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Rhodium Catalysts for C–S Bond Formation

Andrea Di Giuseppe, Ricardo Castarlenas, and Luis A. Oro

Abstract Sulfur-containing molecules are commonly found in chemical biology, organic synthesis, and materials chemistry. The preparation of these compounds through traditional methods usually required harsh reaction conditions. The use of transition-metal-based catalysts has allowed the development of more efficient and sustainable synthetic processes. Rhodium-catalyzed C–S bond formation through the reaction between sulfur sources such as S_8, thiols, or disulfides with organic substrates such as alkynes, allenes, and aryl/alkyl halides is one of the most important methods in the synthesis of thioethers. Here, we summarize recent efforts in the reactions of cross coupling, C–H activation, metathesis, thiolation, carbothiolation, and hydrothiolation for the C–S bond formation catalyzed by rhodium complexes, particularly highlighting the synthetic and mechanistic aspects.

Keywords Alkynes • Allenes • Carbothiolation • C–H activation • Cross coupling • Halides • Hydrothiolation • Thioethers • Thiolation

Contents

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Abbreviations

(S)-BIPHANE	(R,R)-1,2-Bis[(R)-4,5-dihydro-3H-binaphtho(1,2-c:2′,1′-e) phosphepino]benzene
AMLA	Ambiphilic metal ligand activation
Ar^F	3,5-$(CF_3)_2C_6H_3$
Bz	Benzyl
CMD	Concerted metalation deprotonation
Cod	Cyclooctadiene
Coe	Cyclooctene
Cp*	Pentamethylcyclopentadienyl
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
Dppb	1,4-Bis(diphenylphosphino)butane
dppBz	1,2-Bis(diphenylphosphino)benzene
Dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Ferrocenediyl-bis(diphenylphosphine)
Dppp	1,3-Bis(diphenylphosphino)propane
Dpppe	1,5-Bis(diphenylphosphino)pentane
e.e.	Enantiomeric excess
IPr	1,3-Bis-(2,6-diisopropylphenyl)imidazol-2-carbene
Nbd	2,5-Norbornadiene
OAc	Acetate
O^{t}Bu	*tert*-Butoxide
OTf	Triflate
r.t.	Room temperature
^{t}AmOH	2-Methyl-2-butanol
THF	Tetrahydrofuran
Tp	Hydrotris(1-pyrazolyl)borate
Tp*	Hydrotris(3,5-dimethylpyrazol-1-yl)borate

1 Introduction

Sulfur is contained in many synthetic reagents, functional materials, or agrochemicals and represents an essential element for all type of life as it is present in amino acids, vitamins, and cofactors [1]. Several bioactive drugs including β-lactam and sulfonamide antibiotics, nonsteroidal anti-inflammatory agents/analgesics, diuretics, antidiabetics, antiulcer, and antipsychotics contain this oligoelement [1–9]. An increasing demand of these molecules has entailed the development of new efficient and selective synthetic methods via C–S bond formation. From this point of view, catalysis is one of the fundamental pillars of sustainable chemistry, and the design and application of new catalysts and catalytic systems are simultaneously achieving the dual goals of environmental protection and economic benefit [10, 11].

Among all branches of catalysis, transition-metal-based catalysts had always been a mainstay of industrial chemistry, and nowadays a number of outstanding catalytic systems have been developed. In particular, the last 3 decades have witnessed a huge increase in catalytic systems for C–heteroatom bond formation [12–30]. In contrast, the development of catalytic systems able to mediate C–S coupling is relatively scarce. One of the reasons for this underdevelopment is the consideration of sulfurated compounds as potent poisons for organometallic catalysts [31]. The overcome of this established belief has changed this trend, and only recently an amount of transition-metal catalytic systems for C–S bond formation has impressively emerged [32–44]. Among these catalysts, rhodium complexes represent one of the most interesting systems principally due to its tunability that allows the thiofunctionalization of a broad range of substrates using a wide variety of sulfur sources. Particularly, rhodium catalysts are the perfect examples where a high degree of control of the chemo-, stereo-, and regioselectivity can be achieved due to an in-depth understanding of the mechanistic issues that allow for a rational design of the organometallic catalysts.

This review outlines the recent advances in the catalytic C–S bond formation mediated by rhodium complexes with a special attention on the mechanism of the reaction. Transformations which are the topics of other chapter of this volume are not included in this review.

1.1 Rhodium-Catalyzed C–S Bond Formation Reactions

As introduced above, rhodium compounds are really flexible catalysts for C–S bond-forming transformations. A regrouping in two big families of reactions can be formally established: (1) substitution and (2) addition reactions. The former includes all type of transformations in which a **C**–X bond is transformed into a **C**–**S** functionality through the formal substitution of the X (a halogen or a hydrogen) by a thio-substituent arising from the appropriate sulfur source **S**–Y with concomitant formation of X–Y as a by-product (Fig. 1a). Transformations included in this family

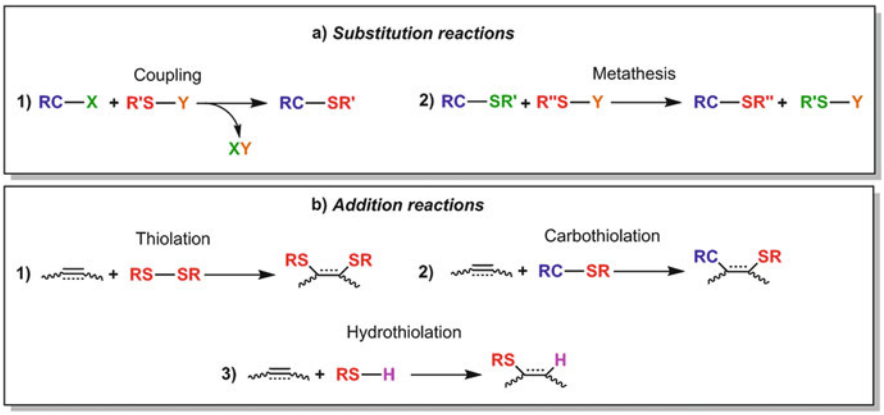

Fig. 1 C–S bond formation catalyzed by Rh: substitution reactions (**a**) and addition reactions (**b**)

are the cross-coupling reactions and the metathesis of thioethers. Substrates involved include alkynes, aromatic compounds bearing a directing group, molecules with an activated C(sp^2)–H or C(sp^3)–H (including heterocycles), halogenated compounds, and thioethers, while the sulfur sources are thiols, disulfides, and α-thioketones.

In the second family of reactions, an appropriate sulfur source S–Y is added into an unsaturation of the substrate. In contrast to the substitution reactions, the hybridization of the carbon where the addition occurs changes from sp^x to sp^{x+1}, and more importantly, a 100% atom efficiency is obtained with no by-product formation, leading to substantial practical advantages in terms of green chemistry. Typical substrates used for these transformations are alkynes and allenes, while the sulfur sources include disulfides, thioethers, and thiols. Depending on the type of thio-substrate added, the reactions are, respectively, named thiolation, carbothiolation, and hydrothiolation (Fig. 1b).

2 Substitution Reactions

The substitution reactions are a widely recognized approach for the coupling of two organic substrates by the construction of new C–C and C–X bonds and the elimination of a small molecule. Depending on the substrates, the following classification can be established for C–S bond formation reactions promoted by rhodium: (1) cross coupling between organic halides with thiols, disulfides (or oligosulfide), or elemental sulfur, (2) coupling via C–H activation between no pre-functionalized organic compounds containing relative acidic C–H bond or bearing directing groups and disulfides or α-thio-substituted ketones as the sulfur source, and (3) metathesis between two sulfurated substrates.

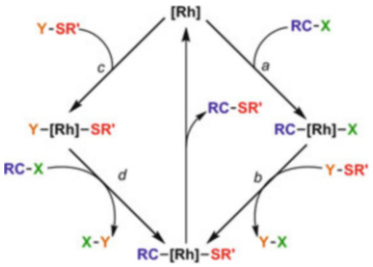

Fig. 2 General reaction mechanism of cross-coupling Rh-catalyzed C–S bond formation

2.1 Cross-Coupling Reactions

The transition-metal-catalyzed cross coupling is a very powerful tool for the creation of C–C and C–heteroatom bonds [45–52]. A general mechanistic framework is described in Fig. 2. In the first step of the cycle, the Rh^{I} precursor activates the C–X bond leading to a RC–Rh^{III}-X species (step a). The transmetalation by the sulfur-containing substrate Y–SR′ provides RC–Rh^{III}–SR′ simultaneously to the elimination of YX (step b). In some cases an additive (bases, phosphine, silane) is required for trapping of the Y and X fragments. In the last step, a C–S reductive elimination gives the coupling product and regenerates the starting Rh^{I} species. Alternatively, the sulfur-containing compound can add first (c) and subsequent reaction with the halogenated substrate yields RC–Rh^{III}–SR′ (d) that evolves by the same pathway.

The formation of C–S bonds by metal-catalyzed cross-coupling reactions was studied for the first time by Migita in 1978 for the Pd-catalyzed coupling of aryl halides with thiols [53]. Starting from this pioneering work, a lot of new catalytic system has been developed using several metals such as Pd, Cu, Ni, Fe, Mn, Co, In, Ag, Bi, or La [54–70]. The development of rhodium-based catalysts for the formation of C–S bonds via cross coupling is relatively recent. The first work was published by Tanaka and coworkers in 2005 [71]. In this report the coupling of thiols and polychloroalkanes in the presence of trimethylamine using $RhCl(PPh_3)_3$ was reported. This reaction serves as a convenient new method to produce formaldehyde dithioacetals and ethylenedithioethers. It was interestingly found that the reaction of thiols and tri- or tetra-chlorinated alkanes such as $CHCl_3$ and CCl_4 gives thioformate and a dithiocarbonic ester, respectively, presumably through hydrolysis of corresponding polythiomethanes by silica gel (Fig. 3a). The reaction of benzyl mercaptan with (R)-(1-chloroethyl)benzene was investigated to gain mechanistic insights, revealing a complete inversion of configuration in the formed sulfide (Fig. 3b). The mechanism proposed in Fig. 3c justifies this observation. The first step is the oxidative addition of the thiol to afford a hydride–thiolate–rhodium(III) species. Elimination of HCl by treatment with Et_3N furnishes rhodium(I)–thiolate intermediates, which reacted with alkyl halides in an S_N2 fashion, thereby furnishing sulfides and regenerating the rhodium(I) active species.

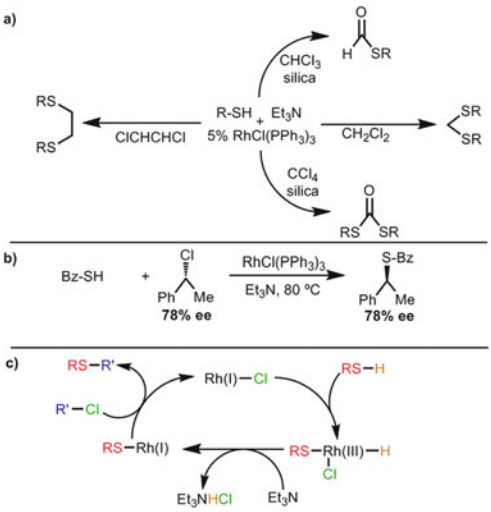

Fig. 3 Coupling of thiols and polychloroalkanes catalyzed by $RhCl(PPh_3)_3$ in the presence of trimethylamine [71]

The heterogeneous version of this reaction was developed by Cai and coworkers by supporting of the Wilkinson's catalyst on MCM 41 derivatized with diphosphine ligand [72]. This system achieves the coupling of thiols with polychloroalkanes or alkyl halides at 30°C or 80°C in the presence of triethylamine, yielding a variety of formaldehyde dithioacetals, ethylenedithioethers, and unsymmetric thioethers in good to excellent yields. The catalyst was easily recycled by simple filtration of the reaction solution and reused for ten consecutive trials without significant loss of activity.

Tanaka and coworkers expanded their methodology to the catalytic enantioselective synthesis of planar-chiral dithiaparacyclophanes [73, 74]. A catalytic system based on the cationic $[Rh(cod)_2]BF_4$ complex and the chiral diphosphine (S)-BINAPHANE was efficient for the catalytic coupling of dithiols and 1,4-bis(bromomethyl)benzenes, yielding dithiaparacyclophanes with enantiomeric excess (e.e.) up to 49% (Fig. 4) [73]. This method represents the first example of asymmetric synthesis of planar-chiral cyclophanes through catalytic enantioselective construction of the *ansa* chains.

An enhancement of this reaction was disclosed by the same research group. A reductive coupling of disulfides with alkyl halides mediated by Wilkinson's catalyst in presence of triethylamine was developed. Molecular hydrogen was used as a reducing agent. This reaction serves as a convenient method to produce unsymmetrical sulfides from disulfides instead of odoriferous thiols (Fig. 5a) [75]. The in situ formation of thiols was demonstrated by the reaction of didodecyl disulfide with molecular hydrogen in the presence of 3% $RhCl(PPh_3)_3$ at 100°C (Fig. 5b). Noteworthy, in spite of $RhCl(PPh_3)_3/H_2$ being a powerful hydrogenating system, the presence of olefins seems to be tolerated. The reaction of $(p\text{-TolS})_2$ with cinnamyl bromide provides the desired cinnamyl sulfide in 76% yield, and almost no hydrogenated phenylpropyl sulfide was generated (Fig. 5c).

Fig. 4 Enantioselective coupling of dithiols with dibromides catalyzed by $[Rh(cod)_2]BF_4$/(S)-BIPHANE [73]

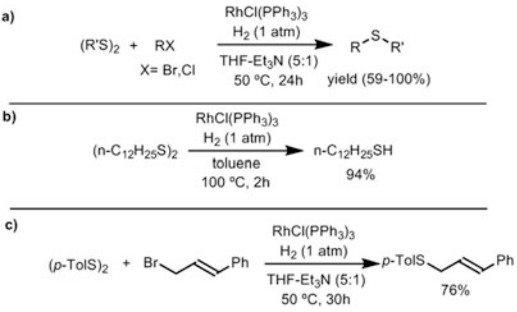

Fig. 5 Reductive coupling of disulfides with alkyl halides mediated by Wilkinson's catalyst in the presence of triethylamine and H_2 [75]

The examples showed above are all referred to $C(sp^3)$–X coupling with a thio-compound. It should be pointed out that nucleophilic substitution on the $C(sp^3)$ atoms occurs readily and usually does not require a catalyst. However, the formation of $C(sp^2)$–S bonds is more challenging and a metallic catalyst is often required. In this context, Yamaguchi and coworkers reported that a catalytic system composed of $RhH(PPh_3)_3$, dppbz, and an excess of triphenylphosphine is efficient for the reaction between aryl fluorides and aliphatic and aromatic disulfides (Fig. 6a) [76]. The reaction proceeds in high yield when electron-withdrawing groups are present in the aryl fluoride, while fluorobenzene is inert. The use of polyfluorobenzenes leads to the production of polyarylthiolation products, with a marked preference for the formation of *p*-difluoride derivatives (Fig. 6b). Interestingly, the reaction of 1-bromo-4-chloro-3-fluorobenzene with di(p-tolyl) disulfide provides selectively the fluorine-substituted product indicating that, in this reaction conditions, the reactivity of aryl fluoride is higher than bromide and chloride counterparts. Triphenylphosphine is fundamental for the reaction acting as a trap of fluoride. In fact, extremely unstable sulfenium fluoride R–SF is formally formed in the reaction. The presence of PPh_3 is crucial to make the reaction thermodynamically favorable converting this compound into more stable products such as triphenylphosphine difluoride and disulfide [40].

A slight modification of the reaction conditions, as the change of dppBz for dppe and THF instead of C_6H_5Cl as solvent, allowed for the coupling of aromatic and aliphatic acid fluorides with disulfides providing the corresponding thioesters (Fig. 7) [77]. Also in this case, fluoride seems to be more reactive than chloride

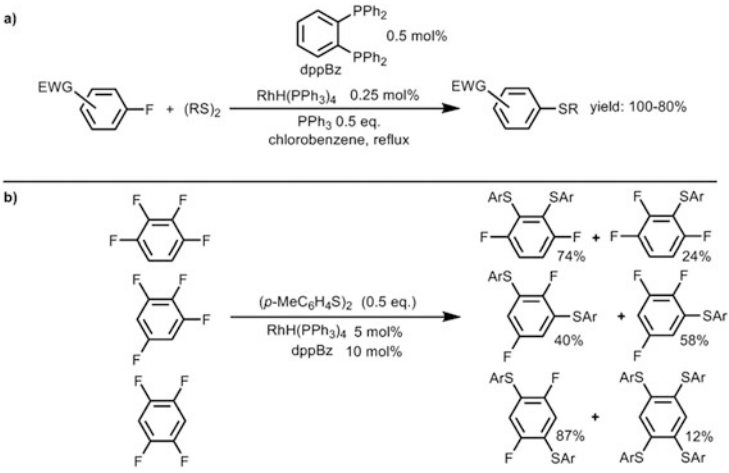

Fig. 6 Reaction between aryl fluorides and disulfides catalyzed by $RhH(PPh_3)_3$ and dppbz in the presence of an excess of triphenylphosphine [76]

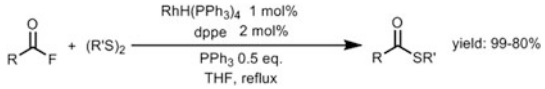

Fig. 7 Reaction between acid fluorides and disulfides catalyzed by $RhH(PPh_3)_3$ and dppe in the presence of an excess of triphenylphosphine [77]

as demonstrated in the reaction of benzoyl fluoride/chloride with di(*p*-tolyl)disulfide in which the former gave the respective thioester in higher yield than the last.

Thiols and disulfides are not the only sulfur source available. In this context, elemental sulfur is attractive because it is cheap, readily available, and easy to handle. Yamaguchi reported the coupling of pentafluorobenzenes with S_8 to give bis(4-substituted 2,3,5,6-tetrafluorophenyl) sulfides in the presence of a catalytic system composed of $RhH(PPh_3)_4$/dppBz and a stoichiometric amount of tributylsilane as fluoride scavenger (Fig. 8a) [78]. An organic trisulfide and a tetrasulfide were also examined, which exhibited notable substrate specificity. Di-tert-butyl tetrasulfide reacted only with very poor aryl monofluorides (containing two electron-withdrawing groups) and 2-fluorobenzothiazole, while di-tert-butyl trisulfide reacted with aryl monofluorides (Fig. 8b). The authors ascribe this difference of reactivity to the variation in S–S bond energy. In fact, elemental sulfur with lower S–S bond energy reacts with the most reactive aryl fluoride (pentafluorobenzenes), while increasing the S–S bond energy (trisulfide > tetrasulfide) results in reactivity with less activated aryl fluorides. A similar correlation will be discussed below for other thiolation reactions.

Aryl fluorides are not the exclusivity for these transformations; also the other aryl halides (chloride, bromide, iodide) are suitable substrates for this reaction [79, 80]. Lee and coworkers have shown that the dimeric complex $[RhCl(cod)]_2$

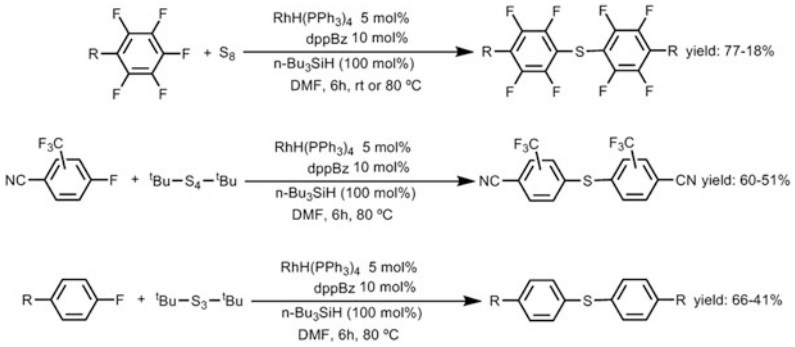

Fig. 8 Reaction between aryl fluoride and S_8 or oligosulfide mediated by $RhH(PPh_3)_4$/dppBz in the presence of *n*-BuSiH [78]

(with 1 equiv. of PPh_3) is able to catalyze the cross coupling of aryl iodide with both aromatic and aliphatic thiols in the presence of a strong base such as NaO^{t}Bu leading to asymmetric diaryl and aryl alkyl thioethers in good to excellent yields (73–99%) [79]. In similar conditions, Ozerov and coworkers extended the precedent work to the use of aryl chlorides and bromides using the pincer complex (POCOP)Rh(H)Cl as a catalyst (Fig. 9) [80]. In this brilliant paper, the mechanism of the process was unveiled due to an in-depth study of each elementary step and the isolation of some intermediates involved in the reaction (Fig. 9b). In the first step, the active Rh^I species (POCOP)Rh (**b**) (unobserved) is generated by dehydrochlorination of **a** with NaO^{t}Bu. The oxidative addition of the aryl halide to this unsaturated fragment generates (POCOP)Rh(Ar)(X) (**c**). The transmetalation of **c** with the in situ produced NaSR provides the aryl-thiolate–Rh^{III} species **d**. Then, C–S reductive elimination gives rise to the Rh^I sulfur adduct (POCOP)Rh(ArSR) (**e**) that after the final thioether, dissociation regenerates the initial active fragment **b**.

2.2 C–S Coupling via C–H Activation

As showed above cross coupling of halogenated substrate with sulfur source, such as thiol disulfides or elemental sulfur, is a powerful tool for the synthesis of thioethers under a variety of conditions (vide supra). However, these methodologies present an important drawback, the prefunctionalization of the substrates. This inconvenience can be overcome by using catalytic systems able to directly functionalize the C–H bonds. Transition-metal-mediated C–H activation is nowadays one of the most important methodologies for the formation of carbon–carbon and carbon–heteroatom bonds with application both in academic and industrial chemistry [81–92]. During the past decade, this approach has been applied to the

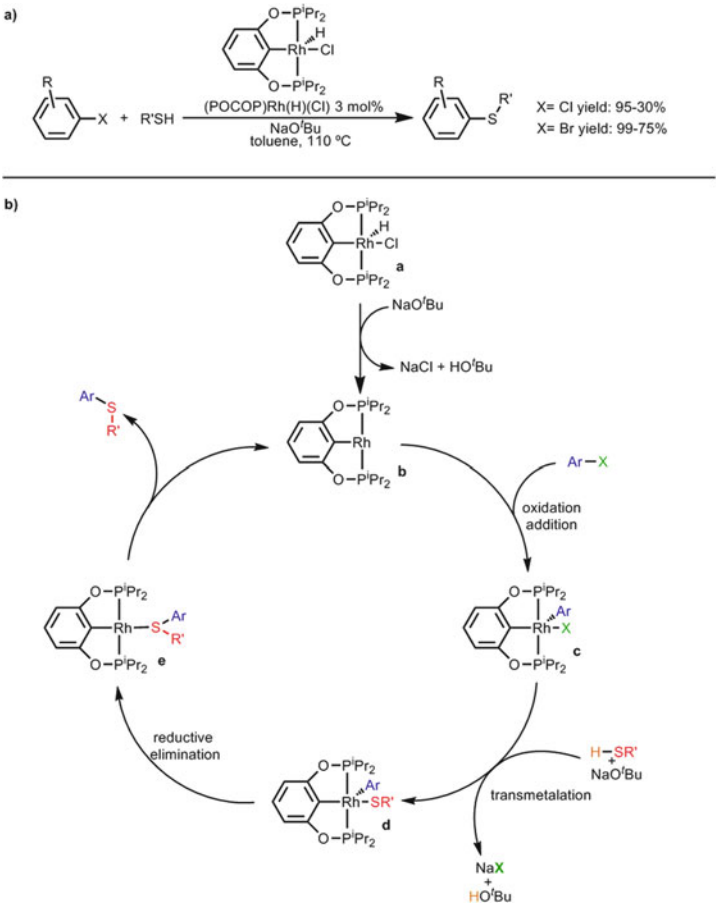

Fig. 9 Cross coupling of aryl chlorides or bromides with thiols catalyzed by (POCOP)Rh(H)Cl in the presence of NaO^{t}Bu [80]

direct thiolation of unfunctionalized substrates using different transition metals such as Pd, Cu, Ru, etc. [93–99].

In the field of the C–H activation, rhodium catalysts have a prominent place, and several systems able to mediate the direct thiolation of C–H bonds have been developed. Two main families can be encountered: (1) the Yamaguchi systems based on the Rh^{I} complex $RhH(PPh_3)_4$ and (2) the systems based on the Rh^{III} complex $[RhCp^*Cl_2]_2$ for the thiolation of aromatic substrates bearing a directing group. The general mechanism of these two catalysts is showed in Fig. 10. In the case of the systems based on $RhH(PPh_3)_4$, the C–H bond oxidatively adds to the Rh^{I} precursor (step a) or, alternatively, it is the Y–S bond (a′), leading to the activated Rh^{III} species C–Rh–H or Y–Rh–S, respectively (Fig. 10a). These species further react with a Y–S or C–H bond (step b or b) to provide thiolate–Rh^{III}–alkyl/alkynyl intermediates with the simultaneous elimination of Y–H. This fundamental step can

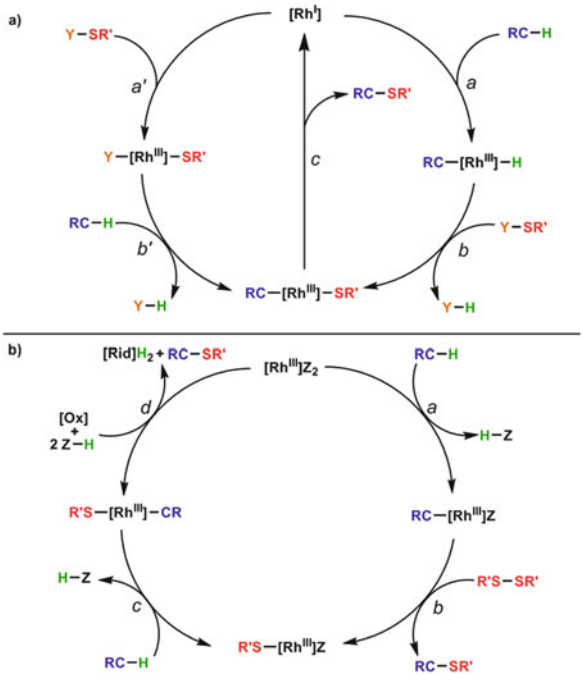

Fig. 10 General mechanisms of reaction for the formation of C–S bond via C–H activation mediated by $RhH(PPh_3)_4$ (**a**) or $[RhCp^*Cl_2]_2$ (**b**)

take place either by the formation of oxidized $[Rh^V(RC)(R'S)(Y)(H)]$ intermediate followed by the reductive elimination of Y–H or by a non-oxidative process via electrophilic substitution, base-mediated (AMLA or CMD) or σ-bond metathesis [100–102]. The final reductive coupling of the C–S bond (c) gives rise to the wanted thiolated substrate RC–SR′ and regenerates the starting Rh^I species. In the case of the $[RhCp^*Cl_2]_2$-based systems, the mechanism is quite different (Fig. 10b). After an activation step in which the chlorido ligands are substituted by more labile anions (Z) (typically triflate), the Rh^{III} species undergo the activation of the C–H bond to form a C–Rh^{III} derivative with concomitant elimination of HZ (step a). This fundamental step can occur by several mechanisms that depend on the substrate and the reaction conditions [100–102]. The reaction of C–Rh^{III} with disulfides via a Rh^V intermediate or by nucleophilic substitution-like reaction affords the coupled product RC–SR′ (step b). Then, Rh^{III}–thiolate intermediate can activate another molecule of substrate leading to a C–Rh^{III}–S (step c), which after reductive elimination step affords another molecule of thioether RC–SR′ (step d). The catalytic cycle is closed by the regeneration of the initial Rh^{III} active species through the oxidation of the final Rh^I complex obtained in step d.

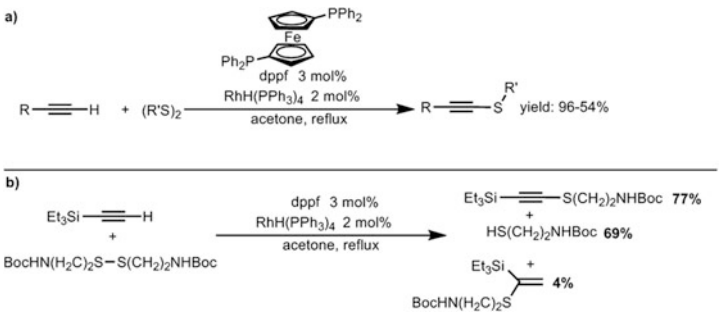

Fig. 11 Alkylthiolation reaction of 1-alkynes with disulfides catalyzed by $RhH(PPh_3)_4$/dppf in acetone [103]

Rhodium(I) Catalytic Systems for C–S Coupling via C–H Activation

The first paper on the direct thiolation of organic substrates via C–H activation mediated by rhodium was presented in 2005 by Yamaguchi and coworkers, who disclosed the thiolation of 1-alkynes with disulfides [103]. Aryl, alkyl, and silyl 1-alkynes were reacted with dialkyl/diaryl disulfides under the catalyst system $RhH(PPh_3)_3$/dppf in acetone. 1-alkyl/arylthio-1-alkynes were obtained in high yield with the simultaneous elimination of thiol (Fig. 11a). Remarkably, this catalytic system is highly chemoselective. In fact, rhodium(I) complexes are efficient catalysts for the addition of disulfides or thiols to alkynes (see Sect. 3). However, in this case the competition between C–H substitution and addition is completely displaced for the former, and only traces of hydrothiolation products were found, as demonstrated with the reaction of trimethylsilylacetylene and bis[2-(^{t}butoxycarbonylamino)]ethyl disulfide (Fig. 11b).

A slight modification of the above catalytic system allowed the α-thiolation of different substrates containing relative acidic C–H bonds (p*K*a 16–18), such as nitroalkanes (and cyclo-nitroalkanes), diethyl malonate, and 1,2-diphenyl-1-ethanone with different disulfides (Fig. 12) [104]. In this report, the dppf is replaced with dppe and the DMA is used as solvent instead of acetone. Noteworthy, this reaction achieves good conversion only when is performed under air atmosphere. In fact, in these conditions thiols are oxidized to disulfide converting the reaction exergonic, then thermodynamically favored.

These reactions, as well as the other thiolation, developed by Yamaguchi with $RhH(PPh_3)_4$, turned out to be in equilibrium that suggest the easy reversibility of the C–S bond cleavage/formation. For this reason, depending on the reaction conditions, it is possible to control the transfer of a thio-group from an organosulfurated compound to another organic substrate. Following this approach, Yamaguchi and coworkers developed many transfer reactions for the thiolation of different types of substrates using in each case an appropriate sulfur source. The methylthiolation of α-phenyl ketones and α-phenylthio ketones was obtained using *p*-cyano-α-methylthioacetophenone as sulfur source in the presence of a catalytic

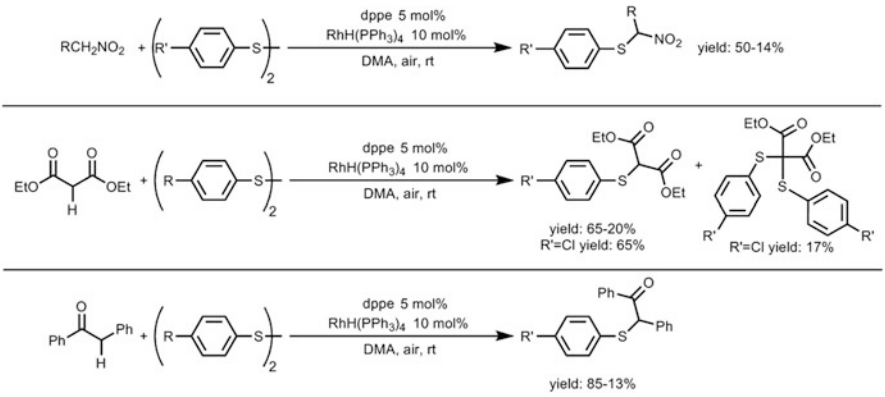

Fig. 12 Alkylthiolation reaction of 1-alkynes with disulfides catalyzed by $RhH(PPh_3)_4$/dppf in acetone [104]

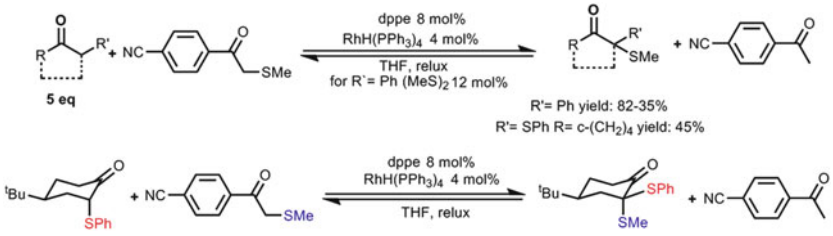

Fig. 13 Methylthiolation of α-phenyl ketones and α-phenylthio ketones with *p*-cyano-α-methylthioacetophenone catalyzed by $RhH(PPh_3)_4$/dppe in THF [105, 106]

amount of $RhH(PPh_3)_4$ and dppe (Fig. 13) [105, 106]. Interestingly, the reaction of diastereomeric 4-(tert-butyl)-2-phenylthiocyclohexanones gave selectively an axial 2-methylthiolated product (Fig. 13).

The same catalytic system can be used for the α-methylation reaction of unactivated ketone giving α-methylthio ketones (Fig. 14a) [107]. In this case the use of *p*-cyano-α-methylthioacetophenone as SMe source is not effective, while good results have been obtained with 1,2-diphenyl-2-methylthio-1-ethanone. Interestingly, the methylthiolation in unsymmetric ketones takes place initially into the more substituted α-carbon, and then a rearrangement to the products thiolated at the less substituted carbons takes place (Fig. 14b). This probably indicates that the former to be the kinetic product and the latter the thermodynamic. Other substrates such as aldehydes, phenylacetate, and phenylacetonitrile have been α-methylthiolated in the same reaction conditions (Fig. 14c).

The usefulness of this catalytic system was also demonstrated in the thioderivatization of heteroarenes such as 1,3-benzothiazoles, 1,3-benzoxazoles, and benzothiophene that give 2-phenylthio derivatives, and the monocyclic heteroaromatics, 1-methyl-1,2,3,4-tetrazole and 2-cyanothiophene, were converted

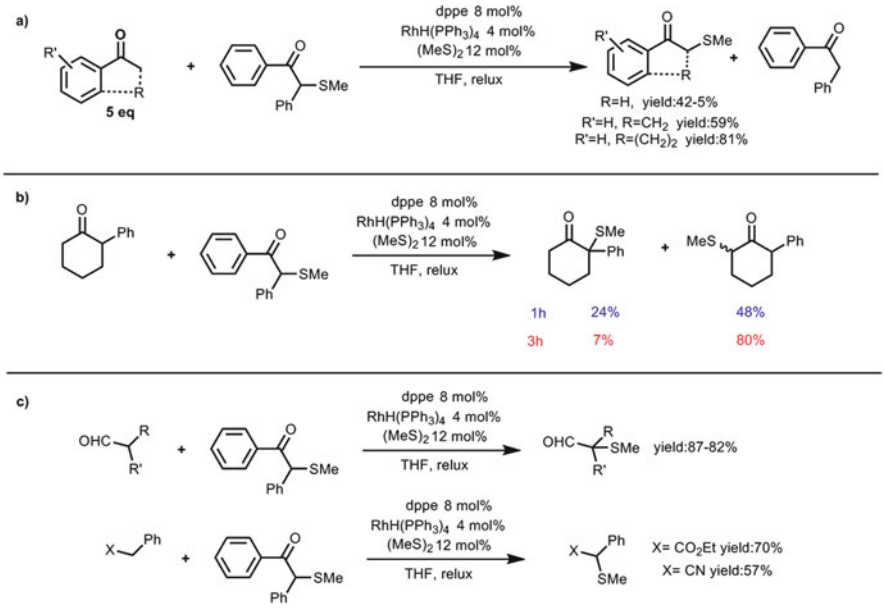

Fig. 14 Methylthiolation of unactivated ketones aldehydes, phenylacetate, and phenylacetonitrile with 1,2-diphenyl-2-methylthio-1-ethanone catalyzed by $RhH(PPh_3)_4$/dppe in THF [107]

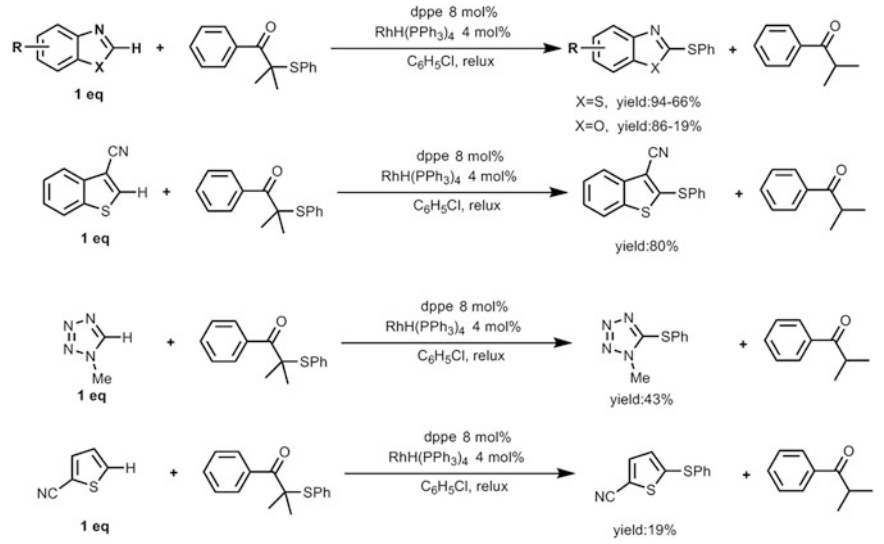

Fig. 15 Phenylthiolation of heteroarenes with α-(phenylthio)isobutyrophenone catalyzed by RhH $(PPh_3)_4$/dppe in C_6H_5Cl [108]

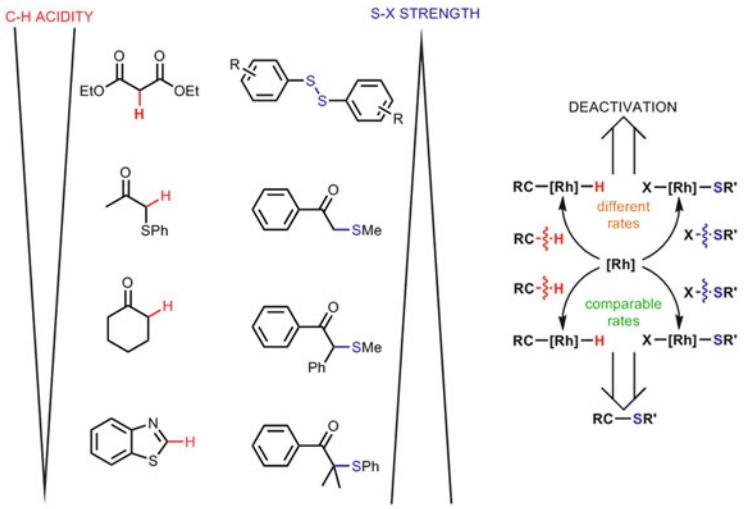

Fig. 16 C–H bond acidity of the substrate vs C–S strength of the S–X bond in the reaction of thiolation mediated by $RhH(PPh_3)_4$

into the 5-phenylthio compounds (Fig. 15) [108]. In this case the author found that the best sulfur source was α-(phenylthio)isobutyrophenone.

As it has been demonstrated with the above examples, the use of an appropriate phenylthio transfer reagent is crucial for the efficient catalyzed conversion of heteroaromatic C–H bonds into C–S bonds. An interesting correlation between the acidity of the C–H of the substrates and the strength of the S–X bond of the thio-source was found. Therefore, relatively acidic compounds such as nitroalkanes or malonate (p*K*a 16–18) reacted with diaryl disulfides in the presence of O_2, while 1-alkynes with a moderate acidic proton (p*K*a 21) reacted with disulfides, and less acidic ketones and heteroarenes (p*K*a 27) interact with different types of thioethers. These observations suggest an inverse correlation between the strength of the S–X bond and the acidity of the C–H proton (Fig. 16). Authors suggest that the favorable combination of substrates and sulfurating reagents is ascribable to kinetic reasons [104]. In fact, when a rhodium complex activates C–H and S–S bonds at comparable rates, thiolation reactions should proceed smoothly. Instead, if the C–H bond activation is much slower than S–S bond activation, the catalyst preferentially interacts with the S–S bond, which retards the total reaction deactivating the catalyst (Fig. 16). For this reason, the wise choice of an appropriate combination of substrate and sulfur source results fundamental to enhance the reaction rate and to drive the reaction to completion before catalyst deactivation.

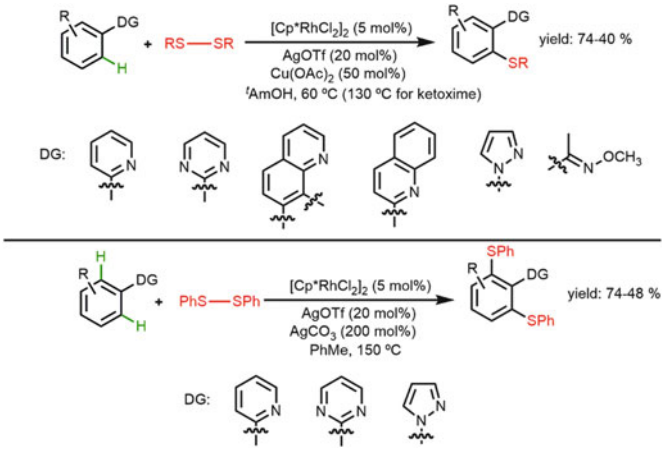

Fig. 17 Direct sulfenylation of arene via C–H activation mediated by $[Cp^*RhCl_2]_2$/AgOTf/$Cu(OAc)_2$ in ^{t}AmOH [112]

Rhodium(III) Catalytic Systems for C–S Coupling via C–H Activation

Aromatic compounds represent one of the most abundant starting materials available for organic synthesis. However, the high stability of the aromatic C(sp^2)–H bonds makes their functionalization really challenging. In the last years, Rh-based systems have been broadly exploited and used for its excellent catalytic proprieties in C–H bond activation and subsequent C–C or C–X formation [83, 109–111]. In particular, complexes containing the [Cp^*Rh^{III}] have been extensively used in the selective C–H activation of aromatic compound bearing directing groups such as pyridine, oxime, and hydrazine, among others.

Catalytic systems based on these species have been just recently applied in the field of the C–S bond formation. In 2014 Li and coworkers reported the first example of Rh^{III}-catalyzed direct C–H thiolation using aryl and alkyl disulfides as sulfur source (Scheme 17) [112]. In this work, the catalytic system $[Cp^*RhCl_2]_2$/AgOTf/$Cu(OAc)_2$ in ^{t}AmOH at 60°C is efficient in the mono-thiolation of several arenes containing pyridines, benzo[h]quinolone, bicyclic quinolone, pyrimidine, pyrazole, and ketoximes. In addition, modification of the reaction conditions allows for a double C–H activation/thioesterification process that affords dithioethers in moderate to good yields (Fig. 17). The broad substrate scope and high efficiency of the direct C–S coupling provide a straightforward way for selective preparation of sulfur-containing heterocycles not easily accessible by conventional cross-coupling reactions.

A mechanism coherent to that explained above was proposed by the authors (Fig. 18). In the first step of the reaction, the chlorido ligands of $[Cp^*RhCl_2]_2$ (**a**) are eliminated using AgOTf providing a more active cationic species containing the fragment $[Cp^*Rh]OTf_2$ (**b**). The pyridine framework coordinates to this Rh^{III} precursor directing the activation of the C–H bond of the arene leading to the

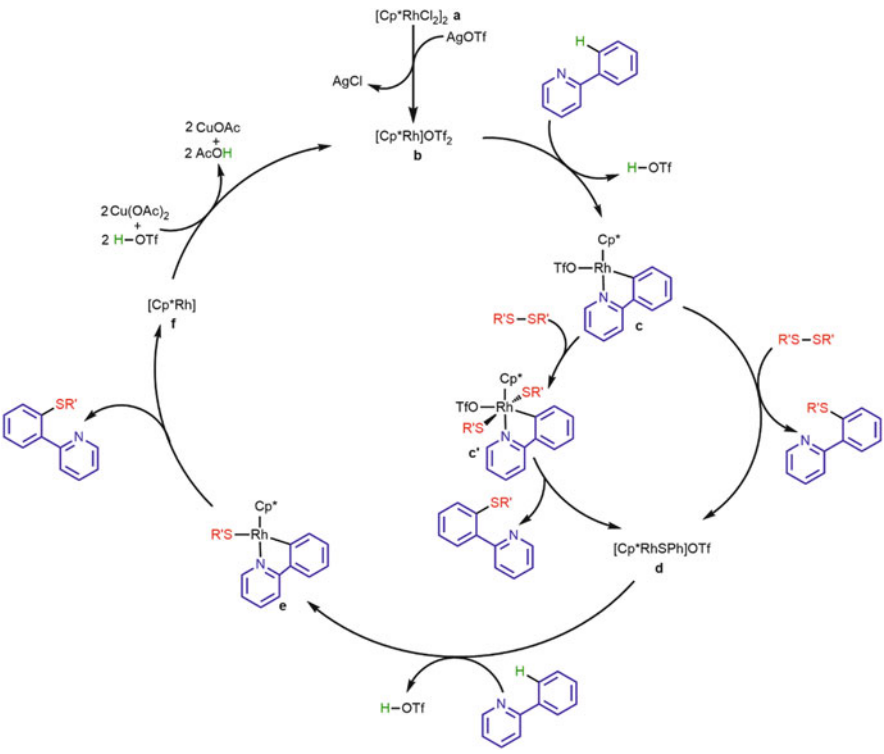

Fig. 18 Catalytic cycle for the direct sulfenylation of phenylpyridine mediated by $[Cp^*RhCl_2]_2$/AgOTf/$Cu(OAc)_2$ [112]

rhodacycle **c**. This derivative can be synthesized independently and prove to catalyze efficiently the thiolation of phenylpyridine with $(PhS)_2$, "bold" demonstrating that effectively is an intermediate of this transformation. Compound **c** reacts with disulfide to afford the phenylthiolated phenylpyridine and the PhS–Rh^{III} species **d**, via a nucleophilic-addition-type reaction (path a) or, alternatively, via an oxidative pathway with the Rh^{V} intermediate **c′** (path b). Complex **d** reacts with another molecule of substrate leading to the five-membered rhodacycle **e**, which then undergoes reductive elimination to afford another molecule of organic product together with a rhodium(I) species **f**. Oxidation of **f** to **b** by the reduction of Cu^{II} to Cu^{I} completes the catalytic cycle.

Following the same catalytic approach, the direct thiolation of other type of substrates has been studied. Zhu and coworkers report in 2015 a convenient and efficient method for sulfuration and olefination of aromatic ketazines via rhodium-catalyzed oxidative C–H bond activation [113]. The catalytic system is composed of $[Cp^*RhCl_2]_2$ as precatalyst, AgOTf for the activation of the Rh complex, and $Cu(OAc)_2$ as final oxidant. The selective phenylthio-etherification of a range of substituted ketazines using phenyl disulfides takes place in DCE at 60°C (Fig. 19). The proposed mechanism according to experimental results of kinetic

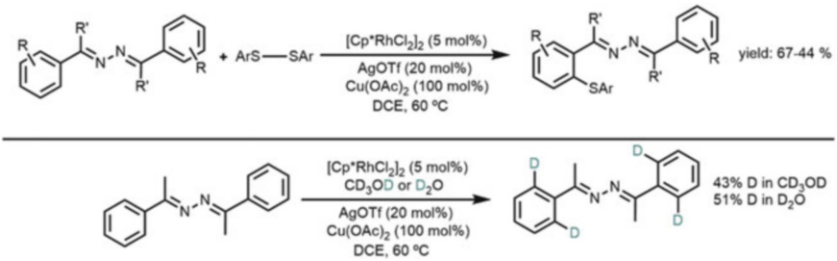

Fig. 19 Selective mono-phenyl thiosulfenylation of ketazines catalyzed by $[Cp^*RhCl_2]_2$/AgOTf/$Cu(OAc)_2$ in DCE [113]

isotopic effect is similar to that described for the previous Cp^*Rh^{III} system (Fig. 18). Notably, H/D exchange experiments revealed that all the four *ortho*-positions on aryl are deuterated, which demonstrated that the catalytic system, thanks to the key role of the directing group, is able to activate each of these C–H bonds (Fig. 19). However, the authors have been able to find adequate reaction conditions for the selective mono-thiolation to occur.

The usefulness of this catalytic system was also demonstrated in the selective C7-thiolation of indoles with disulfides [114]. Indole and indoline scaffolds are ubiquitous structural motifs found in a multitude of pharmaceutical compounds, particularly 7-substituted indoles and indolines. Wang and coworkers elegantly showed that the catalytic C7-thiolation of indolines is achievable by using a readily available and easily removable pyrimidyl group as a directing group. In the optimal conditions, the catalytic system, composed of $[Cp^*RhCl_2]_2$, AgOTf, and $AgCO_3$ (as oxidant) in toluene at 130°C, is able to mediate the thioetherification of a broad type of 1-(pyrimidin-2-yl)indoline derivatives with diphenyl disulfides (Fig. 20a). Notably, the choice of the N-protecting group was found to be crucial for this reaction. In fact, it was demonstrated that acetyl or *N*,*N*-dimethylcarbamoyl directing group did not deliver the corresponding product under the standard conditions of the pyrimidyl derivatives. Finally, the utility of this C7-thiolation reaction was further highlighted by its successful conversion of indolines into indoles. Oxidation with DDQ and removing of the pyrimidyl group with NaOEt afford 7-(phenylthio)-1*H*-indole in 97% yield (Fig. 20b). Also in this case, the proposed catalytic cycle perfectly fits with that showed in Fig. 18.

Alkyl and aromatic disulfides are not the only sulfur source suitable for the C–S formation by rhodium-catalyzed oxidative C–H bond activation. Li and coworkers have recently reported the selective catalytic trifluoromethylthiolation of indoles using *N*-(trifluoromethylthio)saccharin as a source of trifluoromethylthio group ($-SCF_3$) (Fig. 21) [115]. The catalytic system developed for this reaction contains $[Cp^*RhCl_2]_2$, $AgSbF_6$, and $Zn(OTf)_2$. In the opinion of the authors, this last reactive acts as Lewis base for the activation of the *N*-(trifluoromethylthio)saccharin. In fact, when $Zn(OTf)_2$ is replaced by $Cu(OTf)_2$, the product yield decreased sharply, which may indicate that the oxidizing power is not relevant in this reaction system. The selective C-2 trifluoromethylthiolation of indoles *N*-derivatizated by

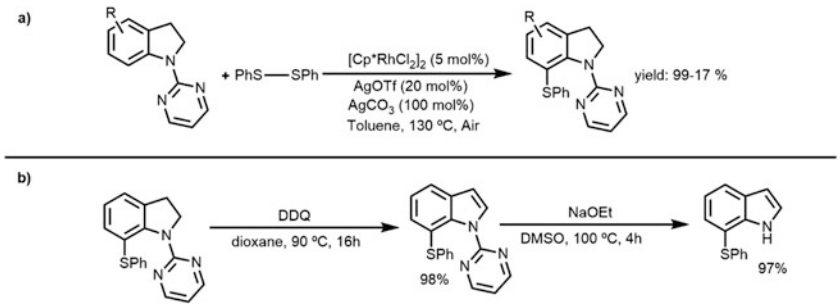

Fig. 20 (**a**) Selective C7-thiolation of indolines with PhSSPh catalyzed by $[Cp^*RhCl_2]_2/AgOTf/AgCO_3$ in toluene; (**b**) conversion of N-protected indolines into indoles [114]

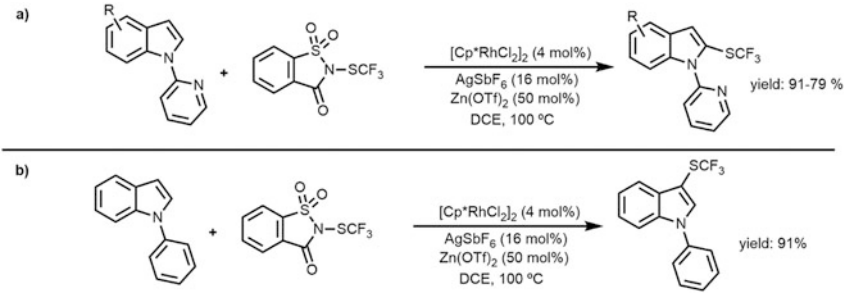

Fig. 21 Selective C2-trifluoromethylthiolation of indolines with *N*-(trifluoromethylthio)saccharin catalyzed by $[Cp^*RhCl_2]_2/AgSbF_6/Zn(OTf)_2$ [115]

2-pyridyl group that acts both as N-protecting and directing groups is operative in DCE at 100°C (Fig. 21a). Arene functionality is not limited to indoles. Trifluoromethylthiolation of 2-phenylpyridine and 2-(1*H*-pyrrol-1-yl)pyridine also occurred in moderate to high yield (Fig. 21a). Remarkably, when 1-phenyl-1*H*-indole was used as a substrate under the standard conditions, the functionalization occurred exclusively at the 3-position (Fig. 21b). This is a demonstration that the selectivity is correlated to the N-substituent. In fact, in the presence of an N-directing group, the reaction occurred via a C–H activation pathway, while, as demonstrated previously by the same research group, in the absence of such a group, the reaction is Lewis acid catalyzed [116].

2.3 Metathesis of Thioethers and Disulfides

The works discussed above account for the reaction of RC–X (X = halogen) or RC–H bonds with an adequate sulfur source (Y–SR′) for the formation of thioethers of type RC–SR′. Another approach for synthesis of new thioethers consists in the

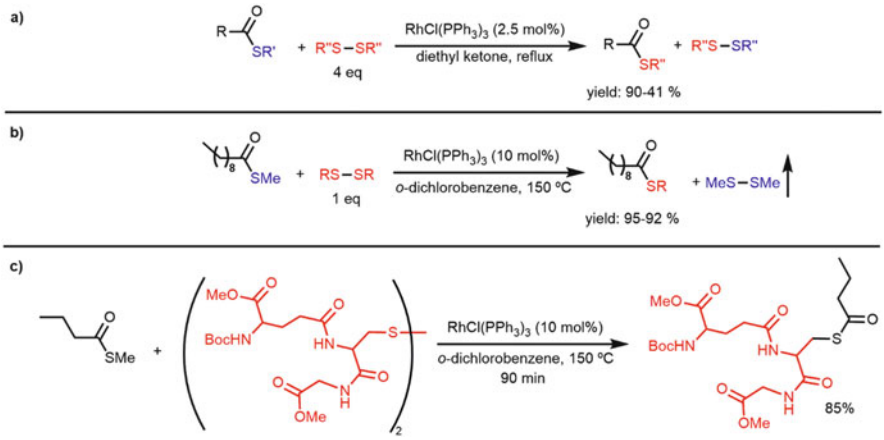

Fig. 22 Alkylthio exchange reaction of thioesters and disulfides [117]

interchange of their thio-groups of two previously sulfurated products (see Fig. 1). This type of transformation is really interesting for the study of fundamental processes in the catalytic C–S bond formation and also extends the available synthetic methods for the synthesis of thio-compounds.

Catalysts able to mediate this type of reaction should have the capacity to establish an equilibrium between the thiolated reagents and the thio-interchanged products, through the activation of their C–S bonds. As showed in Sect. 2.2.1, Yamaguchi and coworkers have demonstrated that $RhH(PPh_3)_4$ is able to activate C–S bonds establishing equilibriums between different types of thio-compounds; thus it was a promising candidate for the metathesis of different sulfur-containing compounds.

Alkoxy exchange between esters is a fundamental reaction catalyzed by acid or base. In contrast, the exchange reaction of the sulfur analogs in similar conditions does not proceed. However, Yamaguchi and coworkers reported the alkylthio metathesis of thioesters and disulfides mediated by Rh^I complexes [117]. The treatment of a thioester and a dialkyl disulfide (4 eq) in refluxing diethyl ketone in the presence of $RhCl(PPh_3)_3$ (or $RhH(PPh_3)_4$) (2.5 mol%) for 1.5 h gave an alkylthio-exchanged thioester (and mixed disulfides) in good to excellent yields (Fig. 22a). The species involved in this reaction are in equilibrium; thus an excess of reactives must be added to shift the equilibrium to the wanted products. However, the use of *S*-methyl thioester shifts the equilibrium to the exchanged thioester using one equivalent of disulfide, since dimethyl disulfide formed can be removed by evaporation (Fig. 22b). This method was effectively applied in a molecule of remarkable biological interests as the glutathione disulfide that was thioesterified with *S*-methyl butanethioate in good yield (Fig. 22c).

A similar catalytic system composed of $RhH(PPh_3)_4$ and dppe is able to mediate the metathesis of α-organothioketones with disulfides [118]. Similar to previously described for C–H activation reactions, the metathesis process is affected by the

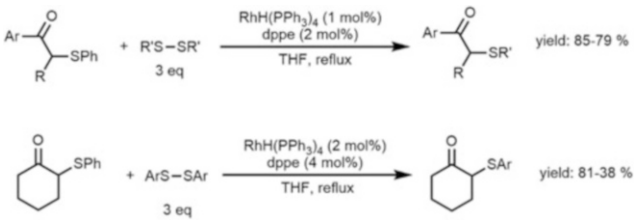

Fig. 23 Organothio exchange reaction of α-organothioketones with disulfides catalyzed by RhH$(PPh_3)_4$/dppe THF at reflux [118]

structure of the substrate: α-phenylthio and α-alkylthio aryl ketones react effectively with diaryl and dialkyl disulfides, while α-phenylthio dialkyl ketones react only with diaryl disulfides (Fig. 23).

In the two examples of metathesis showed above, a thioether (C–S) reacts with a disulfide (S′–S′) to afford the exchange products C–S′ and S–S′. In contrast, the metathesis of two sulfurated organic products CS/C′S′ can undergo two modes of reactivity to yield CS′/C′S and CC′/SS′ derivatives. The control of the reaction mode using a single metal complex is an interesting challenge. Yamaguchi reported that an appropriate choice of the ligands can totally change the reactivity of a catalytic system shifting from CS′/C′S to CC′/SS′ metathesis products [119]. In the presence of a catalytic amount of $RhH(PPh_3)_4$ and the chelating bisphosphine dppf, two 1-alkylthioalkynes exchange alkylthio groups to give equilibrium mixtures of four 1-alkylthioalkynes (CS′/C′S). In contrast, when a monodentate phosphine such as $(p\text{-OMePh})_3P$ or $MePh_2P$ is used, 1,3-butadiynes and disulfides are obtained (CC′/SS′) (Fig. 24a). A feasible explanation for this interesting ligand effect consists in the proposal of a reaction mechanism involving a Rh(V) intermediate (Fig. 24b). Two thioalkynes undergo oxidative addition within a rhodium(I) intermediate (**a**) to give an octahedral rhodium(V) species (**b** and **c**) bearing two alkynyl and two alkylthio ligands. In the opinion of the authors, the *trans*-effect of the different ligands together with the geometrical constrain of the dppf ligand leads to complex **b** in which the alkynyl groups are disposed in *trans*-configuration and the thiolated ligand in *cis*. This configuration does not allow the reductive elimination of the two alkynyl groups to form butadiyne, and only alkylthio exchange proceeds. In the case of monophosphine complex, the two phosphines take the *trans*-configuration, allowing the reductive elimination to form butadiyne or alkylthio-exchanged products.

3 Catalytic Addition of S–X on Unsaturated Substrates

The addition of sulfur–hydrogen, sulfur–carbon, or sulfur–sulfur (S–Y) bond to an acetylenic hydrocarbon represents a powerful tool for the synthesis of vinyl thioethers. This 100% atom-economical methodology meets the demands for the

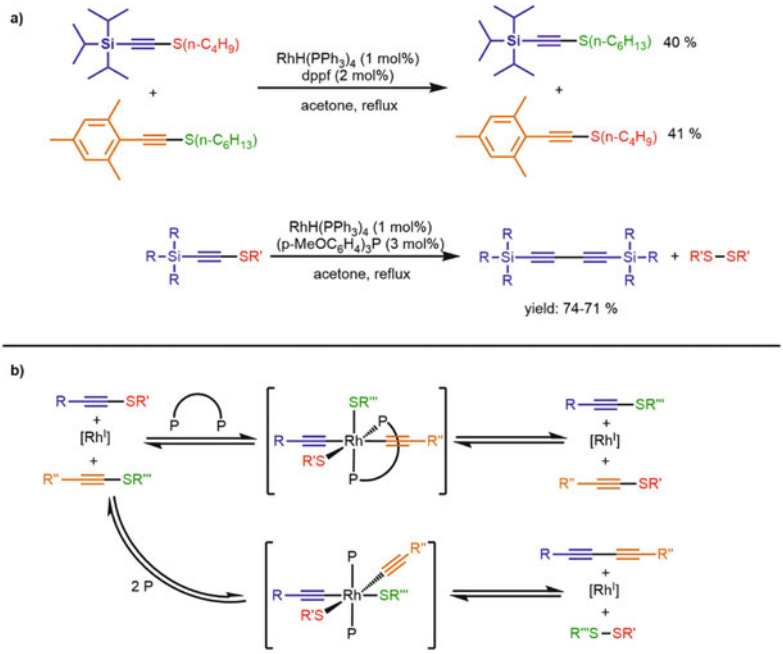

Fig. 24 (**a**) Rhodium mediates CS/C′S′ metathesis reaction: formation of CS′/C′S or CC′/SS′ bonds; (**b**) putative reaction mechanism using bidentate phosphine or monodentate phosphine [119]

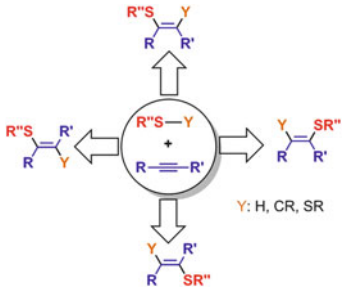

Fig. 25 Addition of thio-compound to alkynes

continuing development of green chemistry. However, an examination of the addition reactions raises other important problems relative to the stereo-/regioselectivity of the transformation (Fig. 25).

The solution to this problem has been found with the development of catalytic systems based on transition metals that are able to mediate the stereo-/regioselective addition of S–Y on a triple bond. From the pioneering work of Newton in 1976 which was described the first catalytic addition of thiols to dimethyl acetylenedicarboxylate using molybdenum complexes [120], several other transition-metal-based catalytic systems have been developed [18, 32, 34,

35, 38, 39, 42, 43]. Also in this transformation, rhodium complexes have a prominent role, providing catalytic systems with very high activity and selectivity in hydrothiolation, thiolation, and carbothiolation of alkynes and allenes. In the case of rhodium, both of these transformations are stereoselective and proceed via a *syn*-addition. However, the regioselectivity of the reaction may change and depends on the metal complex, in particular on the stereoelectronic properties of the ligands that can totally change the final composition of the reaction products. The origin of the selectivity and the role of the ligand in this transformation are more extensively explained in the following sections.

3.1 Addition of S–S and S–C

As shown in Fig. 11, when disulfides were used as substrates in the Rh^{I}-catalyzed reaction with terminal alkynes, 1-alkyl/arylthio-1-alkynes were obtained. Yamaguchi and coworkers have reported a slight modification of this catalytic system leads to a total change of the chemoselectivity. In fact, they showed that the system composed of $RhH(PPh_3)_4$/phosphine with the addition of a small amount of triflic acid leads to 1,2-disubstituted alkenes of *Z* configuration (Fig. 26a) [121]. It should be emphasized that while *E*-bis(thio)-substituted alkenes can be easily obtained under nucleophilic conditions, selective formation of *Z*-isomers has been a challenge for a long time. The catalytic system developed is highly active for both alkylic and aromatic disulfides (including cystine) as well as a wide range of different terminal alkynes with different functional groups (hydroxyl, tert-butyldimethylsilyloxy, ester, or nitrile). In all cases the products were obtained with good to excellent yield, with outstanding *Z*-stereoselectivity (no trace of other isomers was detected). The reaction mechanism can explain the impressive stereoselectivity obtained (Fig. 26b). In the first step, the oxidative addition of the S–S bond to the Rh^{I} takes place leading to the S–Rh^{III}–S complex **a**. Coordination (**b**) and insertion of alkyne into the M–S bond (**c**) and, finally, reductive elimination of the product furnish the final *Z*-1,2-dithiolated alkenes and regenerate the initial Rh^{I} species. The addition of the disulfides in this mechanism is strictly *syn*; then *Z*-1,2-disubstituted alkene is the only isomer that can be formed.

Noteworthy, when allenes were treated with disulfides in the same catalytic conditions, a 1:1 mixture of (*E*)-2-alkylthio-1,3-dienes and (*E*)-2-alkylthio-2-alkane was found (Fig. 27a) [122]. The reaction can be applied to various combinations of monosubstituted allenes and aliphatic disulfides. The proposed catalytic cycle that explains the formation of these two products in 1:1 ratio is showed in Fig. 27b. The oxidative addition of the disulfide to the initial Rh^{I} complex (**a**) gives the dithiolate–Rh^{III} complex **b**. Allene insertion into the Rh–S bond yields the π-allyl complex **c**. Subsequent β-hydride elimination leads to the diene product and the hydride–Rh^{III}–thiolate complex **d**. The formation of the diene instead of the 1,2-dithiolated product **z** is an evidence that in this step of the catalytic cycle, the β-hydride elimination is faster than the reductive elimination with the other thiolate

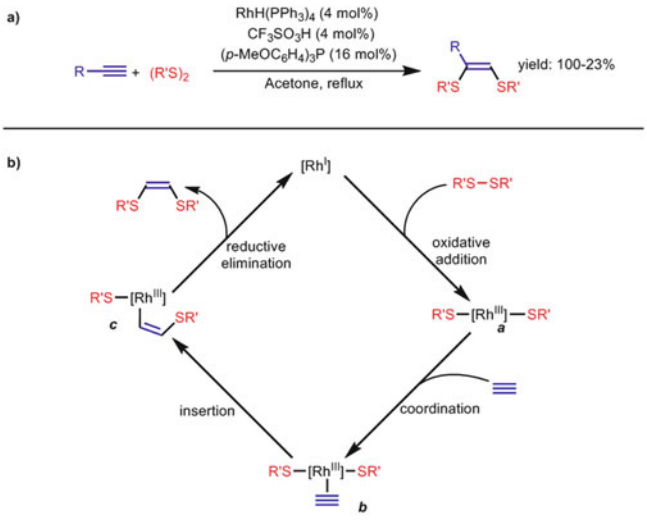

Fig. 26 (**a**) Addition of disulfides to terminal alkynes. (**b**) Putative reaction mechanism [121]

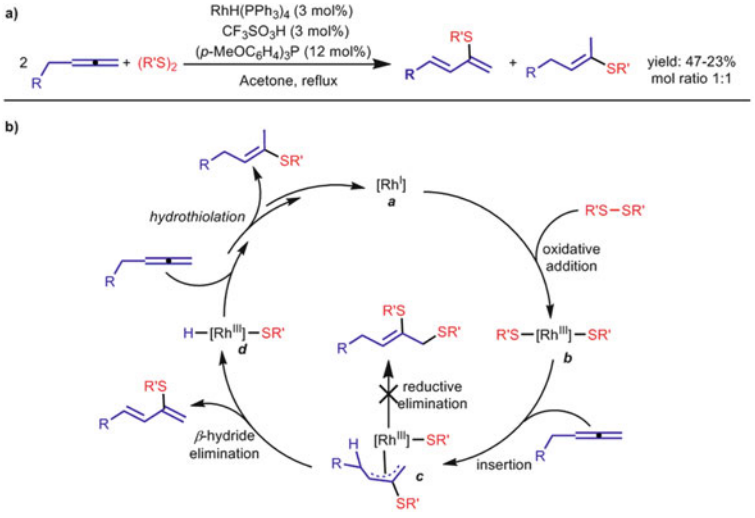

Fig. 27 (**a**) Reaction between allenes and disulfides catalyzed by $RhH(PPh_3)_4$; (**b**) reaction mechanism [122]

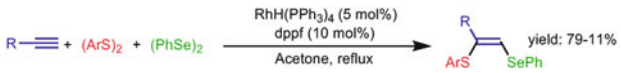

Fig. 28 Rhodium-catalyzed 1-seleno-2-thiolation of 1-alkynes [123]

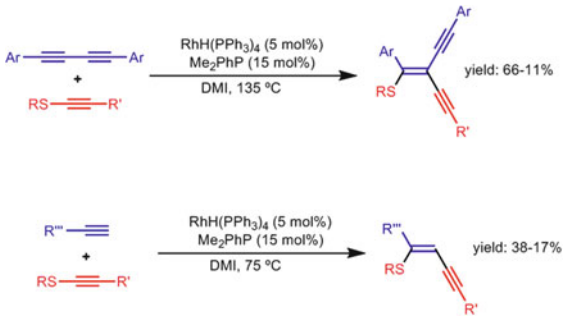

Fig. 29 Carbothiolation of diynes and terminal alkynes with 1-1-alkylthio-1-alkynes catalyzed by $RhH(PPh_3)_4$ [124]

group. Complex **d** then reacts with another molecule of allene (the mechanism of hydrothiolation is described in the next section) giving the (*E*)-2-alkylthio-2-alkane and regenerating the initial Rh^I species.

The addition of seleno- and thio-groups on alkynes can be obtained in similar conditions. $RhH(PPh_3)_4$ and dppf catalyze the regio- and stereoselective additions of diaryl disulfides and diaryl diselenides to 1-alkynes giving (Z)-1-arylseleno-2-arylthio-1-alkenes in moderate to good yields (Fig. 28) [123]. The authors have found that the nature of phosphine and, in particular, the appropriate carbon chain length are fundamental for activity and selectivity of the reaction. In fact, when dppp or dppb was used instead of dppf, the reaction took place in lower yield and selectivity. Dppe and dpppe did not catalyze the reaction.

Another important reaction catalyzed by Rh complexes is the carbothiolation of alkynes. Yamaguchi reported that the catalytic system, $RhH(PPh_3)_4/Me_2PhP$, is able to mediate the carbothiolation reaction of 1-alkylthio-1-alkynes into symmetric diynes (Fig. 29) [124]. The reactions proceed via *syn*-addition to the triple bond. Regioselective ethynilation at the carbon 2 and thiolation into carbon 1 were observed. Terminal alkynes such as 1-decyne and (t-butylthio)acetylene also underwent the carbothiolation but in lower yield than diynes. In this case, the C–C bond formation occurs at C-1 (and C–S at C-2), confirming that for all type of substrates studied, the ethynilation is directed to the less hindered atom of the unsaturated moiety of the substrate.

Another interesting example of Rh-catalyzed carbothiolation was reported by Willis and coworkers [125]. In this work, the efficient addition of aryl methyl sulfides (bearing a carbonyl group in *ortho*-position) to terminal alkynes catalyzed by $[Rh(DPEphos)(ligand)][BAr^F{}_4]$ (ligand = nbd or o-xylene) was showed (Fig. 30a). The process proved to be broad in scope, tolerating a variety of steric and electronic changes to both reaction partners. Importantly, the alkenyl sulfide products were generated as single geometric isomers, suggesting a stereoselective *syn*-addition process. Similar to the reaction mentioned above (Fig. 29a), the reaction proceeds with high regioselectivity leading to the selective arylation of the terminal position of the alkyne (C-1) together with the thiolation of the C-2. The identification of the intermediates through stoichiometric and catalytic experiments allowed the authors to suggest a mechanism of reaction (Fig. 30b). In the first step,

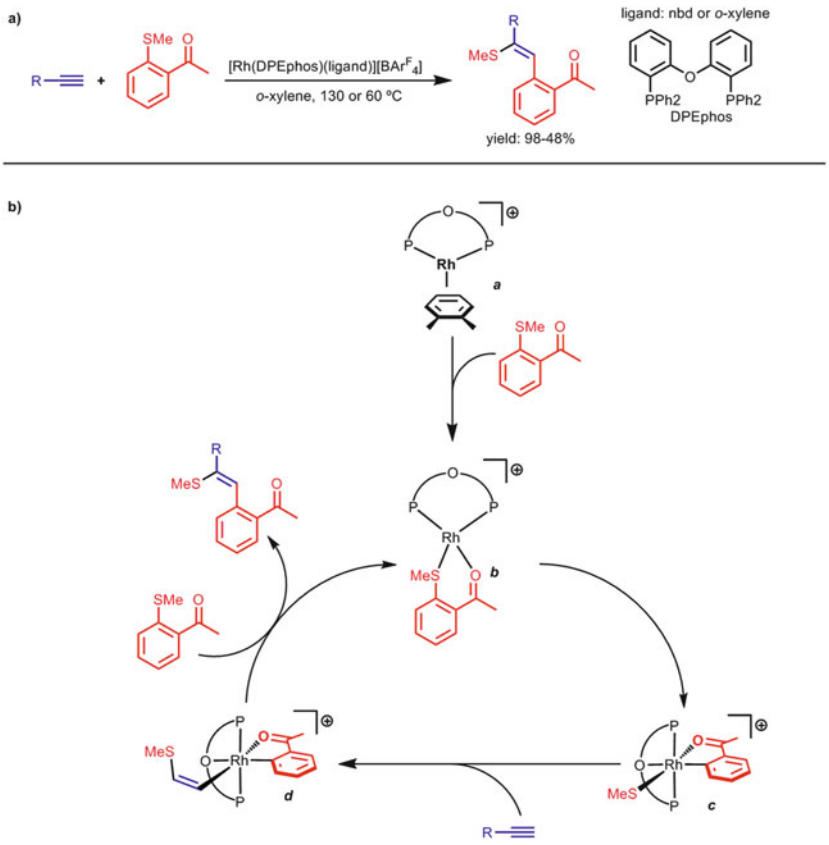

Fig. 30 (**a**) Rhodium-catalyzed reaction of aryl methyl sulfides and terminal alkynes. (**b**) Reaction mechanism [125]

the exchange between the o-xylene and the aryl-thiolate substrate takes place in furnishing complex **b**. The oxidative addition of the Ar–S bond to this complex leads to the Rh^{III} complex **c** that was identified as the resting state of the reaction. The addition of alkyne results in productive turnover by insertion of Rh–S bond (**d**). Subsequent reductive elimination of the thiovinyl and aryl groups results in the overall carbothiolation of the alkyne.

3.2 Hydrothiolation of Unsaturated Substrates

Hydrothiolation constitutes one of the simplest and atom-economical approaches for the introduction of sulfurated functionalities into organic frameworks. Particularly for alkyne hydrothiolation, the control of chemo-, regio-, and stereoselectivity still constitutes a motivating challenge. In this context, rhodium complexes have

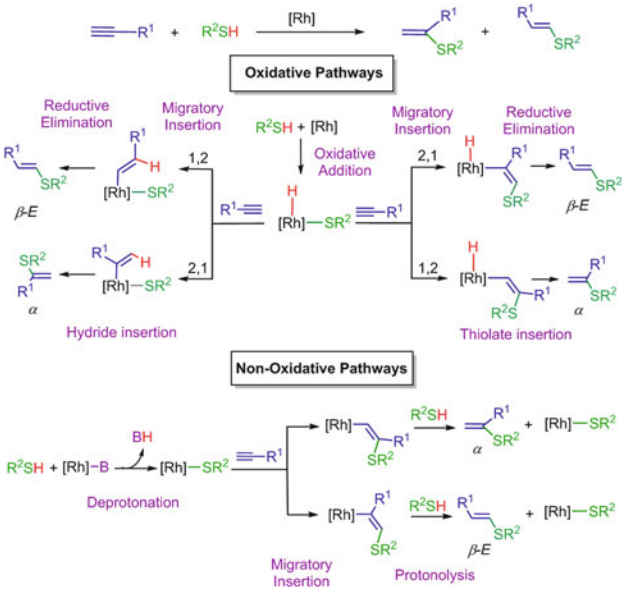

Fig. 31 Regioselectivity in rhodium-catalyzed alkyne hydrothiolation

been revealed as chameleonic species able to direct the regioselectivity upon subtle tuning of the ligands [126–146]. The established mechanisms for this transformation can be mainly divided into oxidative and non-oxidative processes (Fig. 31). The more common route starts by oxidative addition of the S–H bond of the thiol to the metallic precursor. Then, the alkyne can insert into Rh–H or Rh–S bonds with two orientations generating four catalytic pathways. Finally, the C–S reductive elimination step affords α- or β-*E*-vinyl sulfides. Alternatively, a non-oxidative mechanism entails the deprotonation of the thiol to generate a Rh–thiolate species. Then, alkyne insertion and protonolysis by an external thiol afford the corresponding vinyl sulfides. As clearly arising from Fig. 31, the complexity of the process needs for a rational design of the catalysts in order to obtain the desired regioselectivity. In general, the insertion of alkynes into metal–hydride bonds is favored compared to that into metal–thiolates, and 1,2-insertion is preferred over 2,1-insertion, but the metal environment can play an essential role in reversing this trend. Indeed, in some circumstances reductive elimination could be rate limiting; thus the mode of insertion plays a minor role.

The first use of rhodium catalysts for alkyne hydrothiolation was reported by the Ogawa's group [126]. The Wilkinson catalyst $RhCl(PPh_3)_3$ led predominantly to the formation of β-*E* vinyl sulfide. The mechanism was studied by stoichiometric NMR experiments (Fig. 32). The first step consists in the oxidative addition of thiophenol to form *trans*-$HRhCl(SPh)(PPh_3)_2$. Subsequent 1,2-insertion of 1-dodecyne into rhodium–hydride bond yields a stable β-*E*-metal-alkenyl that undergoes reductive elimination with the thiolate ligand to generate a lineal vinyl

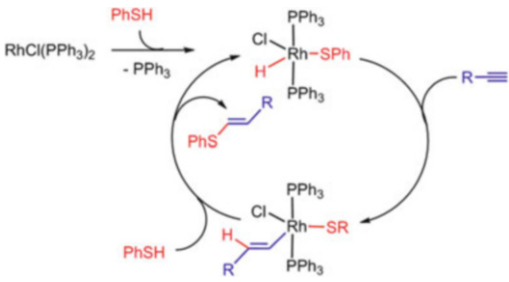

Fig. 32 Catalytic cycle for the formation of β-*E* vinyl sulfides proposed for Wilkinson's catalyst

sulfide. Furthermore, Love et al. have also demonstrated that alkyne insertion takes place into the metal–hydride bond, thereby ruling out a possible competing vinylidene-based pathway [127]. Wilkinson's catalyst is also effective in the oligomerization and polymerization of dithiols with dialkynes [128, 129]. Supported variants based on $RhCl(PR_3)_3$ have also been described [130, 131].

Messerle and coworkers disclosed in 2003 that neutral and cationic rhodium complexes bearing P,N and N,N ligands may act as efficient catalysts for alkyne hydrothiolation (Fig. 33) [132]. The best results were obtained for cationic complexes having P,N bidentate ligands which showed complete selectivity for the *E*/*Z* anti-Markovnikov vinyl sulfide products. Mechanistic studies point to a catalytic cycle initiated by oxidative addition of the thiol to generate hydride–thiolate species followed by alkyne insertion into the hydride ligand. The formation of *Z*-β-vinyl sulfide would require an isomerization of metal-alkenyl intermediates prior to reductive elimination step.

The Love's group contributes to field with an important landmark in 2005 [133]. In contrast to the previous assessment that group 9 transition-metal-based catalysts induce anti-Markovnikov selectivity, these authors elegantly showed that a reverse selectivity could be obtained by hydrotris(3,5-dimethylpyrazolyl)borate (Tp*) rhodium precursors. Furthermore, $Tp^*Rh(PPh_3)_2$ complexes are very active, particularly with the previously unreactive aliphatic thiols, and display broad scope, tolerating a wide range of functional groups such as amines, ethers, nitriles, or silanes. The nature of the Tp moiety was found to be essential for the catalytic activity. Thus, the bis(pyrazolyl)borate precursor found to be less effective than the tris(pyrazolyl)borate analogs, indicating that a k^3-coordination of the ligand should play an important role. Although the full mechanism has not completely been determined, the authors suggest a 1,2-insertion of the alkyne into Rh–S bonds as a key step for selectivity (Fig. 34) [134]. A year after the seminal report of Love's group, Mizobe and coworkers showed that the related precursor Tp*Rh(coe)(NCMe) promotes the hydrothiolation of benzyl and phenylacetylene with thiophenol [138]. In this case, a slightly different mechanism was proposed. A double addition of thiol with concomitant release of molecular hydrogen generates a dithiolate–rhodium complex as the active species. The insertion of the alkyne into a Rh–S bond is therefore the only possibility, thus generating branched vinyl sulfides by subsequent protonolysis. Reactivity studies and the X-ray structural

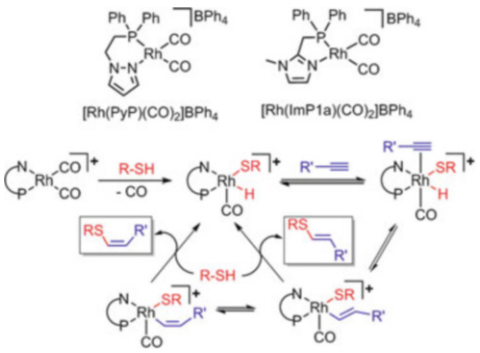

Fig. 33 Rhodium cationic systems favoring anti-Markovnikov selectivity

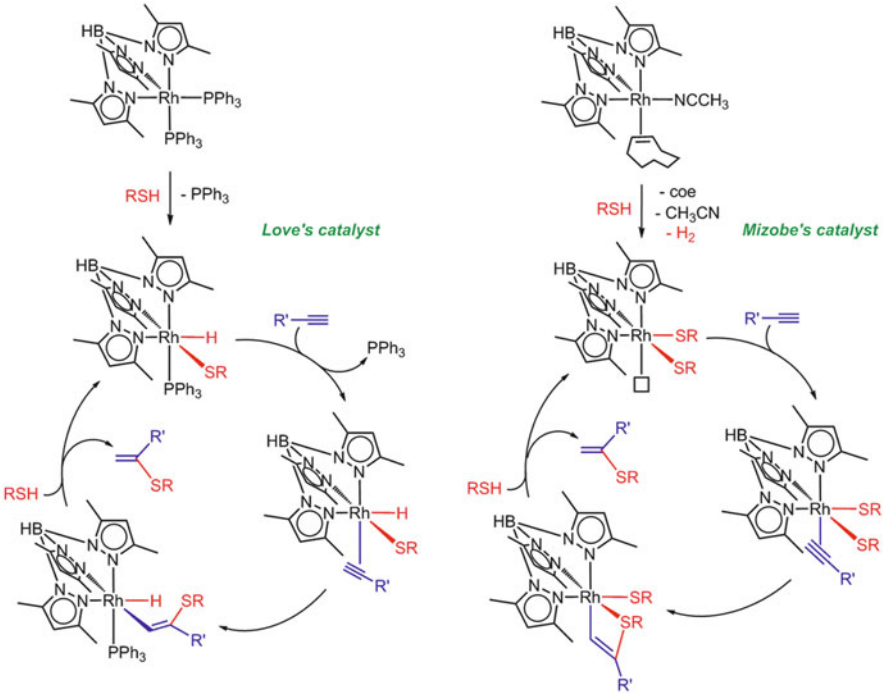

Fig. 34 Proposed catalytic cycles for Tp*Rh precursors leading to Markovnikov-vinyl sulfides

characterization of a rhodium-alkenyl-thioether intermediate strongly support the mechanistic proposal.

Markovnikov selectivity in the formation of vinyl sulfides by alkyne hydrothiolation is also obtained with dinuclear rhodium-phosphino-carbonyl catalysts (Fig. 35) [139]. The reaction can be performed in a mixture of THF/water due to the presence of water-soluble phosphines and is possible to recycle. These results are in stark contrast with those obtained for related monomeric catalysts described

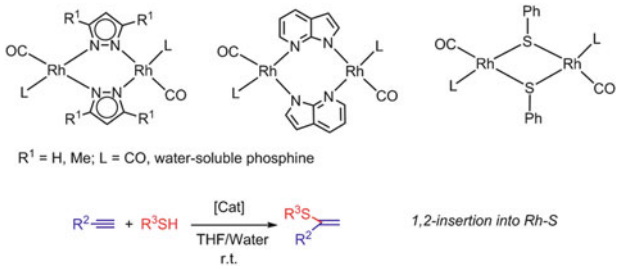

Fig. 35 Markovnikov-selective dinuclear phosphine–carbonyl catalysts

by Messerle (see above). Kinetic measurements indicate that the dinuclear species maintain its entity and the bridges are not cleaved during the catalytic process. Deuterated experiments demonstrate a *syn*-addition of the thiol over the alkynes. The authors propose a 1,2-insertion of the alkyne into the rhodium thiolate bond generated by oxidative addition as responsible for the branched selectivity.

Allenes can also participate in rhodium-mediated hydrothiolation reactions. The approach furnishes α-chiral sulfides and sulfones which are valuable building blocks in organic synthesis [140, 141]. The catalytic system composed of [RhCl(cod)]$_2$ and a chiral phosphine showed higher enantioselectivity for the addition of the sulfur atom to the more substituted carbon of the allene (Fig. 36). Subsequent oxidation affords the chiral sulfones in high yield. Based on deuterium-labeled experiments, the authors propose an initial oxidative addition of the thiol and subsequent hydrometalation of the more substituted double bond of the allene.

Ligand-Controlled Selectivity in Rh–NHC Catalysts

Our group has recently disclosed that rhodium(I)-N-heterocyclic carbene (NHC) catalysts efficiently perform alkyne hydrothiolation under mild conditions [143]. Substitution of a phosphine by a N-heterocyclic ligand in Wilkinson's catalyst resulted in the stabilization of the active species although with slight reduction of initial rate for thiophenol addition to phenylacetylene at room temperature (Fig. 37). Conversion with RhCl(PPh$_3$)$_3$ reaches 80% with a TOF ½ of 300 s^{-1}, whereas 99% of conversion was observed for RhCl(IPr)(PPh$_3$)$_2$ but displaying 55 s^{-1} of TOF ½. Selectivity outcome also changed. The amount of α-vinyl sulfide was increased by the introduction of the carbene moiety. Other Rh–NHC complexes were tested as catalyst for this transformation. The free-phosphine dinuclear catalyst [Rh(μ-Cl)(IPr)(η^2-ethylene)]$_2$ surpassed the activity of Wilkinson's catalyst maintaining the stabilizing effect of carbene. Full conversion was obtained after 1 h with anti-Markovnikov vinyl sulfide preference. The introduction of mononuclear pyridine complex RhCl(IPr)(η^2-coe)(py), obtained by bridge cleavage with the nitrogenated ligand in the dinuclear precursor, remarkably increased the selectivity toward the Markovnikov-type adducts up to 91%, although with a decrease of activity. Indeed, both selectivity increment and activity decrease were magnified by addition of ten

Fig. 36 Asymmetric addition of thiols to allenes

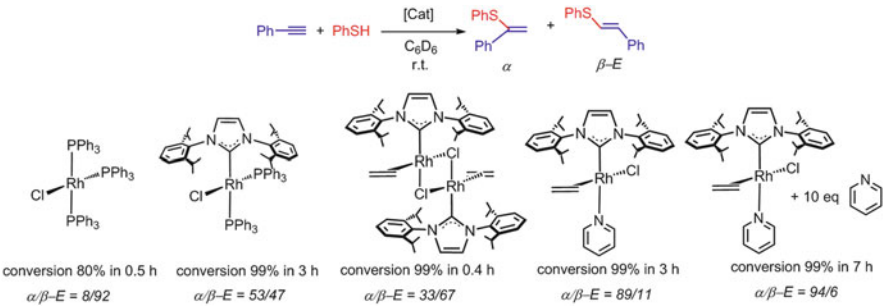

Fig. 37 Introduction of a NHC ligand into rhodium catalysts

equivalents of pyridine to the catalytic precursor. The catalyst was totally inactive in neat pyridine. The use of other nitrogenated bases does not result in an increase of selectivity, indicating that the role of pyridine is played in coordination with the metallic center. Antiradical additives do not affect catalytic outcome thus excluding radical processes as responsible for catalytic activity.

In order to shed light into the pyridine effect over selectivity in Rh–NHC-based catalysts, stoichiometric experiments and theoretical DFT calculations were performed. The first step consists in the oxidative addition of the thiol to form a hydride–thiolate–rhodium species. This type of intermediate was not possible to detect in the absence of pyridine. Then, rate-determining 1,2-alkyne insertion into R–S bond takes place to finally afford the Markovnikov thioether after reductive elimination. A likely explanation for the "pyridine effect" is as follows: the sterically hindered and strongly electron-donating NHC ligand directs the coordination of the pyridine *trans* to it, consequently blocking coordination of the alkyne in this position. Simultaneously, the *trans* influence of the hydride paves the way to a *cis* thiolate-alkyne disposition, which subsequently gives rise to the branched vinyl sulfide regioisomer. The absence of pyridine allows the alkyne to coordinate in the preferred site *trans* to IPr position, and therefore subsequent unselective migratory insertion into hydride or thiolate can occur (Fig. 38).

As previously discussed, the dinuclear precursors of type $[Rh(\mu\text{-}Cl)(NHC)(\eta^2\text{-olefin})]_2$ favor the formation of linear thioethers, whereas the selectivity is switched toward branched *gem*-vinyl sulfides by the mononuclear catalyst RhCl(NHC)(pyridine)(η^2-olefin). An equilibrium between both types of precursors is established rendering the concentration of pyridine essential for the control of regioselectivity. We hypothesized that the equilibrium shift to the mononuclear species by using a

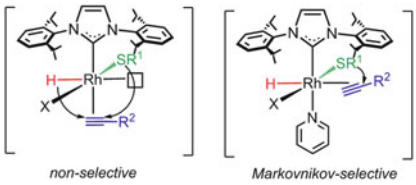

Fig. 38 Interplay between NHC, pyridine, and hydride ligand for Markovnikov selectivity

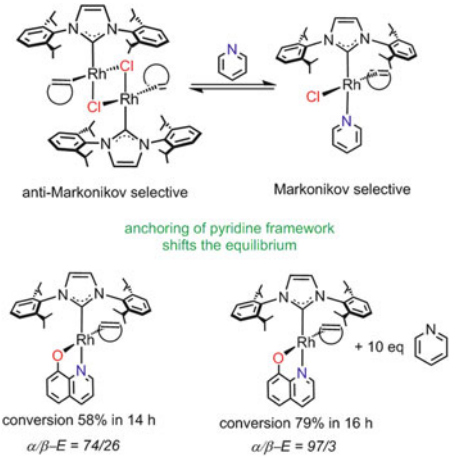

Fig. 39 Selectivity enhancement by anchorage of the N-donor ligand

chelate ligand would increase Markovnikov selectivity. Thus, we design a next generation of catalyst bearing a quinolinolate ligand (Fig. 39) [144]. The catalytic activity is lower, as observed in the aforementioned systems by the addition of pyridine. Selectivity to α-vinyl sulfides of the quinolinolate-based catalysts is high (74–80%), but, unfortunately, lower than expected. Notably, the addition of pyridine results in an increase of the selectivity up to 97%.

Theoretical DFT and experimental results revealed that a different mechanism is operative for the quinolinolate-based catalysts with regard to pyridine systems. The first step is similar for both, the oxidative addition of the acidic thiol. Then, each catalyst takes different routes but reaching the same goal, the branched vinyl sulfide (Fig. 40). Pyridine catalysts undergo 1,2-thiolate insertion with migratory insertion as rate limiting, whereas quinolinolate species evolve by hydride insertion with reductive elimination as rate limiting. These facts exemplify how subtle changes in catalytic structure may result in complete change in the operative mechanism although arriving to the same final result.

The fact that the presence of pyridine as additive is essential in quinolinolate catalysts to reach high selectivity is intriguing. In contrast to RhCl(IPr)(η^2-olefin)(py) precursors, alkenyl intermediates resulting from alkyne insertion into hydride bond can be detected for quinolinolate-based catalysts (Fig. 41). However, we observed that pyridine coordinates to linear alkenyl but not to the bulkier branched one, thus disfavoring the reductive elimination of anti-Markovnikov thioether and therefore increasing Markovnikov selectivity.

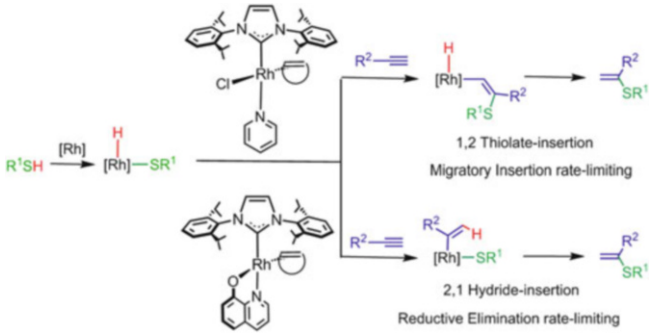

Fig. 40 Mechanistic pathways for pyridine and quinolinolate catalyst precursors

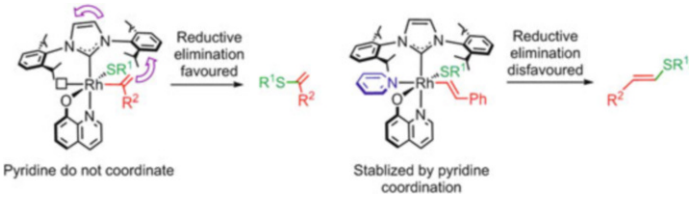

Fig. 41 Role of pyridine in selectivity

Another approach for enhancement of Markovnikov selectivity is the non-oxidative strategy depicted in Fig. 31. A deprotonation of the thiol eliminates the hydride moiety; therefore only the insertion over R–S bond is operative. We have designed dinuclear Rh–NHC precursors bearing hydroxo bridges as internal base able to achieve this task (Fig. 42) [145]. As anticipated, these catalysts display a high selectivity (up to 94%), but a decrease of activity is observed. Low-temperature experiments allow for detection of the square-planar Rh^{I}–thiolate intermediate. Nevertheless, as a consequence of the tendency of pyridine to coordinate *trans* to IPr [146], both thiolate and alkyne are mutually *trans* disposed; therefore insertion step is limited, making this intermediate inactive. However, these species undergo a subsequent thiol addition to generate hydride–dithiol–Rh^{III} species that can evolve in similar pathways that pyridine catalysts do, thus displaying high Markovnikov selectivity.

In view that the non-oxidative mechanism is not operative for Rh-pyridine precursors because of oxidation to Rh^{III} by the free thiol used as a substrate, we envisage that the introduction of a π-acceptor carbonyl group would reduce this step. Indeed, a pyridine moiety gives stability and flexibility to the catalytic system. With these prerequisites established, we chose a 2-hydroxymethylpyridine-Rh-CO catalyst as suitable candidate for improving selectivity (Fig. 43). This precursor displayed the higher selectivity within the family of Rh–NHC catalysts [144]. The catalytic activity is reduced at room temperature, but 98% of conversion was attained at 50°C. The effect of the carbonyl ligand, in addition to reduce Rh^{III}

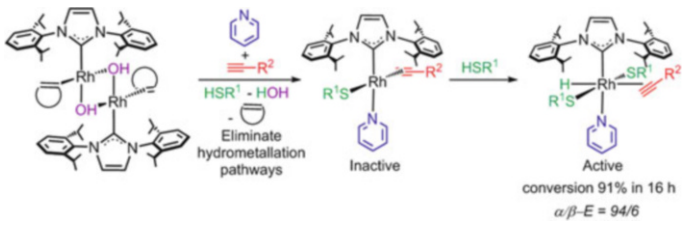

Fig. 42 Mechanism for Rh–hydroxo–NHC catalyst

Fig. 43 Design of NHC–Rh–CO catalysts

oxidation by the thiol, favors a thiolate to alkyne *cis* disposition; therefore the migratory insertion, as the π-acceptor ligand, prefers to coordinate *cis* to carbene in contrast to pyridine that prefer *trans* coordination.

As showed above, the introduction of a NHC ligand into rhodium precursors has provided a fruitful family of alkyne hydrothiolation catalysts. The particular estereoelectronic properties confer stability to active species that result in an enhancement of catalytic activity. The different pathways available for this transformation render the rational design of the ligands essential for controlling selectivity. An in-depth knowledge of the precise mechanism has allowed this task to be achieved successfully. Further work is necessary in order to apply the insights gained for this model system to other hydrofunctionalization reactions.

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