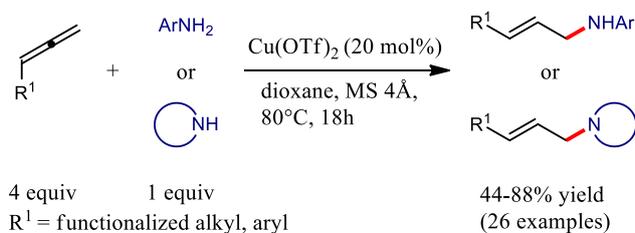
Among the different methodologies reported in the literature, the most commonly spread mechanism for alkene hydroamination catalyzed by late transition metal-based systems is the olefin-activation mechanism by π -coordination. For instance, the most active and general among late transition metal-based systems reported so far for the cyclohydroamination of alkenes and primary or secondary amines, the rhodium monocationic system, $[\text{Rh}(\text{COD})_2]\text{BF}_4/\text{bis}(\text{diethylamino})\text{xantphos}$ ligand, operates in a similar alkene activation pathway as highlighted by detailed mechanistic investigations.^[12] An analogue activation pathway has been demonstrated by extensive mechanistic and theoretical studies for the hydroamination of aminoalkenes catalyzed by $[\text{Ir}(\text{COD})\text{Cl}]_2$.^[13] This postulated activation pathway has been at the origin of the initial and following catalyst developments based on copper,^[14] iron^[15] and zinc^[2] for alkene hydroamination and related hydroamidation reactions in the burgeoning context of first-row late transition metals. In 2012, the Mandal's group investigated the catalytic application of well-defined methyl-zinc complexes stabilized by a symmetrical *N*-alkylsubstituted phenalenyl ligand in alkene hydroamination (Scheme 2).^[3] This study was inspired by the elegant work of Roesky *et al.* on the use of aminotroponimate-ligated and ligand-free methyl zinc complexes for cyclohydroamination of aminoalkenes.^[2] As previously reported by the Roesky group, Mandal *et al.* found that the reaction rate is altered by the ligand *N*-substituent (R^4) following the trend Me (**1-Zn** with $\text{R}^4 = \text{Me}$) \ll *i*Pr (**1a-Zn**) \leq Cy (**1b-Zn**) and that the catalytic activity is significantly improved in the presence of the $[\text{PhNMe}_2\text{H}][\text{B}(\text{C}_6\text{F}_5)_4]$ activator (Scheme 2). As noticed for the intramolecular conversion of functionalized primary and secondary aminoalkenes

into the corresponding 5- and 6-membered rings, the more efficient catalytic systems **1a-Zn** and **1b-Zn** offer, in the presence of co-catalyst [PhNMe₂H][B(C₆F₅)₄], similar catalytic activities to that of Roesky's methylzinc [N-isopropyl-2-(isopropylamino) troponiminato] catalyst (Scheme 2, top). Experimental and computational investigations into the operating mechanism of the reaction were conducted. As anticipated and confirmed by in situ NMR experiment, methyl abstraction of **1a-Zn** by the boron co-catalyst leads to the formation of catalytically active cationic zinc species (Scheme 2, bottom). The reaction rate dependence is first- and inverse order with respect to the catalyst and aminoalkene concentration respectively. Kinetic studies also underline a substantial kinetic isotope effect (KIE) for the cyclohydroamination of primary and secondary aminoalkenes catalyzed by **1a-Zn** and **1b-Zn**. DFT calculations reveal that the alkene activation pathway is energetically the most favorable over the energetically inaccessible amine activation pathway. Simultaneously binding of the zinc species to the olefin and amine functionality affords a more stable species that the one exclusively bound to the olefin or amine. A rapid equilibrium involving all these species may be operating. From all of these investigations, it was suggested by the authors that the reaction occurs by first coordination of the olefin to the electrophilic cationic zinc species **A**, arising from reaction of **1a-Zn** and [PhNMe₂H][B(C₆F₅)₄] (Scheme 2, bottom).^[3a] The latter is in rapid equilibrium with the putative catalyst resting state **B**. Nucleophilic attack of the coordinated alkene by the tethered amine provides the ammonium alkylzinc adduct **C**. Subsequent cleavage of the Zn-C σ -bond by intramolecular turnover-limiting proton transfer generates the product-ligated zinc complex **D** (Scheme 2, bottom).^[3a] The cyclized hydroamination product is released by the incoming aminoalkene leading to the regeneration of the catalytically competent species **A**. DFT calculations show that, among the assessed series of *N*-alkyl-substituted phenalenyl-based zinc complexes, the cationic zinc complex originated from **1b-Zn** has the greatest stability (evaluated by the HOMO-LUMO energy gap) which is at the origin of the highest activity of this complex.^[3b]



Scheme 2. Cationic zinc-catalyzed *exo*-cyclohydroamination of primary and secondary aminoalkenes and its proposed alkene π -coordination mechanism (L = phenalenyl ligand).

In 2017, the group of Monnier and Taillefer described an extension of this olefin-activation strategy to allene-type compounds using copper triflate (II) as catalyst.^[4a] This is the first report of copper-promoted hydroamination of terminal allenes and cyclic secondary amines or aniline derivatives, both partners bearing functional groups (Scheme 3). This process affords regio and stereoselectively the corresponding (*E*)-linear allylamines as the only product of hydroamination under mild reaction conditions, but with a large excess of amine. A joint experimental and theoretical mechanistic study with the group of Ciofini and Grimaud smartly identified the catalytically active species as being a cationic copper (I) species. The regio- and stereoselectivities observed for the linear (*E*)-allylamine product was also rationalized.^[4b,c]



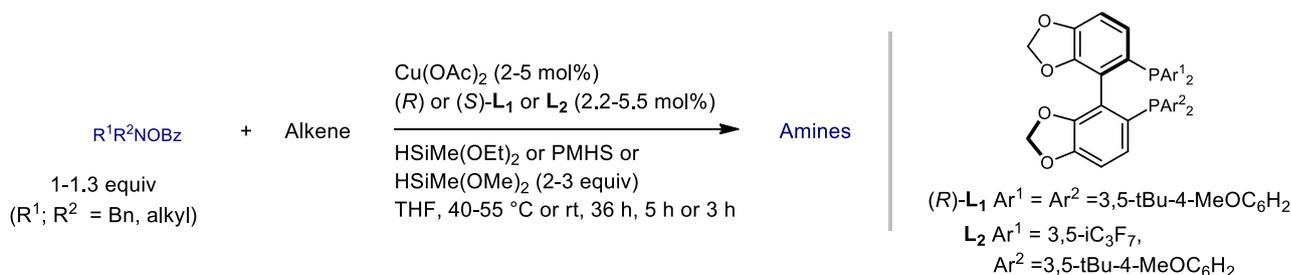
Scheme 3. Regio- and stereoselective copper(II) triflate-catalysed hydroamination of terminal allenes and cyclic secondary amines or anilines.

3.2 Hydrometalation

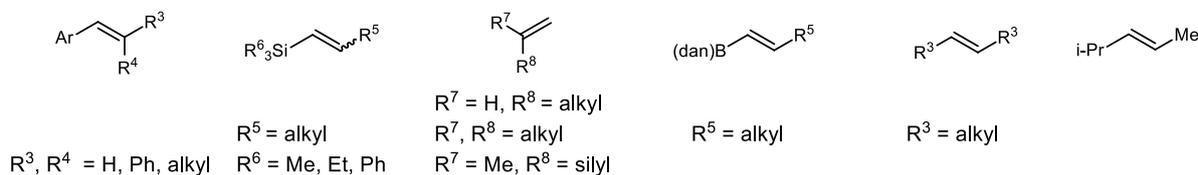
In 2013, taking advantage of the well-known phosphine copper-hydride chemistry^[16] and the electrophilicity^[17] of hydroxylamine esters, an original and mechanistically distinct strategy for the C-N bond formation from arylalkenes and hydroxylamine esters as amine sources was independently reported by the groups of Buchwald^[8] and Miura^[9] and Hirano. This novel strategy relying on an umpolung electrophilic amination approach was an astonishing breakthrough in the field of now-called formal hydroamination.^[18] Both reports highlight that the combination of a chiral biphosphine ligand and a copper(I) or (II) salt in the presence of a hydrosilane reagent are particularly efficient for the regio- and enantioselective intermolecular formal hydroamination of arylalkenes and *O*-

benzoylhydroxylamines.^[8,9] The original Buchwald combination ((*R*)-DTBM-SEGPHOS ((*R*)-**L**₁) / Cu(OAc)₂ / HSiMe(OEt)₂) has a wider scope than the Miura and Hirano combination (((*S,S*)-Me-Duphos or (*R,R*)-Ph-BPE) / CuCl / diethoxymethylsilane / LiOtBu) and is currently the most applied combination^[8,19] The former is indeed efficient for the preparation of a plethora of chiral tertiary amines (chiral branched amines, α -amino-silanes and α -boronic acids, β -chiral amines) from a range of alkene derivatives (functionalized styrenes, *cis/trans*- β -substituted and β - β -substituted arylalkenes, vinylsilanes, alkenyl 1,8-diaminonaphthyl boronates and 1,1-dialkyl-substituted alkenes) in good to excellent yields and with high enantiomeric excesses (Scheme 4).^[8,20] It was noted that both (*E*)- and (*Z*)-vinylsilanes provide the same enantiomer, but (*E*)-isomers are obtained with higher ee values and with faster reaction rates than the corresponding (*Z*)-isomers.^[20b]

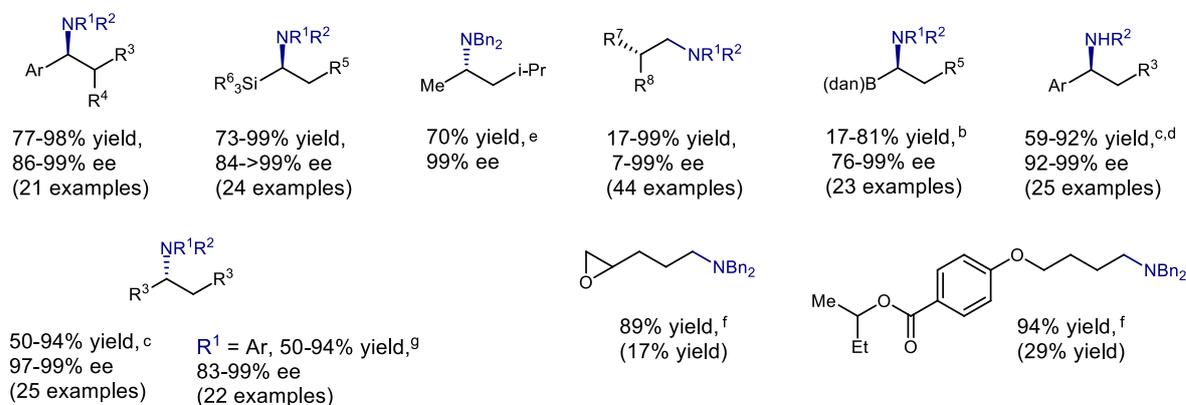
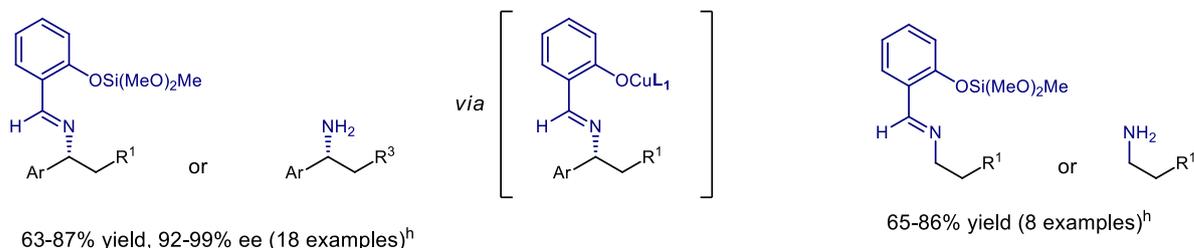
The scope of this Cu-H-based methodology was further expanded to include the formation of chiral secondary amines and the conversion of highly challenging internal alkenes^[22] in high yields.^[21] This scope extension relies on the crucial use of the more electron-rich 4-(dimethylamino)benzoate group on the electrophilic amine partner instead of the previously employed benzoate group (Scheme 4).



Alkenes



Tertiary and Secondary Amines

Schiff Bases and Primary Amines with $R^1R^2NOBz = 1,2\text{-benzoxazole}$ 

Scheme 4. Regio- and enantioselective biphosphine-CuH-catalyzed formal hydroamination of alkene derivatives and electrophilic amines. a) all reactions run with (*R*) or (*S*)-**L**₁ unless otherwise stated. b) with LiOtBu (4 equiv). c) with R²NHOCO₂(*p*-NMe₂C₆H₄). d) with PPh₃ (4.4-8.8 mol%). e) regioselectivity = 82:18. f) with (±)-**L**₂ instead of (±)-**L**₁. g) with ^tBuOH (1 equiv) and PPh₃ (2-6 mol%). h) conversion of the chiral Schiff bases into the primary amines without ee erosion: NH₂OH.HCl, MeOH. dan = 1,8-diamonaphthyl.

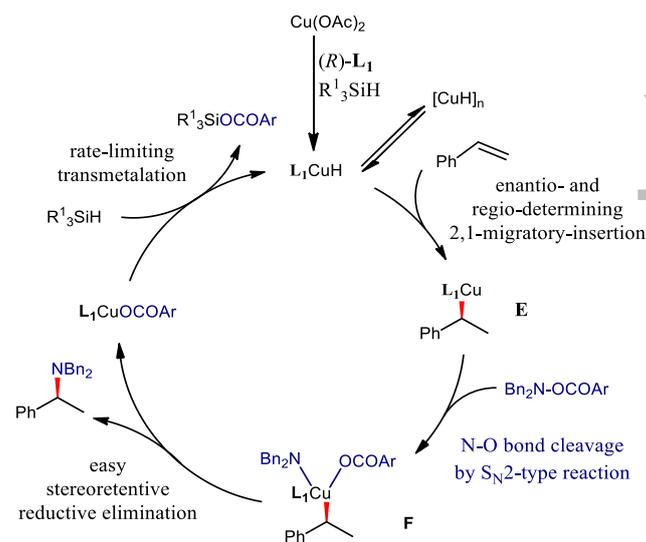
In-depth experimental studies have been conducted on the C-N bond formation reaction of styrenes and *O*-benzoyl-*N,N*-dialkyl-hydroxylamine catalyzed by the system ((*R*)-**L**₁) / Cu(OAc)₂ / HSiMe(OEt)₂.^[23] These studies, completed by computational investigations done with a structurally simplified combination ((1,2-bis(diphenylphosphino)benzene / Cu(OAc)₂ / LiOtBu / Me₃SiH) and electrophilic amine (Me₂NOBz),^[24] support the mechanistic picture displayed in Scheme 5 as proposed by the authors. The initial reaction of the enantiopur

biphosphine ligand **L**₁ / Cu(OAc)₂ with the hydrosilane reagent leads, after reduction and transmetalation, in the generation of catalytically relevant **L**₁Cu(I)-H being monomeric as suggested by the linear relationship ee_{prod} = f(ee_{ligand}).^[23] Nevertheless, the measurement of an apparent fractional order dependence of the reaction rate on the concentration in metal evokes a putative equilibrium of **L**₁Cu(I)-H with its dimer or higher-order species or aggregates.^[25] The Cu-H σ-bond is subsequently engaged in a regioselective alkene 2,1-

migratory insertion with styrene via a four-center planar transition state resulting in the formation of an alkyl copper(I) species **E** (Scheme 5). This hydrometalation step is irreversible and enantio-determining as suggested by deuterium-labelling experiments and the linear free energy relationships between the Hammett electronic parameters of *para*-substituted styrenes and the measured *ee* values. Subsequent N-O bond cleavage of the amine reagent through intramolecular S_N2 displacement promoted by species **E** leads to the formation of species **F**.^[23] An easy and stereoretentive reductive elimination liberates the formal hydroamination product by C-N bond formation and provides $L_1CuOCOAr$. The latter should be the resting state of the catalyst as shown by MS and NMR studies.^[23] Subsequent transmetalation between $L_1CuOCOAr$ and the hydrosilane regenerates the catalytically competent $L_1Cu(I)-H$. From a linear Hammett correlation between the reaction rate and the electronic parameters of the *para*-substituents of the aromatic ring of the amine, it was demonstrated that the reaction rate increases with the electronic richness of the electrophilic amine.^[23] Further studies have shown that the reaction rate is not influenced by the styrene *para*-substituent and displays a first-order dependence on silane concentration and a zero-order dependence on styrene and amine concentration.^[23] These observations are consistent with the transmetalation step being rate-determining.

On the basis of these mechanistic investigations, the observation of a better efficiency of electrophilic amine partners bearing more-electron rich esters may arise from their enhanced ability to restore the active $L_1Cu(I)-H$ during the rate-limiting transmetalation and their diminished non-productive degradation by the catalyst as demonstrated by DFT studies (Scheme 5).^[24] Electronic stabilization of copper species **E** by the neighbouring aryl (or silyl) group and formation of a less sterically hindered alkylcopper intermediate rationalize the observation of a Markovnikov and *anti*-Markovnikov selectivity for arylalkenes (and vinylsilanes) and linear alkenes respectively. Examination of the through-bond and through-space interactions between the Cu(I)-H catalyst ligated to diverse biphosphine and alkylalkenes by DFT calculations shows that the superior reactivity noted with the bulky ligand DTBM-SEGPHOS emanates principally from a better stabilization of the hydrocupration transition state *via* superior dispersion interactions from the *tert*-butyl substituent of the phosphine and the alkyl substituent of the alkene.^[23b] Indeed, for terminal and internal alkenes and in contrast to arylalkenes, the rate-limiting step is the hydrocupration step.^[23] Additionally, the high enantiofacial discrimination of the olefin during the hydrometalation step originates from the spatial orientation of the *tert*-butylsubstituted aryl group of the biphosphine ligand as suggested by DFT studies.^[21a] The understanding of the substrate-ligand interactions was exploited further to design a more efficient biphosphine ligand

for this CuH-catalyzed transformation.^[26] An iterative ligand design approach led to the identification of ligand L_2 (SEGFAST; Scheme 4) as affording a significantly more active copper-hydride catalyst than the previous optimal ligand L_1 . Indeed, L_2 provides a 62-fold rate increase compared to L_1 in the *anti*-Markovnikov hydroamination of terminal alkylalkenes and Bn_2NOBz (Scheme 3).^[26] The alliance of both 3,5-*i*-C₃F₇ and 3,5-*t*Bu-4-MeOC₆H₂ substituents was crucial to achieve the proper balance of stability and reactivity at the catalyst.



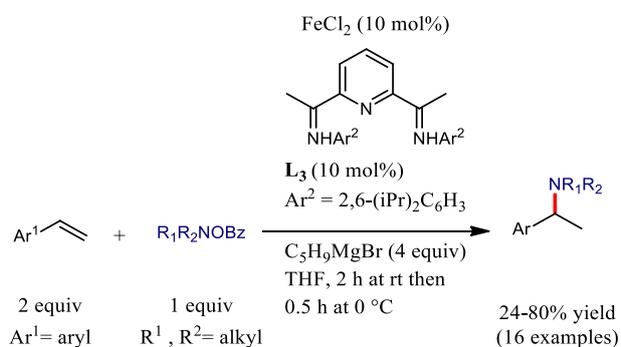
Scheme 5. Proposed mechanism for DTBM-SEGPHOS-CuH-catalyzed hydroamination of styrene and $Bn_2NOCOAr$ proceeding by alkene hydrometalation (L_1 - (R) -DTBM-SEGPHOS).

This mechanistic understanding led, through structure optimizations of the silane, amine transfer agent and use of additives (^tBuOH, PPh₃) to noteworthy enhancement of the scope, efficiency and practicality of the CuH-methodology.^[23a,27,28] For instance, the synthesis of enantioenriched *N*-arylamines could be achieved by the addition of ^tBuOH (1 equiv) and PPh₃ in catalytic amount to the reaction medium.^[28a] The employ of 1,2-benzisoxazole as electrophilic amine partner equivalent to ammonia affords a practical access to enantioenriched α -branched and linear primary amines under mild reaction conditions (Scheme 4).^[28b] The chiral Schiff bases products obtained through this procedure can be quantitatively converted into the corresponding primary amines without enantiomeric excess erosion.

Among the earth-abundant transition metal catalysts covered herein, the DTBM-SEGPHOS-CuH hydroamination methodology offers the wider synthetic utility and should be the methodology of choice for the preparation of a plethora of (chiral) amines classes (e.g linear alkylamines, enamines, α -, γ -, or δ -chiral branched alkylamines, chiral 1,3-amino alcohols) from easily available starting materials with

high levels of chemo-, regio-, and stereocontrol.^[21, 27,28]

In 2014, an analogue electrophilic amination strategy was described for the regioselective Markovnikov hydroamination of aromatic olefins and hydroxylamine esters using the combination iron(II) dichloride/2,6-diiminopyridine as precatalyst and a cyclopentylmagnesium bromide as reducing agent (Scheme 6).^[10] However, the scope of this iron-based protocol is not as broad as that of the CuH methodology as it is inefficient for the conversion of α - and β -methylstyrenes, *p*-Cl and *p*-CF₃-styrene and aliphatic terminal alkenes. Mechanistically speaking, the authors proposed that a Fe-H species is generated (from FeCl₂ and Grignard reagent) and subsequently engaged in a regioselective alkene 2,1-migratory-insertion. Electrophilic amination of the ensuing alkyl iron species leads to C-N bond formation.

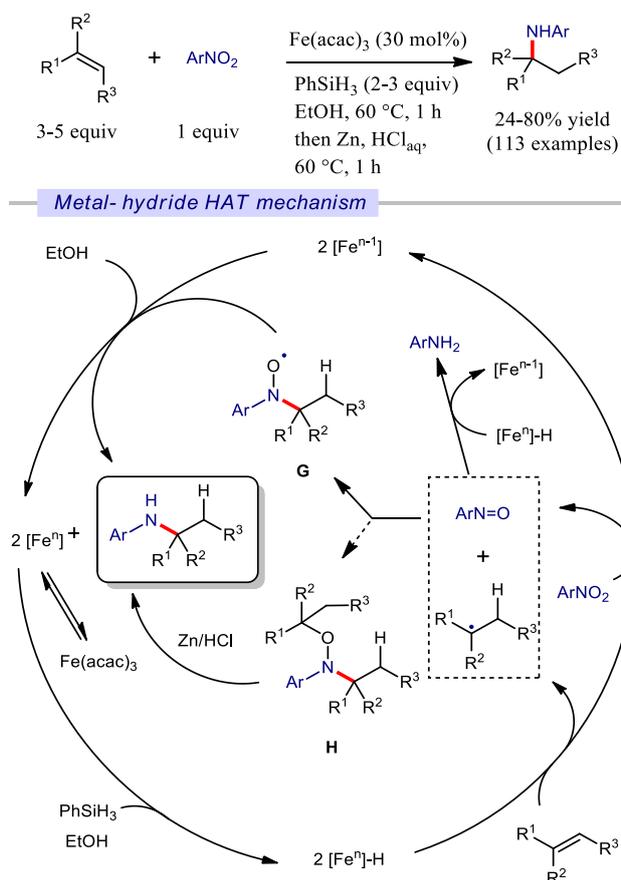


Scheme 6. Regioselective iron-catalyzed Markovnikov hydroamination of aromatic olefins and hydroxylamine esters.

3.3 H-atom transfer

In 2015, the group of Baran described the formal hydroamination of nitroarenes and alkenes using an iron-based methodology which follows a different activation mechanism from alkene π -coordination or hydrometalation.^[11] From their expertise on the H-atom transfer (HAT) promoted by Fe(III)-H for C-C bond radical formations from alkenes^[29] and some literature precedent^[30], the group reports a practical process based on iron hydride chemistry for the preparation of secondary (hetero)aryl amines substituted by secondary or tertiary alkyl from nitro(hetero)arenes and mono and polysubstituted alkenes by C-N bond formation (Scheme 7, top).^[11, 2311] A wide range of hindered secondary (hetero)aryl amines has been synthesized from alkenes and nitroarenes through the use of Fe(acac)₃ (30 mol%) in the presence of an excess of PhSiH₃ (2-3 equivalents). The optimal operating conditions lead to the isolated amines in low to good yields with exclusive Markovnikov selectivity (Scheme 7, top).^[11] In addition to its air and moisture compatibility, this procedure offers a remarkable opportunity for further derivatizations orthogonally to the conventional C-N bond formation methods. Indeed, this methodology

has a wide tolerance for functional groups such as amide, amine, alcohol, thioether, ketone, halide, nitrile, triflate and boronic acid. No or low yields of hydroamination product are obtained with nitroalkanes, leading to a restriction of the methodology to nitro(hetero)arenes with the exception of α -substituted styrenes, 2-nitropyridines, nitroimidazoles and nitrophenyl bearing ortho-esters or free alcohol or thiol.^[11] From control experiments and literature background,^[32] the authors propose that the catalytic cycle follows the general pathway of Scheme 7 (bottom).^[11] This putative mechanism explains the formation of the desired hydroamination products such as amino (hetero)arenes (from the reduction of nitro (hetero)arenes) but also the main by-products such as *N,O*-alkylated products **H**. The initiation step is the *in situ* formation of the species [Feⁿ]-H from Fe(acac)₃ and PhSiH₃ in EtOH.^[33] From the depth experimental and computational studies conducted on the related iron-catalyzed alkene cross-coupling reaction by the groups of Baran, Poli and Holland,^[34] one could speculate that the species [Feⁿ]-H is an unobserved iron(III)-H species. This hydride species reduces both the nitro(hetero)arene and the substituted alkene into the corresponding nitroso(hetero)arene and alkyl radical intermediate respectively by regioselective HAT. After this reduction step, the presumed metallic species would be [Feⁿ⁻¹] (Scheme 7, bottom).^[11] The presence of ArNH₂ isolated as by-product arises from further reduction of the nitroso species by [Feⁿ]-H. Reaction of the nitrosoaryl species with one and two equivalents of the alkyl radical would form the oxygen-centered radical **G** and the *N,O*-dialkyl compound **H** respectively. **G** may then undergo monoelectronic reduction by [Feⁿ⁻¹] to yield the corresponding hydroxylamine anion (Scheme 7, bottom).^[11] The latter is converted to the desired hydroamination product after ethanolsis and second monoelectronic reduction regenerating the [Feⁿ]⁺ cationic species. In the related iron-catalyzed cross-coupling reaction of alkenes and acrylates, these electron transfer-proton transfer sequences that deliver the addition product have been demonstrated to be a concerted proton-coupled electron transfer.^[34b] The authors also suggest that hydroxylamine may also be the result of a hydrogen transfer process between the [Feⁿ]-H species and **G**.^[11] The isolated secondary product **H** resulting from the double alkylation is converted to the formal hydroamination compound by Zn/HCl treatment (Scheme 7, bottom).^[11] Control experiments have clearly established that iron is involved in the activation of both reaction partners (alkene and nitroarene) and that nitroso (hetero)arenes derivatives and hydroxylamines, and not amino(hetero)arenes, are part of the productive process.^[11]



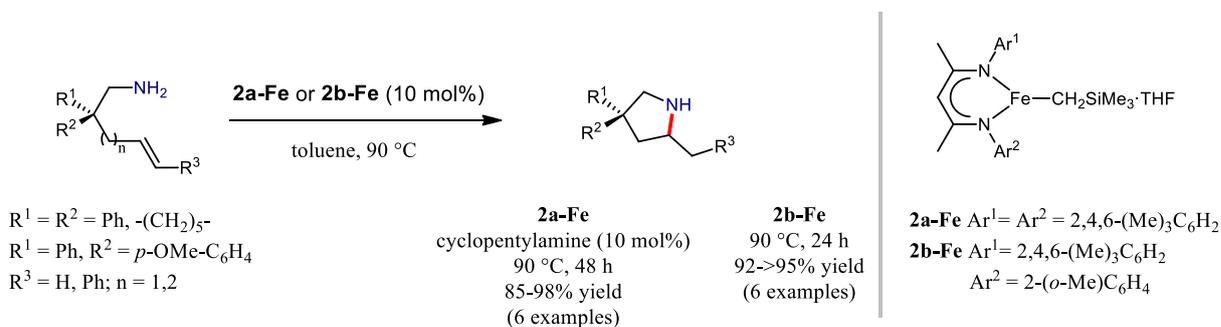
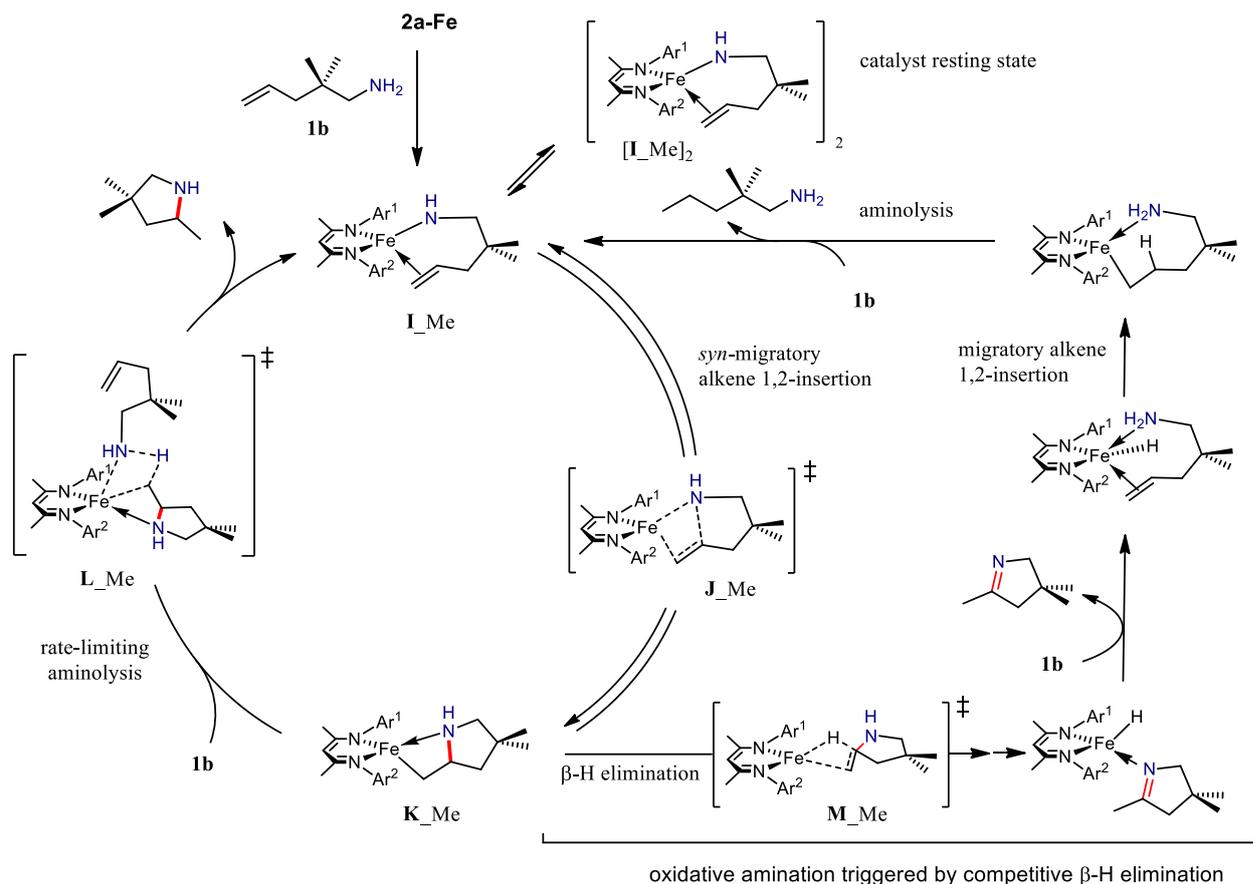
Scheme 7. Proposed metal-hydride H-atom transfer (HAT) mechanism of iron-promoted formal hydroamination of nitro(hetero)arenes and (poly)substituted alkenes.

The groups of Thomas and Shaver and the group of Shenvi have independently improved this iron-hydride protocol from respectively the use of an amine-bis-(phenolate)iron(III) complex (instead of $\text{Fe}(\text{acac})_3$) and isopropoxy(phenyl)silane^[35] (instead of phenylsilane).^[36] Under these conditions, the reaction can be run at ambient temperature and under lower catalyst loading than the Baran's original report.

4 Amine deprotonation pathway

The activation pathway by initial amine deprotonation is mainly encountered in hydroamination with basic catalysts based on Group 1-5 elements.^[11] In the last few years, this activation pathway was extended to earth-abundant, first-row late transition metals in the objective to develop more functional tolerant and sustainable hydroamination catalysts for the cyclization of electronically unbiased primary amines.^[5,6,7] In 2014, this activation mode was employed to develop an unreported iron-based methodology for alkene hydroamination of unprotected primary amines using well-defined low coordinate β -diketiminatoiron(II) alkyl complexes as catalysts.^[5] Stimulated by previous works,^[37] the group of Hannedouche has indeed explored the reactivity of these complexes in the

cyclohydroamination of primary aminoalkenes (Scheme 8, top). They demonstrated that the isolated C_2 -symmetric β -diketiminatoiron(II) alkyl complex **2a-Fe** was an efficient structurally-defined catalyst for the selective hydroamination of primary amines tethered to alkenes, leading to the formation of 5- and 6-membered heterocycles in good to excellent yields (Scheme 8, top).^[5] This methodology is however not suitable for the cyclohydroamination of substrates without a geminal disubstitution on the tether or with 1,2-dialkyl-substituted alkenes.^[5] In their preliminary study,^[5] the authors highlight that the addition of a catalytic amount of cyclopentylamine enhances the reaction selectivity in favor of the hydroamination product (versus the oxidative products) from 83% (without cyclopentylamine) to 96%. However, this selectivity enrichment was done at the expense of the reaction rate. More recently, a combined experimental and computational mechanistic study of this transformation promoted by catalyst **2a-Fe** (without cyclopentylamine) was undertaken.^[38] Kinetic analysis of the cyclohydroamination reaction of 2,2-diphenylpent-4-en-1-amine provides the empirical second-order rate law $v = k[\mathbf{2a-Fe}]^1[\text{aminoalkene}]^1$, a primary KIE ($k_{\text{H}}/k_{\text{D}}$) of 2.7 (90 °C) and the activation entropy value of $\Delta S^\ddagger = -13.4 \text{ cal}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$. These data suggest a highly-order transition state associated with the turnover-limiting step of the catalytic cycle involving the participation of a single adducted aminoalkene and the breaking of a N-H bond.^[38] The formation of iron amido complexes **I** (**I**_{Me} and **I**_{Ph}), isolated and characterized as centrosymmetric amido-bridged dimers [**I**]₂, advocate the amine deprotonation pathway by the alkyl catalyst (Schemes 8, bottom and 9). Additionally, the formation of insertive products from direct reactivity of isolated dimer [**I**_{Ph}]₂ without the assistance of an additional proton source and the *syn*-stereochemistry of the cyclisation are in favor of a C-N bond formation proceeding by alkene migratory-1,2-insertion via a stepwise σ -insertive mechanism.^[38] This insertive type mechanism has been previously proposed for hydroamination reactions catalyzed by rare earth and alkaline complexes.^[39] The catalytic efficiency of complex [**I**_{Ph}]₂ was similar to complex **2a-Fe** suggesting the participation of the latter in the catalytic cycle.^[5] The detailed computational survey of the conceivable mechanistic avenues for the hydroamination pathway suggests that an alternative concerted pathway is less favored in the presence of a more kinetically accessible σ -insertive mechanism.^[38] This concerted pathway evolving concomitant C-N/C-H bond formation via a multi-center transition state structure, was put forward as a distinct operating hydroamination mechanism for some rare-earth-, alkaline- and Group 4-based catalysts.^[39]

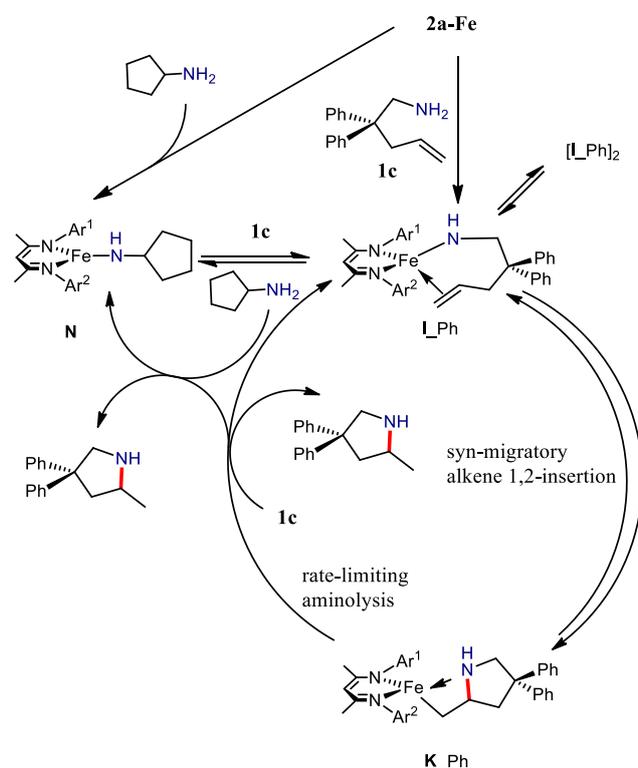
Stepwise σ -insertive mechanism

Scheme 8. Cyclohydroamination of primary amines tethered to alkenes catalyzed by β -diketiminatoiron(II) alkyl complexes **2a-Fe** and **2b-Fe** and the proposed operating stepwise σ -insertive mechanism.

On the basis of these accumulated experimental and computational data, a stepwise σ -insertive mechanism is proposed by the authors as the operating mechanism for the cyclohydroamination reaction catalyzed by **2a-Fe** (without cyclopentylamine) as displayed in Scheme 8 (bottom) for substrate **1b**.^[38] Initial σ -bond metathesis between **2a-Fe** and aminoalkene **1b** delivers the catalytically relevant monomeric species **I_Me**, which is in equilibrium with its amido dimer $[\text{I_Me}]_2$ being likely the catalyst resting state. Subsequent facile and reversible *syn*-migratory-1,2-insertion of the pendant alkene into the Fe-N σ -bond via the transition state structure **J_Me** leads to the transient insertive complex **K_Me**.

Complex **K_Me** can undergo rate-limiting aminolysis (protodemetalation) of its Fe-C σ -bond with aminoalkene **1b** via transition state structure **L_Me**, providing the hydroamination product after liberation and regenerating of active catalyst complex **I_Me** (Scheme 8, bottom).^[38] Competitively, insertive alkyl complex **K_Me** can evolve through β -H elimination. In-depth DFT calculations have also been conducted on the mechanistic pathway for rival oxidative amination and have shown that the kinetically viable, competitive β -H elimination pathway features two-state reactivity and takes place through two-spin crossover transition states.^[38] This pathway accounts for the formation of oxidative amination products

(imine and reduced aminoalkene) as side-products according to the elementary steps described in Scheme 8 (bottom). The reaction selectivity originates from the competitive avenues for turnover-limiting protodemetalation and β -H elimination pathways. The selectivity enhancement in presence of additional cyclopentylamine may originate from the participation of this additive in the rate-limiting step that leads to the formation of amido complex **N** which is proposed to be in equilibrium with the catalytically active species **I**_{Ph} (Scheme 9).^[5,38] This proposal is based on the independent synthesis of **N** which affords similar catalytic efficiency as **2a-Fe**. The detrimental effect of the additive on the reaction rate may be ascribed to the presence of this equilibrated process.^[38]



Scheme 9. Proposed mechanism for the hydroamination of primary amines tethered to alkenes catalyzed by β -diketiminatoiron(II) alkyl complexes **2a-Fe** highlighting the putative role of the cyclopentylamine additive.

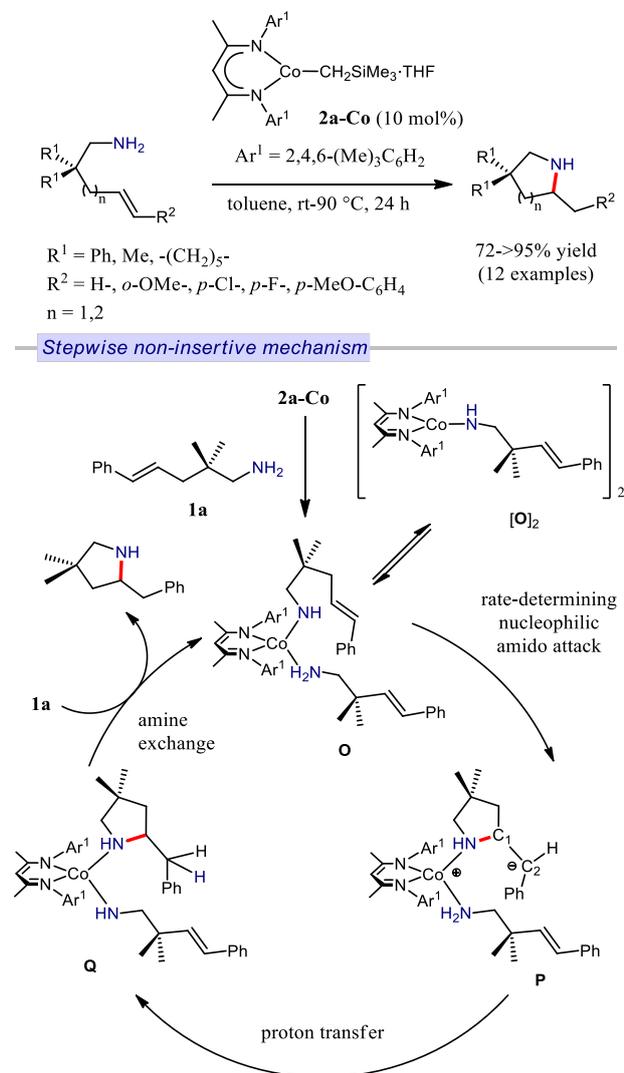
To bypass this drawback in catalyst reactivity linked to the use of cyclopentylamine additive, an alternative strategy involving rational modification of the β -diketiminato ligand was recently explored to target high hydroamination selectivity.^[41] From their mechanistic DFT investigations^[38] and a previous computational study^[40] the authors hypothesized that enhancing the steric demands around the metal should disfavor the competitive β -H elimination pathway and consequently afford higher selectivity in favor of the hydroamination product. Investigations of the catalytic behavior of diverse well-defined C_1 -

symmetric β -diketiminatoiron(II) alkyl complexes featuring steric and electronic variations on one of the *N*-aryl substituents of the ligand scaffold highlight that complex **2b-Fe** bearing a potentially coordinative *ortho*-methoxy substituent is a significantly more active and selective catalyst for the cyclohydroamination of primary aminoalkenes (Scheme 8).^[41] A hydroamination selectivity of 95% is reached at 93% conversion of **1c** after only 250 min of reaction with **2b-Fe** meanwhile a reaction time of up to 48h was needed to attain such selectivity with **2a-Fe**/cyclopentylamine. The better efficiency of **2b-Fe** may be ascribed to the coordinating ability and/or steric hindrance of the *ortho*-methoxy substituent as suggested by comparative studies.^[41]

In 2009, a similar σ -insertive mechanism by amine activation was proposed as putative operating mechanism for the copper-catalyzed cyclohydroamination of primary and secondary aminoalkenes using Cu(Ot-Bu)/4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) as catalytic system.^[7]

In 2018, the groups of Hannedouche, Ujaque and Lledós reported that the well-defined low coordinate β -diketiminatocobalt(II) alkyl **2a-Co** as cobalt analogue of **2a-Fe** has the ability to catalytically promote the *exo*-cyclohydroamination of primary aminoalkenes under mild conditions (Scheme 10, top).^[6] This report is the first example of cobalt-catalyzed alkene hydroamination with unprotected primary amines.^[42] Contrary to the iron catalyst, the introduction of a phenyl ring at the terminal position of the alkene was compulsory to achieve hydroamination reactivity avoiding alkene isomerization as the dominant pathway. This cobalt methodology allows the formation and isolation of diverse *gem*-disubstituted pyrrolidines and piperidines in satisfactory yields (Scheme 10).^[6] However, it does not proceed with trisubstituted alkenes or substrates unbiased toward cyclization.^[6] The reaction mechanism has been examined by deuterium-labelling, kinetics and stoichiometric experiments and DFT calculations. From these studies, a novel mechanism distinct to the above iron-catalyzed hydroamination methodology was suggested as the operative pathway by the authors (Scheme 10, bottom). This stepwise non-insertive mechanism features a turnover-limiting nucleophilic attack of the amido moiety of monomeric cobalt(II) complex **O** (formed by σ -bond metathesis between **2a-Co** and aminoalkene **1a** and coordination of a second molecule of **1a** to the non-coordinated tethered alkene affording the zwitterionic species **P** (Scheme 10, bottom).^[6] The catalytically competent species is proposed to be the amidoalkene-aminoalkene cobalt adduct **O**, which is in rapid equilibrium with its dimer [**O**]₂. The latter was isolated and fully characterized in the solid-state similarly to [**I**_{Me}]₂. Subsequent rapid proton transfer from the amine group of the coordinated substrate to the methylene anion at the C₂ carbon of **P** affords neutral species **Q** (Scheme 10,

bottom). Displacement of the hydroamination product by another aminoalkene molecule regenerates the catalytically competent species. DFT calculations highlight no direct interaction between the metal center and the C₂ carbon of **P**, underlining the non-insertive character of the mechanistic proposal.^[6]



Scheme 10. Hydroamination of primary amines tethered to alkenes catalyzed by β -diketiminatocobalt(II) alkyl complex **2a-Co** and the proposed operating stepwise non-insertive mechanism.

These computational studies reveal that this non-insertive mechanism prevails energetically over alternative operating mechanisms along with the alkene π -coordination, stepwise σ -insertive or concerted non-insertive pathways.^[6] The experimentally determined second-order rate law $v = k[2aCo]^1[aminoalkene]^1$, *syn*-stereochemistry of the addition process and activation parameters as well as the no KIE observation are consistent with the proposed stepwise non-insertive mechanism. The stereochemistry of the cyclization was rationalized by the fact that the proton transfer step from **P** to **Q** is

faster than the C₁-C₂ bond rotation as demonstrated by DFT calculations (Scheme 10, bottom).^[6]

5 Conclusion

This review gives an overview of the mechanistic investigations conducted on the most relevant advances in the burgeoning area of alkene (formal) hydroamination promoted by earth-abundant 3d transition metal catalysts involving iron, cobalt, copper and zinc. This emphasizes the diversity of alkene- and amine-activation strategies encountered to unlock some of the remaining challenging of the field. The fruitful exploitation of the well-developed biphosphine ligated copper-hydride chemistry and the iron hydride hydrogen atom transfer reactions for alkene activation in the context of C-N bond formation has led to outstanding breakthroughs in terms of scope, (stereo)selectivities and applicability. However, despite the unquestionable impacts of these formal hydroamination strategies, their global atom- and -step efficiency diverge from the direct N-H addition on alkenes of classical hydroamination reaction. Successful developments in this direction have been gained by zinc, iron and cobalt catalysts via a more classical alkene π -coordination or amine deprotonation pathways. These efforts deserve to be underscored and sustained. For the CuH- and Fe-catalyzed hydroamination proceeding by alkene and amine activation respectively, the understanding of the operating mechanisms have already led to some noteworthy improvements in terms of activity. Undeniably, the insights gathered through these mechanistic studies will trigger further development in catalyst design and one- and two-electron reactivity control in the exciting field of 3d metal-catalyzed alkene hydroamination.

Acknowledgements

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REVIEW

Alkene Hydroamination via Earth-Abundant Transition Metal (Fe, Co, Cu and Zn) Catalysis: A Mechanistic Overview

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