I.P.Beletskaya, C.Nájera, M.Yus
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Catalysis and regioselectivity in hydrofunctionalization reactions of unsaturated carbon bonds. Part II. Hydroamination

Irina P. Beletskaya,[a]* Carmen Nájera,[b] Miguel Yus [b]

[a] *Department of Chemistry, Lomonosov Moscow State University, Leninskie Gory 1, stroenie 3, 119991 Moscow, Russian Federation*
[b] *University of Alicante, Ctra. San Vicente s/n, 03690 San Vicente del Raspeig, Alicante, Spain*

This review continues consideration of the regioselectivity problem in the catalyzed hydrofunctionalization of unsaturated organic compounds and addresses hydroamination of unsaturated hydrocarbons. Particular parts of the review deal with reactions of alkenes, alkynes, allenes and dienes. It is shown that the selectivity of hydroamination depends on the natures of the reactants and the catalyst. Conditions of the reactions are described; in some cases, reaction mechanisms are discussed. Reactions for which divergent regioselectivity is possible are noted.
The bibliography includes 249 references.

Dedicated to the memory of V.V.Markovnikov.

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1. Introduction

The addition of substrates with an element – hydrogen bond to compounds containing unsaturated carbon – carbon bonds is an atom-economic reaction that has attracted particular attention of synthetic chemists in recent years. Among such processes is hydroamination, which is widely used in organic synthesis. However, the real efficiency of a transformation depends on its selectivity. In some cases, it is important not only to conduct a reaction, but also to ensure the regioselectivity for this reaction, although in some of the examples presented below, stereo- and enantioselectivity are discussed.

Using catalysis, it became possible to perform hydroamination of unsaturated hydrocarbons, which is a thermodynamically unfavourable reaction. Amines are a highly important class of organic compounds, widely used both in fundamental chemical research and in industrial processes and for the preparation of drugs and materials. The development of a one-step method for their synthesis using cheap and readily available starting compounds such as alkenes, alkynes, allenes and dienes became a challenge for organic chemists. It is not surprising that the possibility to use various types of catalysis drew attention of a big number of chemists to hydroamination by amines, amides, hydrazines, hydroxylamines and just ammonia. New activation pathways (electrocatalysis, photocatalysis) and new substrates appeared for these processes and, what is most important, bifunctionalization of unsaturated compounds became possible. Hydroamination reactions are well reviewed.[1–22] However, many of them are focused either on one class of unsaturated compounds or on one type of catalysis. We will restrict ourselves to the discussion of the addition of amines and amides to these compounds. As in Part I of the review,[23] devoted to hydroformylation, hydrosilylation and hydroborylation reactions, the attention here is focused on the regioselectivity problem and on the possibility to convert the same substrate to either purely Markovnikov or purely anti-Markovnikov isomer (divergent regioselectivity) by changing the catalyst or conditions, with both products being of synthetic value. The addition of amines to activated alkenes (Michael reaction),[24,25] which can take place without a catalyst, is beyond the scope of this review. Usually,

I.P.Beletskaya. Academician, Doctor of Chemical Sciences, Head of the Laboratory of Organoelement Compounds at the Department of Chemistry, Moscow State University.
Telephone: +7(495)939 – 3618, e-mail: beletska@org.chem.msu.ru
Current research interest: chemistry of organoelement compounds including transition metals and lanthanides; homogeneous transition metal catalysis in organic chemistry, new catalysts, asymmetric organocatalysis.
C.Nájera. Full Professor of Organic Chemistry (Catedrática) Faculty of Sciences, Department of Organic Chemistry, University of Alicante (Spain).
Telephone: +43(965)903 – 728, e-mail: cnajera@ua.es
Current research interest: sulfones, α-amino acids, peptide coupling reagents, palladium-catalyzed reactions, gold-catalyzed reactions, asymmetric metal catalysis, asymmetric organocatalysis, 1,3-dipolar cycloadditions, alkylation reactions with alcohols.
M.Yus. Full Professor of Organic Chemistry (Catedrática) Faculty of Sciences, Department of Organic Chemistry, University of Alicante (Spain).
Telephone: +43(965)903 – 548, e-mail: yus@ua.es
Current research interest: synthetic organic chemistry, metal-based homogeneous and heterogeneous catalysis.

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aza-Michael reactions proceed under mild conditions, although they are restricted to a certain range of substrates. In the case of terminal alkenes, these reactions always give anti-Markovnikov products.

The following abbreviations are used in the review:

9-BBN — 9-borabicyclo[3.3.1]nonane,

(*R*,*R*)-BenzP* — (*R*,*R*)-(+)-1,2-bis(*tert*-butylmethylphosphino)benzene,

BINAP — (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,

bmp — di(1-pyrazolyl)methane,

Boc — *tert*-butyoxycarbonyl,

$(Bpin)_2$ — bis(pinacolato)diboron,

CAAC — cyclic alkylaminocarbenes,

Cat — catalyst,

Cbz — benzyloxycarbonyl,

COD — cycloocta-1,5-diene,

COE — cyclooctene,

Cp — cyclopentadienyl,

Cp* — 1,2,3,4,5-pentamethylcyclopentadienyl,

Cy — cyclohexyl,

dba — dibenzylideneacetone,

DCB — *o*-dichlorobenzene,

DCE — dichloroethane,

DFT — density functional theory,

dipp — 2,6-diisopropylphenyl,

dippf — 1,1′-bis(diisopropylphosphino)ferrocene,

DMAP — 4-dimethylaminopyridine,

DME — dimethoxyethane,

DPEPhos — bis[2-(diphenylphosphino)phenyl] ether,

dppb — 1,4-bis(diphenylphosphino)butane,

dppe — 1,2-bis(diphenylphosphino)ethane,

dppf — 1,1′-bis(diphenylphosphino)ferrocene,

dppp — 1,2-bis(diphenylphosphino)propane,

DPPPent — 1,5-bis(diphenylphosphino)pentane,

dppr — 1,1′-bis(diphenylphosphino)ruthenocene,

(*R*)-DTBM-SEGPHOS — (*R*)-(−)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi(1,3-benzodioxole),

dr — diastereomeric ratio,

ee — enantiomeric excess,

er — enantiomeric ratio,

EWG — electron-withdrawing group,

Fu — furyl,

Ind — indenyl,

Johnphos — 2-(di-*tert*-butylphosphino)biphenyl,

Jospophos — (2*S*)-1-{(1*S*)-1-[bis(1,1-dimethylethyl)phosphino]ethyl}-2-[(*S*)- phenylphosphinyl]ferrocene,

Josiphos — (*R*)-1-[(SP)-2-(dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine,

LED — light-emitting diode,

Ment — menthyl,

(*R*,*R*)-MethylNorphos — 1,1′-{(1R,2*R*,3*R*,4*S*)-5-methylbicyclo[2.2.1]hept-5-ene-2,3-diyl}bis(1,1-diphenylphosphine),

MW — microwave irradiation,

Naph — naphthyl,

neat — solvent free,

Nf — nonafluorobutanesulfonyl (nonaflyl),

NFSI — *N*-fluorodi(benzenesulfonyl)amine,

NMP — *N*-methyl-2-pyrrolidone,

NPs — nanoparticles,

N-Xantphos — 4,6-bis(diphenylphosphino)-10*H*-phenoxazine,

OPNB — 4-nitrobenzoate,

PhthN — *N*-phthalimido,

pip — piperidine,

PPTS — pyridinium 4-toluenesulfonate,

Py — pyridyl,

rr — regioisomeric ratio,

rt — room temperature,

SEGPHOS — 5,5′-bis(diphenylphosphino)-4,4′-bi(1,3-benzodioxole),

Solv — solvent,

TBS — *tert*-butyldimethylsilyl,

TFA — trifluoroacetic acid,

TFE — trifluoroethanol,

Tf — trifluoromethanesulfonyl (triflyl),

THD-Dipp — 1,3-bis(2,6-diisopropylphenyl)hexahydro-2*H*-1,3-diazepin-2-ylidene,

TMDSO — 1,1,3,3-tetramethyldisiloxane,

TMEDA — tetramethylethylenediamine,

TMS — trimethylsilyl,

Tol — methylphenyl (tolyl),

(*R*,*R*)-TolylRenophos — (2*R*,3*R*)-2,3-bis[bis(4-methylphenyl)phosphino]bicyclo[2.2.1]heptane,

TON — turnover number of the catalyst,

Tp — tris(pyrazolyl)borate,

TPPTS — trisodium triphenylphosphine-3,3′,3″-trisulfonate,

TRIP-thiol — 2,4,6-tri(isopropyl)benzenethiol,

Ts — *p*-toluenesulfonyl (tosyl),

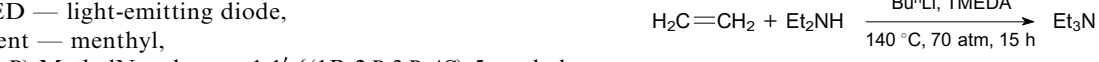
Xantphos — 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

2. Hydroamination of alkenes

The problem of hydroamination of unactivated alkenes has been repeatedly addressed using various catalytic methods in different years. Classical approaches imply the use of Lewis and Brønsted bases and acids as catalysts for these reactions. Although some of the reactions are still relevant for industry, most of them are mainly of historical value. For example, aminomercuration,[26–28] which has played an important role in the development of addition reactions,[29] is now barely used because of toxicity of mercury compounds.

Base catalysis of reactions of unactivated alkenes with amines requires drastic conditions. Indeed, in 1954, Howk *et al.*[30] carried out reactions of ammonia and primary amines with alkenes in the presence of alkali metals and their hydrides. Another example is n-butyllithium-catalyzed addition of diethylamine to ethylene at 140 °C and 70 atm (Scheme 1).[31]

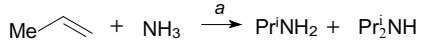
Scheme 1



TMEDA is tetramethylethylenediamine

Alkali metal amides, including rubidium and cesium amides, are often used as bases.[32] In the presence of these catalysts at a temperature of 101 °C and high substrate pressures (84 – 118 atm), ammonia adds to ethylene, giving a mixture of ethyl-, diethyl- and triethylamine; the maximum overall conversion is 67% in the case of $CsNH_2$. The same catalyst was employed to perform the Markovnikov addition of ammonia to propylene giving isopropylamine as the major product. However, despite the drastic conditions, the conversion of alkene in this reaction is moderate (~12%) (Scheme 2).

Scheme 2

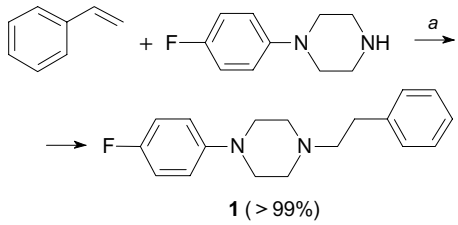


(*a*) $CsNH_2$ or $NaNH_2$, 139 °C, 17.5 h

Under base catalysis, aniline adds to ethylene.[33] The catalytic activity is inherent in the intermediate formed *in situ* from sodium amide and aniline; the reaction requires a temperature of 270 °C and a pressure of 27 atm.

The application of similar procedures for more reactive alkenes is possible under markedly milder conditions. In 1998, Beller and Breindl[34] carried out hydroamination of styrene with a piperazine derivative catalyzed by n-butyllithium. The reaction proceeded at 120 °C and at atmospheric pressure. This afforded the desired anti-Markovnikov product **1** with an excellent selectivity (> 99%) and in high yield (> 99%) (Scheme 3).

Scheme 3



1 (> 99%)

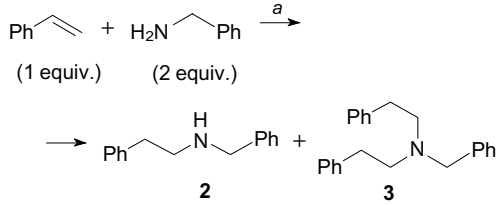
(*a*) Bu^nLi (10 mol.%), THF, 120 °C, 20 min

Decrease in the catalyst amount to 2.5 mol.% actually does not reduce the yield, while in the presence of 1 mol.% of the catalyst, the yield is 62%. In 2004, Beller and co-workers[35] succeeded in conducting this reaction with various piperazine derivatives. As the catalyst amount increased to 20 mol.%, the reaction proceeded at room temperature and gave good yields of products.

The history of studying base-catalyzed hydroamination is considered in most detail in a review of Beller and co-workers.[3]

Hultzsch and co-workers[36] reported the anti-Markovnikov addition of benzylamine to styrene under the action of $LiN(TMS)_2$ (TMS is trimethylsilyl) in the presence of chelating donor diamine ligand $\mathbf{L^1}$ (Scheme 4).

Scheme 4

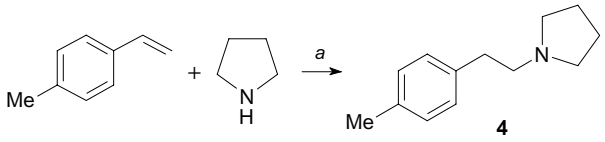


(*a*) $LiN(TMS)_2$, $\mathbf{L^1}$, C_6D_6, 120 °C, 45 min; $\mathbf{L^1}$ = TMEDA

Despite the excess of benzylamine, tertiary amine **3**, resulting from addition of the formed secondary amine **2** to styrene, was detected in the reaction mixture. The authors were able to optimize the reaction conditions for the synthesis of the linear product: the ratio of amines **2** and **3** was 20 : 1 with the total yield being 67%.

Later, Barrett *et al.*[37] demonstrated that calcium and strontium amides $[M(N(TMS)_2)_2]_2$ catalyze hydroamination reactions of substituted styrenes (vinylarenes) with primary and secondary amines giving anti-Markovnikov products. For example, in the transformation shown in Scheme 5, the strontium salt is more active than the calcium complex, which is manifested as a higher yield of product **4**.

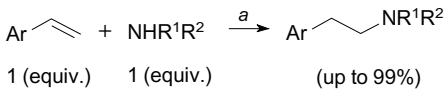
Scheme 5



(*a*) $[M(N(TMS)_2)_2]_2$ (5 mol.%), neat, 60 °C; M = Ca (60 h; 70%), Sr (28 h; 84%); neat is solvent free

Recently, Schulz and co-workers[38] carried out the anti-Markovnikov addition of secondary aliphatic amines to vinylarenes under the action of the solid base $LiCH_2TMS$ in THF at room temperature (Scheme 6).

Scheme 6

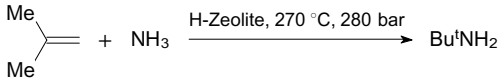


(*a*) $LiCH_2TMS$ (1.5 mol.%), [D_8]-THF, 21 °C, 0.5–120 h

However, attempts to carry out these reactions with high enantioselectivity for α-methylstyrene in the presence of a chiral ligand did not meet with success.

Acid catalysis is associated, first of all, with industrial processes for the synthesis of amines using zeolites.[39] One of such processes is the synthesis of *tert*-butylamine by the Markovnikov addition of ammonia to 2-methylpropene (isobutene) (Scheme 7).[40–42] The reaction proceeds under very drastic conditions; the substrate conversion is reasonable as regards industrial processes (24%), but because of high temperature, recycling of unreacted 2-methylpropene and ammonia is fairly expensive.

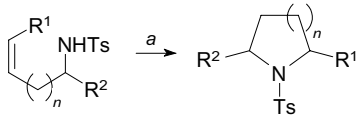
Scheme 7



The first patents on hydroamination in the presence of zeolites were granted to BASF back in the late 1980s, but research in this promising area is still in progress. The latest existing patent[43] is dated 2013. The authors used lithium ion-doped boron zeolites to prepare amines by the reaction of alkenes with ammonia and primary and secondary amines. A publication of 2019[44] is devoted to the mechanism and kinetics of this reaction and to the catalytic activities of various zeolites.

In 2002, Schlummer and Hartwig[45] reported aminocyclization catalyzed by Brønsted acids (Scheme 8). The reaction takes place in the presence of either trifluoromethanesulfonic acid or H_2SO_4. The choice of the catalyst for attaining the best yields of the product depends on the nature of the substrate.

Scheme 8

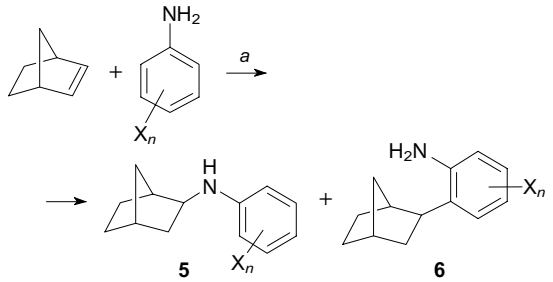


(up to 99%)

(*a*) TfOH (20 mol.%) or H_2SO_4 (20 mol.%), PhMe, 100 °C;
R^1 = H, Ar; R^2 = H, Pr^i; n = 1, 2; Tf is trifluoromethanesulfonyl (triflyl), Ts is *p*-toluenesulfonyl (tosyl)

Bergman and co-workers[46] carried out intermolecular hydroamination of norbornene with aniline derivatives catalyzed by $Ph_3CB(C_6F_5)_4$ (Scheme 9). The reaction pathway depends on the nature of the substrate, since hydroamination competes with hydroarylation. For X_n = 4-Cl and 3,5-$(CF_3)_2$, the target product **5** was formed selectively in 55% and 80% yields; in other cases, mixtures of isomers **5** and **6** were isolated.

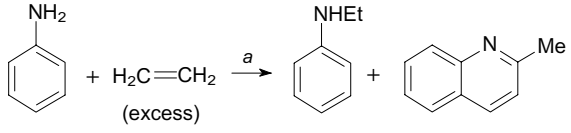
Scheme 9



(*a*) $Ph_3CB(C_6F_5)_4$ (5 mol.%), C_6D_6, 135 °C, 48 h; X_n = H, 4-Cl, 4-OMe, 4-Me, 2,6-Me_2, 3,5-$(CF_3)_2$

Hydroamination catalyzed by metal salts and complexes is now used most widely and is developed most extensively as an addition reaction to unsaturated compounds. For example, the parent alkene, ethylene, is known to be hydroaminated by aniline with a ruthenium complex as a catalyst to give *N*-ethylaniline and 2-methylquinoline in 48 : 52 ratio (71% total yield) (Scheme 10).[47]

Scheme 10

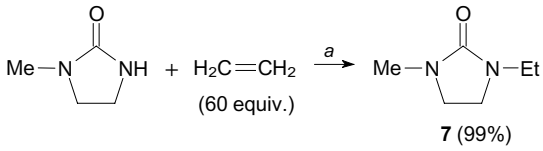


(*a*) [Ru] (5 mol.%), PhH, 80 °C;
[Ru] = $[(PCy_3)_2(CO)(Cl)Ru{=}CH{-}CH{=}CMe_2]^+BF_4^-$;
Cy is cyclohexyl

In the presence of Au^I complex and silver salt, hydroamination of ethylene and terminal alkenes with cyclic ureas results in high yields (Scheme 11).[48]

The hydroamination of unactivated alkenes remains problematic up to now. Considerable efforts are taken in this respect, because it is obvious that such an atom-economic and efficient reaction will be an excellent alternative to other methods for amine synthesis. It is known that alkenes tend to undergo electrophilic addition, while the catalytic reactions covered in this review correspond to

Scheme 11

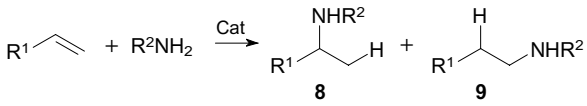


(*a*) AuCl, AgOTf, 1,4-dioxane, 100 °C, 20 h

nucleophilic addition. However, nucleophilic addition should be preceded by activation of the double bond by metal complexes. There is a competition between the complex formation of the metal with the double bond and with the amino group. The coordination to amine gives rise to a complex in which both the Lewis acidity of the metal and the nucleophilicity of the amine decrease. For this reason, moderately basic amines are usually employed for these reactions; most often, these are various amides and even cyclic ureas, which are weakly coordinated to the metal and readily deprotonated.

In the consideration of these reactions, regioselectivity comes to the forefront because both Markovnikov (**8**) and anti-Markovnikov isomers (**9**) can be formed (Scheme 12).

Scheme 12

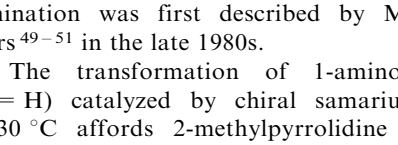


Cat is catalyst

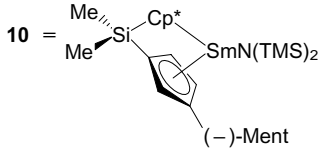
Below we mainly consider intermolecular reactions, although a few intramolecular reactions of this type are also known; these reactions are especially successful, resulting in the preparation of practically valuable nitrogen-containing heterocyclic products. The intramolecular hydroamination reactions are catalyzed by lanthanide or alkaline earth metal complexes and follow a mechanism different from the mechanism of transformations catalyzed by transition metal complexes. The intramolecular hydroamination was first described by Marks and co-workers[49 – 51] in the late 1980s.

The transformation of 1-aminopent-4-ene (n = 1, R = H) catalyzed by chiral samarium complex **10** at −30 °C affords 2-methylpyrrolidine with enantiomeric excess (*ee*) of up to 72%, while 1-aminohex-5-ene (n = 2, R = H) is converted to 2-methylpiperidine (Scheme 13).[5] This reaction was also performed for the homologues with

Scheme 13



(*a*) [Sm] (**10**) (5 mol.%), C_6D_6; n = 1, 2; R = H, Me;
Cp* is 1,2,3,4,5-pentamethylcyclopentadienyl, Ment is menthyl;



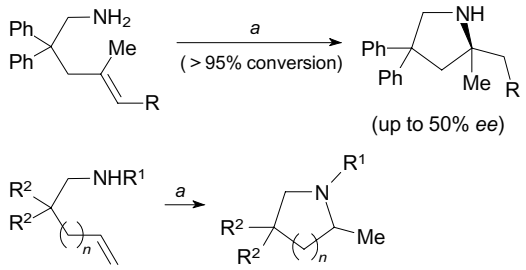
R = Me; the degree of conversion of the substrate exceeded 99%.

The cyclization of aminoalkenes induced by yttrium complexes **11**, **12** (Scheme 14) [52–54] or by calcium and magnesium salts **13**, **14** (Scheme 15) proceeds in a similar way.[37] The mechanism of these transformations includes the formation of metal amide **15**, double bond insertion into the N–M bond (M = Ln, Ca, Mg) and protonolysis yielding cyclic amine (Scheme 16).[17]

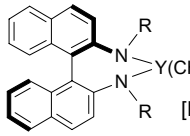
The intermolecular hydroamination of unactivated alkenes is still a problematic reaction, being restricted to a certain type of amines and catalysts. Specific features of these reactions are not only the difficulty in selecting the catalyst and conditions, but also the regioselectivity: usually the Markovnikov isomer is predominantly formed (see Scheme 12).

One of few examples of the intermolecular hydroamination of unactivated alkenes catalyzed by chiral lanthanide complexes was described by Hultzsch and co-workers [55, 56] (Scheme 17). Chiral yttrium and lutetium complexes **16a–e** were used to catalyze the Markovnikov addition of benzylamine to hept-1-ene. The highest yields and enantiomeric excesses of amine **17** were attained when yttrium complex **16a** (R = $SiPh_3$) was taken as the catalyst.

Scheme 14

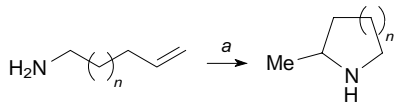


(*a*) [Y] (**11** or **12**) (6 mol.%); R = H, Me, Ph; *n* = 1, 2; R^1 = Me, Bn; R^2 = H, Me, Ph; R^2–R^2 = $(CH_2)_5$

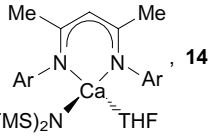
[Y] = 

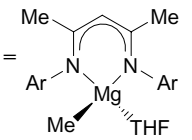
[R = Bn (**11**), cyclo-C_5H_9 (**12**)]

Scheme 15



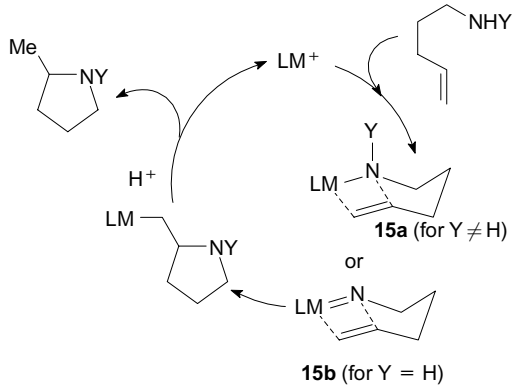
(*a*) [Ca] (**13**) or [Mg] (**14**)

13 = 

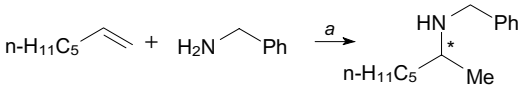
, **14** = 

(Ar = 2,6-$Pr^i_2C_6H_3$)

Scheme 16

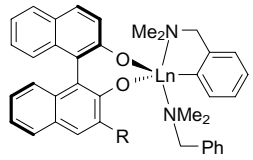


Scheme 17



17 (65%, 58% *ee*)

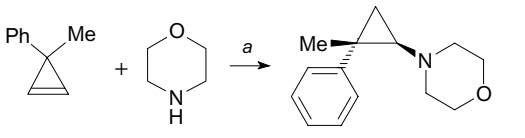
(*a*) [Ln] (**16a–e**), C_6D_6 or [D_8]-PhMe, 150 °C;

16a–e = 

[Ln = Y: R = $SiPh_3$ (**a**), $SiPh_2Cy$ (**b**), $SiPh_2Bu^t$ (**c**), $Si(C_6H_3Me_2$-3,5)$_3$ (**d**); Ln = Lu, R = $SiPh_3$ (**e**)]

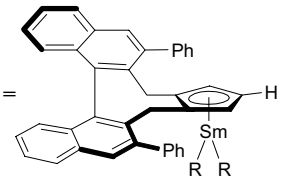
The hydroamination of cyclopropene, especially asymmetric one, is of high relevance, since it results in the synthesis of chiral aminocyclopropanes — important fragments of biologically active compounds and pharmaceuticals. Hou and co-workers [57] performed a reaction of this type using chiral half-sandwich complexes of lanthanides as catalysts, with samarium complex **18** being the catalyst of choice (Scheme 18). Apart from aminocyclopropane **19a**, analogous products **19b–d** were obtained by this method; the diastereomeric ratio (*dr*) was greater than 20 : 1 for all products.

Scheme 18



19a (95%, 99% *ee*)

(*a*) [Sm] (**18**) (5 mol.%), PhMe, 25 °C, 12 h;

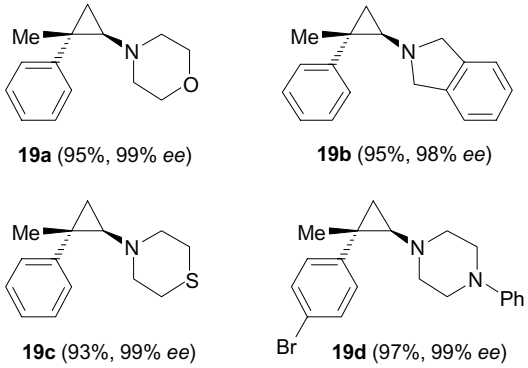
18 = 

(R = $CH_2C_6H_4NMe_2$-2)

However, the catalysis by late transition metals is most interesting for researchers. These reactions of ethylene and other alkenes were described for platinum salts and complexes as catalysts. For example, Brunet and co-workers [58, 59] demonstrated that the platinum salt $PtBr_2$ in the ionic liquid Bu^n_4PBr catalyzes the reaction of aniline with hex-1-ene at 150 °C to give Markovnikov product **20** with high regioselectivity [**20** : (**21** + **22**) = 95 : 5] (Scheme 19).

The effects of the halogen atom in the PtX_2 catalyst (X = Hal), the basicity of amine and the nature of alkene on

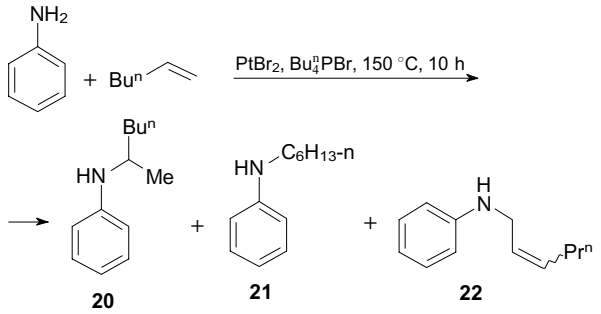
Structures 19



19a (95%, 99% *ee*) **19b** (95%, 98% *ee*)

19c (93%, 99% *ee*) **19d** (97%, 99% *ee*)

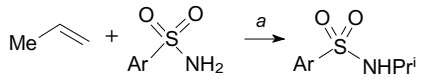
Scheme 19



the catalyst activity, regioselectivity and deactivation were studied for this reaction by experimental and computational methods.[60]

A high Markovnikov selectivity is also inherent in the hydroamination of propylene with *p*-toluenesulfonamide or weakly basic anilines. This reaction is catalyzed by the $(COD)Pt(OTf)_2$ complex (COD is cycloocta-1,5-diene) combined with the $AgBF_4$-activated $[PtCl_2(C_2H_4)]_2$ platinum dimer (Scheme 20).[61]

Scheme 20



(*a*) $(COD)Pt(OTf)_2$ (10 mol.%), $[PtCl_2(C_2H_4)]_2$, $AgBF_4$, DCB, 90 °C, 12 h; DCB is *o*-dichlorobenzene

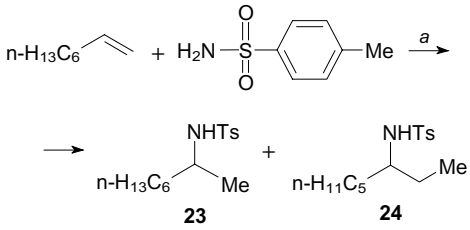
Gold complexes proved to be the most active catalysts in the reaction of alkenes with amides. Thus $Ph_3PAuOTf$-catalyzed hydroamination of oct-1-ene on treatment with *p*-toluenesulfonamide affords a mixture of isomers **23** and **24** (2 : 1 ratio) in a total yield of 85% (Scheme 21).[62]

The AuCl – AgOTf-catalyzed hydroamination of ethylene and terminal alkenes with cyclic ureas was reported by Widenhoefer and co-workers[48] (Scheme 22).

Analogous intramolecular cyclizations catalyzed by gold complex result in high yields of the corresponding Markovnikov products **25** and **26** (Scheme 23).[63]

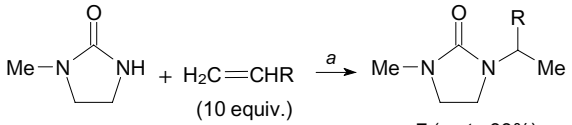
Despite the fact that asymmetric hydroamination has been studied so far by considering the intramolecular cyclizations of aminoalkenes,[5, 50, 64, 65] it is also known for intermolecular reactions of unactivated alkenes (see Scheme 17).[55, 56] Widenhoefer and co-workers[48] showed that chiral gold complex $(\mathbf{L^2})(AuCl)_2$ catalyzes the reactions

Scheme 21



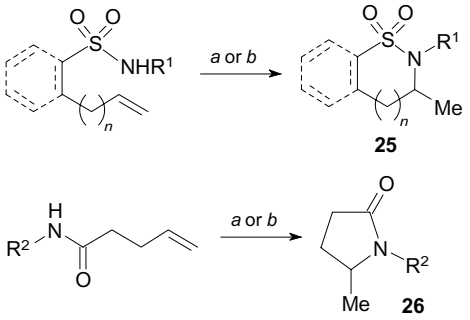
(*a*) $Ph_3PAuOTf$, PhMe, 85 °C

Scheme 22



(*a*) AuCl, AgOTf, 1,4-dioxane, 100 °C, 20 h; R = H, Me, Et, n-C_6H_{13}

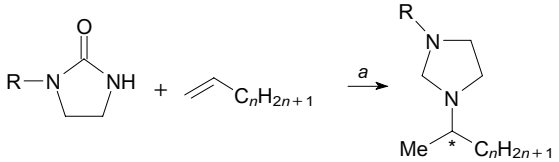
Scheme 23



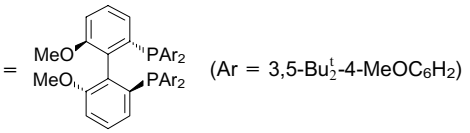
(*a*) $(PPh_3)AuOTf$ (1 – 5 mol.%), PhMe, 100 °C, 12 – 18 h;
(*b*) $(PPh_3)AuOTf$ (1 – 5 mol.%), DCE, MW, 30 min; *n* = 0, 1, 2;
R^1 = H, Et, Bu^t; R^2 = Ar, Bz, Ts; DCE is dichloroethane, MW is microwave irradiation

of terminal alkenes with cyclic ureas to afford Markovnikov product **27** in a high yield and with good enantioselectivity (Scheme 24).

Scheme 24



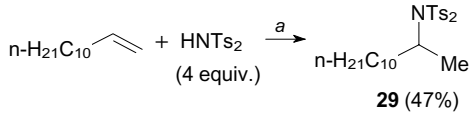
(*a*) $(\mathbf{L^2})(AuCl)_2$, AgOTf, *m*-xylene, 100 °C, 48 h; **27** (75% – 79%, 71% – 79% *ee*)



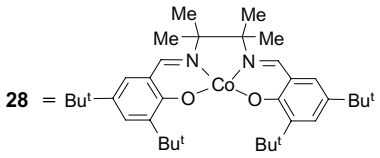
Zhou *et al.*[66] reported the addition of various activated nucleophiles, mainly oxygen-containing ones, to unactivated alkenes catalyzed by cobalt(III) complex. The complex was prepared *in situ* from Co^{II} complex **28** in the presence of

hypervalent iodine and 1,1,3,3-tetramethyldisiloxane (TMDSO). The addition of secondary activated amine under these conditions furnished Markovnikov product **29** in a moderate yield (Scheme 25).

Scheme 25

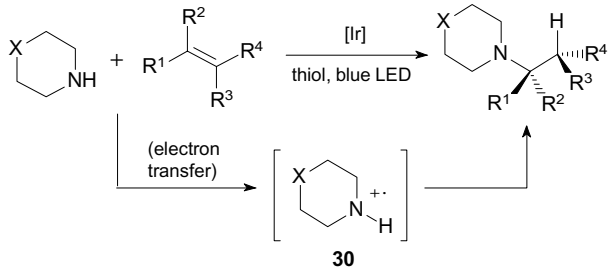


(*a*) [Co] (**28**) (3.3 mol.%), PhIO (2 equiv.), TMDSO (2 equiv.), EtOAc (0.3 M), rt, 18 – 38 h;



The problem of regioselective preparation of the anti-Markovnikov isomer remained unsolved for a long time. Quite recently, Knowles and co-workers [67, 68] proposed a general method for the synthesis of such products by a photocatalyzed reaction between unactivated alkenes and primary or secondary alkylamines in the presence of iridium complex and thiol as a hydrogen atom donor (Scheme 26). This radical reaction passes through the formation of aminium radical cation **30** upon irradiation with a blue light-emitting diode (blue LED).

Scheme 26

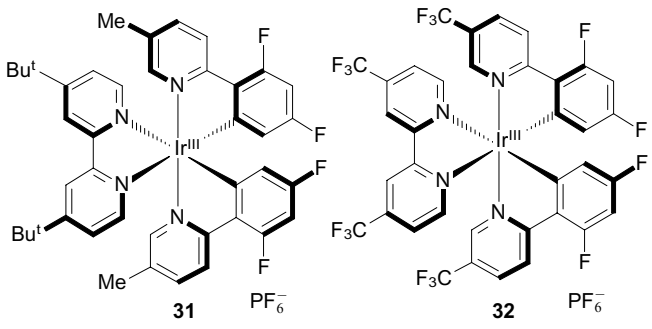


X = O, CH_2, *etc.*; R^1, R^2 = H, Alk; R^3, R^4 = Alk

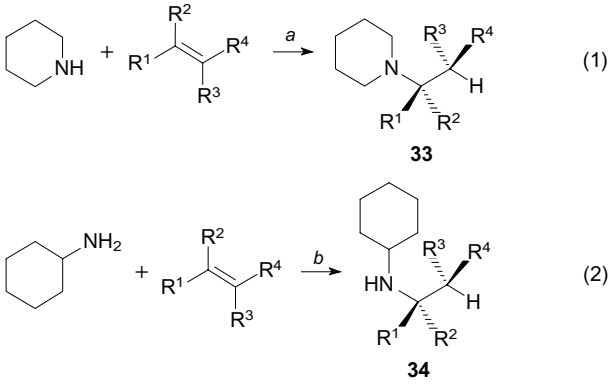
For these reactions, complexes **31** and **32** were proposed as photocatalysts and 2,4,6-triisopropylbenzenethiol (TRIP-thiol) was used as a proton transfer catalyst.

In the case of secondary amines (*e.g.*, piperidine), the reaction with alkenes in the presence of complex **31** gives the expected products **33** in high yields [Scheme 27, reaction (1)]: the yield of amine **33a** [$R^1 = R^2 = H$, $R^3 - R^4 = (CH_2)_5$] reaches 98%. The application of complex **32** in this reactions is of little utility.[67, 68] However, particularly complex **32** showed a better performance in the reaction of primary amines (*e.g.*, cyclohexylamine) with unactivated alkenes [67] [see Scheme 27, reaction (2)]: the yield of amine **34a** ($R^1 = R^2 = H$, $R^3 = Me$, $R^4 = CH_2Bu^t$) was 72%.

Structures 31, 32



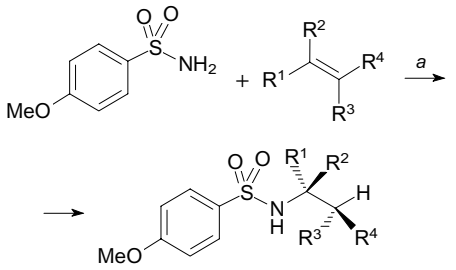
Scheme 27



(*a*) [Ir] (**31**) (2 mol.%), TRIP-thiol (50 mol.%), PhMe, blue LED, rt;
(*b*) [Ir] (**32**) (2 mol.%), TRIP-thiol (30 mol.%), 1,4-dioxane, blue LED, rt;
R^1, R^2 = H, Alk; R^3, R^4 = Alk

The addition of primary and secondary sulfonamides to unactivated alkenes in the presence of indicated photocatalysts also follows an anti-Markovnikov regioselectivity (Scheme 28).[69]

Scheme 28

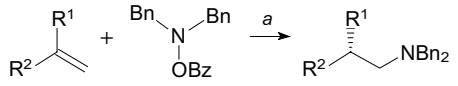


(*a*) [Ir] (2 mol.%), $Bu^n_4NOP(O)(OBu^n)_2$ (20 mol.%), TRIP-thiol (30 mol.%), $PhCF_3$ (0.1 M), blue LED, rt

Zhu and Buchwald [70] obtained anti-Markovnikov product **35** using a basically different (electrophilic) aminating reagent: *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine. The $Cu(OAc)_2$ – silane system, which generates CuH, served as the catalyst. In the presence of an appropriate chiral ligand, such as (*R*)-(−)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi(1,3-benzodioxole] {(*R*)-DTBM-SEGPHOS, [**L**^{3}]*}, these reactions can be used to obtain chiral amine **35a** ($R^1 = CH_2OTBS$, $R^2 = Bu^t$; TBS is *tert*-butyldimethylsilyl) with high enantioselectivity (Scheme 29).

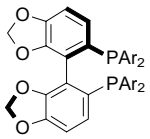
A hypothesized mechanism of the reaction in the general form is depicted in Scheme 30. Although this transformation leads to the hydroamination product, the presented reaction equation (see Scheme 29) is fairly formal, as noted by Hartwig and co-workers.[71]

Scheme 29

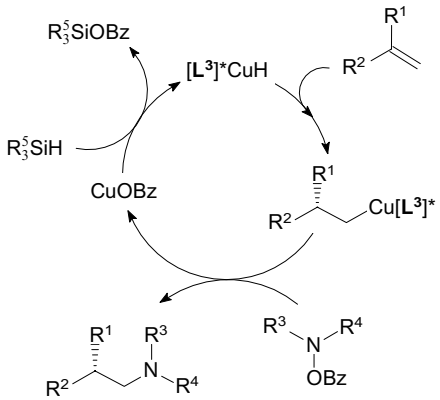


35 (up to 91%, up to 99% *ee*)

(*a*) [CuH](**L**^{3})*, $(EtO)_2MeSiH$, THF, 40 °C, 36 h;

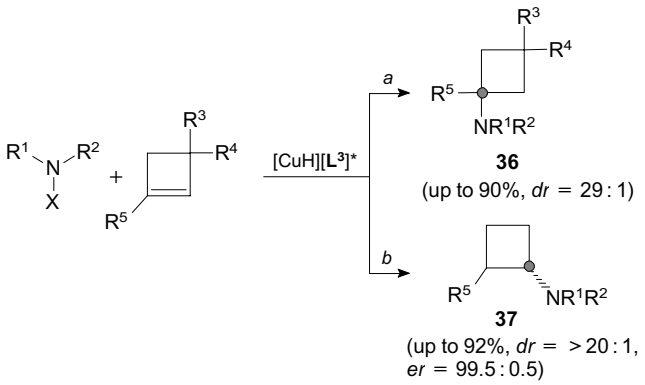
(**L**^{3})* =  (Ar = 3,5-Bu^t_2-4-$MeOC_6H_2$)

Scheme 30



One more interesting example of enantioselective amination in which the steric factors of the reactants change the regioselectivity was described by Buchwald and co-workers.[72] The reaction of cyclobutenes with *O*-benzoylhydroxyamines is highly diastereo- and enantioselective and gives products **36** or **37**, depending on substituents in the substrates (Scheme 31).

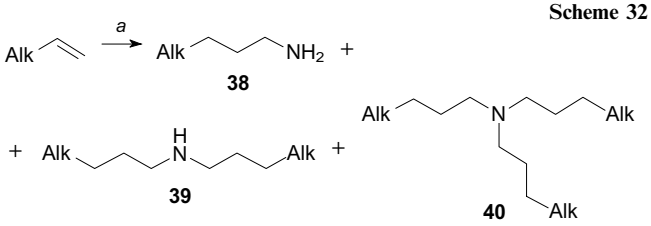
Scheme 31



(*a*) for X = OBz, R^5 = Ar: $R^3 = R^4$ = H; R^3 = Me, R^4 = Ph; $R^3 - R^4 = (CH_2)_5$; (*b*) for X = OC(O)($C_6H_2Me_3$-2,4,6), R^5 = Ar, Alk. Silyl: $R^3 = R^4$ = H; R^1, R^2 = Alk; *er* is the enantiomeric ratio

A separate group of reactions is comprised of hydroaminomethylation reactions: simultaneous treatment of an alkene with synthesis gas and an amine, which was described by Reppe and Vetter[73] back in 1953. Usually these reactions are catalyzed by rhodium complexes,[73 – 77] and when ammonia is used, they give mixtures of mono- (**38**), di- (**39**) and trisubstituted (**40**) amines[78] (Scheme 32).

Scheme 32

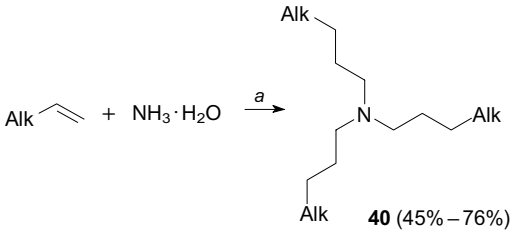


(*a*) [Rh], NH_3, CO/H_2

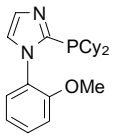
In the presence of bimetallic Rh/Ir catalyst in the two-phase system, primary amine **38** was obtained with 90% selectivity.[79, 80]

Beller and co-workers[78] employed the ruthenium carbonyl complex with 2-phosphine-substituted imidazole **L**^{4} (in 1 : 1.1 ratio) to catalyze hydroamination. The reaction furnished tertiary amines **40** in good yields and with excellent anti-Markovnikov selectivity (the ratio of normal to branched products reached 99 : 1) (Scheme 33).

Scheme 33



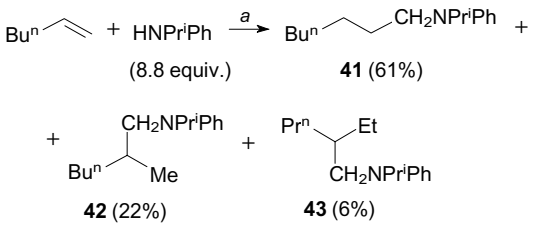
(*a*) $Ru_3(CO)_{12}$ (0.2 mol.%), **L**^{4}, CO/H_2 (1 : 4, 50 bar), THF, PhMe, 120 °C, 20 h;

L^4 = 

Liu *et al.*[81] described the aminomethylation in the presence of a heterogeneous catalyst composed of gold nanoparticles supported on cobalt oxide. The authors believe that cobalt particles generated *in situ* also possess catalytic activity. The reaction of terminal alkene with high excess of amine yields a mixture of a linear (**41**) and branched (**42**, **43**) isomers, with the former predominating. The best outcome with 100% conversion of the substrate and a great predominance of linear product **41** was obtained under conditions indicated in Scheme 34.

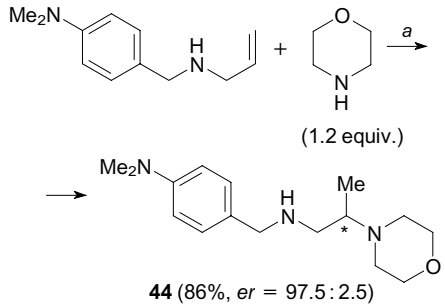
Allylic derivatives of amines and alcohols were also subjected to hydroamination catalyzed by various transition metal complexes. Using rhodium complex with chiral ligand

Scheme 34

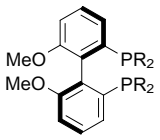


(*a*) Au/Co_3O_4, CO/H_2, heptane, 120 °C, 3.5 h

Scheme 35



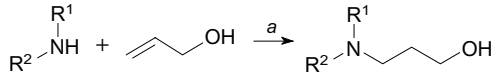
(*a*) $Rh(COD)_2BF_4$ (5 mol.%), (**L**^{5})* (5 mol.%), DME (0.25 M), 60 °C, 16 h; DME is dimethoxyethane, Fu is furyl;

(**L**^{5})* =  (R = 2-Fu)

(**L**^{5})*, chiral diamines **44**, resulting from Markovnikov addition of morpholine, were prepared (Scheme 35).[82]

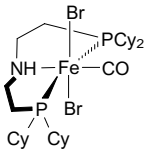
The hydroamination of allylic alcohols with secondary amines catalyzed by iron complex **45** affords anti-Markovnikov products: γ-amino alcohols **46** (Scheme 36).[83] In the case of alkyl- and arylamines, the yields of products **46** (R^1 = Alk, Ar) reach 99%, while for amides [R^1 = C(O)Alk], they do not exceed 85%.

Scheme 36



46

(*a*) [Fe] (**45**) [(1–2) mol.%], $NaHBEt_3$ [(2–4) mol.%], K_3PO_4 (40 mol%), CyH, N_2, 60 °C, 12–24 h; R^1 = Alk, Ar, C(O)Alk; R^2 = H, Alk;

45 = 

A similar result was obtained previously for ruthenium complex.[84]

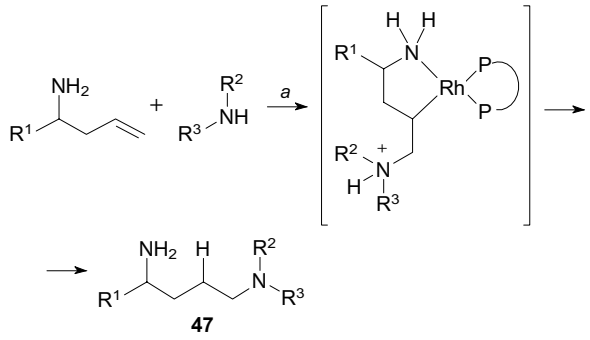
Anti-Markovnikov isomer **47** is also produced upon Rh-catalyzed hydroamination of homoallylic amines in the presence of AgOTs and 1,1′-bis(diphenylphosphino)ferrocene (dppf, **L**^{6}) (Scheme 37).[85]

However, hydroamination of allylamines and -imines catalyzed by rhodium complex [(**L**^{7})Rh(COD)]BF_4 [**L**^{7} is bis[2-(diphenylphosphino)phenyl] ether (DPEPhos)] gives rise to Markovnikov products, for example, compound **48**, in a quantitative yield (Scheme 38).[86,87]

Early studies of hydroamination catalyzed by late transition metal complexes were carried out for norbornene, which has a high reactivity towards the addition reactions because of the strained double bond.[88–90]

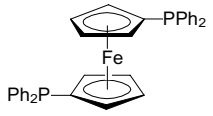
The hydroamination of cyclohexene (Scheme 39) and cyclopentene or norbornene with *p*-toluenesulfonamide or weakly basic anilines catalyzed by the $(COD)Pt(OTf)_2$ complex and the $[PtCl_2(C_2H_4)]_2$ platinum dimer activated by $AgBF_4$ gives expected product **49** in a high yield

Scheme 37

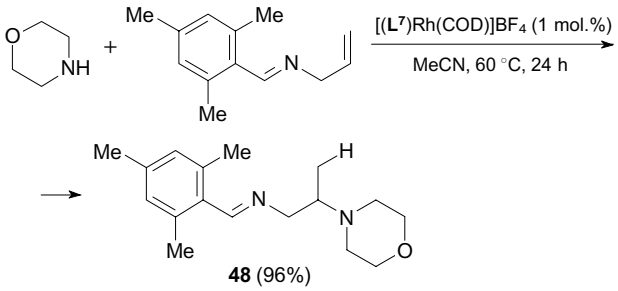


47

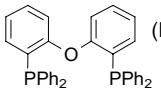
(*a*) $[(COD)RhCl]_2$ (2.5 mol.%), **L**^{6} (5 mol.%), AgOTs (5 mol.%), DME, 60–100 °C, 48 h; R^1–R^4 = Alk; P⌒P = **L**^{6};

L^6 =  (dppf)

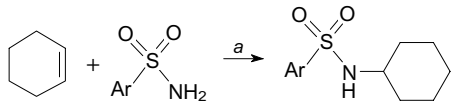
Scheme 38



48 (96%)

L^7 =  (DPEPhos)

Scheme 39



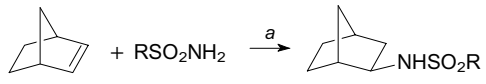
49

(*a*) $(COD)Pt(OTf)_2$ (10 mol.%), $[PtCl_2(C_2H_4)]_2$, $AgBF_4$, DCB, 90 °C, 12 h

(>95%).[61] The same reaction proceeds smoothly with the gold complex $Ph_3PAuOTf$ as the catalyst: the yield of product **49** is 90%.[62]

The $[(PhO)_3P]AuCl$–AgOTf system was used to perform reactions of norbornene with various sulfonamides; for arenesulfonamides, toluene served as the solvent (Solv), while in the case of methanesulfonamide, 1,4-dioxane was used (Scheme 40).[91]

Scheme 40

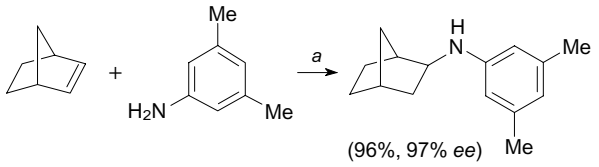


(up to 96%)

(*a*) $[(PhO)_3P]AuCl$, AgOTf, Solv, MW, 90 °C, 30 min; R = Ar, Alk

The addition of aniline derivatives (*e.g.*, *m*-xylidine) to norbornene catalyzed by iridium complex with chiral phosphine ligand (**L^3**)* [(*R*)-DTBM-SEGPHOS] in the presence of potassium bis(trimethylsilylamide) (KHMDS) proceeds enantioselectively giving high yields of products (Scheme 41).[92]

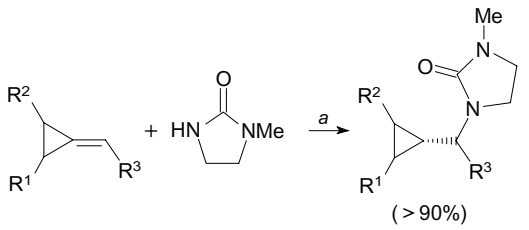
Scheme 41



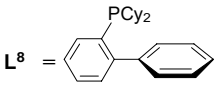
(*a*) $[Ir(COE)_2Cl]_2$ (0.5 mol.%), (**L^3**)* (1 mol.%), 1% base, KHMDS (1 mol.%), 70 °C, 12 h; COE is cyclooctene

Catalysis by cationic gold complex with biphenyl ligand **L^8** allows for the anti-Markovnikov regio- and diastereoselective (> 95%) addition of secondary amines and amides to alkylidenecyclopropanes (Scheme 42).[93]

Scheme 42



(*a*) [(**L^8**)Au(NCMe)]$^+$ SbF_6^- (5 mol.%), 1,4-dioxane, 80 °C, 18 h; R^1, R^2 = Alk, Ph, Bn; R^3 = H, Me;



Copper salts catalyze the regioselective hydroamination of styrenes [reaction (1) in Scheme 43], norbornene [reaction (2)] and cyclohexa-1,3-diene [reaction (3)] on treatment with sulfonamides under mild conditions either in the absence of a ligand or in the presence of (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, **L^9**) or 1,2-bis(diphenylphosphino)ethane (dppe, **L^{10}**) ligand.[94,95] Apart from these complexes, Lewis acid ($InBr_3$) can also catalyze hydroamidation, although in this case, the reaction requires higher temperature (120 °C) and a higher concentration of the catalyst [see reaction (4) in Scheme 43].[96]

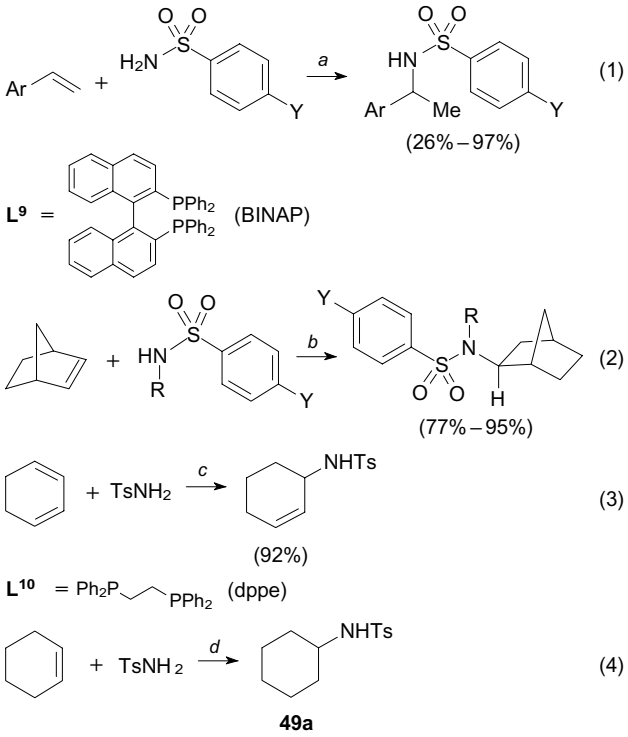
Vinylarenes form a separate class of alkenes. Initially, Lewis acids were used as catalysts for hydroamination of vinylarenes, which gave rise to Markovnikov products.

The addition of cyclic amines (for example, morpholine) to styrenes catalyzed by a palladium complex in the presence of trifluoromethanesulfonic acid also affords Markovnikov isomer — compound **50** (Scheme 44).[97]

A similar reaction pathway is involved in the addition of anilines to vinylarenes catalyzed by palladium complexes with various phosphine ligands: dppf (**L^6**), (*R*)-BINAP [(*R*)-**L^9**], dppe (**L^{10}**), 1,1′-bis(diphenylphosphino)ruthenocene (dppr, **L^{11}**) and 1,1′-bis(diisopropylphosphino)ferrocene (dippf, **L^{12}**) (Scheme 45).[98 – 104]

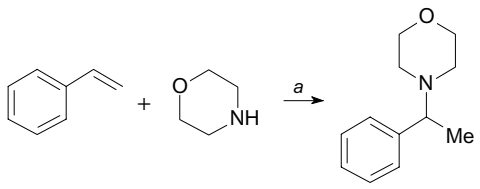
The asymmetric version of this reaction was effected by Ogasawara *et al.*,[102] who used palladium complexes with

Scheme 43



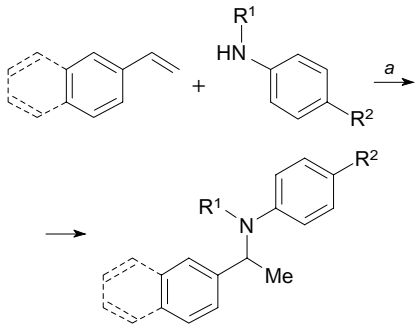
(*a*) $Cu(OTf)_2$ (5 mol.%), **L^9** (5 mol.%), 1,4-dioxane, 75 °C, 18 – 36 h; (*b*) $Cu(OTf)_2$ (10 mol.%), 1,4-dioxane, 85 °C, 18 h; (*c*) $Cu(OTf)_2$ (5 mol.%), **L^{10}** (5 mol.%), 1,4-dioxane, 55 °C, 18 h; (*d*) $InBr_3$ (20 mol.%), PhMe, 120 °C, 18 – 36 h; Y = NO_2, Me; R = H, Bn

Scheme 44

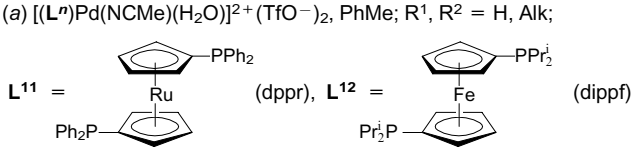


(*a*) $Pd(O_2CCF_3)_2$ (5 mol.%), **L^6** (10 mol.%), TfOH (20 mol.%), 1,4-dioxane, 120 °C, 24 h

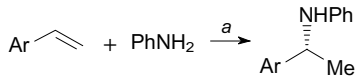
Scheme 45



(*a*) [(**L^n**)Pd(NCMe)(H_2O)]$^{2+}$$(TfO^-)_2$, PhMe; R^1, R^2 = H, Alk;

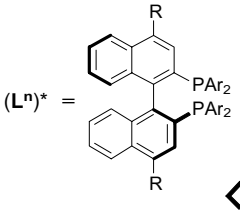


Scheme 46

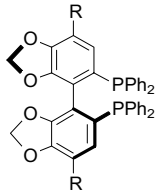


(up to 90%, up to 85% *ee*)

(*a*) [((*S*)-(**L**^{n})*)Pd(NCMe)$_2$]$^{2+}$(TfO$^-$)$_2$, PhMe, 75 °C, 40 h;



[R = H: Ar = Ph (*n* = 9), 4-MeC$_6$H$_4$ (*n* = 13), 3,5-Me$_2$C$_6$H$_3$ (*n* = 14); Ar = Ph: R = Me (*n* = 15), Ph (*n* = 16), P(O)(OEt)$_2$ (*n* = 17), TMS (*n* = 18)];

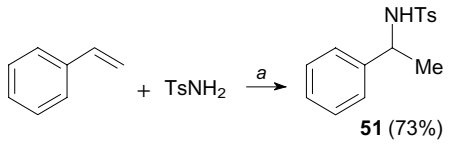


[R = H (**L**^{19}), Bu^t (**L**^{20})]

chiral ligands: 4,4′-R$_2$-derivatives of (*S*)-BINAP [(**L**^{9})*, (**L**^{13})*–(**L**^{18})*] and (*S*)-SEGPHOS [(**L**^{19})*, (**L**^{20})*] [SEGPHOS is 5,5′-bis(diphenylphosphino)-4,4′-bi(1,3-benzodioxole)] (Scheme 46).

The reactions of amides with vinylarenes give Markovnikov isomers in the presence of various catalysts;[105–108] in particular, iron salts were used to prepare sulfonamide **51** (Scheme 47).[106]

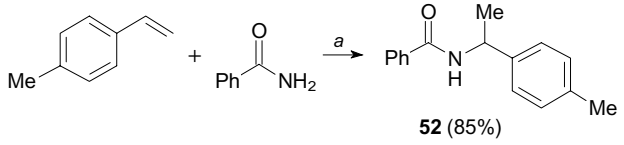
Scheme 47



(*a*) FeCl$_3$ (10 mol.%), 1,4-dioxane, 120 °C

The addition of benzamide to vinylarenes catalyzed by the Pt^{II}–phosphine **L**^{21} system has been described.[107] Under these conditions, 4-methylstyrene is converted to product **52** in a high yield (Scheme 48).

Scheme 48

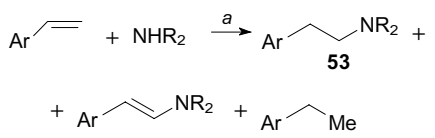


(*a*) [PtCl$_2$(C$_2$H$_4$)$_2$]$_2$–**L**^{21} (5 mol.%), 140 °C, 24 h; **L**^{21} = (4-F$_3$CC$_6$H$_4$)$_3$P

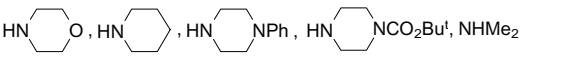
The preparation of anti-Markovnikov products in these reactions was problematic. Currently, there are several known examples of anti-Markovnikov addition to vinylarenes.[37, 109–112] The first example of this type was reported by Hartwig and co-workers[109] in 2003. The authors obtained anti-Markovnikov isomer **53** as the major product in the reaction of secondary amines with vinylarenes catalyzed by the rhodium complex [Rh(COD)(DPEPhos)]BF$_4$ (Scheme 49). The best ratio of anti-Markovnikov product **53** to the corresponding enamine (9 : 1) was found for the reaction of 2-vinylpyridine with dimethylamine.

The application of ruthenium complex **54** in the presence of 1,5-bis(diphenylphosphino)pentane ligand (DPPPent, **L**^{22}) and trifluoromethanesulfonic acid to catalyze the reaction of styrene with morpholine gives rise to anti-

Scheme 49

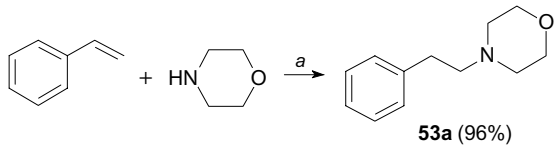


(*a*) [(**L**^{7})Rh(COD)]BF$_4$, PhMe, 70 °C;

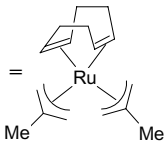
HNR$_2$ = 

Markovnikov product **53a** with a high selectivity (Scheme 50).[110, 113]

Scheme 50

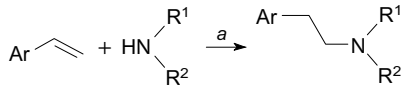


(*a*) [Ru(COD)(2-methylallyl)$_2$] (**54**) (5 mol.%), **L**^{22} (7 mol.%), TfOH (10 mol.%), 1,4-dioxane, 100 °C, 24 h;

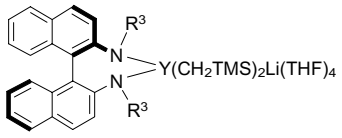
L^{22} = Ph$_2$P–(CH$_2$)$_4$–PPh$_2$ (DPPPent); **54** = 

An equal regioselectivity is observed for reactions catalyzed by lanthanum[51] and yttrium complexes (**11**, **12**, **55a**,**b**, **56**)[111] (Scheme 51).

Scheme 51

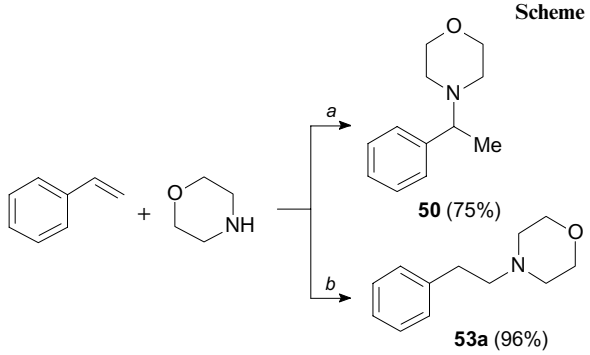


(*a*) [Y] (**11**, **12**, **55a**,**b**, **56**) (10 mol.%), [D$_8$]-PhMe, 130 °C; R^1 = Me, R^2 = Bn (**b**); R^1–R^2 = (CH$_2$)$_4$ (**c**);

[Y] = 

[R^3 = Bn (**11**), cyclo-C$_5$H$_9$ (**12**), 2-MeOC$_6$H$_4$CH$_2$ (**55a**), 2,4,6-Me$_3$C$_6$H$_2$CH$_2$ (**55b**), (9-Antryl)CH$_2$ (**56**)]

Scheme 52



(*a*) Pd(O$_2$CCF$_3$)$_2$ (5 mol.%), **L**^{6} (10 mol.%), TfOH (20 mol.%), 1,4-dioxane, 120 °C, 24 h; (*b*) [Ru] (**54**) (5 mol.%), **L**^{22} (7 mol.%), TfOH (10 mol.%), 1,4-dioxane, 100 °C, 24 h

Using the presented data, it is possible to derive a regiodivergent pair of reactions in which the selectivity is controlled by the catalyst (Scheme 52).

3. Hydroamination of alkynes

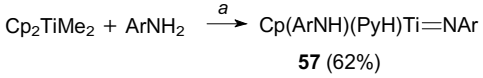
Owing to the nature of a triple bond, which tends to undergo nucleophilic rather than electrophilic addition, hydroamination of alkynes proved to be an easier task for metal catalysis than the hydroamination of unactivated alkenes considered above. However, for the formation of amines, an additional reduction step is required in this case.

While considering these reactions, it is reasonable to start from catalysis by early transition metals, because these catalysts were the first to be studied for these reactions at the end of the 20th century. In this case, the reaction mechanism differs considerably from the mechanism inherent in the catalysis by other metals. As will be seen from the subsequent examples, the addition may give predominantly either Markovnikov or anti-Markovnikov isomer; in some cases, a relatively small ligand modification can induce switching from one pathway to the other; and the resulting enamine can isomerize to imine.

The rapid development of catalyzed intermolecular hydroamination of alkynes started from the pioneering works of Bergman's,[114,115] Rothwell's[116] and Livinghouse's[117] research groups, which used imide complexes of Group 4 metals. Subsequently, detailed studies of alkyne hydroamination catalyzed by titanium (more rarely, zirconium) complexes were performed under the direction of Bergman,[118] Doye,[119] Odom,[120] Richeson[121] and Beller.[122] The authors paid attention not only to the catalyst performance, but also to the selectivity of reactions with these catalysts.

Bergman and co-workers[118] utilized Ti and Zr cyclopentadienyl (Cp) complexes; in the presence of aniline, they were converted to amide – imide complexes such as compounds **57** (Scheme 53).

Scheme 53

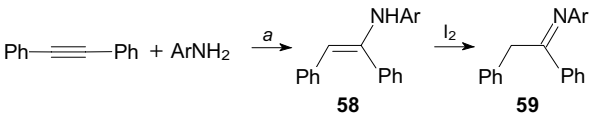


(*a*) PyH, PhMe, 75 °C; Py is pyridyl

These complexes catalyzed the reaction of anilines with diphenylacetylene to give enamine **58**, which isomerized to imine **59** under the action of catalytic amounts of iodine (Scheme 54).

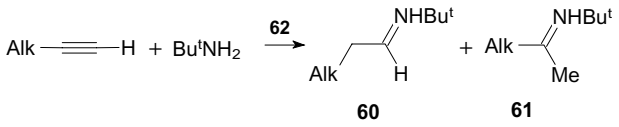
In 2002, Beller and co-workers[123] reported the first example of the preparation of anti-Markovnikov product **60** (rather than Markovnikov product **61**) in the reaction of terminal alkynes with *tert*-butylamine catalyzed by the titanium complex $[(\eta^5\text{-Cp})_2\text{Ti}(\eta^2\text{-C}_2(\text{TMS})_2)]$ (**62**)

Scheme 54



(*a*) [Ti] (**57**) (3 mol.%), C_6D_6, 75 °C

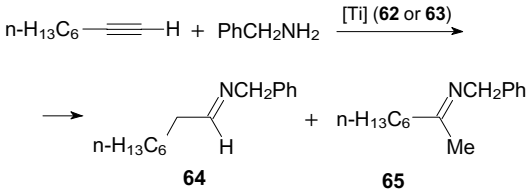
Scheme 55



(Scheme 55). The selectivity of this reaction reached 100% and the yield of product **60** was as high as 98%.

An experimental and theoretical study of the reaction regioselectivity as a function of the nature of amine, alkyne and catalyst was reported.[122] It was shown that aliphatic amines are more prone to form anti-Markovnikov isomers, while aromatic amines tend to form Markovnikov products, although selection of the catalyst may change this trend. For example, the pathway of reaction between of oct-1-yne and benzylamine is controlled by a minor change in the nature of the ligand (Cp in complex **62** and Cp* in complex **63**); it is possible to compose a divergent pair of reactions in which either isomer **64** or **65** prevails (Scheme 56).

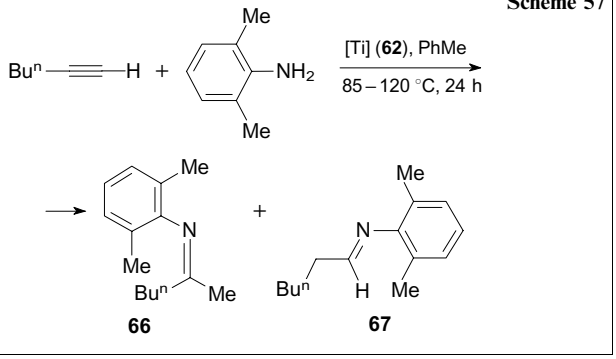
Scheme 56



Cat	Yield of **64** (%)	Yield of **65** (%)
$[(\eta^5\text{-Cp})_2\text{Ti}(\eta^2\text{-C}_2(\text{TMS})_2)]$ (**62**)	82	18
$[(\eta^5\text{-Cp}^*)_2\text{Ti}(\eta^2\text{-C}_2(\text{TMS})_2)]$ (**63**)	19	81

Unlike aliphatic amines, sterically hindered aromatic amines form Markovnikov products with a high selectivity: the ratio of products **66** and **67** is 99 : 1 (the total yield is 94%) (Scheme 57).

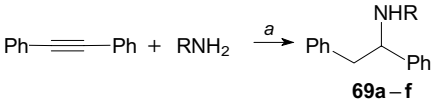
Scheme 57



A more active catalyst, $[\text{Ind}_2\text{TiMe}_2]$ (**68**) (Ind is indenyl), was proposed by Doye and co-workers.[124] The reaction of diphenylacetylene with various amines resulted in high yields of compounds **69a** – **f** and, in some cases, took 3 hours (Scheme 58). In the case of product **69f**, 62% of the initial alkyne was recovered from the reaction mixture.

In the reactions of terminal alkynes, the yields of products were somewhat lower; in the case of *tert*-butylamine, the anti-Markovnikov isomer was formed almost

Scheme 58



69a–f

(*a*) 1) [Ind_2TiMe_2] (**68**) (3 mol.%), PhMe, 105 °C, 3–48 h; 2) $NaBH_3CN$, $ZnCl_2$, MeOH, 25 °C, 20 h

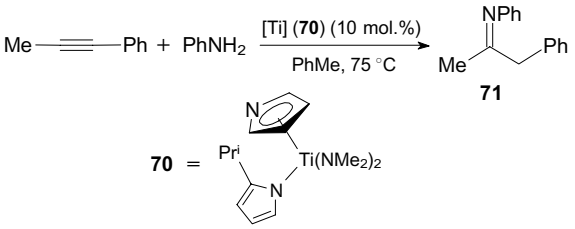
Compound **69**	R	Time /h	Yield (%)
a	Pr^n	3	89
b	Bu^t	5	84
c	cyclo-C_5H_9	3	91
d	4-MeC_6H_4	24	98
e	Ph_2CH	5	90
f	Bn	48	30

selectively with both aliphatic and aromatic alkynes. Similarly to an earlier result,[122] in the case of cyclopentylamine, the anti-Markovnikov isomer prevailed, while the reactions of aromatic amines with aliphatic alkynes gave mainly the Markovnikov product.

A detailed study of the catalytic activity of various titanium indenyl complexes in the hydroamination reactions was carried out by Oñate and co-workers.[125] In the case of terminal alkynes, these transformations also afforded mixtures of Markovnikov and anti-Markovnikov isomers, although in some cases, the authors were able to attain the selective formation of either of the isomers, in full agreement with the results of an earlier publication.[122]

Other highly active titanium catalysts of hydroamination are (2,2′-diaryldipyrrolylmethane)- and bis(2-arylpyrrol-1-yl)titanium complexes described by Swartz and Odom.[126] Complex **70** proved to be most active, as evidenced by studying the rate of reaction of aniline with an internal alkyne, 1-phenylpropyne, which gave imine **71** (Scheme 59).

Scheme 59



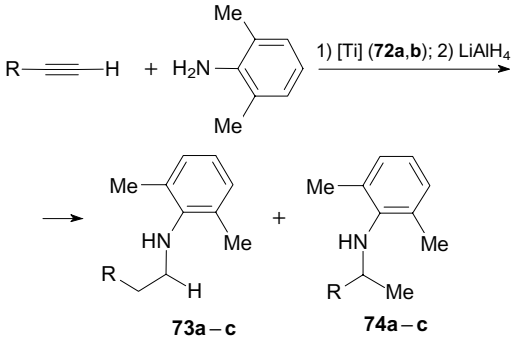
71

70 =

Schafer and co-workers[7] investigated catalysis and regioselectivity of the hydroamination of terminal alkynes in the presence of titanium amidate complexes. Depending on substituents in complexes **72a**,**b** and the nature of the alkyne, the reaction with 2,6-dimethylaniline selectively gave either anti-Markovnikov (**73a–c**) or Markovnikov (**74a–c**) product (Scheme 60).

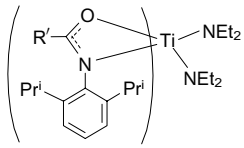
For both complexes, anti-Markovnikov isomer **73** prevailed in the reaction with aromatic alkynes; however, in the case of complex **72a**, this difference was pronounced and the reaction can be considered to be regioselective. Meanwhile, in the reaction of aliphatic alkyne (R = Bu^n) catalyzed by **72a** and **72b**, Markovnikov product **74c** predominated. In the reactions of aliphatic alkynes with aliphatic amines

Scheme 60



73a–c **74a–c**

72a,**b** =



[R′ = Ph (**a**), C_6F_5 (**b**)]

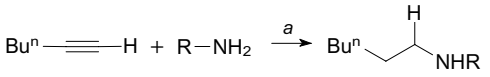
Compounds **73**, **74**	R	Cat	Yield (%)	**73** : **74**
a	Ph	**72a**	62	49 : 1
a	Ph	**72b**	69	3 : 1
b	4-$MeOC_6H_4$	**72a**	57	49 : 1
c	Bu^n	**72a**	72	1 : 49
c	Bu^n	**72b**	84	1 : 49

($BnNH_2$, Bu^tNH_2), the anti-Markovnikov isomer was formed either selectively or exclusively with both catalysts.

In 2014, Schafer and co-workers[127] investigated the selectivity of addition of a large group of aliphatic and aromatic amines to aliphatic and aromatic alkynes using titanium bis(amidate)bis(amide) complex **75** as the catalyst. The reactions of aromatic amines with aromatic alkynes yield mainly the anti-Markovnikov isomer. In the case of aliphatic alkynes, the situation changes: depending on the nature of the alkyne and substituents in the aniline aromatic ring, it is possible to select a combination of reactants that would mainly afford the Markovnikov isomer. The best product yield (with the Markovnikov isomer predominating according to the data of Shafer and co-workers[7]) was attained in the reaction of hex-1-yne with 2,6-dimethylaniline. The reactions of aliphatic amines with aliphatic alkynes result in the formation of anti-Markovnikov products in good yields. It was demonstrated that the resulting mixture of enamine and imine can be subsequently reduced with various reducing agents to give secondary amines **76a–e** (Scheme 61).[128]

The pioneering studies on alkyne hydroamination in the presence of Group 4 metal complexes were followed by the

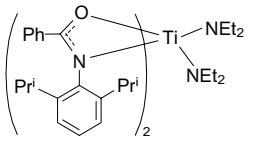
Scheme 61



76a–e (70%–88%)

(*a*) 1) [Ti] (**75**) (5 mol.%), PhH, 65 °C, 24 h; 2) [H]; R = Pr^i (**a**), Bu^t (**b**), Bn (**c**), All (**d**), 3,4-$(MeO)_2C_6H_3(CH_2)_2$ (**e**);

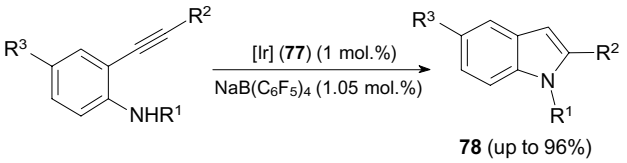
75 =



works in which this reaction was catalyzed by lanthanides [12, 129, 130] and late transition metals (Pd, Rh, Ir).[4, 6] In recent years, the use of gold complexes made a pronounced contribution to the development of this research area.[4, 131, 132]

The intramolecular hydroamination of alkynes has been studied rather comprehensively; these reactions are considered most fully in a review of Gooßen and co-workers.[20] Iridium complex **77** efficiently catalyzes the aminocyclization of substituted *o*-alkynylanilines. The yields of indoles **78** in this reaction directly depend on the nature of substituents in the benzene ring (the reaction proceeds with the greatest difficulty in the presence of electron-withdrawing substituents) (Scheme 62).[133]

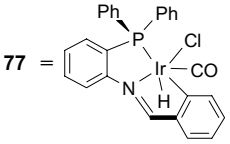
Scheme 62



78 (up to 96%)

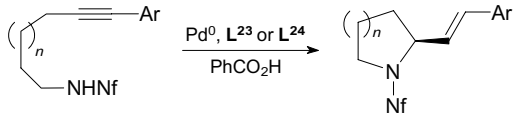
R^1, R^2 = Alk; R^3 = H, Me, NO_2, Cl;

77 =



Narsireddy and Yamamoto [134] implemented the intramolecular asymmetric aminocyclization giving heterocycles **79**. As catalysts, they used zerovalent palladium complexes with chiral ligands: 1,1′-{(1*R*,2*R*,3*R*,4*S*)-5-methylbicyclo[2.2.1]hept-5-ene-2,3-diyl}bis(1,1-diphenylphosphine) [(*R*,*R*)-MethylNorphos, **L[23]**] and (2*R*,3*R*)-2,3-bis[bis(4-methylphenyl)phosphino]bicyclo[2.2.1]heptane [(*R*,*R*)-TolylRenorphos, **L[24]**] (Scheme 63).

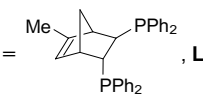
Scheme 63



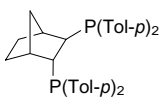
79 (up to 95%, up to 95% *ee*)

n = 1, 2; Nf is nonafluorobutanesulfonyl (nonaflyl),
p-Tol is 4-methylphenyl (tolyl);

L[23] =



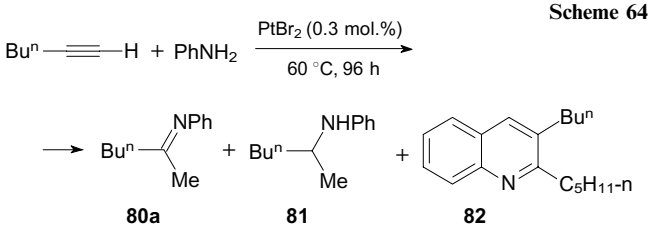
, **L[24]** =



The intermolecular hydroamination of alkynes was studied using a variety of transition metal complexes, although these studies were started relatively recently.

Divalent platinum salts induce the Markovnikov addition of aniline to terminal alkynes. In the reactions with aliphatic alkynes (*e.g.*, hex-1-yne), the formation of the major product **80a** is accompanied by the formation of branched amine **81** and substituted quinoline **82** as by-products.[135] In the authors' opinion, heterocycle **82** results from dimerization of the anti-Markovnikov addition product (linear imine), the subsequent heterocyclization, deamination and dehydrogenation. The major branched product **80** is reduced to amine **81** (Scheme 64).

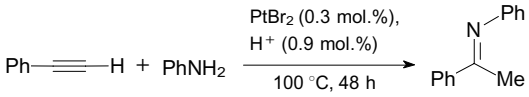
Scheme 64



80a **81** **82**

A similar reaction of phenylacetylene is regioselective: the catalyst turnover number (TON) in the preparation of imine **83a** is 146 (Scheme 65).

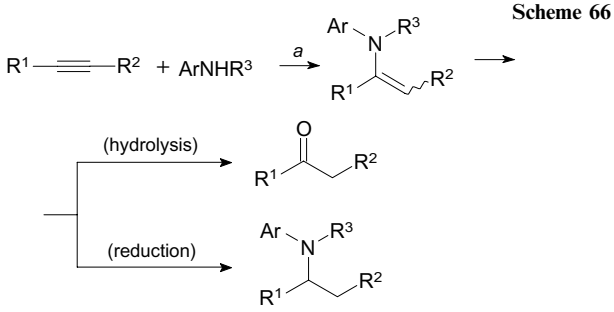
Scheme 65



83a (42%)

Yamamoto and co-workers [136] performed palladium-catalyzed intermolecular hydroamination of unactivated internal alkynes with primary and secondary aromatic and alkylaromatic amines (Scheme 66). After hydrolysis or reduction, the corresponding ketones or amines were formed.

Scheme 66



(*a*) [Pd(**L[10]**)$(H_2O)_2$](TfO)$_2$, 1,4-dioxane, 80 °C; R^1, R^2 = Alk, Ar; R^3 = H, Me

Allyl palladium complex **84** catalyzes the Markovnikov addition of primary and secondary amines to phenylacetylene.[137] The reaction with aromatic primary amines proceeds much more easily than with aliphatic amines: the yields of products **83a**,**b** are higher than the yields of **83c**,**d** and **85a**,**b** (Scheme 67).

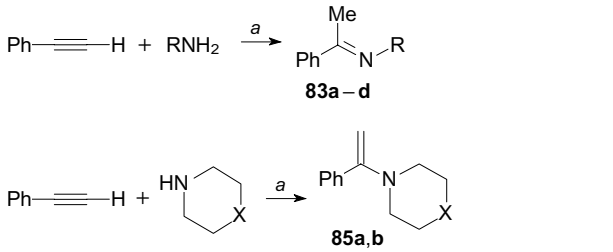
The intermolecular hydroamination of phenylacetylene with anilines occurs under the action of catalyst **77**.[133] The reaction selectively gives Markovnikov isomers **86** (Scheme 68).

Ruthenium carbonyl also catalyzes the Markovnikov addition of amines to arylacetylenes yielding enamines **87** (Scheme 69).[138]

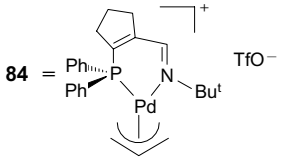
In the presence of NH_4PF_6 additive, anilines can add not only to aromatic, but also to aliphatic alkynes, with product yields depending on the nature of the amine (Scheme 70).[139]

Binuclear ruthenium complex **88** with the (dimethylsilyl)cyclopentadienyl ligand is able to catalyze the selective Markovnikov addition of aromatic amines to phenylacety-

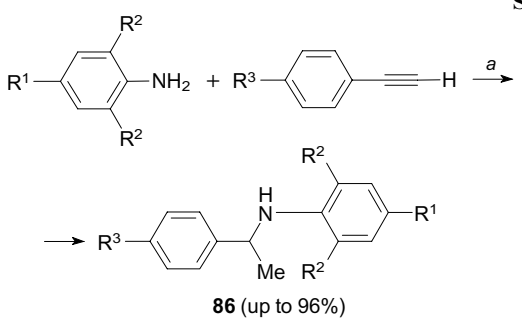
Scheme 67



(*a*) [Pd] (**84**) (5 mol.%), THF, 70 °C, 22 h;
83: R = Ph (**a**, 75%), *p*-Tol (**b**, 67%), Bn (**c**, 12%), Cy (**d**, 6%);
85: X = O (**a**, 62%), CH_2 (**b**, 38%);

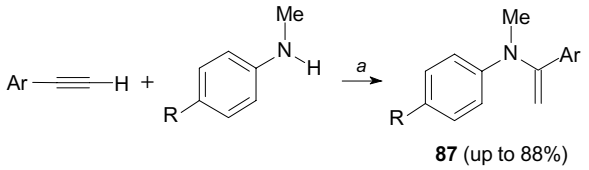


Scheme 68



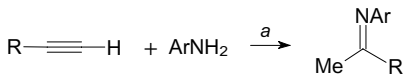
(*a*) 1) [Ir] (**77**) (1 mol.%), 2) Et_3SiH, 3) H_2O; $R^1 – R^3$ = H, Alk

Scheme 69



(*a*) $Ru_3(CO)_{12}$ (0.05 mol.%), 70 °C, 18 h; R = H, Alk

Scheme 70



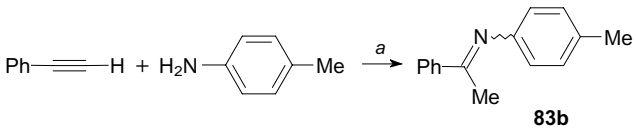
(*a*) $Ru_3(CO)_{12} – NH_4PF_6$ (0.1 mol.%); R = Alk (up to 63%), Ar (up to 95%)

lene; however, the yields of, for example, product **83b** in this reaction are moderate (Scheme 71).[140]

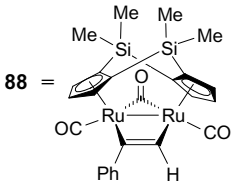
The first example of *N*-arylamide addition *via* the N – H bond to unactivated alkynes was described by Watanabe and co-workers.[141] The reaction of arylamides with oct-1-yne catalyzed by ruthenium carbonyl affords the linear anti-Markovnikov isomer — (*E*)-enamide **89** (Scheme 72).

Allylic ruthenium complex [Ru(COD)(2-methylallyl)$_2$] (**54**) catalyzes the anti-Markovnikov addition of amides to aliphatic alkynes. The stereoselectivity of this reaction can

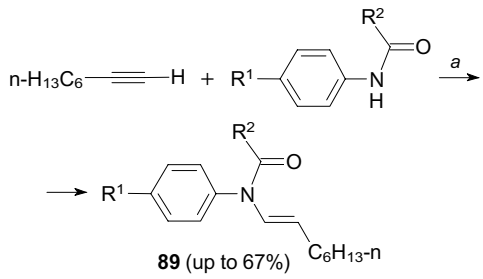
Scheme 71



(*a*) [Ru] (**88**) (3.3 mol.%), HBF_4;



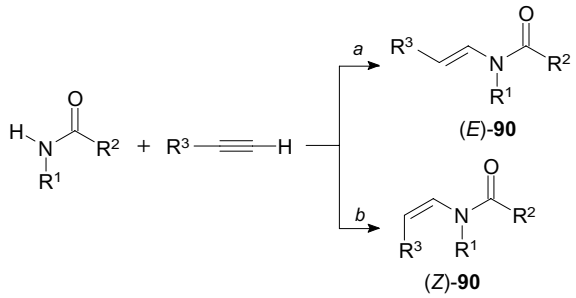
Scheme 72



(*a*) [$Ru_3(CO)_{12}$] (4 mol.%), PCy_3 (8 mol.%), PhMe, 180 °C, 15 h;
R^1, R^2 = Alk

be controlled: depending on the ligand used, either *E* or *Z* isomer of enamides **90** is formed as the major product (Scheme 73).[142]

Scheme 73

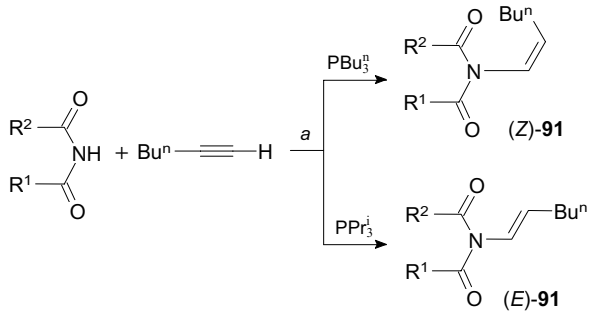


(*a*) [Ru(COD)(2-methylallyl)$_2$] (**54**), PBu^n_3, DMAP;
(*b*) [Ru(COD)(2-methylallyl)$_2$] (**54**), $Cy_2PCH_2PCy_2$, H_2O;
$R^1 – R^3$ = Alk; DMAP is 4-dimethylaminopyridine

Similarly, the addition of imides to unactivated alkynes has the anti-Markovnikov regioselectivity. The reactions catalyzed by a system consisting of allyl ruthenium complex **54**, scandium triflate and phosphine ligand give either *E* or *Z* isomer of compound **91** as the major product, depending on the nature of the ligand (Scheme 74).[143]

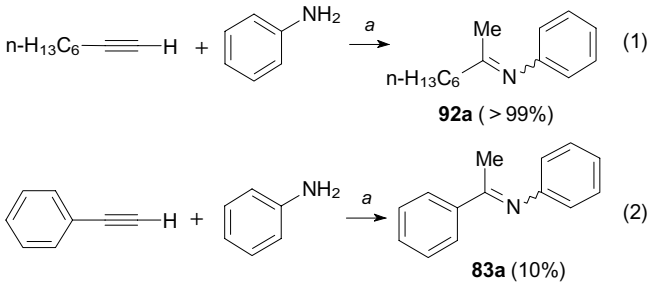
The reaction of aliphatic alkyne (oct-1-yne) with aromatic primary amine catalyzed by the [Rh(COD)$_2$]BF_4 – 2 PCy_3 system taken in a quantity of 2.5 mol.% affords Markovnikov isomer **92a** in a very good yield [Scheme 75, reaction (1)].[144] The addition of aniline to phenylacetylene catalyzed by the same system

Scheme 74



(*a*) [Ru] (**54**), $Sc(OTf)_3$, DMF, 100 °C; R^1, R^2 = Alk

Scheme 75

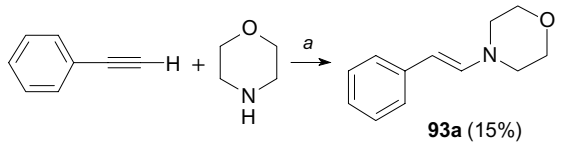


(*a*) $[Rh(COD)_2]BF_4 - 2\,PCy_3$, THF, 100 °C

proceeds markedly less smoothly [see Scheme 75, reaction (2)].

The opposite regioselectivity is inherent in the addition of aliphatic secondary amine to phenylacetylene; however, the yield of anti-Markovnikov product **93a** is also unsatisfactory (Scheme 76).

Scheme 76



(*a*) $[Rh(COD)_2]BF_4 - 2\,PPh_3$

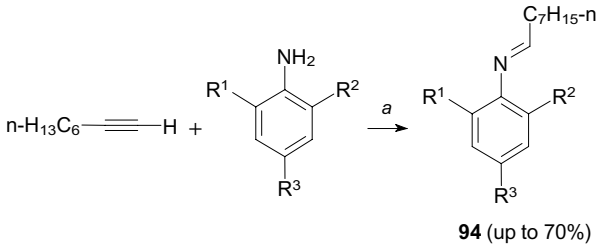
The application of a similar catalyst, $[Rh(\mathbf{L^{25}})(COD)]BPh_4$, in the reaction of oct-1-yne with substituted anilines leads to anti-Markovnikov isomers **94**. The major difference from the previous protocol is the presence of bulky *N*,*N*-ligand $\mathbf{L^{25}}$ (Scheme 77).[145]

When electron-donating substituents are present in the aniline aromatic ring, the yields of the products reach 70%, while the conversion of unsubstituted aniline is only 25%.

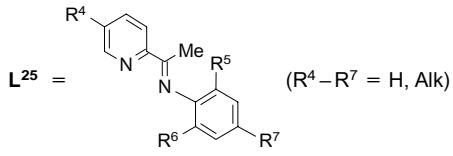
The $TpRh(CH_2{=}CH_2)_2$ catalyst [Tp = tris(pyrazolyl)-borate] combined with triphenylphosphine ensures the anti-Markovnikov addition of secondary (including cyclic) and primary aliphatic amines to aliphatic alkynes yielding enamines **95** or imines **96** (Scheme 78).[146] Under the action of this catalytic system, amines barely add to aromatic alkynes, giving only traces of the product.

The formation of heterocyclic compounds, 1,2-dihydroquinolines **97**, *via* the $[Cp^*RhCl_2]_2$-catalyzed reaction of aniline with terminal alkynes has been reported

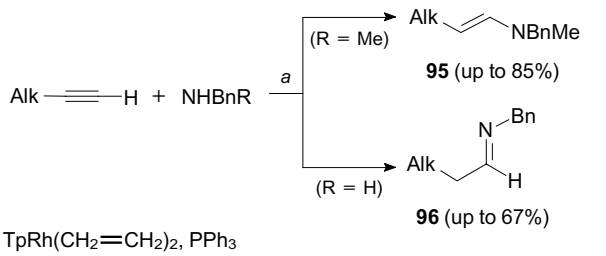
Scheme 77



(*a*) $[Rh(\mathbf{L^{25}})(COD)]BPh_4$; $R^1 - R^3$ = H, Me, Pr^i;



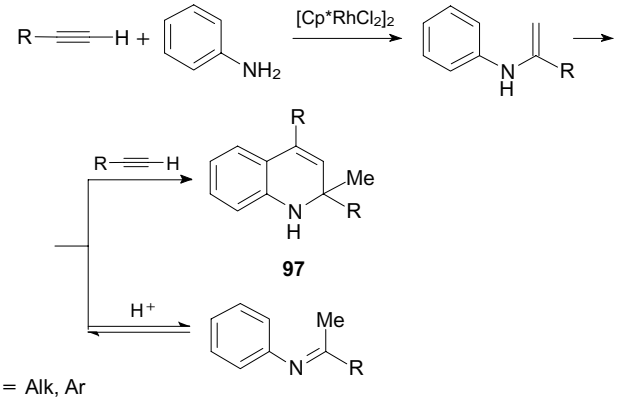
Scheme 78



(*a*) $TpRh(CH_2{=}CH_2)_2$, PPh_3

(Scheme 79).[147] In the authors' opinion, the process starts with the Markovnikov addition, which is followed by alkyne insertion. The conditions were optimized in relation to the addition of 3-methoxyaniline to phenylacetylene, with the best yields being attained when HBF_4 was used as an additive, 2 mol.% of the Rh catalyst was taken, and the reaction was conducted in toluene at 100 °C.

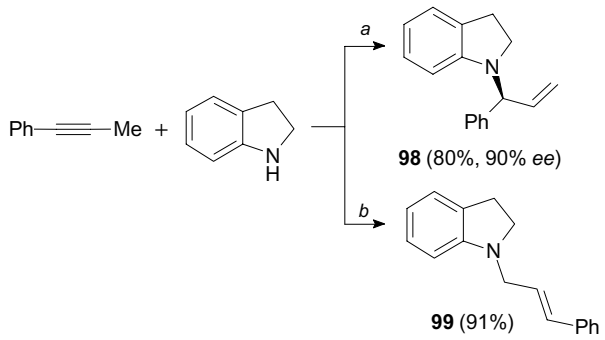
Scheme 79



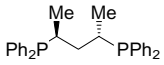
R = Alk, Ar

The first example of regio- and enantioselective Rh-catalyzed hydroamination giving a branched (**98**) or a linear (**99**) isomer was reported by Chen *et al.*[148] The regioselectivity was controlled by the type of acid added: phthalic acid and 3,5-dimethylbenzoic acid and 1,2-bis(diphenylphosphino)propane (dppp, $\mathbf{L^{26}}$) were used to prepare the linear isomer, while ligand $\mathbf{L^{27}}$ was utilized for the enantioselective synthesis of the branched isomer. Without an acid, the reaction did not take place (Scheme 80).

Scheme 80



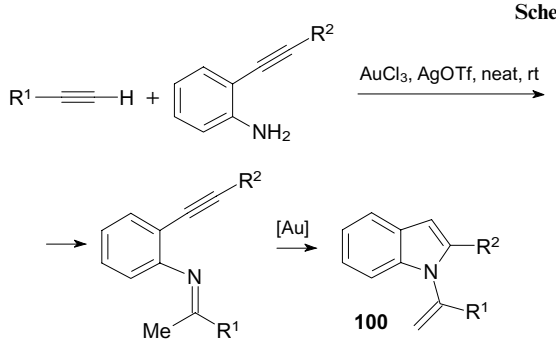
(*a*) [Rh(COE)$_2$Cl$_2$], **L^{26}**, 3,5-Me$_2$C$_6$H$_3$CO$_2$H, THF, 70 °C, 18 h;
(*b*) [Rh(COE)$_2$Cl$_2$], **L^{27}**, 1,2-(HO$_2$C)$_2$C$_6$H$_4$, THF, 70 °C, 18 h;

L^{26} = Ph$_2$P⌒PPh$_2$, **L^{27}** = 

In recent years, considerable attention has been paid to gold-catalyzed transformations. Gold salts and complexes are especially efficient in activating triple bonds.[8, 131, 132] Gold as a catalyst for the hydroamination of alkynes proved to be highly useful. Here we do not address the mechanisms of these reactions,[149] because the Markovnikov regioselectivity was observed in all cases. Reactions of alkynes that contain functional groups, which allow the synthesis of double hydroamination products or more complex products,[150, 151] are also beyond the scope of this review. The syntheses resulting in the generation of new stereocentres (*i.e.*, transformations in which hydroamination is accompanied by hydroarylation) are not considered either.[152] All these issues are not related to the regioselectivity problem, although they are highly important and require special consideration.

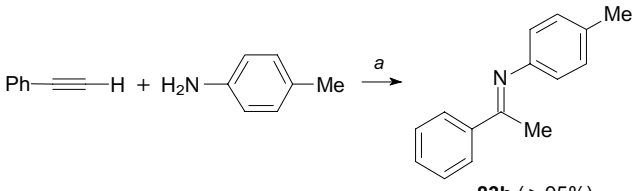
It is known that intramolecular hydroamination of *o*-alkynylaniline catalyzed by various Lewis acids is a modern method for indole synthesis.[153] Li and co-workers [154] demonstrated that reactions of *o*-alkynylanilines with terminal alkynes catalyzed by Au^{II} complex give rise to *N*-alkenylindoles **100**. Presumably, this double hydroamination involves an intermolecular hydroamination step, which is followed by iminocyclization (Scheme 81).

Scheme 81

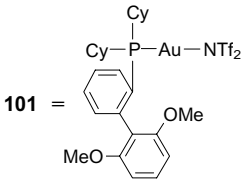


Leyva and Corma [155] proposed two active catalysts based on gold(I) and phosphine ligands, Au(S-Phos)NTf$_2$ (**101**) and Au(PPh$_3$)NTf$_2$ (**102**), for the hydroamination of alkynes. The catalysts can easily be recovered by precipitation upon the addition of hexane and efficiently reused (they withstand 3 to 5 cycles, depending on the particular reaction) and allow conduction of the processes at room temperature. This always results in the formation of the Markovnikov product, but the selectivity of these catalysts in the reactions of aromatic and aliphatic alkynes is different. For example, *p*-toluidine and phenylacetylene react in the presence of catalyst **101** to give imine **83b** in an excellent yield (Scheme 82), while the use of complex **102** results in a substantially lower product yield.

Scheme 82

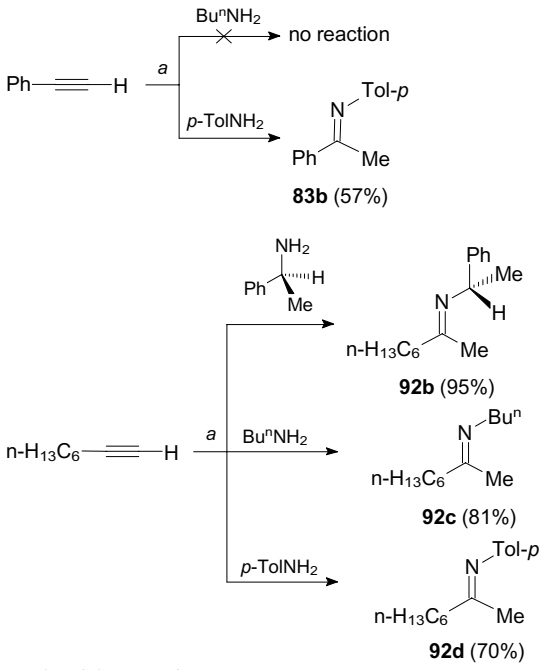


(*a*) [Au] (**101**) (1 mol.%), CH_2Cl_2, rt, 24 h;

101 = 

Relatively high (~70%) product yields were detected in the reactions of aromatic amines with aliphatic alkynes. Meanwhile, when complex **101** serves as the catalyst, alkylamines do not react with alkynes. In the case of catalyst **102**, the situation is absolutely different: with this catalyst, reactions of aromatic amines with both types of alkynes, but especially with aromatic alkynes, proceed less efficiently; aliphatic amines with aromatic alkynes do not react at all; however, reactions of aliphatic amines with aliphatic alkynes give excellent yields of products (Scheme 83).

Scheme 83

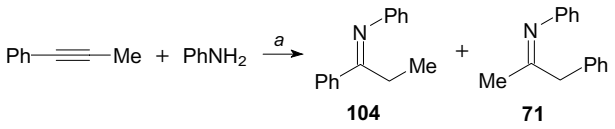


(*a*) [Au] (**102**) (5 mol.%), neat, rt, 24 h

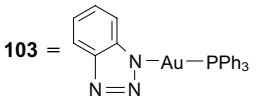
Apparently, this effect of the ligand in the Au catalyst is due to an intricate combination of electronic effects in the amine and in the alkyne and in the formed π-complex.

Shi and co-workers [156] proposed anionic and neutral triazole ligands for the hydroamination of alkynes. These ligands form complexes with Au^{I}; they are stable at a temperature of 80 °C and catalyze reactions of internal and terminal (aromatic and aliphatic) alkynes at low concentrations (1 mol.%). The highest activity was found for catalyst **103**; however, for attaining high yields of products **71** and **104** (91%; 1 : 6 ratio), the presence of $H_3PO_4 \cdot 12\,WO_3$ co-catalyst is required (Scheme 84).

Scheme 84

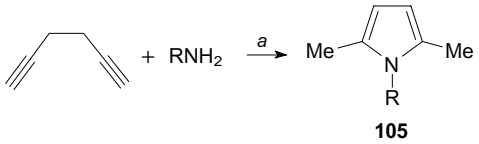


(*a*) [Au] (**103**) (1 mol.%), $H_3PO_4 \cdot 12\,WO_3$ (2 mol.%), PhMe, 80 °C;



The reactions of hexa-1,5-diyne with anilines afford substituted pyrroles **105** in high yields, with the highest yield being 97% for R = Ph (Scheme 85).

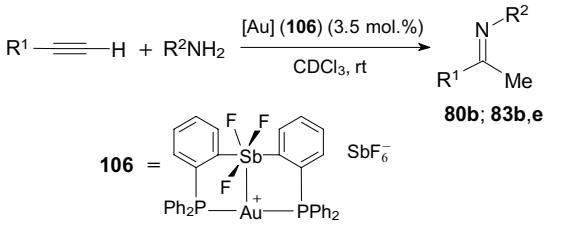
Scheme 85



(*a*) [Au] (**103**) (1 mol.%), $H_3PO_4 \cdot 12\,WO_3$ (2 mol.%), PhMe, 80 °C

Yang and Gabbaï [157] proposed conducting hydroamination with aromatic amines in the presence of cationic gold complex **106**; this catalyst proved to be very active towards transformations involving terminal aromatic and aliphatic alkynes. Owing to the donor – acceptor bond between gold and antimony atoms, the Lewis acidity of gold in this complex is increased (Scheme 86).

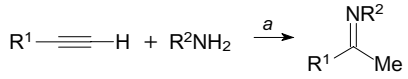
Scheme 86



Compound	R^1	R^2	Time /min	Yield (%)
80b	Bu^n	*p*-Tol	60	61
83b	Ph	*p*-Tol	40	92
83e	Ph	2,4-$Pr^i_2C_6H_3$	70	83

Cationic gold complexes in the presence of heteropoly acids catalyze the Markovnikov addition of anilines and phenylhydrazines to aromatic and aliphatic alkynes to afford the corresponding ketimines (Scheme 87).[158]

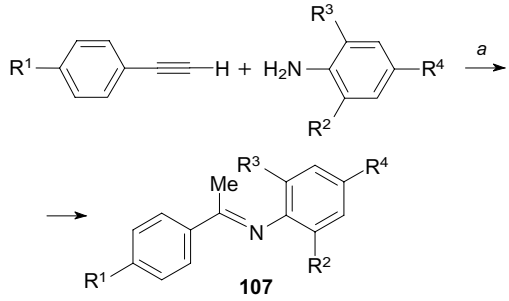
Scheme 87



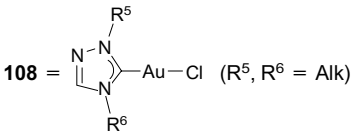
(*a*) [Ph_3AuMe], NH_4PF_6, neat; R^1 = Alk, Ar; R^2 = Ar, NHAr

Markovnikov isomer **107** was obtained by the reaction of phenylacetylenes with anilines catalyzed by gold(I) complexes with 1,2,4-triazole-containing *N*-heterocyclic carbenes **108**, which was accompanied by enamine – imine rearrangement (Scheme 88).[159]

Scheme 88

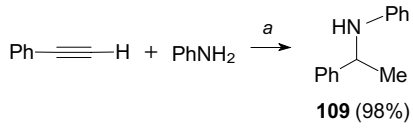


(*a*) [Au] (**108**) (2 mol.%), $AgBF_4$ (2 mol.%), MeCN, 90 °C, 24 h;
$R^1 - R^4$ = H, Alk;



Beletskaya and co-workers [160] showed that cationic gold complex with phosphine ligand $(C_6F_5)_3PAuNTf_2$ catalyzes the Markovnikov addition of anilines to alkynes under mild conditions (at room temperature under solvent-free conditions), giving high yields of products (*e.g.*, 98% in the case of compound **109**), with the catalyst being easily reused (Scheme 89).

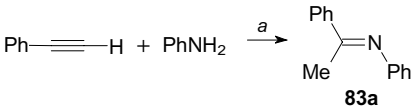
Scheme 89



(*a*) 1) $(C_6F_5)_3PAuNTf_2$ (1 mol.%), neat, rt; 2) $NaBH_4$, MeOH

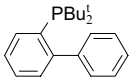
Xu and co-workers [161] investigated reactions catalyzed by cationic gold complexes and the effect of silver additives on the reaction pathway. The reaction of phenylacetylene with aniline catalyzed by cationic gold complex with the 2-(di-*tert*-butylphosphino)biphenyl ligand (Johnphos, **L**[28]) is accompanied by the enamine – imine rearrangement and results in the formation of Markovnikov product **83a** (for conversion of >90%). An excess of silver salt in the

Scheme 90



83a

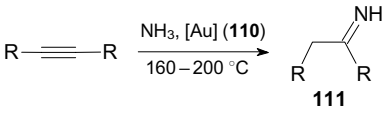
(*a*) [(**L**^{28})AuOTf] (0.5 mol.%), CD_2Cl_2, rt;

L^{28} =  (Johnphos)

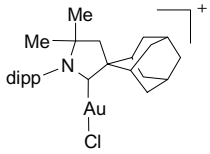
reaction mixture substantially retards the reaction (Scheme 90).

Bertrand and co-workers[162] prepared fairly unusual gold carbene complexes such as **110**, which were able to catalyze reactions of alkynes, including internal ones, with ammonia, giving products **111** in good yields (Scheme 91).

Scheme 91

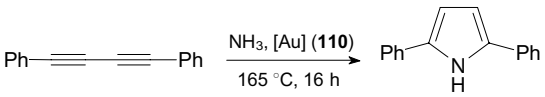


111

110 =  [KB(C$_6$F$_5$)$_4$]$^-$ (dipp is 2,6-diisopropylphenyl)

The reactions of ammonia with terminal alkynes have the Markovnikov regioselectivity. In the case of diphenylbutadiyne, 1,4-diphenylpyrrole (**112**) is formed in a high yield (Scheme 92).[162]

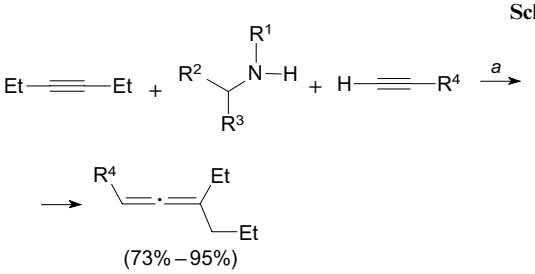
Scheme 92



112 (87%)

Bertrand and co-workers[163] also developed a method for the preparation of allenes by hydroamination of alkynes catalyzed by the same cationic gold complex **110**. The reaction involves two alkyne molecules and a secondary amine molecule, no fragment of which is present in the product (sacrificial reagent) (Scheme 93). The first step is the Markovnikov or anti-Markovnikov (depending on the nature of alkyne) addition of secondary amines to terminal alkynes catalyzed by Au complex **110**.

Scheme 93

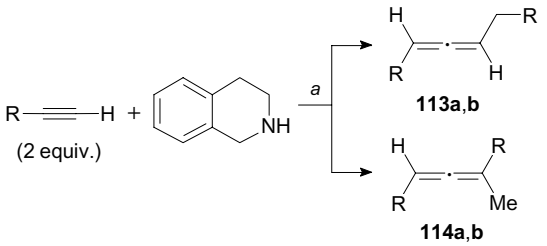


(73%–95%)

(*a*) [Au] (**110**) (5 mol.%) (–R^{2}R^{3}C=NR^1)

The same gold complex catalyzes *in situ* coupling of the intermediate with one more equivalent of the starting alkyne (or another terminal or internal alkyne) to give imine (Scheme 94). In the case of R = Bu^t or TMS, the reaction selectively gives the products of coupling with the anti-Markovnikov isomer (**113a**,**b**), while for R = Bu^n or Cy, the coupling product with the Markovnikov isomer (**114a**,**b**) is selectively formed.

Scheme 94



113a,**b**

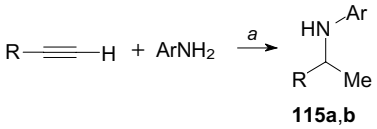
114a,**b**

(*a*) [Au] (**110**), C_6D_6, 120 °C, 16 h, –imine; **113**: R = Bu^t (**a**, 89%), TMS (**b**, 47%); **114**: R = Bu^n (**a**, 68%), Cy (**b**, 79%)

Hammond and co-workers[164] demonstrated that gold nanoparticles (NPs) supported on titanium oxide, in the presence of the $H_3PO_4 \cdot 12\,WO_3$ co-catalyst, are active towards hydroamination of phenylacetylenes and aliphatic alkynes with anilines, for example, to prepare compounds **115a**,**b**. With this heterogeneous catalyst, good yields of products are also attained in the reaction of secondary aliphatic amine (*e.g.*, morpholine) with phenylacetylene and in the aminocyclization of substituted *o*-alkynylanilines (the yield of indole **78** for R^1 = Ph, R^2 = 5-F is 97%). However, these reactions require large amounts of the catalyst and microwave irradiation (Scheme 95).

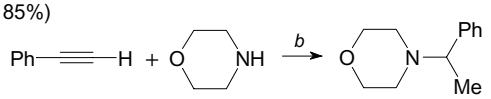
Corma *et al.*[165] investigated the catalytic activity of Au^{I}- and Au^{III}-based heterogeneous catalysts supported on various materials towards the reactions of aromatic and aliphatic alkynes with aniline, resulting in Markovnikov products as the corresponding imines. The best results were obtained for the Au^{III}/MCM-41-Sn$_G$ catalyst, where

Scheme 95

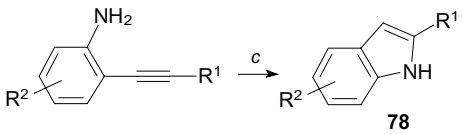


115a,**b**

R = 2-MeC$_6$H$_4$, Ar = Ph (**a**, 92%); R = n-C$_6$H$_{13}$, Ar = 4-FC$_6$H$_4$ (**b**, 85%)



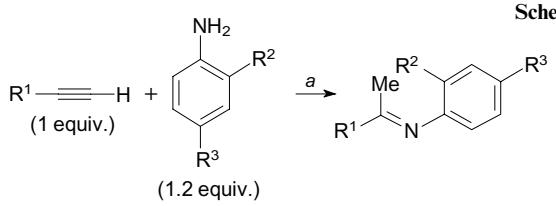
50 (76%)



78

(*a*) 1) Au-NPs/TiO_2 (0.2 mol.%), $H_3PO_4 \cdot 12\,WO_3$ (0.2 mol.%), neat, 80 °C, 12 h; 2) [H]; (*b*) 1) Au-NPs/TiO_2 (1 mol.%), PhMe, MW, 80 °C, 1 h; 2) [H]; (*c*) Au-NPs/TiO_2 (5 mol.%), PhMe, MW, 120 °C, 1 h; R^1, R^2 = H, Alk, Ar, F, Cl

Scheme 96

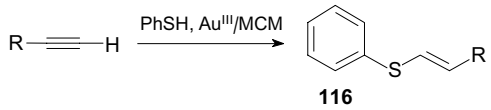


(*a*) Au^{III}/MCM-41-Sn_G (5 mol.%), THF, 70 °C, 1 – 1.5 h; $R^1 - R^3$ = Alk

MCM-41-Sn_G is tin-containing mesoporous mesostructured silicate. The reaction often gives quantitative yields of products and does not require the presence of acid; the catalyst retains activity after four reaction cycles (Scheme 96).

The use of the Au^{III}/MCM-41 catalyst containing no Sn is much less efficient, but provides the same (Markovnikov) regioselectivity of the reaction. It is of interest that the hydrothiolation in the presence of this catalyst furnishes anti-Markovnikov products **116** (Scheme 97).[166]

Scheme 97

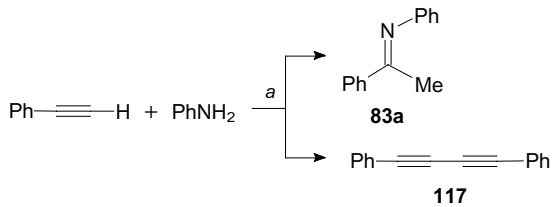


116

R = Alk, Ar

Zhu and co-workers[167] found that the reaction of aniline with alkynes is catalyzed by gold nanoparticles Au-NPs/ZrO_2 under visible irradiation at low temperature. They also found that the visible light may change the pathway of the Au_2Co-NPs-catalyzed reaction of aniline with phenylacetylene (plasmonic switching). The visible irradiation of the reaction mixture ($\lambda > 400$ nm, ~ 0.5 W cm^{-2}) induces complete conversion of substrates to give the Markovnikov product of hydroamination (imine **83a**),[168] since the excited aniline is concentrated on the catalyst. Meanwhile, when the reaction is conducted in the dark, phenylacetylene homocoupling product, diyne **117**, is formed (55% conversion) (Scheme 98).

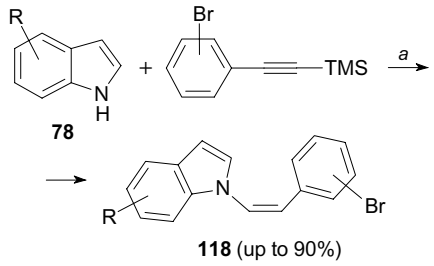
Scheme 98



(*a*) Au_2Co-NPs/ZrO_2

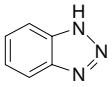
Considering industrial applications, a relevant problem is the replacement of noble metals by less expensive and more readily available catalysts; therefore, it is necessary to mention the importance of studies in which organic reactions are catalyzed by copper salts and complexes. Verma and co-workers[169] described the hydroamination of TMS-protected phenylacetylenes with indoles in the presence of monovalent copper and ligand **L**^{29}, resulting in the synthesis of anti-Markovnikov isomer **118**. The authors showed that

Scheme 99



118 (up to 90%)

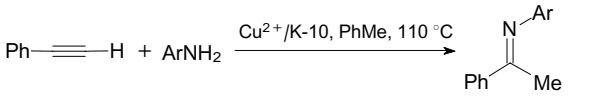
(*a*) CuI (10 mol.%), **L**^{29} (20 mol.%), KOH, DMSO, 120 °C;

R = H, Alk; **L**^{29} = 

in the case of bromo-substituted alkynes, hydroamination prevails over *N*-arylation (Scheme 99).

The hydroamination of phenylacetylene with substituted anilines catalyzed by Cu^{2+} cations supported on acid-activated montmorillonite K-10 aluminosilicate proceeds selectively and furnishes Markovnikov isomer **83** (Scheme 100).[170,171] In the presence of electron-donating substituents in aniline, the yields of products are quantitative.

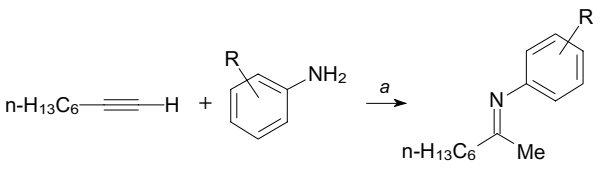
Scheme 100



83 (up to 99%)

Robbins and Hartwig[172] employed the simple CuCl catalyst for the selective preparation of the Markovnikov isomer *via* the reactions of aromatic or aliphatic alkynes with anilines. The yield of the product formed upon the reaction of phenylacetylene with 4-$Bu^nC_6H_4NH_2$ proved to be moderate (55%). Conversely, in the reactions of anilines with aliphatic oct-1-yne, good yields of products **92** were attained (Scheme 101).

Scheme 101

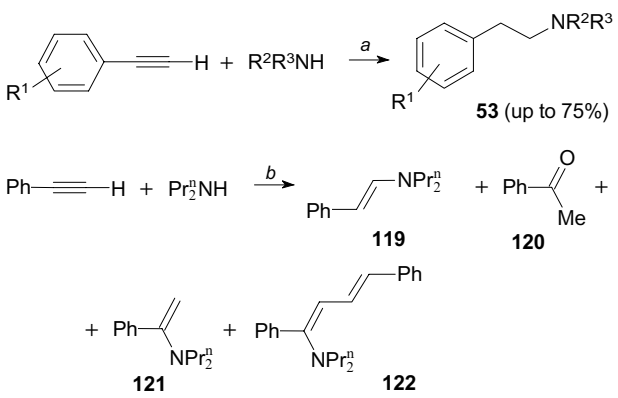


92 (up to 84%)

(*a*) CuCl (25 mol.%), THF, 100 °C

Taillefer and co-workers,[173] who made a weighty contribution to the revival of the Ullmann reaction, studied also addition reactions to unsaturated bonds. They were the first to show that the copper-catalyzed addition of aliphatic amines to terminal alkynes follows the anti-Markovnikov pathway and gives the *E*-configured enamines. After optimization of the conditions, it was found that secondary alkylamines add to arylacetylenes under the action of CuCN to give anti-Markovnikov products in high yields [80% in *N*-methyl-2-pyrrolidone (NMP) and 90% without a solvent]; these products can be reduced to the corresponding amines **53** (Scheme 102).[174] The

Scheme 102



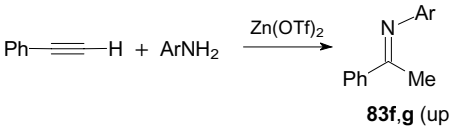
(*a*) 1) CuCN, 2) [H]; (*b*) [Cu] (15 mol.%), N_2, 120 °C, 8 h

[Cu]	Solv	Yield (%)			
		119	**120**	**121**	**122**
CuCl	NMP	40	17	23	15
CuCN	–	90	5	5	0

dependence of the selectivity of this reaction on the catalyst and the solvent was demonstrated considering the reaction of phenylacetylene with di-n-propylamine, which can give products **119** – **122**. When the reaction was carried out in NMP, the products of hydrolysis of the Markovnikov isomer were also detected in minor amounts. The neat reaction has a substantially better selectivity and allows for the synthesis of anti-Markovnikov isomer **119** in a high yield (up to 90%).

Selective formation of Markovnikov isomers **83f**,**g** is observed in the zinc triflate-catalyzed hydroamination of phenylacetylene with anilines carried out in a two-phase system: polar phase (1-ethyl-3-methylimidazolium trifluoromethanesulfonate ionic liquid)/organic phase (n-heptane) (Scheme 103).[175]

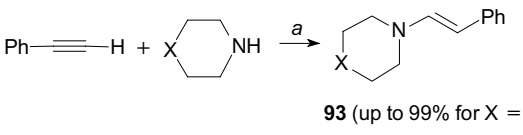
Scheme 103



Ar = 4-Pr^{i}C$_6$H$_4$ (**f**), 4-FC$_6$H$_4$ (**g**)

A catalyst based on tungsten carbonyl [W(CO)$_4$(pip)$_2$] (pip is piperidine) provides the anti-Markovnikov addition of cyclic amines to arylacetylenes to afford products **93** in high yields; however, this catalyst shows a poor performance for reactions with aliphatic alkynes (Scheme 104).[176]

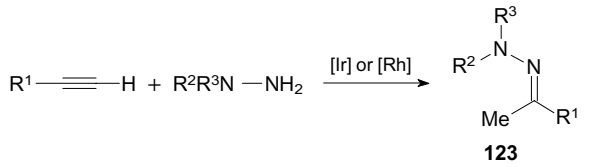
Scheme 104



(*a*) [W(CO)$_4$(pip)$_2$] (1.6 mol.%), neat, 60 – 90 °C, 1 – 5 h;
X = O, NAlk, CH_2

Quite a few publications are devoted to the addition of hydrazine and its derivatives to alkynes. Markovnikov isomer **123** is formed in a good yield upon the addition of phenylhydrazine to aromatic alkynes in the presence of rhodium or iridium catalysts. The presence of alkyl substituents in one of the reactants considerably increases the yields of products. Iridium complex [Ir(bmp)(CO)$_2$]B(C$_6$F$_5$)$_4$ [bmp is di(pyrazol-1-yl)methane] proved to be a more efficient catalyst than rhodium complex [Rh(CO)$_2$Cl]$_2$: in the former case, the product yield for R^1 = Ar reached 74% (Scheme 105).[177]

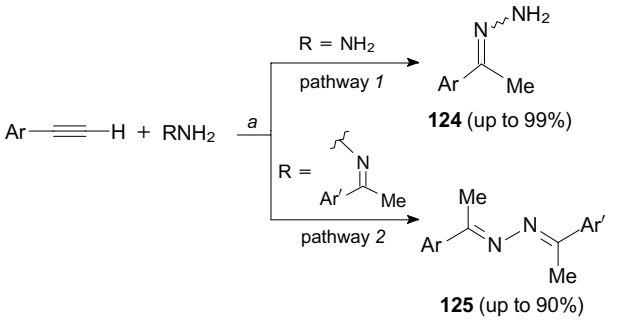
Scheme 105



R^1 = Alk, Ar; R^2, R^3 = Alk

Bertrand and co-workers[178] studied the reactions of hydrazine and its derivatives with phenylacetylene catalyzed by copper salts and complexes. They described the CuCl-catalyzed Markovnikov addition of hydrazine to phenylacetylene and other aromatic alkynes; under these conditions, the yields decreased in the presence of carbene ligands (Scheme 106, pathway *1*). Product **124** thus formed can further react with the starting alkyne (if the alkyne is taken in excess) or, after isolation in pure form, it can react with another aromatic acetylene, being converted to unsymmetrical azines (diazadienes) **125** in good yields (see Scheme 106, pathway *2*).

Scheme 106

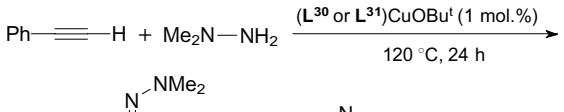


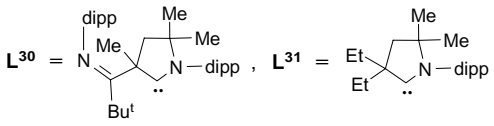
(*a*) CuCl (5 mol.%), KB(C$_6$F$_5$)$_4$ (5 mol.%), C$_6$D$_6$, 100 °C, 12 h

The addition of dimethylhydrazine to phenylacetylene in the presence of CuOBu^t complexes with carbene ligands has the anti-Markovnikov selectivity: the reaction gives a mixture of products **123a** and **126** in which the latter predominates (95% total yield). It is noteworthy that specific ligand **L**^{30}, proposed by Bertrand and co-workers,[179] provides for a considerably more selective course of the reaction than ligand **L**^{31}, which is traditional cyclic alkylaminocarbene (CAAC) (Scheme 107).

Gold salts and complexes are efficient catalysts for the addition of hydrazines to alkynes. Hashmi and co-workers[180] proposed unusual carbene ligand for the hydroamination of phenylacetylenes with hydrazine. Under the action of gold complex **127** with this ligand, the addition of

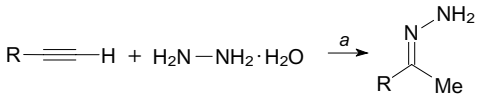
Scheme 107





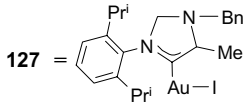
Ligand	**123a** : **126** ratio
L^{30}	4 : 96
L^{31}	23 : 77

Scheme 108



124a – c

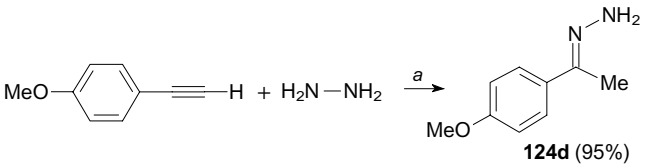
(*a*) [Au] (**127**) (5 mol.%), $KB(C_6F_5)_4$ (5 mol.%), PhH, 20 °C;
R = Ph (**a**, 90%), Bn (**b**, 73%), Bu^n (**c**, 51%);



hydrazine to aliphatic and aromatic alkynes resulted in good or high yields of products **124a – c** (Scheme 108).

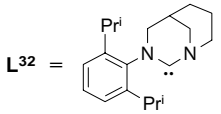
Bertrand and co-workers[181] found that cationic gold complex with carbene ligand **L**^{32} catalyzes the hydroamination of terminal alkynes with unsubstituted hydrazine to give hydrazone **124d** in a high yield (Scheme 109).

Scheme 109



124d (95%)

(*a*) (**L**^{32})AuCl (5 mol.%), $KB(C_6F_5)_4$ (5 mol.%), PhH, 90 °C, 4 h;

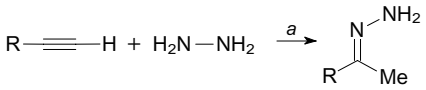


Another cationic gold complex, compound **110**, proved to be equally efficient in the hydrazine addition to aliphatic alkynes (Scheme 110).[182]

Gold complex **128** with phosphine ligand catalyzes the addition of hydrazine to terminal alkynes at room temperature with good product yields. The reaction proceeds most efficiently when electron-withdrawing substituents are present in the benzene ring (Scheme 111).[183]

The mechanism of hydrazine addition to compounds with unsaturated bonds catalyzed by cationic gold complexes with carbene ligands has been discussed in detail;[184]

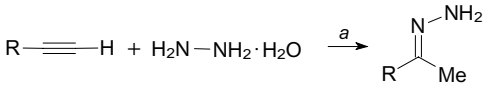
Scheme 110



124b,**c**,**e**

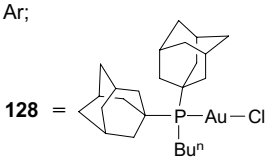
(*a*) [Au] (**110**) (5 mol.%), 100 °C, 3 h; R = Bn (**b**, 95%), Bu^n (**c**, 89%), Cy (**e**, 92%)

Scheme 111



124 (up to 98%)

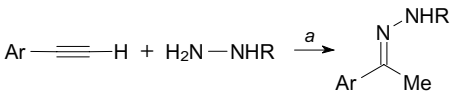
(*a*) [Au] (**128**) (1 mol.%), $LiB(C_6F_5)_4 \cdot 2.5\,Et_2O$ (1 mol.%), PhH, 25 °C, 4 h; R = Alk, Ar;



the same publication presents density functional theory (DFT) calculations for these reactions.

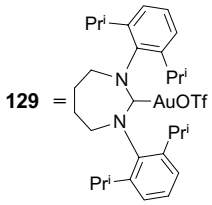
Nechaev and co-workers[185] studied the addition of tosylhydrazine and Boc-substituted hydrazine (Boc is *tert*-butoxycarbonyl) to aromatic alkynes catalyzed by the gold complex [(THD-Dipp)AuOTf] (**129**), where THD-Dipp is 1,3-bis(2,6-diisopropylphenyl)hexahydro-2*H*-1,3-diazepin-2-ylidene. The reactions were carried out without a solvent with a small amount of the catalyst, which resulted in the formation of Markovnikov products **130** and **131** in good yields (Scheme 112).

Scheme 112



130, **131** (up to 97%)

(*a*) [Au] (**129**) (0.25 mol.%), neat, 100 °C; R = Ts (**130**), Boc (**131**);

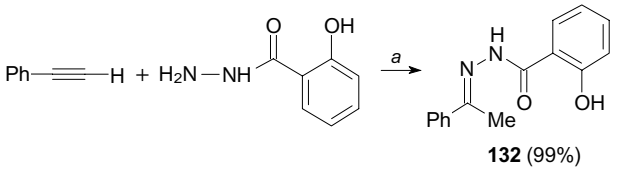


Kukushkin and co-workers[186] described the hydrazide addition to terminal alkynes in the presence of the gold complex $Ph_3PAuNTf_2$. The reactions with aromatic alkynes proceed more easily than reactions with aliphatic alkynes; in both cases, Markovnikov regioselectivity is observed. For example, using this complex as a catalyst, compound **132** was obtained in a quantitative yield (Scheme 113).

Semicarbazides add to aromatic alkynes under similar conditions.[187] For example, product **133** was isolated in a good yield (Scheme 114).

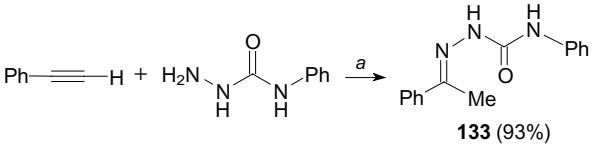
To conclude the Section, we present an example of divergent regioselectivity for the reaction of phenylacetylene

Scheme 113



(*a*) $Ph_3PAuNTf_2$ (6 mol.%), PhCl, 60 °C, 2 h

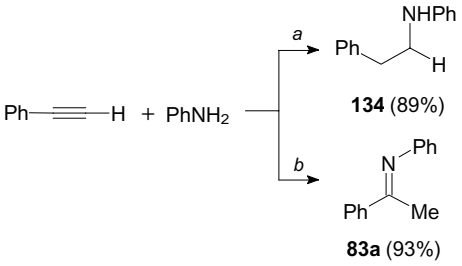
Scheme 114



(*a*) $Ph_3PAuNTf_2$ (3 mol.%), PhCl, 60 °C, 5 h

to aniline carried out under similar conditions in the presence of titanium complex **75** (Ref. 128) or the Cu/K-10 catalyst (Scheme 115).[171] In the former case, amine **134** was isolated after reduction of the anti-Markovnikov isomer, while in the latter case, imine **83a** was formed as the Markovnikov addition product.

Scheme 115



(*a*) [Ti] (**75**), PhH, 70 °C, 0.5 h; (*b*) Cu/K-10, PhMe, 110 °C, 4 h

4. Hydroamination of allenes

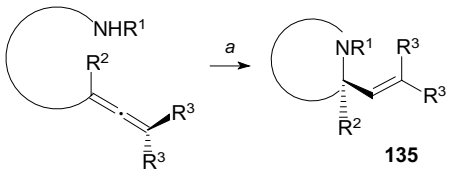
The use of available raw materials, terminal allenes, for the catalytic functionalization such as hydroamination opens up the way for the synthesis of branched allylamines, which are an important class of allyl derivatives.

Similarly to the Sections devoted to alkenes and alkynes, this Section starts with examples of intramolecular hydroamination catalyzed by either Brønsted acids[188] or various metal complexes,[189, 190] including lanthanide complexes.[191] The enantioselective cyclization of ω-aminoalkylallenes in the presence of Rh catalyst with ligand $\mathbf{L^{33}}$ results in the synthesis of α-vinyl heterocyclic derivatives **135** (Scheme 116).[192]

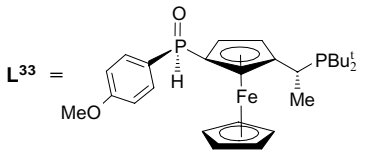
Liu and co-workers[193] employed intramolecular fluoroamination of allenes catalyzed by silver salt in the presence of electrophilic fluorine to prepare fluoro-2,5-dihydropyrrole **136a**; this is a good example of double bond bifunctionalization. Compound **136b** resulting from hydroamination was formed as a by-product (Scheme 117).

The mechanism of this reaction depicted in Scheme 118 accounts for the formation of both products.

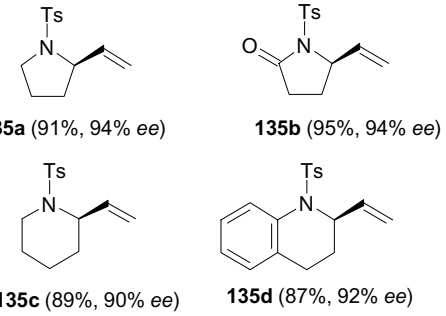
Scheme 116



(*a*) $[Rh(COD)Cl]_2$ (2 mol.%), $\mathbf{L^{33}}$ (2 mol.%), Solv (0.2 M), Δ, 12 h;



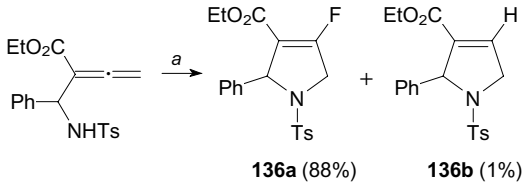
Examples of products



135a (91%, 94% *ee*) **135b** (95%, 94% *ee*)

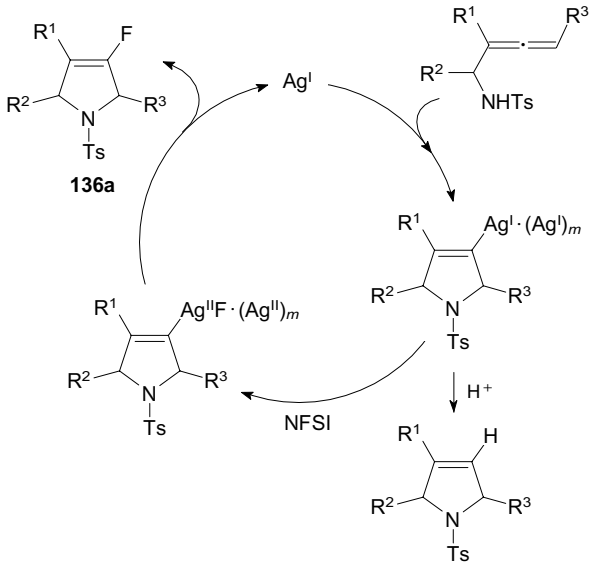
135c (89%, 90% *ee*) **135d** (87%, 92% *ee*)

Scheme 117



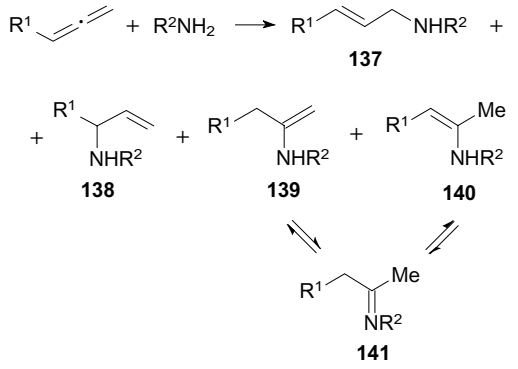
(*a*) NFSI (1.5 equiv.), $AgNO_3$ (20 mol.%), K_2CO_3 (2 equiv.), Et_2O, rt; NFSI is *N*-fluorodi(benzenesulfonyl)amine

Scheme 118



The intermolecular hydroamination of allenes can, in principle, afford linear and branched isomers: allyl- (**137**, **138**) and vinylamines (**139**, **140**); the latter can isomerize to ketimines **141** (Scheme 119).

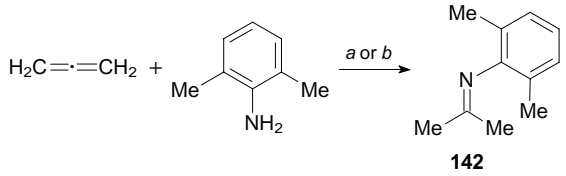
Scheme 119



These reactions were performed using early transition metal (Ti, Zr) and noble late transition metal (Pt, Pd, Rh) catalysts and, subsequently, cheaper and more readily available Ni and Cu catalysts. Gold catalysis has been developed most extensively in recent years.

Allene hydroamination was performed by Bergman and co-workers [194] with early transition metal (zirconium and titanium) complexes as catalysts. For example, the reaction of allene with anilines is catalyzed by the zirconium complex $Cp_2Zr(NHC_6H_3Me_2\text{-}2,6)_2$ and gives ketimine **142** in 83% yield (Scheme 120, conditions *a*).

Scheme 120

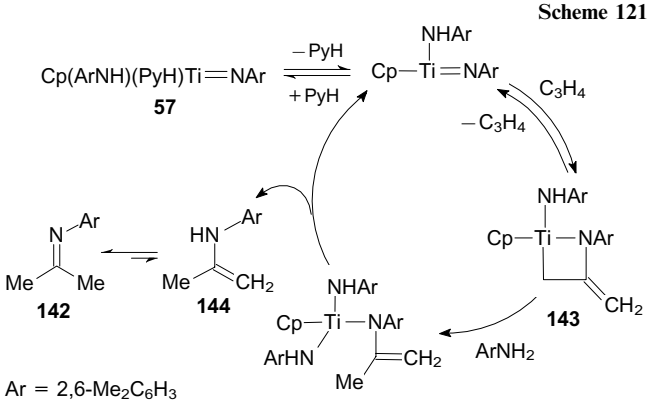


(*a*) $Cp_2Zr(NHC_6H_3Me_2\text{-}2,6)_2$ (2.7 mol.%), 90 °C, 2 days;
(**b**) Cp_2TiMe_2 (10 mol.%), C_6D_6, 45 °C

This transformation can also be catalyzed by the titanium complex Cp_2TiMe_2; the product yield exceeds 95% with the reaction half-period being 30 min (see Scheme 120, conditions *b*).[118] In the presence of aniline and pyridine, Cp_2TiMe_2 is converted to the active complex Cp(ArNH)(PyH)Ti=NAr (**57**). The cycloaddition of complex **57** to allene gives intermediate **143** (for Ar = 2,6-$Me_2C_6H_3$); on treatment with 2,6-xylidine, this intermediate regenerates the catalyst and gives product **144**, which isomerizes to imine **142** (Scheme 121).

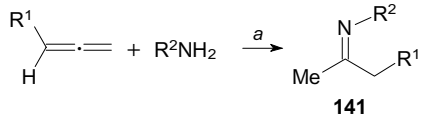
Later, Ayinla and Schafer [195] employed bis(amidate)-bis(amido)titanium complex **72a** as a precatalyst for hydroamination of substituted allenes. Monosubstitited allenes were allowed to react with aromatic and aliphatic (primary) amines. The reaction conditions were substantially different: for aromatic amines, the reaction temperature was 85 – 90 °C and the reaction time was 16 h, whereas in the case of aliphatic amines, longer heating (24 h) at 120 °C is required (Scheme 122). In all cases, ketimines were formed in good to high yields. Meanwhile, the reaction with 1,1-

Scheme 121



Ar = 2,6-$Me_2C_6H_3$

Scheme 122

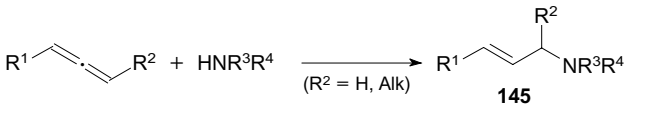


(*a*) [Ti] (**72a**) (5 mol.%); R^1 = Ph, Bz; R^2 = Pr^i, Bu^t, Ph, 2,4-$Me_2C_6H_3$, Bn

disubstituted allenes did not proceed under these conditions.

The addition of amines to allenes catalyzed by late transition metal complexes leads to the formation of a C – N bond with terminal, less substituted, carbon atom. Usually, this gives allylamines **145** (Scheme 123), although there are exceptions. The reaction is catalyzed by Pd, Pt, Rh, Cu, Ag and Au complexes or salts.

Scheme 123



Note that allylamines are components of many natural products and biologically active molecules (Fig. 1);[196] therefore, the development of general and selective methods for allylamine synthesis attracts considerable attention. The intermolecular addition of amines to allenes catalyzed by transition metal complexes can serve as an efficient synthetic route to allylamines.

The first publications on the intermolecular hydroamination of allenes catalyzed by transition metal complexes date back to the mid-1990s.[197, 198] The palladium-catalyzed intermolecular hydroamination of substituted allenes with secondary aliphatic amines afforded a mixture of target allylamines **146** and diene amines **147** (Scheme 124).[197] The authors were able to optimize conditions in such a way that some of the reactions gave predominantly the target allylamine: for example, in the case of diethylamine ($R^1 = R^2$ = Et), the yields of products **146a** and **147a** were 72% and 19%, while in the case of pyrrolidine, the target allylamine **146b** [$R^1 - R^2 = (CH_2)_4$] was formed as the only product in 89% yield.

Yamamoto and co-workers [198] demonstrated that the reactions of monosubstituted allenes with secondary aliphatic and aromatic amines catalyzed by Pd complexes with

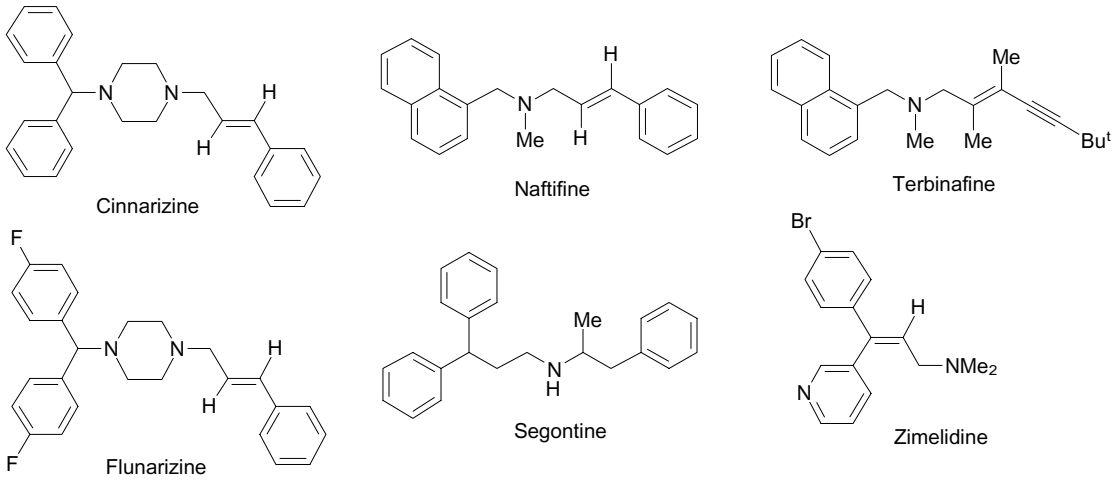
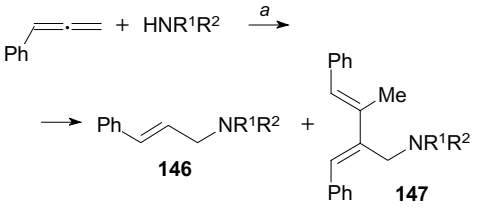


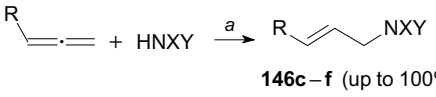
Figure 1. Pharmaceutical drugs containing an allylamine moiety.

Scheme 124



(*a*) $Pd(dba)_2$ (10 mol.%), Ph_3P (2 equiv.), $Et_3N \cdot HI$, THF, 65 °C, 22 h; R^1, R^2 = Alk; dba is dibenzylideneacetone

Scheme 125



(*a*) Pd^0, **L**^{6}, AcOH, THF, 80 °C; X = Y = CH_2CO_2Et (**c**, up to 99%), Bn (**d**, up to 99%), Ph (**e**, 67%); X = 2-Naph, Y = Ph (**f**, 62%); Naph is naphthyl

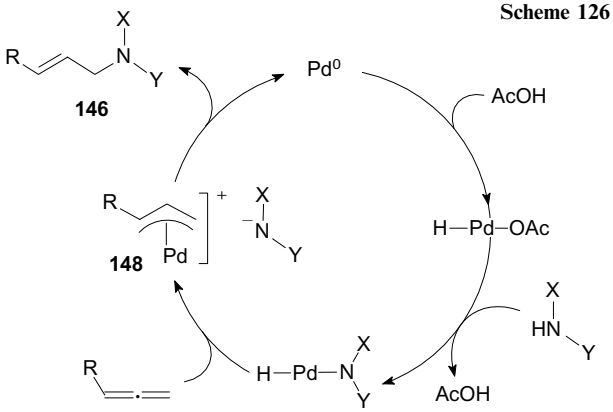
ligand **L**^{6} in the presence of acetic acid also afford linear products (Scheme 125).

The catalytic cycle proposed for this reaction includes the formation of HPdOAc, which is converted to the complex HPdNXY; the latter reacts with allene giving π-allylpalladium intermediate **148**, which is converted to anti-Markovnikov product **146** (Scheme 126).

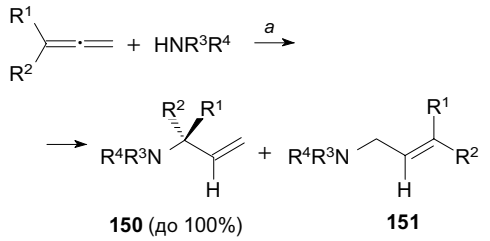
Schmidt and co-workers [196, 199] demonstrated that cationic allyl palladium complex **149** with the 3-iminophosphine ligand exhibits high catalytic activity towards the reactions of mono- or disubstituted allenes with alkylamines and anilines under mild conditions. Depending on the kinetic or thermodynamic control, branched (**150**) or linear (**151**) products are formed (Scheme 127). A short-term (1 – 10 min) reaction with anilines affords branched compounds **150** in up to 100% yields; when the reaction time increases to 20 h, it is possible in some cases (for example, for 1,1-diphenylallene) to obtain up to 100% of linear product **151**.[200]

In the presence of another allyl palladium complex (**152**), selective preparation of linear (thermodynamic) prod-

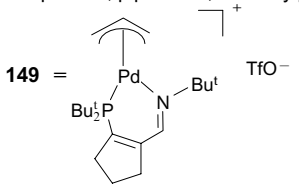
Scheme 126



Scheme 127



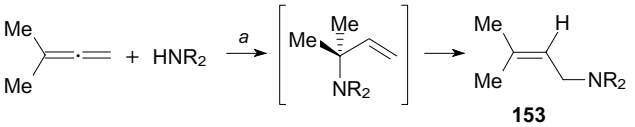
(*a*) [Pd] (**149**), 1 – 10 min; R^1 = H, Alk, Ar; R^2 = Alk, Ar; R^3R^4NH is aniline, anisidine, cyclohexylamine, 2-octylamine, morpholine, piperidine, 1-methylpiperazine, pyrrolidine;



ucts is possible. For example, 3-methylbuta-1,2-diene reacts with secondary, in particular cyclic, amines at room temperature giving allylamines **153** in high yields and with conversion of > 98% (Scheme 128).[199]

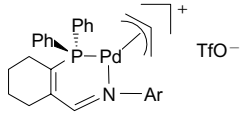
Thus, a regiodivergent pair of allene hydroamination reactions controlled by ligands in palladium complexes is

Scheme 128



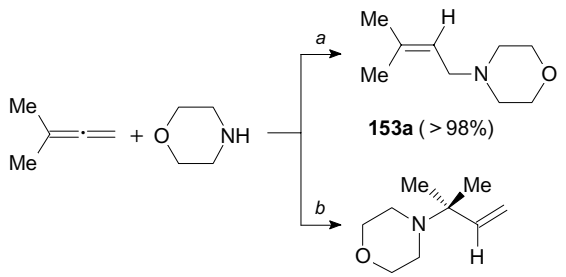
153

(*a*) [Pd] (**152**) (5 mol.%), C_6D_6, 25 °C, 1 – 30 h;

152 =  (Ar = 2,6-$Me_2C_6H_3$)

Amine	Time /h
Morpholine	4
Pyrrolidine	6
Indoline	24
Diethylamine	3
n-Butyl(methyl)amine	4

Scheme 129



153a (> 98%)

150a (95%)

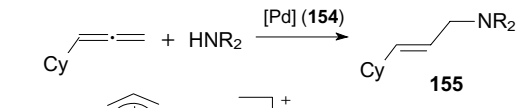
(*a*) [Pd] (**152**) (5 mol.%), C_6D_6, 25 °C, 4 h; (*b*) [Pd] (**149**) (5 mol.%), C_6D_6, 25 °C, 0.5 h

presented in Scheme 129 in relation to the reaction of 3-methylbuta-1,2-diene with morpholine.

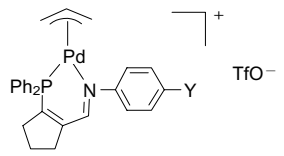
The use of modified allylpalladium 3-(iminophosphine) complex with aryl substituents at the nitrogen atom (**154**) to catalyze reactions of cyclohexylallene with a series of cyclic amines resulted in the synthesis of linear products **155** in high yields (Scheme 130).[201] The electronic effect of the substituent in the *para*-position of the aryl moiety was shown to influence the reaction pathway.

In 2010, Toups and Widenhoefer[202] accomplished the addition of secondary amines to monosubstituted allenes catalyzed by platinum complexes with bidentate ligands in

Scheme 130



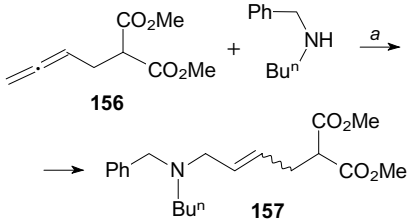
155

154 = 

Amine	Yield (%)
Morpholine	87
Pyrrolidine	81
Piperidine	88
1,2,3,4-Tetrahydroisoquinoline	85

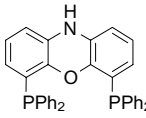
the presence of AgOTf. In the reaction of allene **156** with benzyl(n-butyl)amine, the highest yields of product **157** were obtained using dppf (**L**[6]) and 4,6-bis(diphenylphosphino)-10*H*-phenoxazine (N-Xantphos, **L**[34]) (Scheme 131).

Scheme 131



156 **157**

(*a*) (**L**[34])$PtCl_2$ (5 mol.%), AgOTf (5 mol.%), PhMe, 80 °C, 24 h;

L[34] =  (N-Xantphos)

Ligand	Yield of **157** (%)	*E* : *Z* ratio
L[6]	81	10 : 1
L[34]	91	6.7 : 1

Other amines and allenes are also converted to the corresponding allylamines in high yields and with predominant contents of the *E* isomers.

Unlike complexes of other metals, rhodium complexes used as catalysts lead to the formation of the branched isomer. This reaction makes it possible to prepare chiral allylamines, which are in demand as building blocks for organic synthesis. Breit and co-workers[203] reported the asymmetric hydroamination of monosubstituted allenes with anilines catalyzed by chiral rhodium complexes. The best result was attained in the reaction catalyzed by rhodium complex with (*R*)-1-[(SP)-2-(dicyclohexylphosphino)-ferrocenyl]ethyldicyclohexylphosphine ligand (Josiphos, **L**[35]). The addition of the aniline amino group to cyclohexylallene involved the substituted carbon atom and gave product **158** in a high yield and with good enantioselectivity (Scheme 132). The developed procedure was successfully applied for hydroamination of cyclohexylallene and other allenes on treatment with *p*-anisidine (examples of products **159** are presented in Scheme 132).

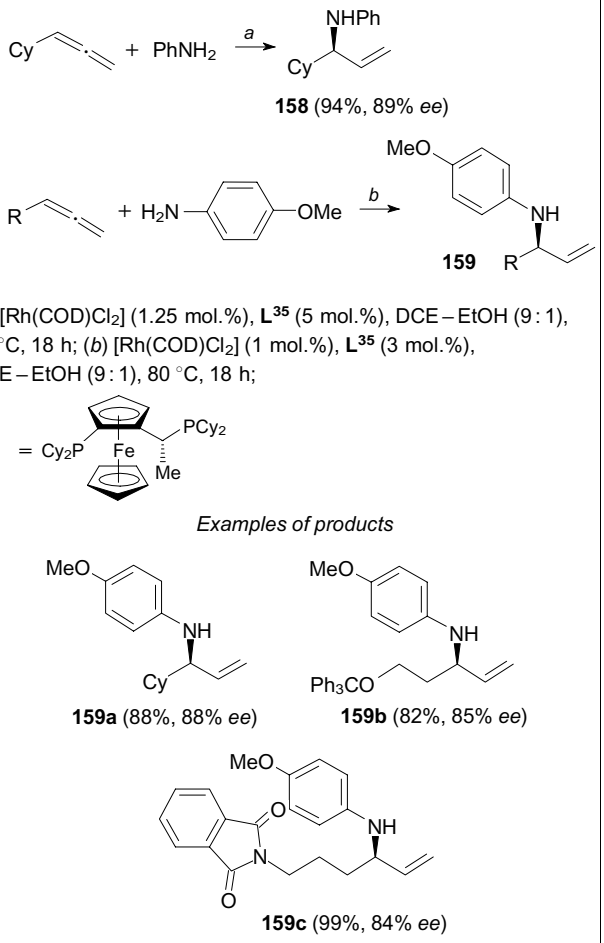
A catalytic cycle involving participation of allylrhodium intermediate **160** was proposed for this reaction (Scheme 133).

Tafazolian and Schmidt[204] reported the first example of nickel catalysis of the hydroamination of allenes with secondary amines. In the presence of allyl Ni complex **161**, cyclic amines react with monosubstituted allenes to give allylamines **162** in good to high yields (Scheme 134); in the case of 1,1-dimethylallene, the yields are good (up to 80%). However, this reaction could not be carried out for primary aromatic or aliphatic amines.

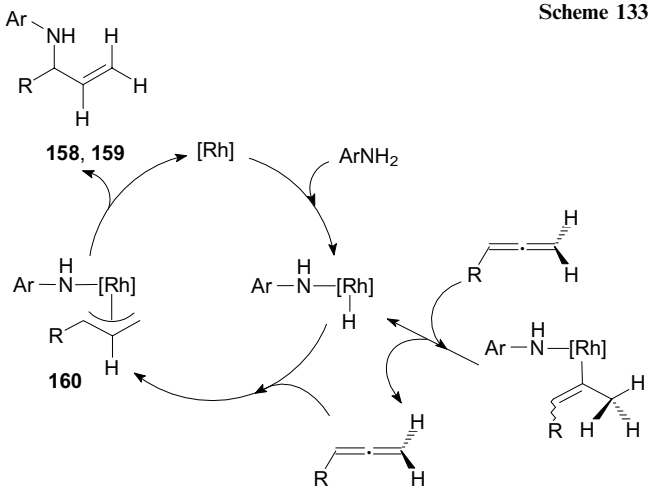
An interesting mechanism was proposed for this reaction: first, alkene forms new Ni complex **163**, in which reductive elimination and proton transfer take place, instead of the nucleophilic attack on the allyl group (Scheme 135).

Recently, Taillefer and co-workers[205, 206] reported the $Cu(OTf)_2$-catalyzed hydroamination of terminal allenes, including allenamides and *N*-allenylcarbamates, with ani-

Scheme 132



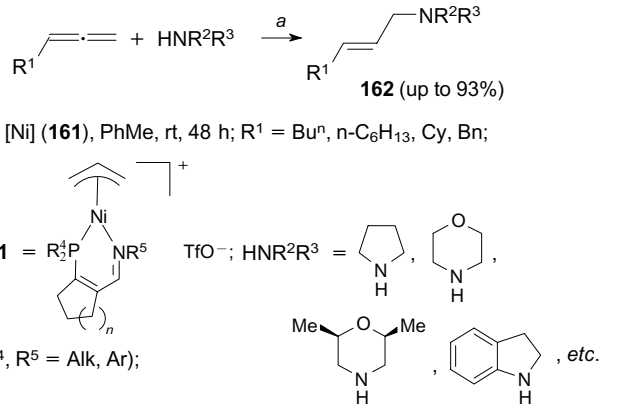
Scheme 133



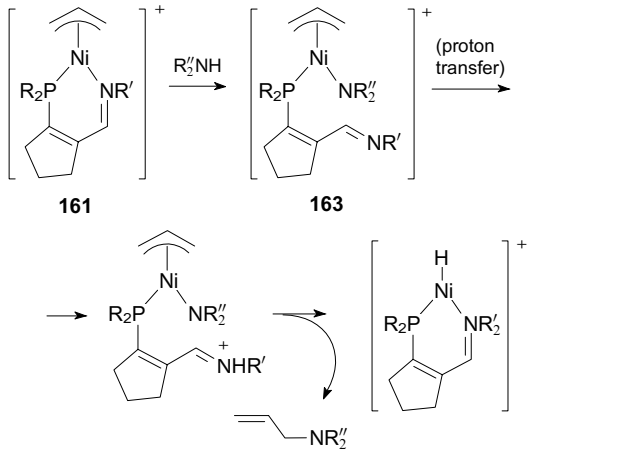
line derivatives and cyclic amines (Scheme 136). The authors demonstrated that the true catalyst is Cu^{I}. The reaction results in the formation of anti-Markovnikov products **162** and **164**, which mainly or exclusively have the *E* configuration. In the case of phenylallene, the yields of products **164** reach 85%.

A great part of studying the allene hydroamination belongs to reactions catalyzed by gold salts or complexes. Most often, these reactions are intramolecular and can be carried out in the asymmetric version, using compounds

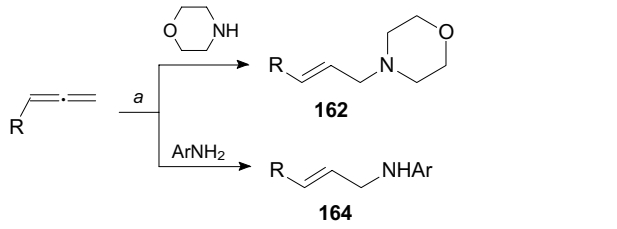
Scheme 134



Scheme 135



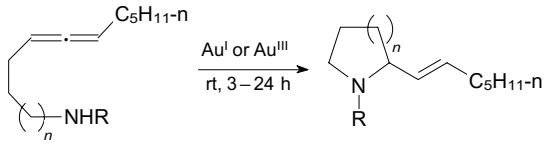
Scheme 136



with a protected amino group, for example, amides.[189, 190, 207 – 215] The reactions are usually selective and enable the synthesis of five- and six-membered nitrogen-containing heterocycles under mild conditions. Since these transformations are beyond the scope of this review, we will give only the most interesting examples of the asymmetric hydroamination of allenes catalyzed by Au^{I} or Au^{III} compounds.

Yamamoto and co-workers[215] carried out intramolecular hydroamination of chiral allene **165** ($n = 1$, 96% *ee*), obtained from (*S*)-(−)-1-octyn-3-ol; the chirality was thus transferred to the resulting pyrrolidine **166** (94% *ee*) (Scheme 137). However, the authors did not determine the absolute configuration of the product. The corresponding piperidines **166** ($n = 2$) were prepared in a similar way. The highest yield of the product (99%) was attained for R = Ts, $n = 1$, for the reaction time of 3 h.

Scheme 137

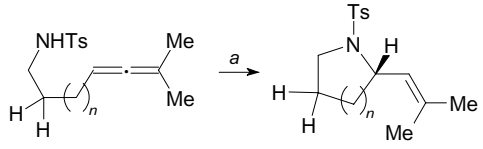


165 **166** (53% – 99%)

n = 1, 2

Toste and co-workers [213] performed a similar cyclization catalyzed by chiral binuclear gold complex with the ligand (*R*)-(**L^{14}**)* [(*R*)-xylylBINAP] and obtained vinyl-substituted pyrrolidines and piperidines **167** with high entatioselectivity (Scheme 138).

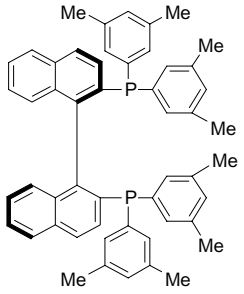
Scheme 138



167 (98%, 99% *ee*)

(*a*) [(*R*)-(**L^{14}**)*](AuOPNB)$_2$ (3 mol.%), DCE, rt, 15 h; n = 1, 2; OPNB is 4-nitrobenzoate;

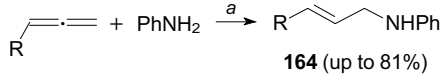
(*R*)-(**L^{14}**)* =



[(*R*)-xylylBINAP]

In 2006, Nishina and Yamamoto [216] described the $AuBr_3$-catalyzed intermolecular hydroamination of terminal and internal allenes on treatment with anilines. The reactions proceeded under mild conditions and afforded linear allylamines **164** (Scheme 139). For the product with R = Ph, the yield was 78%.

Scheme 139



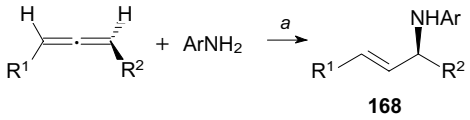
164 (up to 81%)

(*a*) $AuBr_3$ (10 mol.%), THF, 30 °C; R = n-C_8H_{17}, Cy, Bn, Ar

In the case of 1,3-disubstituted chiral allenes, chiral allylamine is formed with high enantioselectivity (high chirality transfer). For example, the reaction of 1-phenylbuta-1,2-diene with aniline **168** (Ar = R^1 = Ph, R^2 = Me) gave a product in 68% yield with 88% *ee* (Scheme 140).[217]

Duncan and Widenhoefer [218] showed that hydroamination of monosubstituted and 1,1- and 1,3-disubstituted allenes with aniline and *N*-alkylaniline derivatives results in high product yields when Au^{I} complex with biphenylphosphine ligand **L^{28}** is used as the catalyst (Scheme 141). In the reaction of NH-anilines with 1,1-dimethylallenes, the formation of monoallylated product **169** may be accompanied by the formation of bis-product **170**; in the case of

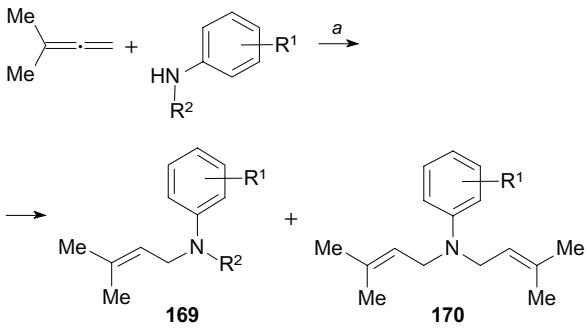
Scheme 140



168

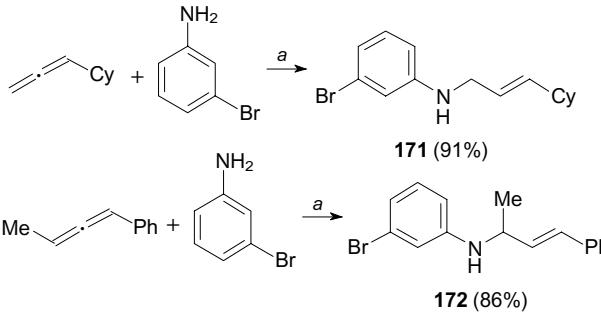
(*a*) $AuBr_3$ (10 mol.%), THF, 30 °C; R^1, R^2 = Alk, Ar

Scheme 141



169 **170**

169: R^2 = H: R^1 = H (73%), 2-Br (87%); R^2 = Me: R^1 = H (73%), 4-Br (94%)

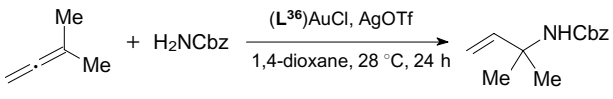


(*a*) Au^{I}, **L^{28}**, AgOTf (5 mol.% each), 1,4-dioxane, 45 °C

4-bromo- and 4-nitroanilines, the latter is formed in a quantitative yield. The reaction of 3-bromoaniline with substituted allenes affords allylanilines **171** and **172** in high yields.

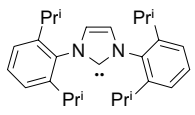
In these reaction, Au^{I} complex with phosphine ligand has a considerable advantage over gold complex (**L^{36}**)AuCl with carbene ligand (see below). Note, however, that these carbene complexes showed excellent performance in the reactions of terminal and internal allenes with N-unsubstituted carbamates.[219] The reactions of monosubstituted and 1,1- and 1,3-disubstituted allenes with benzylcarbamate catalyzed by Au^{I} carbene complex usually afford iso-compounds, for example, compound **173**, in high yields (Scheme 142).

Scheme 142



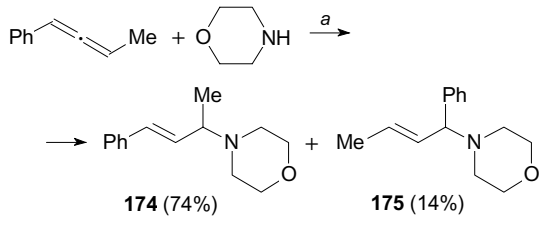
173 (96%)

Cbz is benzyloxycarbonyl; **L^{36}** =



The first example of allene hydroamination with aliphatic amine (morpholine) catalyzed by gold complexes was published in 2007.[220] A variety of Au^{I} phosphine complexes were used as catalysts in this reaction, which resulted in linear allylamines, the yields of which strongly depended on both the nature of phosphine ligand and the nature of substituents in the allene. In the case of 1,3-disubstituted allene (for example, 1-phenylbuta-1,2-diene), morpholine added predominantly to the less sterically hindered position, thus giving compound **174**, while isomeric compound **175** was isolated as a by-product (Scheme 143).

Scheme 143

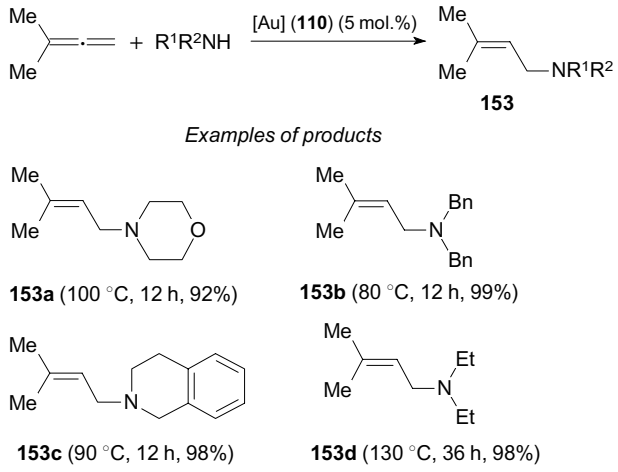


174 (74%) **175** (14%)

(*a*) $ClAuPPh_2$(*p*-Tol) (10 mol.%), AgOTf (10 mol.%), PhMe, 80 °C, 12 h

Bertrand and co-workers[221] effected the addition of various primary and secondary amines to terminal allenes using a catalytic system comprising cationic gold complex **110** and (alkyl)(amino)carbene ligand (Scheme 144).

Scheme 144



153

Examples of products

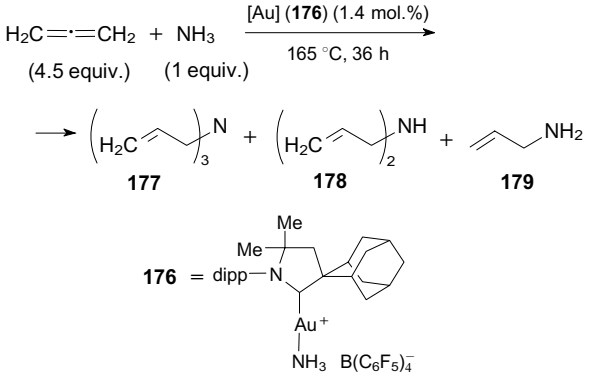
153a (100 °C, 12 h, 92%) **153b** (80 °C, 12 h, 99%)

153c (90 °C, 12 h, 98%) **153d** (130 °C, 36 h, 98%)

Using derivative **176** of this catalyst, Bertrand and co-workers[162] carried out the addition of ammonia to allenes. Depending on the reactant ratio, this reaction with ammonia yields a mixture of mono-, di- and triallylamines of various compositions, with a nitrogen atom occurring in an unsubstituted or less hindered position. In the case of a 4.5-fold excess of the allene, the **177** : **178** : **179** product ratio was 76 : 6 : 1. By adjusting the reactant ratio, it is possible to obtain triallylamine with a selectivity of up to 91% (Scheme 145).

The reaction proved to be feasible even for tetrasubstituted allene; however, because of steric hindrance, the regioselectivity changed, and the reaction stopped after the monohydroamination step giving vinylamine **180**, containing the amino group in position 2 (Scheme 146).

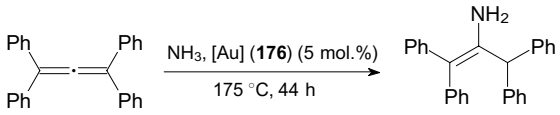
Scheme 145



177 **178** **179**

176 = dipp—N(Me)(Me) with Au^{+} NH_3 $B(C_6F_5)_4^-$

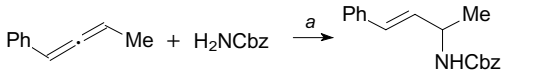
Scheme 146



180 (79%)

The intermolecular enantioselective hydroamination of internal allenes under the action of benzylcarbamate is catalyzed by gold complex with chiral ligand $\mathbf{L^2}$ (Scheme 147).[222] After recrystallization, the enantioselectivity of product (*S*)-**181** is 96%.

Scheme 147



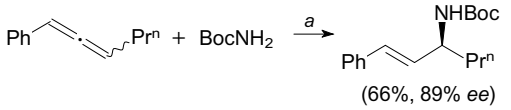
(*S*)-**181** (89%, 72% *ee*)

(*a*) [($\mathbf{L^2}$)$(AuCl)_2$] (2.5 mol.%), AgX (5 mol.%), 1,4-dioxane, 24 °C, 24 h

The asymmetric amidation of unsymmetrical internal allenes was reported by Toste and co-workers,[223] who employed gold(I) complex with acyclic diaminocarbene ligand $\mathbf{L^{37}}$ (Scheme 148).

Since enamides possess a unique reactivity, it is not surprising that reactions of allenamides, containing this

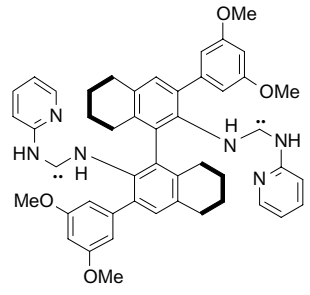
Scheme 148



(66%, 89% *ee*)

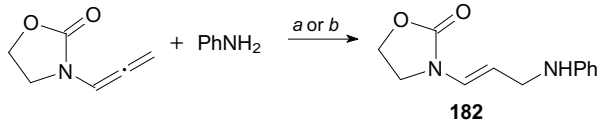
(*a*) [($\mathbf{L^{37}}$)*$(AuCl)_2$] (2.5 mol.%), AgOTf (12 mol.%), 1,4-dioxane, rt, 24 h;

($\mathbf{L^{37}}$)* =



moiety, with nucleophiles attract particular attention of researchers.[224] The hydroamination of allenamides with aromatic amines catalyzed by cationic Au^I complexes furnishes allylamines in good to high yields.[225] For example, in the presence of $Au(PPh_3)OTf$, the yield of compound **182** is 86%, while in the case of $Au(PPh_3)NTf_2$, the yield is 84% (Scheme 149).

Scheme 149



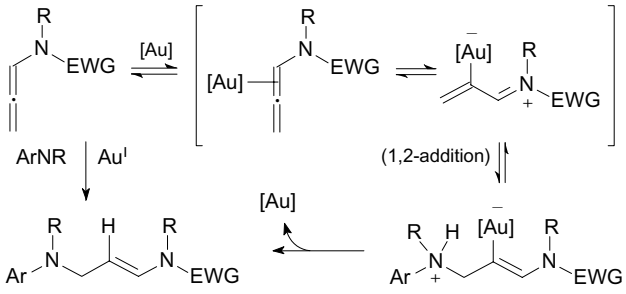
182

(*a*) $Au(PPh_3)OTf$ (5 mol.%), CH_2Cl_2; (*b*) $Au(PPh_3)NTf_2$ (5 mol.%), CH_2Cl_2

Kimber and co-workers[225] proposed a mechanism for this reaction (Scheme 150). Further transformation of these compounds may give practically valuable products.[226]

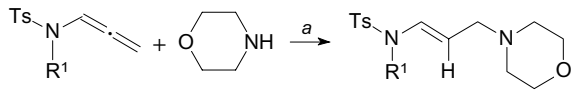
The copper-catalyzed allene hydroamination protocol[205] was utilized to carry out reactions of *N*-allenylsulfonamides.[227] Scheme 151 shows the reaction of this type for the synthesis of derivatives of secondary amines **183**.

Scheme 150



EWG is electron-withdrawing group

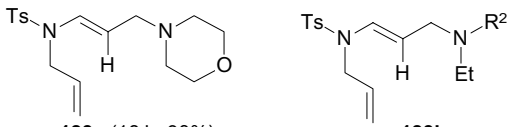
Scheme 151



183

(*a*) $[Cu(NCMe)_4]PF_6$ (5 mol.%), THF, 25 °C, 18 – 72 h; R^1 = Alk, Ar, *etc.*

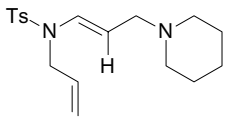
Examples of products



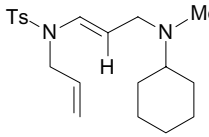
183a (18 h, 90%)

183b,**c**

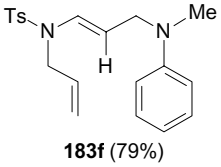
R^2 = Et (**b**, 82%), Bu^n (**c**, 82%)



183d (85%)



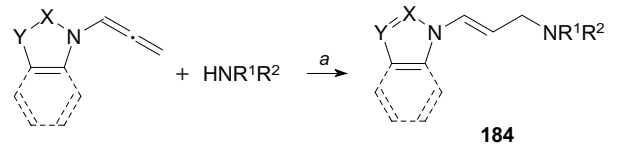
183e (76%)



183f (79%)

Under similar conditions, the corresponding *N*-allenylazoles react regio- and stereoselectively with secondary amines to give heterocyclic allylamines **184** (Scheme 152).[228]

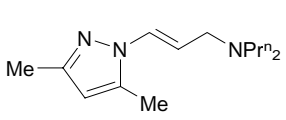
Scheme 152



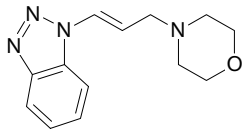
184

(*a*) $[Cu(NCMe)_4]PF_6$ (5 mol.%), THF, rt or 60 °C, 0.25 – 72 h; X = CH, N; Y = CH, N

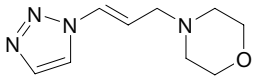
Examples of products



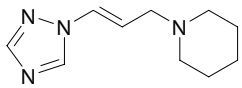
184a (4 h, 95%)



184b (15 min, 84%)



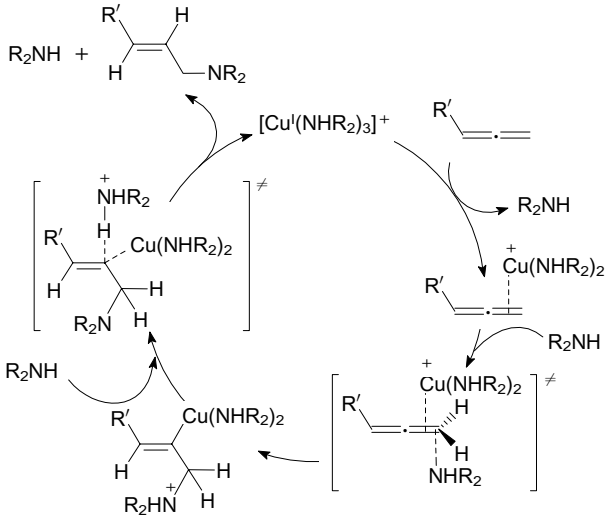
184c (30 min, 99%)



184d (4 h, 84%)

A catalytic cycle including the formation of Cu intermediates was proposed for this reaction (Scheme 153).

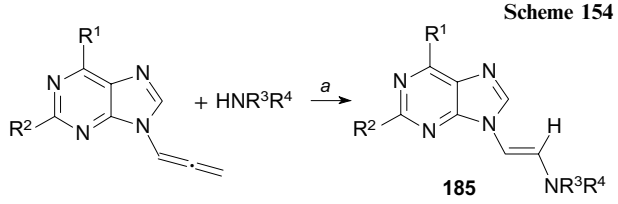
Scheme 153



There is a known example of AgF-catalyzed hydroamination of the allene moiety in purine bases, in which various amines — primary ($BnNH_2$), secondary, cyclic and aromatic ones — add to the terminal carbon atom under mild conditions to give products **185** in high yields (Scheme 154).[229]

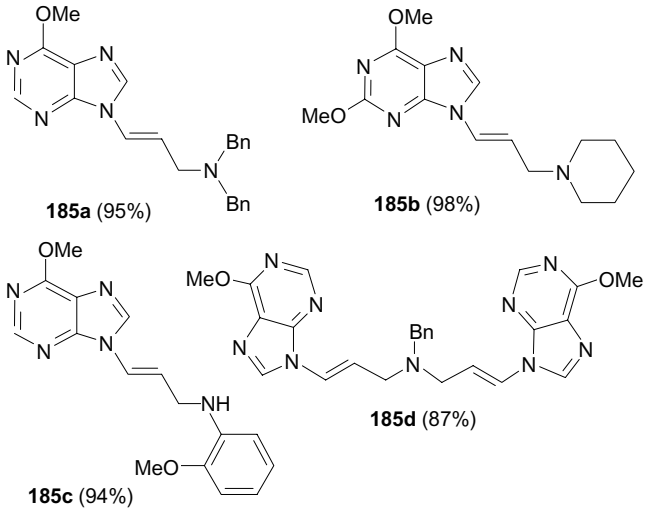
Alonso and Muñoz[230] investigated the reaction of azoles with activated allenes. The Au^I-catalyzed addition of azoles involved the unsubstituted position of allene and yielded linear allylazoles **186**. When platinum salt $PtCl_2$ was used as the catalyst, the regioselectivity completely changed:

Scheme 154

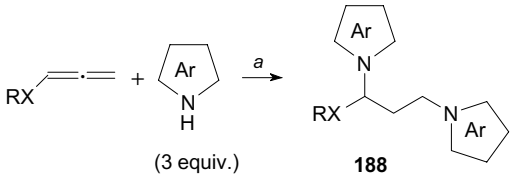


(*a*) AgF (3 mol.% – 5 mol.%), MeCN, 80 °C, 2 – 4 h

Examples of products

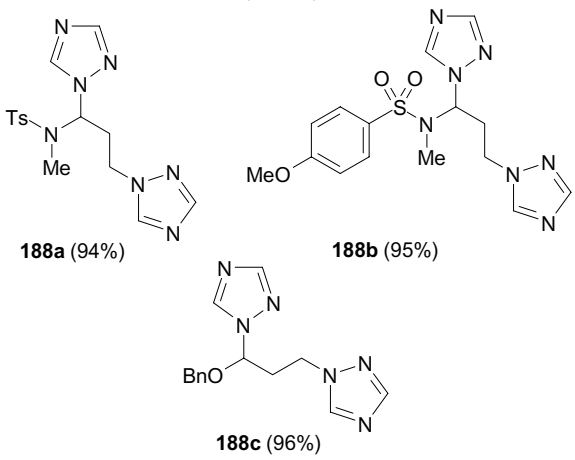


Scheme 156



(*a*) $Au(PPh_3)NTf_2$ (2.5 mol.%), $PtCl_2$ (10 mol.%), 1,4-dioxane (0.2 M), MW, 100 – 150 °C, 1 – 3 h; RX = TsNMe, BnO, PhS, *etc.*

Examples of products



allylazole **187** was formed upon the addition of azole at the substituted position. Thus, this is an example of divergent regioselectivity controlled by the catalyst (Scheme 155).

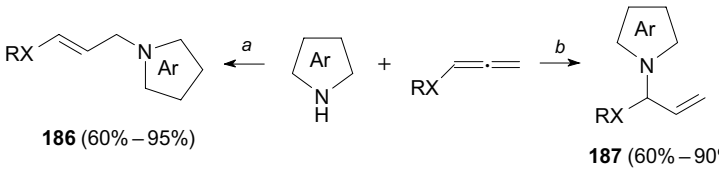
Finally, the bimetallic Au – Pt catalyst exhibited a higher activity than single Au or Pt, giving rise to product **188** substituted at both positions of the allene (Scheme 156).

The reaction of pyrazoles with terminal allenes catalyzed by chiral rhodium complex was regio- and enantioselective and gave branched allylpyrazoles **189** using (2*S*)-1-{(1*S*)-1-[bis(1,1-dimethylethyl)phosphino]ethyl}-2-[(*S*)-phenylphosphinyl]ferrocene (Jospophos, **L**[38]) as the ligand (Scheme 157; for product **189a**, the isolated yield is given).[231] Note that the azole attack was directed on the substituted position. For compound **189a**, the ratio of the isomeric products of addition to the pyrazole N(1) and N(2) atoms was > 99 : 1.

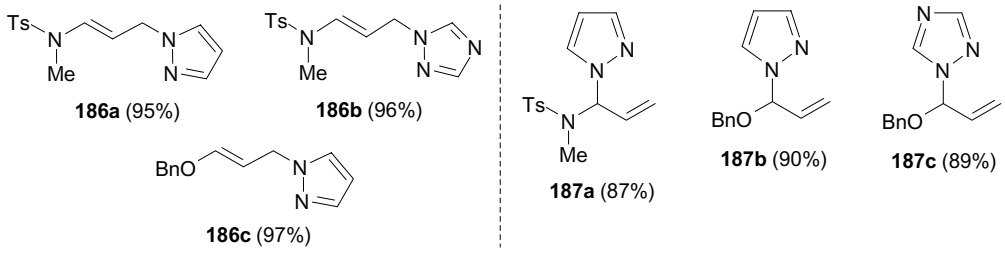
The compounds thus obtained were then subjected to various transformations: for example, compounds **189f** was converted to the anticancer agent (*R*)-ruxolitinib (**190**) (Scheme 158).

An interesting example of formal π-hydroamination of allenes that follows a different mechanism was reported by Wu and co-workers[232] for the Pd^{II}-catalyzed multicomponent reaction of arylallenes with arylboronic acids and nitroarenes in the presence of $Mo(CO)_6$, giving products **191** (Scheme 159).

Scheme 155

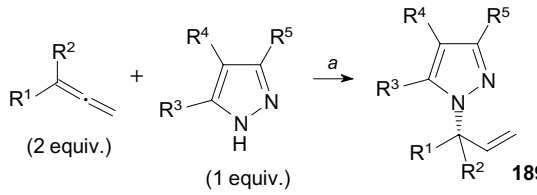


Examples of products

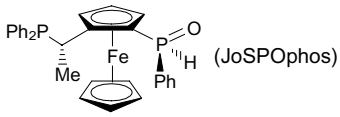


(*a*) $Au(PPh_3)NTf_2$ (2.5 mol.%), 1,4-dioxane (0.2 M), MW, 100 °C, 30 min – 3 h; (*b*) $PtCl_2$ (10 mol.%), 1,4-dioxane (0.2 M), MW, 100 °C, 10 min – 1.5 h; RX = TsNMe, BnO, PhS, *etc.*; Ar in the five-membered ring means aromatic azole

Scheme 157

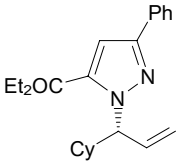


(*a*) [Rh(COD)Cl]$_2$ (2 mol.%), **L^{38}** (5 mol.%), PPTS (20 mol.%), PhMe (0.2 M), 80 °C, 16 h; R^1 = Alk, TMS, Bn, *etc.*; R^2 = H, Me; R^3 = R^5 = H, Me; R^3 = H, Me, CO_2Et; R^4 = Me, Ph, Cl, Br, I, NO_2, CO_2Et, Bpin, CF_3, C(O)H; R^5 = H, Me, Ph;
PPTS is pyridinium 4-toluenesulfonate, $(Bpin)_2$ is bis(pinacolato)-diboron, PhthN is *N*-phthalimido;

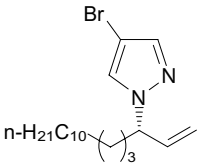
L^{38} = 

(JoSPOphos)

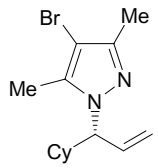
Examples of products



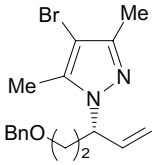
189a (78%, 95% *ee*)



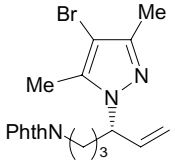
189b (98%, 90% *ee*)



189c (93%, 98% *ee*)

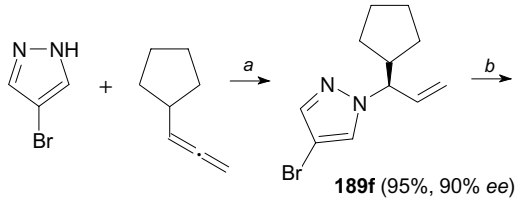


189d (94%, 89% *ee*)

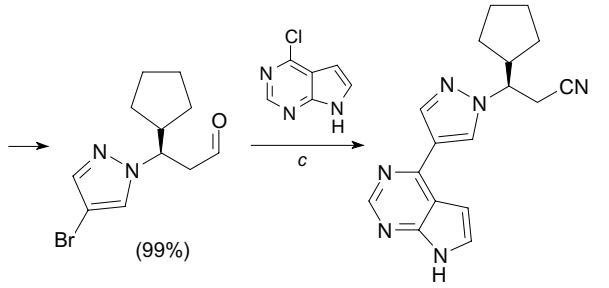


189e (99%, 89% *ee*)

Scheme 158



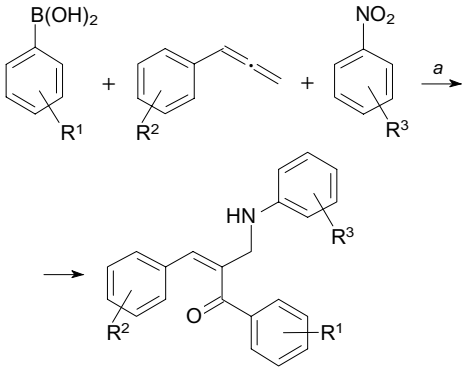
189f (95%, 90% *ee*)



190 [(*R*)-Ruxolitinib, 81%]

(*a*) [Rh(COD)Cl]$_2$ (2 mol.%), **L^{38}** (**5** mol.%), PPTS (20 mol.%), PhMe, 80 °C, 24 h; (*b*) 1) 9-BBN, THF, rt; 2) H_2O_2, NaOH, rt; (*c*) 1) I_2, NH_4OH, THF, rt (90% yield; after recrystallization, 79% with 98% *ee*); 2) $(Bpin)_2$, [Pd(dppf)Cl$_2$] (5 mol.%), KOAc, DMSO, 90 °C; 3) [Pd(PPh$_3$)$_2$Cl$_2$] (5 mol.%), K_2CO_3, 1,4-dioxane – H_2O (2 : 1), 120 °C; 9-BBN is 9-borabicyclo[3.3.1]nonane

Scheme 159

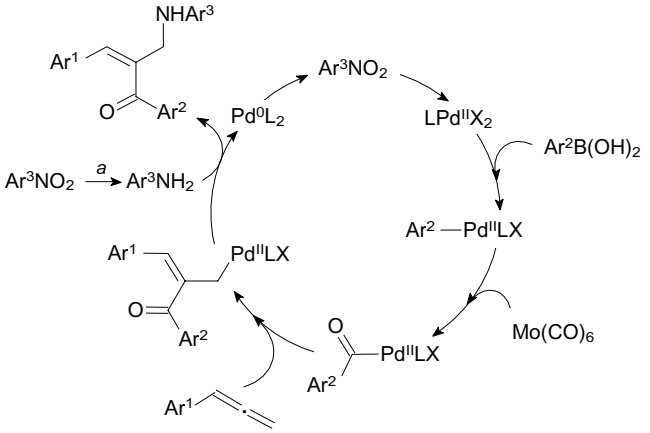


191 (38% – 62%)

(*a*) [Pd(cinnamyl)Cl]$_2$ (2.5 mol.%), **L^{27}** (5 mol.%), $Mo(CO)_6$ (1 equiv.), $KHCO_3$ (2 equiv.), H_2O (5 equiv.), MeCN, 100 °C; R^1 = H, 2-Me, 3-Me, 4-Me, 3-OMe, 4-OMe, *etc.*; R^2 = H, 2-Me, 3-Me, 4-Bu^t, 4-F, *etc.*; R^3 = H, 2-Me, 3-Et, 4-OMe, 2-F, 4-F, 4-SMe, *etc.*

During the reaction, nitroarenes are converted to anilines. The authors suggest a mechanism in which amination takes place at the C(sp^3) – PdX bond (Scheme 160).

Scheme 160



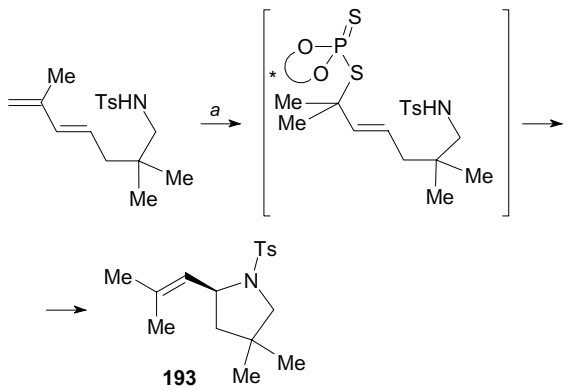
(*a*) [Pd], H_2O, $Mo(CO)_6$

5. Hydroamination of dienes

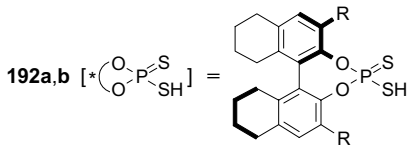
The catalytic hydroamination of 1,3-dienes to yield allylamines is of considerable interest, as these compounds are widely used in pharmaceutics and are incorporated in many natural molecules. In recent years, these reactions have attracted great attention. The huge industrial output of buta-1,3-diene (> 10 million tons per year) suggests that its functionalization is a highly relevant task.[233] Meanwhile, intermolecular hydroamination of both buta-1,3-diene and its derivatives has not yet been adequately studied.

There are known intramolecular hydroamination and hydroamidation reactions of dienes, including asymmetric ones,[234 – 236] carried out using various types of catalysts. Toste and co-workers[236] described asymmetric intramolecular hydroamidation of dienes catalyzed by chiral Brønsted acids **192a**,**b** (organocatalysis) (Scheme 161; as substituents for catalyst **192a**, *tert*-butyl groups are given in the Supplementary Information). Vinyl-substituted *N*-tosylpyrrolidine **193** was obtained under these conditions with enantiomeric excess of 96%.

Scheme 161

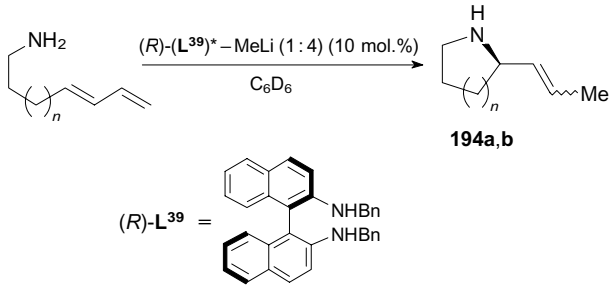


(*a*) **192a**,**b** (10 mol.%), PhF, 15 or 23 °C; R is 10-[3.5-di(*tert*-butyl)-phenyl]anthracen-9-yl (**a**, 96% yield), 10-(2,4,6-trimethylphenyl)-anthracen-9-yl (**b**, 98% yield);



Collin and co-workers[235] studied the intramolecular asymmetric hydroamination catalyzed by chiral lithium salts. In the presence of chiral ligand (*R*)-(**L**^{39})* at 95% conversion of the substrate, *E*-configured products **194a**,**b** are mainly formed in high yields, but with moderate enantioselectivity (Scheme 162).

Scheme 162

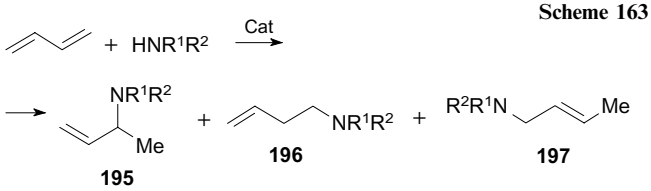


Compound **194**	*n*	*T*/°C	Time/h	Yield (%)	*E* : *Z*
a	1	20	0.17	68	98 : 2
b	2	50	21	62	89 : 11

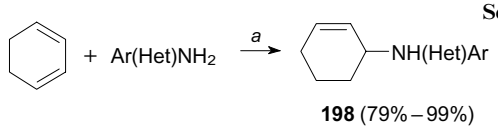
The reactions of unsubstituted diene with amines are expected to give products of 1,2- [Markovnikov (**195**) and anti-Markovnikov isomers (**196**)] and 1,4-addition (**197**) (Scheme 163).

In 2001, Hartwig and co-workers[237] carried out the palladium-catalyzed reaction of cyclohexa-1,3-diene with various (hetero)aromatic amines in the presence of a catalytic amount of trifluoroacetic acid (TFA) and obtained allylamines **198** in high yields (Scheme 164). In the case of anilines with electron-withdrawing groups, a longer reaction time was required.

Scheme 163



Scheme 164

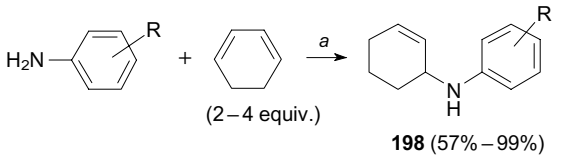


(*a*) $Pd(PPh_3)_4$ (2 mol.%) or $[Pd(\pi\text{-All})Cl]_2$ (5 mol.%) – PPh_3 (10 mol.%), TFA (10 mol.%), PhMe, 25 or 100 °C, 24 – 48 h

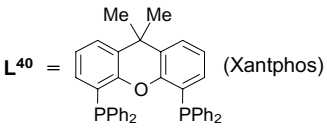
Similar reactions of cycloheptadiene and also methyl- and 2,3-dimethylbuta-1,3-dienes also proceed successfully.

The use of allyl palladium complex with 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene ligand (Xantphos, **L**^{40}) isolated in advance enabled the reaction of cyclohexa-1,3-diene with electron-deficient anilines under mild conditions over a period of 24 h (Scheme 165).[104]

Scheme 165

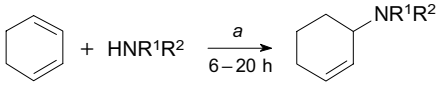


(*a*) [(**L**^{40})Pd(π-All)Cl]$_2$ (2 mol.%), THF, 25 – 50 °C, 24 h; R = 3-NO_2, 4-NO_2, 3-CO_2H, 3-Ac, 4-Ac, 2-CN, 3-CN, 4-CN, 2-CO_2Et, 2-SMe, 4-SMe, *etc.*;

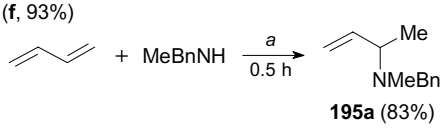


Palladium catalysis, which was used by Hartwig and co-workers[238] for aromatic amines, proved to be inefficient for alkylamines. However, nickel complexes $Ni(COD)_2$ or $[AllNiCl]_2$ with dppf ligand (**L**^{6}) in the presence of a minor amount of TfOH were active towards the reactions of primary, secondary and cyclic amines with cyclohexa-1,3-diene giving products **199a** – **f** in high yields (Scheme 166).

Scheme 166



$R^1 = R^2$ = Et (**a**, 78%); $R^1 - R^2 = (CH_2)_5$ (**b**, 82%), $(CH_2)_2O(CH_2)_2$ (**c**, 80%); R^1 = Me, R^2 = Bn (**d**, 89%); R^1 = H: R^2 = Bu^n (**e**, 89%), Bn (**f**, 93%)



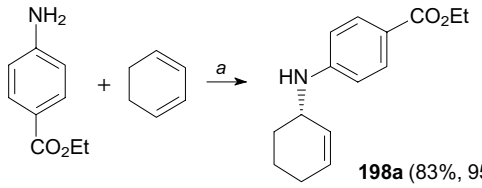
(*a*) $Ni(COD)_2$ – **L**^{6} (5 mol.%), TfOH (20 mol.%), PhMe, 25 °C

Under these conditions, buta-1,3-diene reacted rapidly, without telomerization, giving a minor amount of other isomers (~5%), together with the major Markovnikov product **195a**. However, the reactions of 2- and 2,3-sub-

stituted butadienes proceeded with difficulty and required large catalyst concentrations and elevated temperature.

The asymmetric version of hydroamination of cyclohexadiene in the presence of chiral (*R*,*R*)-diaminocyclohexyl ligand **L[41]**, called the Trost ligand, resulted in highly enantioselective synthesis of chiral amine **198a** (Scheme 167).[237]

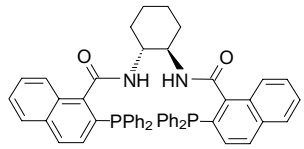
Scheme 167



198a (83%, 95% *ee*)

(*a*) [Pd(π-All)Cl]$_2$ (5 mol.%), **L[41]** (11 mol.%), rt, 120 h;

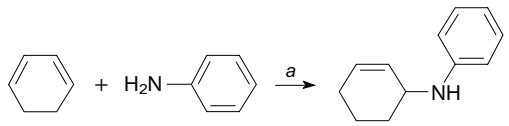
L[41] =



The reaction of dienes with alkylamines follows a more complicated pathway; in this case, preparation of the expected allylamine in a high yield is rarely possible, because of the readily proceeding telomerization.[239]

In 2001, Ozawa and co-workers [99] proposed well-defined active (η^3-All)Pd complex **200**, which ensured the formation of product **198b** in a high yield upon the reaction of aniline with cyclohexa-1,3-diene carried out at room temperature for 5 h (Scheme 168).

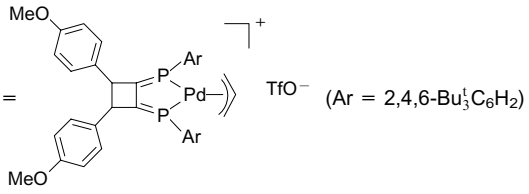
Scheme 168



198b (91%)

(*a*) [Pd] (**200**) (2 mol.%), PhMe, rt, 5 h;

200 =

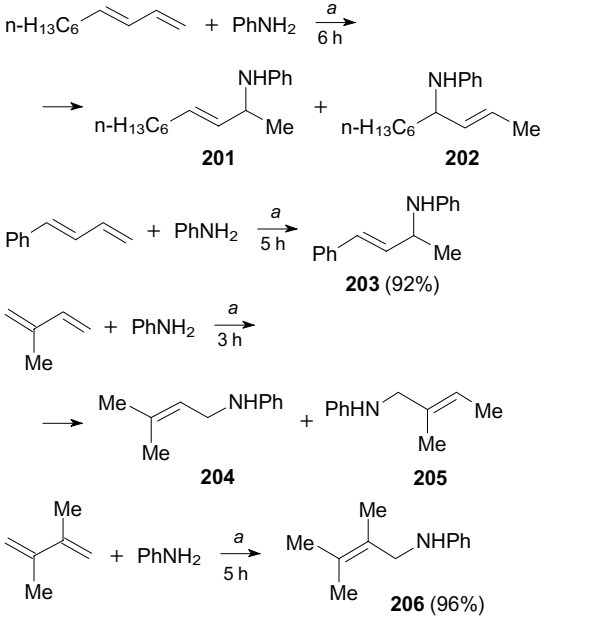


(Ar = 2,4,6-Bu$^t_3$C$_6$H$_2$)

Equally high yields of products **201** – **206** were obtained for acyclic dienes. In the case of linear dienes (aliphatic and aromatic ones), the Markovnikov isomer resulting from 1,2-addition was formed as the major or the only product, while in the case of branched isomers, 1,4-addition products were obtained (Scheme 169). Isomer mixtures were produced from deca-1,3-diene (80% total yield, **201** : **202** = 80 : 20) and 3-methylbuta-1,3-diene (92% total yield, **204** : **205** = 88 : 12).

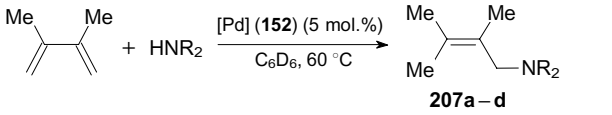
Active Pd catalyst **152** with *N*-aryl-3-iminophosphine ligand was proposed by Schmidt and co-workers [199] for the hydroamination of 2,3-dimethylbuta-1,3-diene with cyclic and acyclic secondary amines. On going from cyclic to acyclic amines, the yield of the products of 2,3-dimethyl-

Scheme 169



(*a*) [Pd] (**200**) (2 mol.%), PhMe, rt

Scheme 170



207a – **d**

Compound **207**	R^1R^2NH	Conversion of substrate (%)	
		24 h	72 h
a	Morpholine	89	–
b	Indoline	69	87
c	Pyrrolidine	40	56
d	Diethylamine	38	55

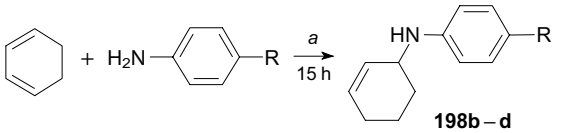
1,3-butadiene hydroamination, compounds **207a** – **d**, decreased (Scheme 170).

In 2014, Beller and co-workers [240] proposed a new Pd catalyst, Pd(COD)Cl$_2$ – DPEPhos (**L[7]**), for the reaction of unactivated dienes mainly with aromatic amines. When they used aromatic amines with electron-donating substituents and cyclic 1,3-dienes, the product yields were high (up to 95%). In the case of linear *E*- and *Z*-dienes, the yields were lower, but in all cases, 1,4-addition products were formed as the only (see **204**, **208**) or major (see **209**, **210**) products (Scheme 171).

The selective formation of 1,4-addition product **204** (formally, the anti-Markovnikov isomer) was attributed to the formation of palladium hydride as a catalyst due to the presence of HCl. A catalytic cycle was proposed for these reactions (Scheme 172).

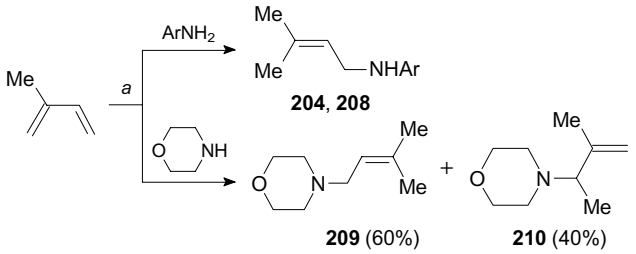
Malcolmson and co-workers [241, 242] found conditions under which the Pd catalysis allows for enantioselective hydroamination of acyclic dienes on treatment with aliphatic amines. Using Pd complex with phosphinooxazoline ligand **L[42]**, they carried out the 1,2-addition of secondary alkylamines to acyclic substituted dienes, *e.g.*, 1-phenylbuta-1,3-diene, with the predominant formation of Markovnikov isomer **211a** – **d** with high enantioselectivity. The

Scheme 171



198b – d

R = H (**b**, 95%), OMe (**c**, 94%), CF_3 (**d**, 77%)

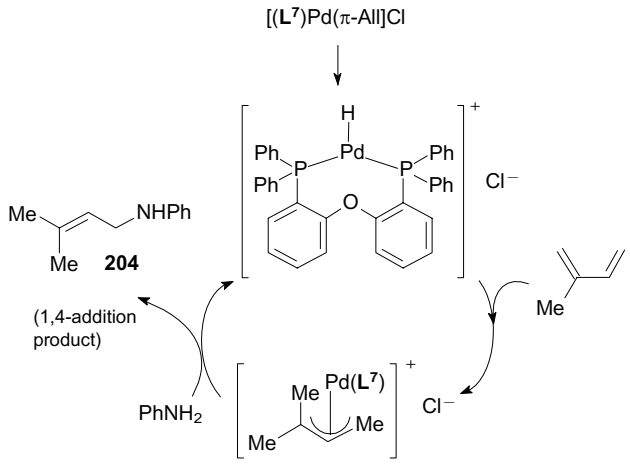


204, **208**

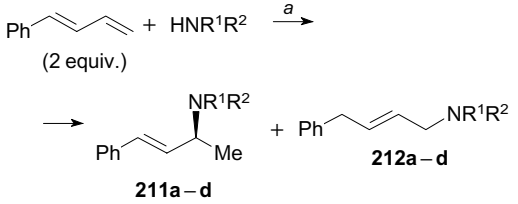
209 (60%) **210** (40%)

(*a*) [Pd(COD)Cl]$_2$ (5 mol.%), **L^7** (5 mol.% – 10 mol.%), PhMe, 100 °C, 10 – 17 h; Ar = Ph (**204**, 70%), 4-MeOC$_6$H$_4$ (**208**, 75%)

Scheme 172

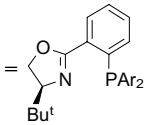


Scheme 173



211a – d **212a – d**

(*a*) [Pd(π-All)Cl]$_2$ (2.5 mol.%), **L^{42}** (5 mol.%), $AgBF_4$ (6 mol.%), CH_2Cl_2;

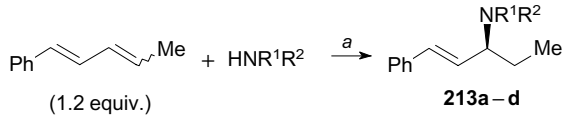
L^{42} =  [Ar = 3,5-(F$_3$C)$_2$C$_6$H$_3$]

Compounds **211**, **212**	R^{1}R^{2}NH	*T*/°C	Time /h	Yield (%)	*er*	**211** : **212** ratio
a	Morpholine	0	3	91	95.5 : 4.5	14 : 1
b	Piperidine	22	20	84	95 : 5	17 : 1
c	BnNHMe	0	3	77	95.5 : 4.5	> 20 : 1
d	Bn$_2$NH	30	20	60	94 : 6	> 20 : 1

1,4-addition products **212a – d** were detected as by-products (Scheme 173).

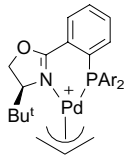
Similarly, the addition of secondary amines to internal dienes under optimized conditions proceeds with high regio- and enantioselectivity and good product yields. However, the success depends on not only the catalyst and the counter-ion, but also on the nature of the diene (Scheme 174).[242] The highest yields of compounds **213a – d** were observed in the presence of palladium complex **214**.

Scheme 174

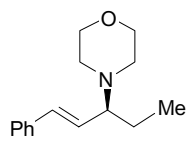


(1.2 equiv.) **213a – d**

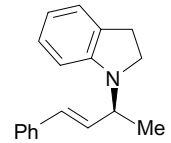
(*a*) [Pd] (**214**) (5 mol.%), Et_3N (3 equiv.), hexane – Et_2O (1 : 1), 22 °C, 20 h;

214 =  $B(C_6F_5)_4^-$ (Ar = 3,5-(F$_3$C)$_2$C$_6$H$_3$)

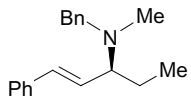
Examples of products



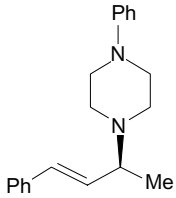
213a (71%, *er* = 96.5 : 3.5)



213b (78%, *er* = 98.5 : 1.5)



213c (62%, *er* = 88.5 : 11.5)



213d (65%, *er* = 94.5 : 5.5)

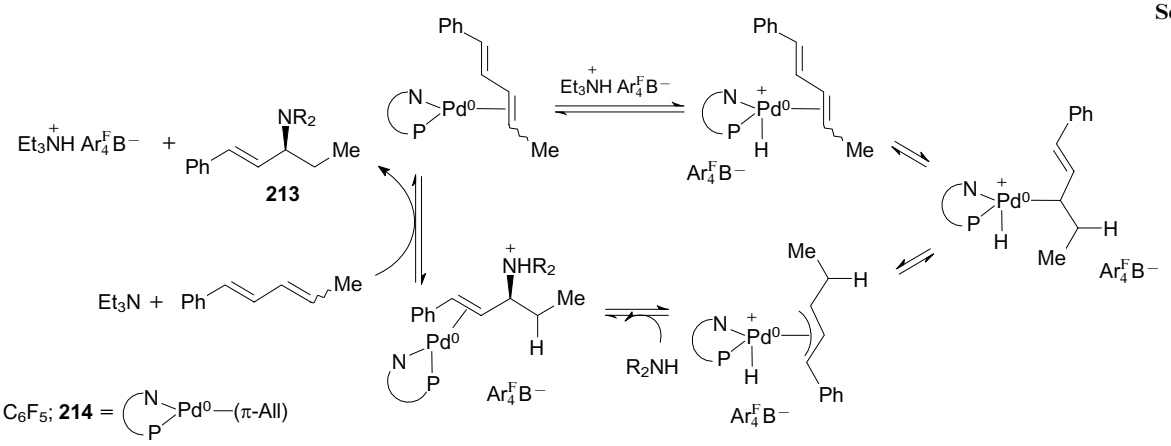
Catalytic cycle proposed for this transformation is presented in Scheme 175.

The cationic ruthenium complex [Ru] = $[(PCy_3)_2(CO)(Cl)Ru{=}CH{-}CH{=}CMe_2]^+BF_4^-$, described by Yi and Yun,[47] which is considered above for the hydroamination of ethylene, catalyzes the reactions of buta-1,3-dienes with primary arylamines and secondary benzocyclic amines with predominant formation of Markovnikov isomers **203**, **215a – c** as mixtures with 1,4-addition products **216a – c** (Scheme 176).

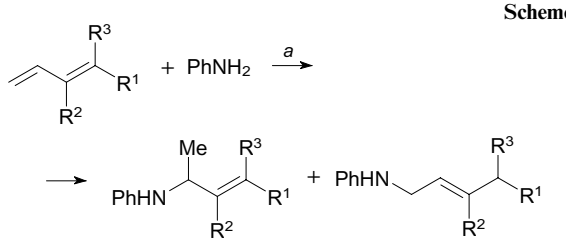
Unsubstituted buta-1,3-diene also reacts with indoline to give mainly Markovnikov product **217** (97% total yield, **217** : **218** = 73 : 27) (Scheme 177).[47]

Yang *et al.*[243,244] investigated the rhodium-catalyzed hydroamination of dienes. As in the palladium-catalyzed reactions, monosubstituted 1,3-diene reacts with indoline according to the 1,2-addition pathway to give the Markovnikov isomer. In the presence of a chiral Jospophos analogue, ligand **L^{43}**, allylamines **219** are formed in high yields and with high enantioselectivity; only in some cases, was 1,4-addition product **220** detected. The presence of catalytic amounts of acid, its pK_a value and steric properties were fundamentally important for this reaction, which was

Scheme 175



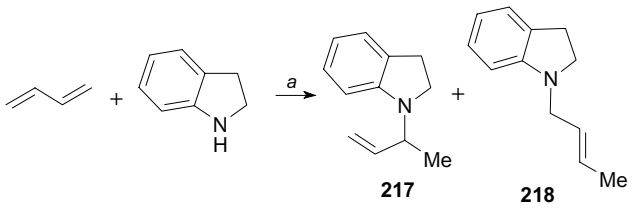
Scheme 176



(*a*) $[(PCy_3)_2(CO)(Cl)Ru{=}CH{-}CH{=}CMe_2]^+BF_4^-$ (5 mol.%), PhH, 20 – 90 °C, 24 – 36 h

R^1	R^2	R^3	Products (ratio)	Yield (%)
H	H	H	**215a** + **216a** (70 : 30)	97
Ph	H	H	**203** + **216b** (95 : 5)	50
H	Me	H	**215b** + **216c** (90 : 10)	68
Me	H	Me	**215c**	35

Scheme 177



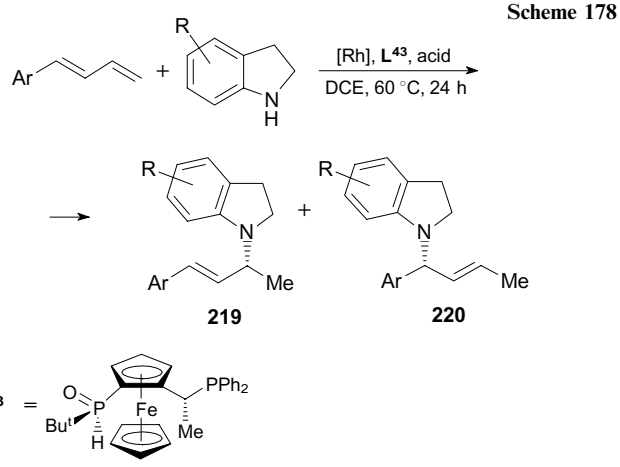
(*a*) $[(PCy_3)_2(CO)(Cl)RuH]$ (5 mol.%), $HBF_4 \cdot Et_2O$ (10 mol.%)

studied in relation to the synthesis of compound **219a** (Ar = Ph, R = H) (Scheme 178).[243]

By varying the natures of the ligand and the Brønsted acid and using *rac*-BINAP (*rac*-**L**^{9}) and mandelic acid (pK_a 3.3 and 3.4 in DCE and water, respectively), the authors prepared for the first time homoallylic amine **221** as the major product. This product is formed *via* 1,2- rather than 1,4-addition (see structure **222**) against the Markovnikov rule (Scheme 179).[244] The mechanism of this reaction has not yet been adequately studied, especially if the reversibility of the diene insertion into the Rh – H bond is taken into account.

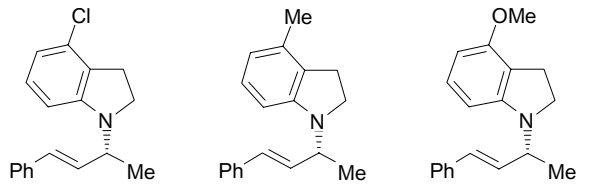
Under similar conditions with the $[Rh(COD)_2]SbF_6$ catalyst (5 mol.%), compounds **221a** – **c**, **223a** – **c** were prepared from appropriate reactants.

Scheme 178

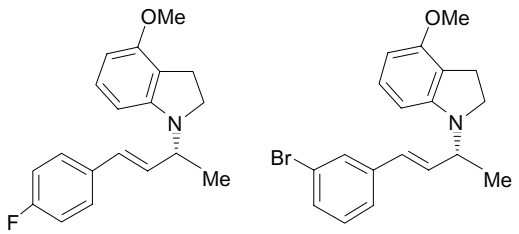


[Rh]	Acid (pK_a)	Yield (%)	*ee* (%)	**219a** : **220a** ratio
$[Rh(COD)Cl]_2$	3,5-$Me_2C_6H_3CO_2H$ (4.2)	84	82	> 20 : 1
$[Rh(COD)Cl]_2$	Ph_3CCO_2H (3.3)	80	90	> 20 : 1
$[Rh(COD)OMe]_2$	Ph_3CCO_2H (3.3)	81	96	–

Examples of products

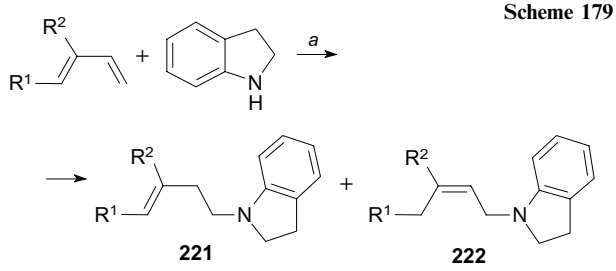


219b (87%, 96% *ee*) **219c** (80%, 96% *ee*) **219d** (80%, 97% *ee*)



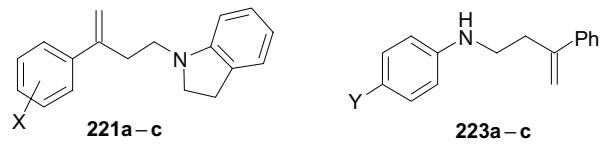
219e (83%, 98% *ee*, *rr* = > 20 : 1) **219f** (82%, 97% *ee*, *rr* = > 20 : 1)

Scheme 179



(*a*) $[Rh(COD)Cl]_2$ (2.5 mol.%), *rac*-**L**[9] (5 mol.%), $PhCH(OH)CO_2H$ (50 mol.%), DCE, 80 °C, 15 h; R^1, R^2 = H, Alk, Ar

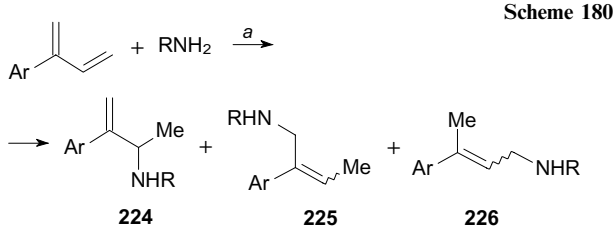
Structures 221, 223



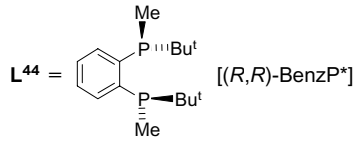
221: X = H (**a**, 83%, *rr* = >20 : 1), 2-Me (**b**, 60%, *rr* = >20 : 1), 3-OMe (**c**, 82%, *rr* = >20 : 1); **223**: Y = CO_2Et (**a**, 40%, *rr* = 5 : 1), F (**b**, 61%, *rr* = 10 : 1), OMe (**c**, 63%, *rr* = 11 : 1); *rr* is regioisomeric ratio

In 2019, Mazet and co-workers[245] reported the enantioselective hydroamination of branched dienes with aliphatic amines catalyzed by chiral nickel complex in the presence of the (*R*,*R*)-(+)-1,2-bis(*tert*-butylmethylphosphino)benzene ligand [(*R*,*R*)-BenzP*, **L**[44]]. The authors showed that in the case of branched isomers, Markovnikov product **224** (3,4-addition product) can be obtained in high yield and with high enantioselectivity and that 1,4-addition products **225**, **226** are formed in minor amounts (Scheme 180).

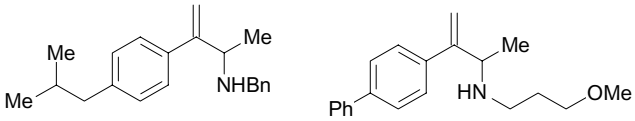
Scheme 180



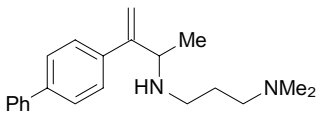
(*a*) $[Ni(COD)_2]$ (5 mol.%), **L**[44] (5 mol.%), TFE (1 equiv.), mesitylene, 23 °C, 22–144 h; TFE is trifluoroethanol;



Examples of products



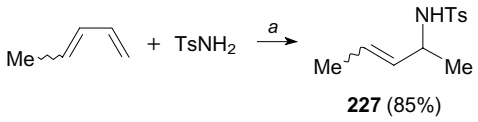
224a (84%, 91% *ee*, *rr* = 8 : 1) **224b** (88%, 93% *ee*, *rr* = 7 : 1)



224c (86%, 96% *ee*, *rr* = 9 : 1)

The addition of sulfonamides to dienes, like the addition to alkenes, is catalyzed by cationic gold complex and gives the Markovnikov product as a result of 1,2-addition to the less hindered position (Scheme 181).[91] For example, compound **227** was formed as a 1 : 7 mixture of *Z* and *E* isomers.

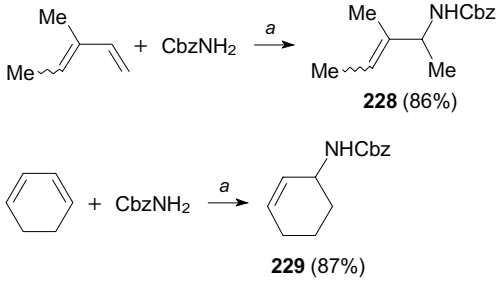
Scheme 181



(*a*) $[(PhO)_3PAuCl]$, AgOTf, PhMe, MW, 90 °C, 0.5 h

In the case of gold catalysis, 1,3-dienes react with carbamates and give analogous products, for example, compounds **228** and **229** (Scheme 182).[246]

Scheme 182



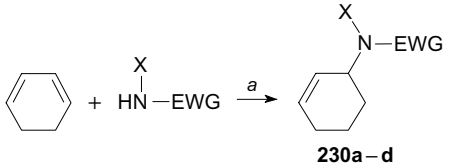
(*a*) $Ph_3PAuOTf$ (5 mol.%), DCE, N_2, dark, overnight

Unfortunately, it was impossible to compose a regiodivergent pair for the reactions of 1,3-dienes, as the authors who obtained Markovnikov[245] and anti-Markovnikov[244] isomers used different amines.

Shibasaki and co-workers[247] developed a catalytic system based on $Bi(OTf)_3$ and $Cu(MeCN)_4PF_6$ with dppe (**L**[10]) ligand, which catalyzed the monohydroamination of 1,3-dienes with various carbamates, sulfonamides and carboxamides to give allylamines in good yields. The authors suggested that the use of copper minimizes the side telomerization of 1,3-dienes, while the presence of the PF_6^- ion accelerates the addition in comparison with the competing polymerization. Scheme 183 depicts the conditions of formation of products **230a**–**d**.

Under the same conditions, acyclic 1,3-dienes react with carbamate to afford either 1,2- and/or 1,4-addition

Scheme 183

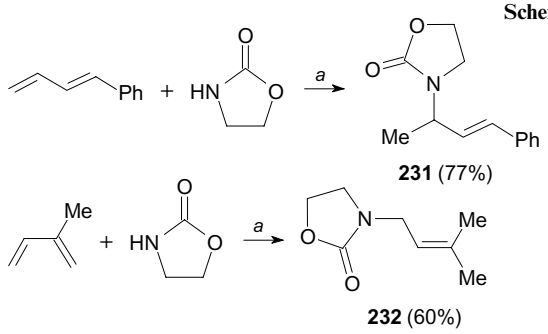


(*a*) $Bi(OTf)_3$ (10 mol.%), $Cu(MeCN)_4PF_6$ (6 mol.%), **L**[10] (4 mol.%), 1,4-dioxane; X = H, Alk

Compound **230**	N(X)EWG	*T*/°C	Time/h	Yield (%)
a	$NHCO_2Me$	50	18	96
b	cyclo-[NC(O)O$(CH_2)_2$]	50	18	92
c	NHTs	50	3	84
d	$NHC(O)C_6H_4CF_3$-4	90	17	77

products, with the ratio of the isomeric products depending on the starting diene. 1-Phenylbuta-1,3-diene was converted to 1,2-addition product **231**, while isoprene (2-methylbuta-1,3-diene) formed 1,4-addition product **232** (Scheme 184).[247]

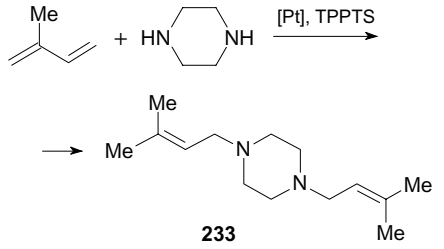
Scheme 184



(*a*) $Bi(OTf)_3$ (10 mol.%), $[Cu(MeCN)_4]PF_6$ (10 mol.%), **L[10]** (4 mol.%), 1,4-dioxane, 50 °C, 18 h

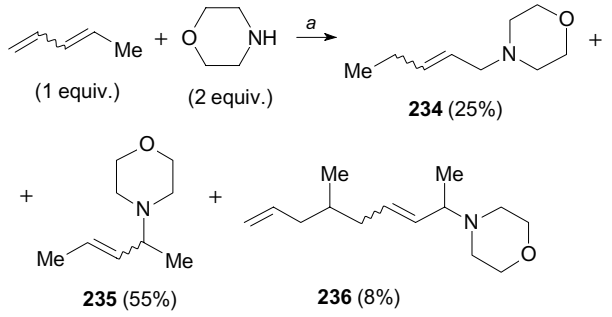
The hydroamination of isoprene catalyzed by soluble platinum complex in the presence of trisodium triphenylphosphine-3,3′,3″-trisulfonate (TPPTS) occurs as 1,4-addition and gives mainly anti-Markovnikov product **233** (Scheme 185).[248]

Scheme 185



As in the case of isoprene, in the hydroamination of piperylene with morpholine, the key problem is telomerization.[249] By using a Pd catalyst with the 1,4-bis(diphenylphosphino)butane ligand (dppb, **L[45]**) in 1 : 2 ratio, one can control this side process and obtain hydroamination products **234** – **236**, with 1,4-addition product **235** predominating (Scheme 186). The reaction selectivity is 90% for 88% conversion of the substrate.

Scheme 186



(*a*) $Pd(O_2CCCl_3)_2$ (0.3 mol.%), **L[45]** (0.3 mol.%), MeOH, 100 °C, 16 h;

L[45] = Ph_2P ⌒ PPh_2 (dppb)

6. Conclusion

The purpose of this review, dedicated to Vladimir Vasil'evich Markovnikov, is to show that his discovery of isomerism is of fundamental importance for modern chemistry, which is concerned about economic and environmental problems. The origin of these problems is the formation of mixtures of two regioisomers instead of one desired isomer, *i.e.*, the lack of selectivity of reactions. Owing to the industrial demands, not only anti-Markovnikov isomers, but also Markovnikov isomers, especially in the enantiopure state, are required in modern chemistry. This is why it is important to control the reaction selectivity, *i.e.*, to carry out regiodivergent reactions, which means that it is possible to prepare either of the isomers, most often, by varying the catalysts. Moreover, the anti-Markovnikov isomer should have a definite stereoconfiguration, while the Markovnikov product should have a definite enantio configuration. Unfortunately, hydroamination reactions are not very illustrative in this respect. Fundamental studies of these transformations mainly refer to intramolecular reactions, which usually represent the construction of complex nitrogen-containing polycyclic systems. In the intermolecular amination of unsaturated compounds, the anti-Markovnikov isomer required for industry is usually a major product, while the chiral Markovnikov isomer is not yet in high demand. However, both trends certainly require expanding the range of catalysts, which would give rise to additional regiodivergent reactions. We hope that the isomeric products formed in these reactions would be called 'Markovnikov' and 'anti-Markovnikov' products in the memory of our great forerunner, rather than linear and branched products.

It is quite obvious that for a country possessing huge hydrocarbon reserves, the problem of functionalization and difunctionalization of alkenes, alkynes, allenes and dienes is of high relevance. For solving this problem, it is necessary, first of all, to find proper catalytic systems. Among functionalization reactions, hydroamination is the newest one. However, since amines represent an important class of organic compounds and the addition of compounds with N – H bonds to substrates with saturated carbon – carbon bonds serves as the most direct and efficient method for the preparation of diverse amines, the number of publications on this topic has markedly increased in recent years. In this review, we did our best to cover the key studies on this topic to allow the reader to get a comprehensive view. It is quite clear that there is room for further research in this area and many results will appear in the near future.

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