

Review

# Thiosemicarbazone Complexes of Transition Metals as Catalysts for Cross-Coupling Reactions

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**Abstract:** Catalysis of cross-coupling reactions under phosphane-free conditions represents an important ongoing challenge. Although transition metal complexes based on the thiosemicarbazone unit have been known for a very long time, their use in homogeneous catalysis has been studied only relatively recently. In particular, reports of cross-coupling catalytic reactions with such complexes have appeared only in the last 15 years. This review provides a survey of the research in this area and a discussion of the prospects for future developments.

**Keywords:** thiosemicarbazone; metal complex; transition metal catalysis; cross-coupling reaction; Heck reaction; Suzuki reaction; Sonogashira reaction; Kumada reaction; Buchwald–Hartwig reaction

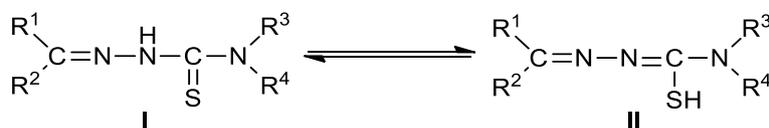
## 1. Introduction

Catalysis by means of transition metal complexes is now a well-established tool for the organic chemist, and the continued interest in the field has led to increasingly more effective and efficient systems for carrying out a wide range of reactions, both on a laboratory and on an industrial scale. The benefits of transition metal catalysis are that the reactions are often very clean and have very high turnovers, meaning that waste products are kept to a minimum, which is one of the precepts of Green Chemistry. In addition, improvements in catalyst design are continually being made and thus allow the use of milder conditions, immobilisation on solid supports, biphasic systems for ease of separation, more benign solvents, etc. Research in the area of transition metal catalysed carbon–carbon and carbon–heteroatom coupling reactions has led to a wide variety of very efficient and useful procedures which are now most often known by the names of the scientists who pioneered their use such as Suzuki–Miyaura, Mizoroki–Heck, Negishi, Sonogashira, Kumada–Tamao–Corriu, Migita–Kosugi–Stille, Tsuji–Trost, Buchwald–Hartwig [1–9]. These procedures are mainly based on palladium although other metals have been shown to be effective in a number of cases. Phosphane ligands have traditionally been the ligands of choice for transition metal catalysis and particularly so for coupling reactions. Such systems are generally rather stable and have been refined to a very great extent. However, since phosphanes can often be water- and air-sensitive, a number of efforts have been made to develop catalysts which avoid them and instead to employ ligands with C, N, O, or S donor groups [10], e.g., *N*-heterocyclic carbenes, carbocyclic carbenes, oxazolines, Schiff bases, amines, imidazoles, hydrazones, semicarbazones, thiosemicarbazones, thioureas, amidates, and so on. This review focuses on complexes of thiosemicarbazones and on how they can play a role in these developments.

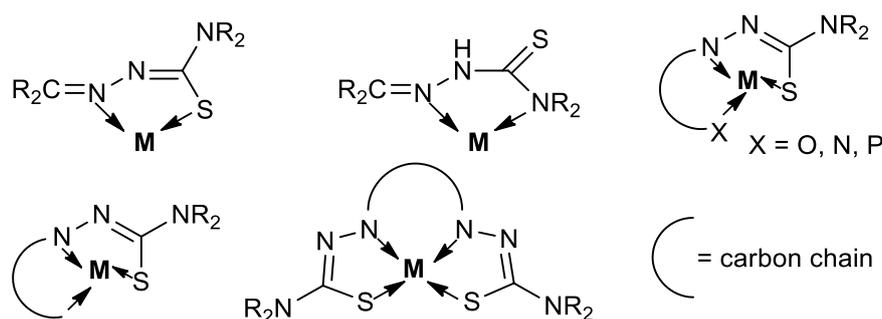
The use of thiosemicarbazones, as well as other closely related chalcogen compounds, as ligands in metal complexes has proved to be a fruitful field of study for many years but initial reports on their application in catalysis did not appear until the 1990's [11–14], while their use in coupling

reactions was only first reported several years later [15,16]. One of the primary motivations for research into these complexes has been the various areas in which they have been proposed for application. For example, apart from their activity as catalysts, which will be covered in more detail in this review, many thiosemicarbazone metal complexes have been widely studied as potential treatments for various types of cancer, for viral, bacterial, or fungal infections, and for neurodegenerative diseases, or for malaria [17–26]. Thiosemicarbazone metal complexes have also found potential application in medical imaging [27,28], while thiosemicarbazones themselves show promise as metal ion sensors and for the scavenging of metals due to their selective and specific coordination properties [28–34]. Although related compounds such as isothiosemicarbazones, dithiocarbazates, and selenosemicarbazones have so far found less application in the catalysis of coupling reactions and will not feature in this review, it is appropriate to mention that a number of metal complexes have nevertheless been reported and that they too have been studied in areas such as oxidation processes [35–37], cytotoxicity [38–47], antimicrobials [48], imaging [49,50], and antioxidants [43,51,52].

Another important aspect of thiosemicarbazones as ligands is the wide variety of coordination modes which can be adopted. Numerous structural studies have been carried out and this area has been the subject of a number of reviews [17,53–55]. An equilibrium mixture of thione (I) and thiol (II) tautomers exists in solution (Scheme 1). The simplest thiosemicarbazones, without any additional potential donor sites, can adopt a bidentate configuration either in their neutral form or in their deprotonated form as an anionic ligand. Many thiosemicarbazones, however, also have additional functionality which provides further potential donor sites and thus enables tridentate or higher degrees of denticity (Scheme 2). This becomes important when dealing with carbon–carbon coupling reactions, and especially those involving palladium complexes, since pincer-type Pd(II) complexes are known to efficiently catalyse carbon–carbon coupling reactions [56], and it has been hypothesised that the tridentate coordination of the pincer ligand stabilises the metal–carbon bond during the catalytic cycle [57].



Scheme 1. Tautomerism of thiosemicarbazones.



Scheme 2. Representative coordination modes of thiosemicarbazones.

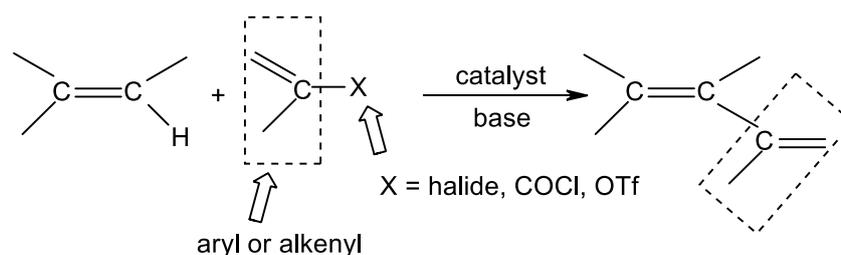
This versatility of coordination, together with the relative ease with which these ligands can often be prepared, has provided a considerable impetus into the study of their metal complexes, and particularly how it can be exploited for the development of new catalysts. Reactions which have been studied using these systems include oxidation [58–74], transfer hydrogenation [75–77], reduction [14], silane alcoholysis [12,13,78], condensation reactions [79–81], and the cyclopropanation of olefins [82,83], as well as coupling reactions which are described here. Some of these have also previously been covered by Kumar et al. in reviews of the role of organochalcogen ligands in Mizoroki–Heck and Suzuki–Miyaura reactions [84–86]. The present review is organised according to

the nature of the bond formed, i.e. carbon–carbon or carbon–heteroatom, with further subdivisions within these categories. It should be noted that, as with many other catalytic systems, the complexes used should usually more accurately be referred to as pre-catalysts since the active species are often formed in the reaction system. Indeed, there may be more than one active species formed, giving rise to a catalytic “cocktail” [87,88]. There have been numerous studies concerning the mechanism of coupling reactions catalysed by transition metal complexes which discuss the nature and formation of these cocktails as well as other related features of these reactions such as the aggregation of complexes or their de-aggregation, leaching effects, the role of nanoparticles and so on [89–92] but relatively little such work has been done, however, on thiosemicarbazone complexes. This aspect is therefore very much in its infancy and the present review will attempt to highlight the most significant studies in this area.

## 2. Carbon–Carbon Coupling Reactions

### 2.1. Mizoroki–Heck Reaction

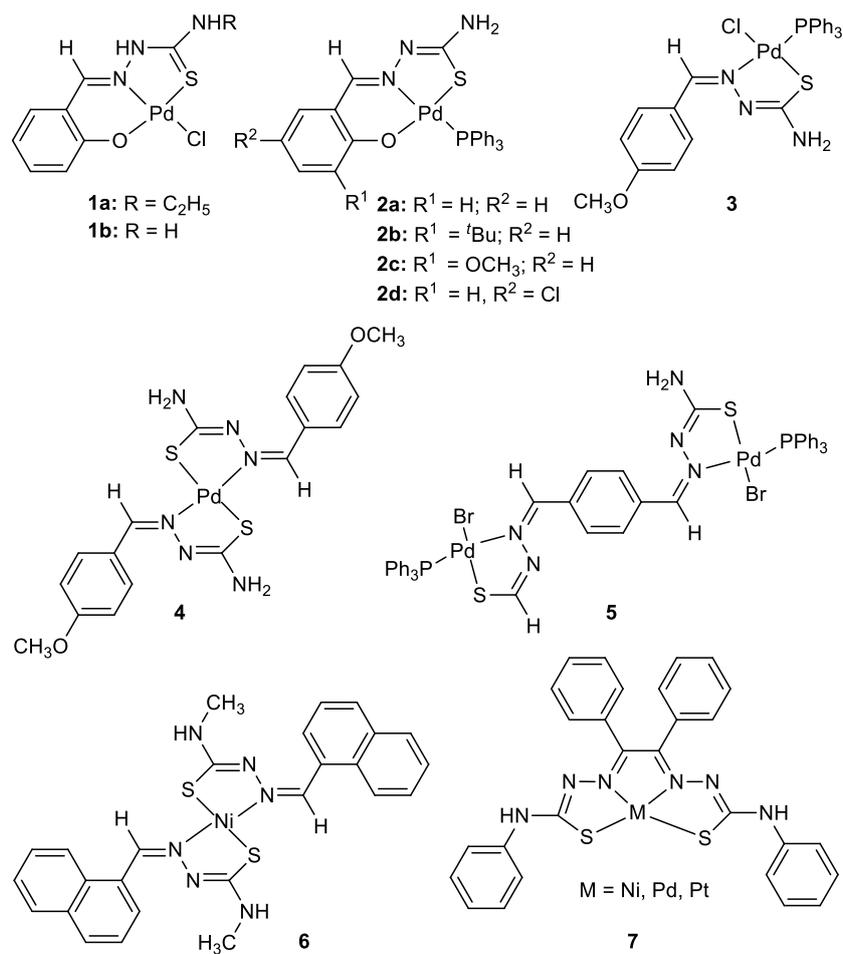
The palladium catalysed coupling of alkenes and aryl halides was discovered independently by Mizoroki and Heck (Scheme 3). The numerous modifications and variations of this reaction have been so extensively reviewed that there is even a review of reviews on the subject [93]. Metal complexes of thiosemicarbazones that have been used as catalysts for this reaction are shown in Figure 1.



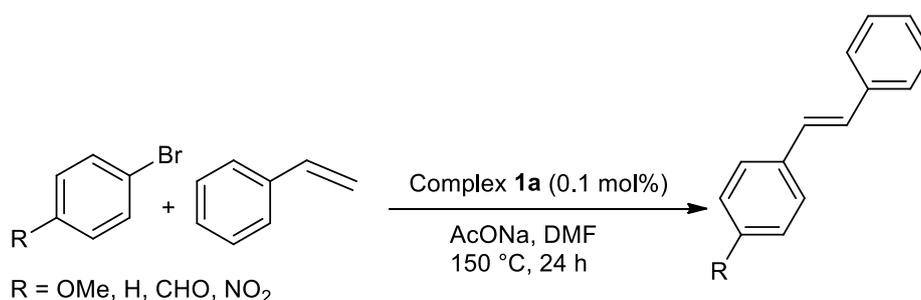
Scheme 3. Mizoroki–Heck reaction.

The first reported use of a thiosemicarbazone in the Heck reaction was in 2004 by the groups of Kovala-Demertzi and Kostas using a palladium complex of salicylaldehyde *N*(4)-ethylthiosemicarbazone (**1a**) (Figure 1) [15]. The crystal structure of the complex indicated that the ligand behaved as a tridentate ligand with N, S and O bonded to the metal. The reaction of styrene with a range of aryl bromides in the presence of varying concentrations of the complex was carried out in DMF (dimethylformamide) at 150 °C both in air and also under an argon atmosphere (Scheme 4). It was found that, as is normally the case for the Heck reaction, the catalytic activity was greater for aryl bromides with electron-withdrawing groups and decreased in the order  $\text{NO}_2 > \text{CHO} > \text{H} > \text{OMe}$ , leading to the conclusion that the oxidative addition of the aryl bromide to the complex was the rate-determining step. The use of an inert atmosphere in general gave better results, particularly for the least active aryl bromides and for low catalyst concentrations. However, the complex was stable enough in air under the reaction conditions to catalyse the reaction for the more activated aryl bromides, and turnover numbers (TONs) ranging from 120 to 14,000 and turnover frequencies (TOFs) in the range 5–583  $\text{h}^{-1}$  were found. Using similar systems, **2**, involving derivatives of salicylaldehydethiosemicarbazone with an additional  $\text{PPh}_3$  ligand, Xie et al. studied the catalysis of the Heck reaction of iodobenzene with methyl acrylate [94]. Having found that the methoxy-derivative **2c** gave the best yields in initial experiments, they examined the reaction with a range of other aryl iodides and aryl bromides, and with different solvents and bases. Generally, good to very good yields were obtained using aryl iodides and various acrylate esters under an argon atmosphere with DMF as solvent,  $\text{K}_2\text{CO}_3$  as base, a temperature of 110–130 °C and a catalyst loading of at least 0.01 mol%. Using  $\text{Na}_2\text{CO}_3$ , lower catalyst loading also gave good results and this base was used in the reactions of the aryl bromides (Scheme 5). In the latter

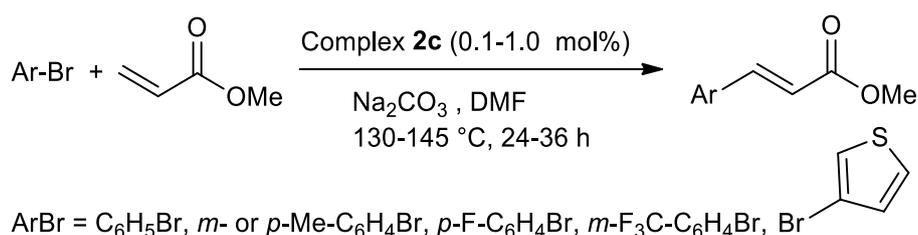
case, catalyst loadings of 0.1 or 1 mol% were necessary in order to obtain acceptable yields. Bidentate thiosemicarbazone complexes of palladium were investigated as catalysts in coupling reactions by Paul et al. [95]. They found that, in the Heck reaction, the complexes **3** and **4** displayed catalytic behavior at 0.5 mol% catalyst loading for the reaction between some aryl bromides and *n*-butyl acrylate (Scheme 6). The authors used Cs<sub>2</sub>CO<sub>3</sub> as base and either ethanol-toluene or PEG (polyethylene glycol) as solvent at 110–150 °C. Although the results were only moderately good, this system could have much room for optimization taking into account the observation of Xie et al. (see above) that PEG was a poor solvent for the similar system that they examined and that K<sub>2</sub>CO<sub>3</sub> was a superior base than Cs<sub>2</sub>CO<sub>3</sub>.



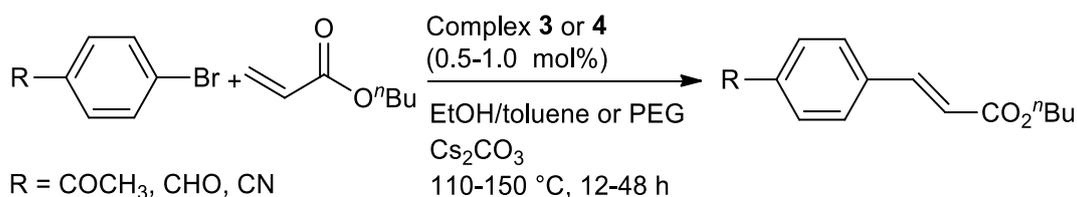
**Figure 1.** Representative metal complexes of thiosemicarbazones as catalysts for the Mizoroki–Heck and other coupling reactions.



**Scheme 4.** Heck reaction of aryl bromides with styrene catalysed by complex **1a**: The first reported use of a thiosemicarbazone in the Heck reaction.

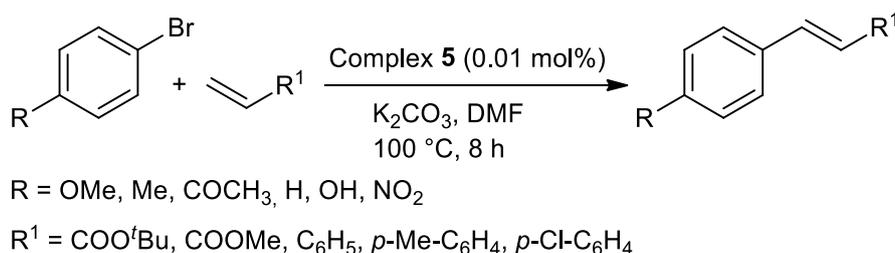


**Scheme 5.** Heck reaction of aryl bromides with methyl acrylate catalysed by complex 2c.



**Scheme 6.** Heck reaction of aryl bromides and *n*-butyl acrylate catalysed by complexes 3 or 4.

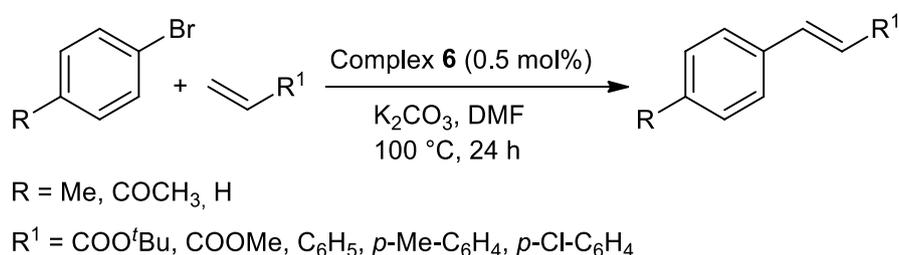
The dinuclear bis-bidentate palladium complex 5, which also possesses  $\text{PPh}_3$  ligands coordinated to the metal, was prepared and structurally characterized by Prabhu and Ramesh who subsequently made a systematic study of its catalytic activity in the Heck reaction of *p*-bromoacetophenone with *t*-butyl acrylate, examining the effect of temperature, solvent, base and catalyst loading [96]. Inorganic bases such as  $\text{K}_2\text{CO}_3$  or  $\text{Na}_2\text{CO}_3$  were superior to amines, DMF was the optimal solvent and a temperature of  $100\text{ }^\circ\text{C}$  provided the best results within a reasonable time. Catalyst loadings of 1 or 0.1 mol% gave quantitative yields but it is worth noting that the reaction proceeds even at very low catalyst loading of 0.00001 mol%, and, although the yield in this case is low (11%), the turnover number (1,100,000) and the turnover frequency ( $137,500\text{ h}^{-1}$ ) are still impressive. Using optimized conditions, the authors were able to demonstrate the activity of the complex for a wide range of electron-withdrawing and electron-donating aryl bromides with methyl and *t*-butyl acrylate, styrene, *p*-methylstyrene, and *p*-chlorostyrene (Scheme 7). TONs of 6,000 to 9,800 and TOFs in the range  $750\text{--}1225\text{ h}^{-1}$  were reported.



**Scheme 7.** Heck reaction of aryl bromides with acrylate esters or substituted styrenes catalysed by complex 5.

The above studies all involved complexes of palladium but there have also been reports of the application of thiosemicarbazone nickel complexes to coupling reactions. One of the main motivations for this is the relatively low cost of nickel compared with palladium while, on the other hand, the main difficulty that needs to be surmounted is the well-established high efficiency of palladium complexes. It is also conceivable that there are important mechanistic differences in the mode of action of the complexes of the two metals but, for thiosemicarbazone complexes at least, no systematic studies have yet been carried out. The first report of the application of thiosemicarbazone nickel complexes to the Heck reaction was by Datta et al., who prepared and characterized three complexes with 2-hydroxyaryl thiosemicarbazone ligands [97]. Dinuclear complexes with tridentate *N,S,O*-coordination were formed which were reacted with  $\text{PPh}_3$ , pyridine, or bipyridine to give mononuclear complexes that retained

the tridentate coordination. The complexes were examined for their catalytic efficiency in the reaction of *p*-bromoacetophenone, *p*-bromobenzonitrile, and *p*-bromobenzaldehyde with butyl acrylate in DMF at 130 °C. Catalyst loadings of 2 mol% were found to give good yields but TONs (18–50) and TOFs ( $2.1 \times 10^{-4} \text{ sec}^{-1}$ ) were modest compared with TONs of analogous palladium complexes (8000). One encouraging feature, however, was that coupling reactions of aryl chlorides also proceeded with yields of a similar order of magnitude to the more reactive aryl bromides and iodides. Better results, at least as far as aryl bromides are concerned, were obtained using the nickel complex **6** reported by Suganthi et al. [98]. Using optimized conditions, this bis(thiosemicarbazone) nickel complex catalysed the reaction between a series of aryl bromides and methyl and *t*-butylacrylate, styrene, *p*-methylstyrene and *p*-chlorostyrene (Scheme 8). Using catalyst loadings of 0.5 mol%, moderate to very good conversions were obtained with turnover numbers ranging from 120 to 188 and turnover frequencies in the range 5–8 h<sup>-1</sup>. However, it is significant that, compared with the system mentioned above [97], no catalytic activity was observed in the coupling of 4-chloroacetophenone with *t*-butyl acrylate in DMF/K<sub>2</sub>CO<sub>3</sub> even after 24 h at elevated temperatures.



**Scheme 8.** Heck reaction of aryl bromides with acrylate esters or substituted styrenes catalysed by Ni complex **6**.

Very recently, a comparative study has been made of similar thiosemicarbazone complexes of nickel, palladium, and platinum [99]. Using a tetradentate bis-thiosemicarbazone ligand, Lima et al. synthesized the complexes **7**. The tetradentate coordination was verified by X-ray diffraction structural determinations and the complexes were subsequently studied in the Heck reaction of iodobenzene with styrene. The palladium complex was an active catalyst at loadings of 3.5 mol% or above in a reaction carried out in DMF at 120 °C using triethylamine as the base. The platinum and nickel complexes showed activity but much less than the Pd complex. The palladium system appears to show much less catalytic activity than previously reported complexes and this may be due to the lack of free coordination sites in the tetracoordinated complex. On the other hand, it should be noted that the use of an organic base instead of an inorganic one is known to play a significant role and this also should be taken into account. It is also not clear from the report whether an inert atmosphere was employed. The authors performed preliminary DFT calculations from which they postulate that the process involving the tetradentate Pd complex does not follow the typical reaction mechanism for Heck catalysts involving an initial Pd(0)-Pd(II) oxidative-addition step. The calculations indicated a partial charge of +1.154 on the metal in the palladium complex compared to a much lower charge of +0.284 on the metal in the nickel one. Taking into account the increased catalytic activity of the Pd complex, and on the basis of their calculations for the likely steps in the catalytic cycle, the authors suggest that the reaction proceeds via an initial Pd(II)-Pd(IV) oxidative-addition of the aryl halide followed by olefin insertion and reductive elimination.

Published reports of the use of thiosemicarbazone complexes as described above for the Mizoroki–Heck reaction are summarised in Table 1 for indicative reactions.

**Table 1.** Mizoroki–Heck reactions catalysed by thiosemicarbazone complexes: representative conditions and yields <sup>1</sup>.

Metal	T (°C)	Solvent	Time (h)	Ligand <sup>2</sup>	Base	Catalyst (mol%)	Yield (%)	Ref.
Pd	150	DMF	24	O,N,S	NaOAc	0.1	46–95	[15]
Pd	130–145	DMF	24–36	O,N,S	Na <sub>2</sub> CO <sub>3</sub>	0.1–1.0	50–90	[94]
Pd	110–150	EtOH/toluene or PEG	12–48	N,S	Cs <sub>2</sub> CO <sub>3</sub>	0.5–1.0	57–80	[95]
Pd	100	DMF	8	N,S	K <sub>2</sub> CO <sub>3</sub>	0.01	60–97	[96]
Ni	130	DMF	24	O,N,S	Cs <sub>2</sub> CO <sub>3</sub>	2.0	36–99	[97]
Ni	110	DMF	24	N,S	K <sub>2</sub> CO <sub>3</sub>	0.5	60–94	[98]
Pd	120	DMF	5–24	S,N,N,S	Et <sub>3</sub> N	3.5	67–82 <sup>3</sup>	[99]

<sup>1</sup> conditions refer to reactions involving aryl bromides and (substituted) styrenes or acrylates. <sup>2</sup> ligand donor atoms.

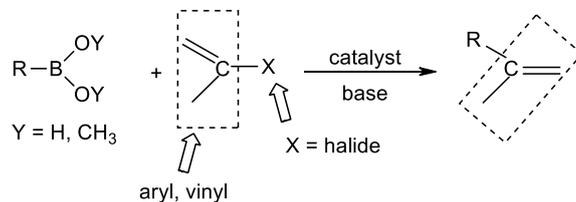
<sup>3</sup> for the reaction of PhI with styrene.

## 2.2. Suzuki–Miyaura and Related Reactions

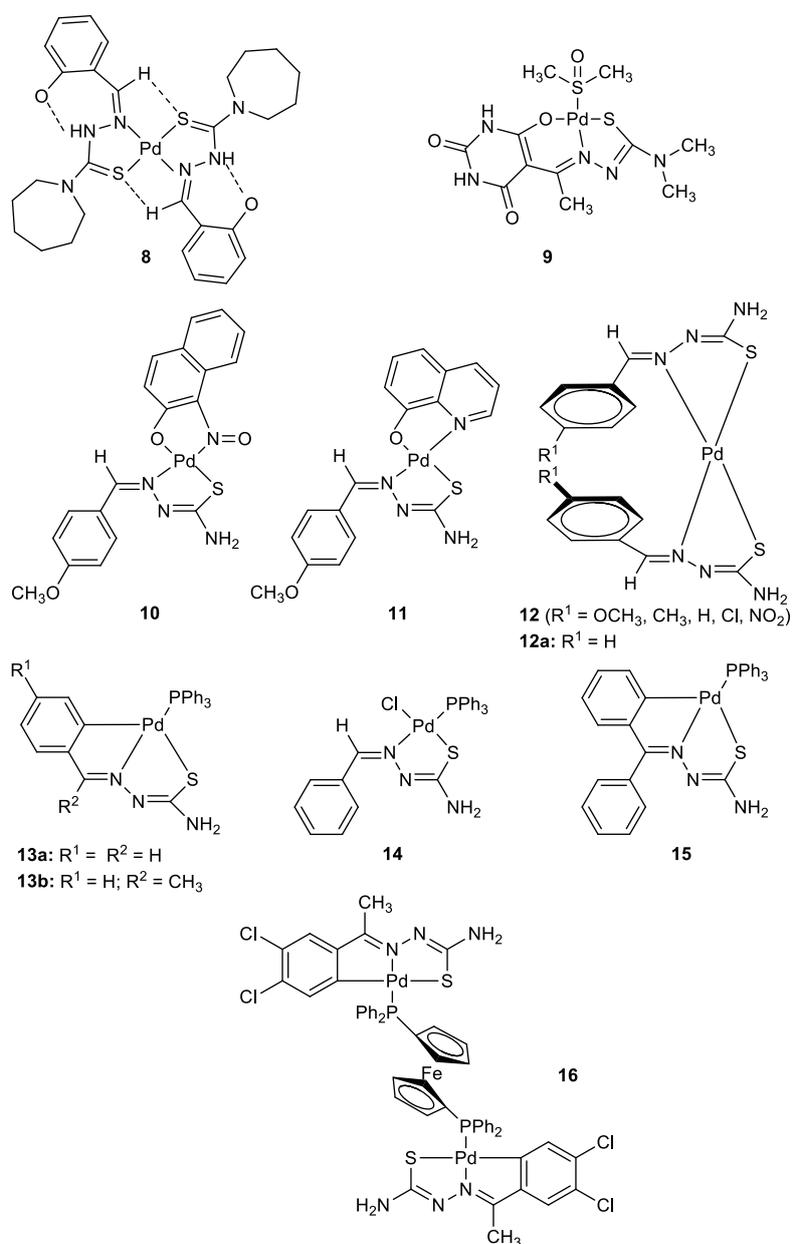
The coupling of alkenyl, alkynyl, and aryl halides with boronic acids and related derivatives by palladium complexes, first reported in 1979 by Miyaura and Suzuki, led to intense research activity aiming at optimising the reaction and extending its application to increasingly more demanding systems (Scheme 9). Numerous reviews have appeared and continue to appear on the subject [2,3]. Representative metal complexes of thiosemicarbazones that have been used as catalysts for this reaction are shown in Figures 2–4; see also in Figure 1.

The first report of the use of thiosemicarbazone complexes in this reaction was by Kostas et al., who studied the cross-coupling of aryl halides with phenylboronic acid (Scheme 10) [16]. The complexes **1a** and **1b** used were derived from salicylaldehyde (Figure 1), and one of them (**1a**) having already been successfully used in the Heck reaction as mentioned above [15]. The complexes are air-stable and this therefore enabled the reactions to be carried out without the need for an inert atmosphere. In addition, they are moisture-stable and in fact the addition of one equivalent of water was found to be beneficial. Aryl bromides with varying substitution were used and, as had been previously observed in reactions with other catalysts, the best results were obtained with electron-withdrawing substituents. Catalyst loadings of 0.1 mol% gave moderate to very good conversions for most substrates in reactions in DMF at 100 °C using Na<sub>2</sub>CO<sub>3</sub> as base, but even lower loadings of 0.001 mol% were also active systems, albeit with lower conversions. TONs ranging from 400 to 49,000 and TOFs in the range 17–2042 h<sup>-1</sup> were reported. The reaction with aryl chlorides was also catalysed by these complexes but, as expected, with somewhat lower TONs (260–370) and TOFs (11–15 h<sup>-1</sup>). These complexes were less active than some previously reported P-systems but have the important advantage of being phosphane free and requiring less demanding conditions. In a subsequent paper, the same group reported on the synthesis and characterisation of a new palladium thiosemicarbazone complex **8** (Figure 2) [100]. The thiosemicarbazone was again derived from salicylaldehyde but with a tertiary amino end group derived from hexamethyleneimine. The crystal structure determination of the bis-ligand palladium complex demonstrated that the two ligands were coordinated in a bidentate fashion via N and S donors. In contrast with the complexes in the previous study, the oxygen on the salicylaldehyde portion was not involved in direct bonding to the metal but was connected via a hydrogen bond to the unsubstituted thioamide nitrogen. This complex did not demonstrate catalytic activity in the Suzuki–Miyaura reaction using the conditions employed in the previous work, and it was proposed that this is because the metal is bonded to two thiosemicarbazone moieties by four intramolecular bonds, resulting in inhibition of the addition of the aryl halide to the metal during the catalytic cycle. However, using microwave irradiation, positive results were obtained for the reaction of bromobenzene and *p*-nitrobromobenzene with phenylboronic acid (Scheme 11). As in the previous study, the addition of water was found to be beneficial and good yields were obtained after up to 60 min irradiation using DMF as solvent and Na<sub>2</sub>CO<sub>3</sub> as base. Catalyst loadings of 0.1 mol% were used for reactions with bromobenzene and 0.001 mol% for those with *p*-nitrobromobenzene. TONs of up to 37,000 and TOFs

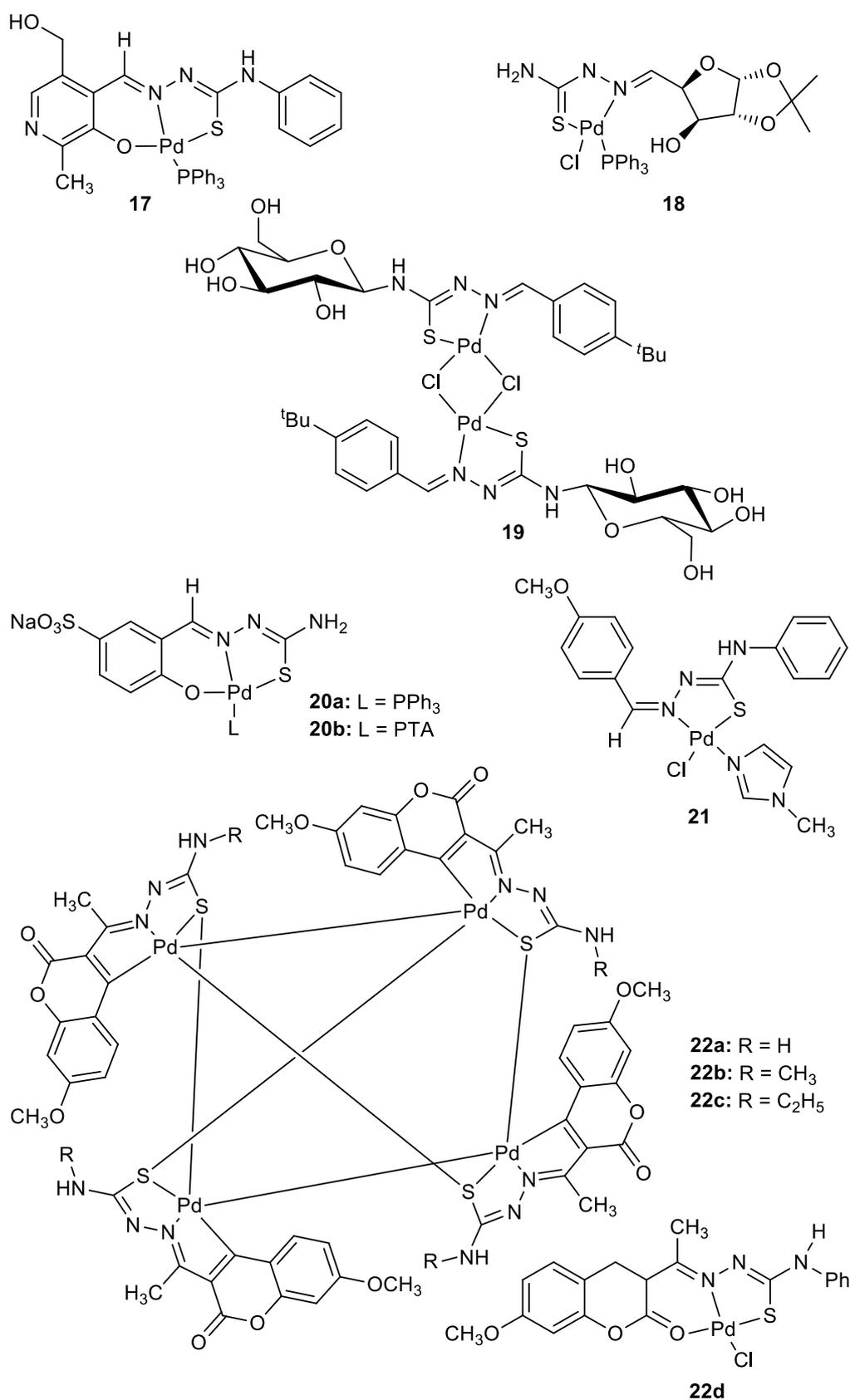
of up to  $617 \text{ min}^{-1}$  were recorded. The reaction of phenylboronic acid with *p*-nitrochlorobenzene was also successful under these conditions. The observation that conventional heating failed to promote the reaction prompted the authors to postulate that the acceleration of the reaction was due to specific microwave effects [100,101].



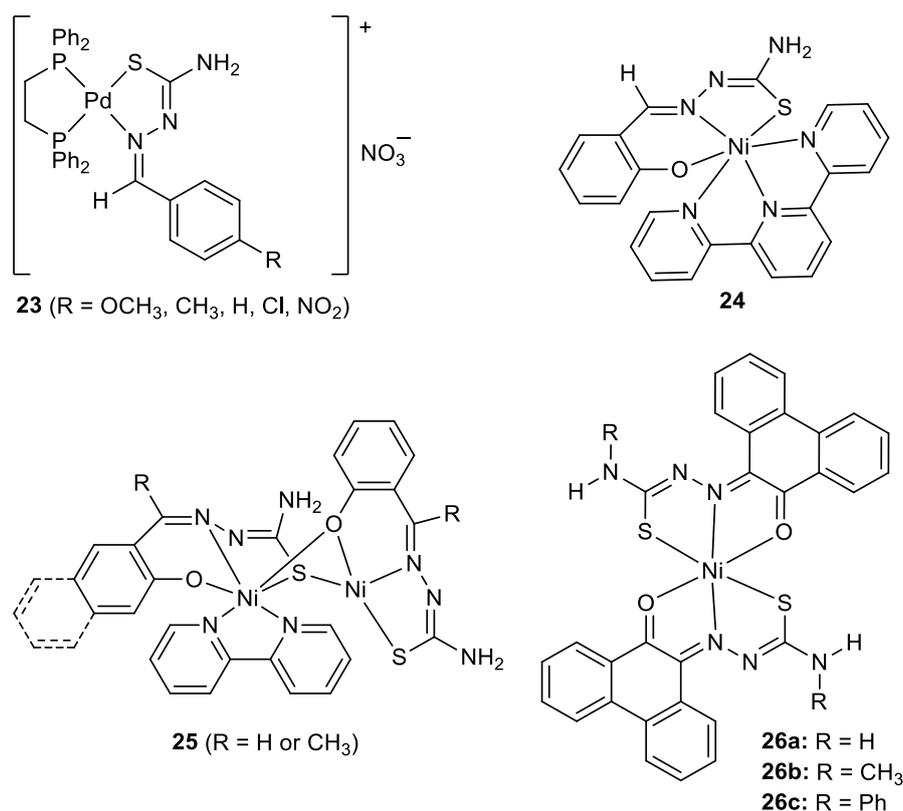
**Scheme 9.** Suzuki–Miyaura reaction.



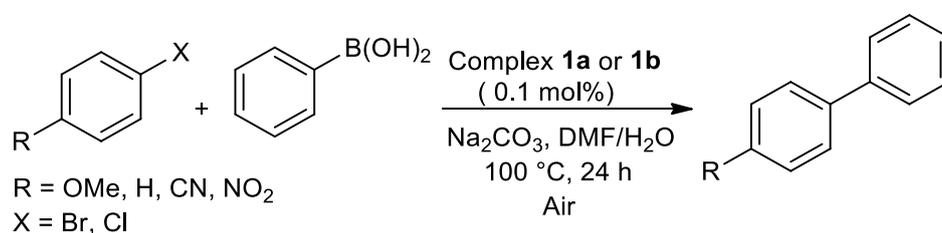
**Figure 2.** Representative metal complexes of thiosemicarbazones as catalysts for the Suzuki–Miyaura and other coupling reactions (Part A).



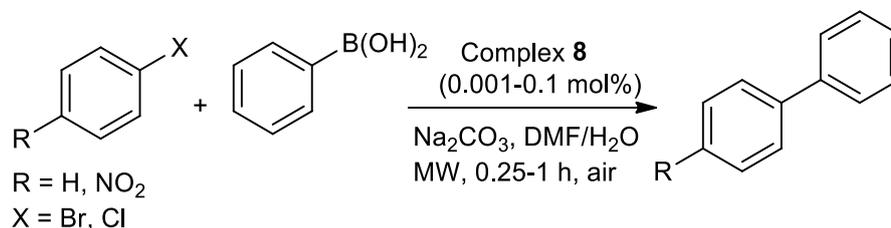
**Figure 3.** Representative metal complexes of thiosemicarbazones as catalysts for the Suzuki–Miyaura and other coupling reactions (Part B).



**Figure 4.** Representative metal complexes of thiosemicarbazones as catalysts for the Suzuki–Miyaura and other coupling reactions (Part C).



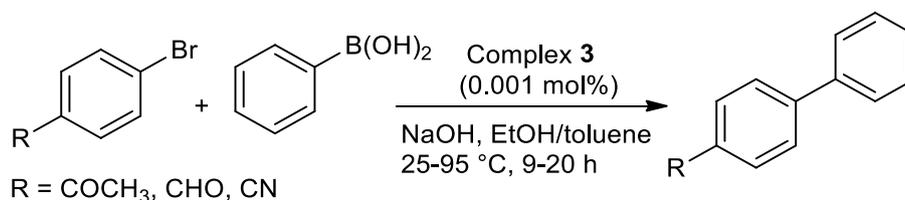
**Scheme 10.** Suzuki reaction of aryl halides with phenylboronic acid catalysed by complex **1a** or **1b**: The first reported use of a thiosemicarbazone in the Suzuki reaction.



**Scheme 11.** Microwave-promoted Suzuki–Miyaura cross-coupling of aryl halides with phenylboronic acid catalysed by complex **8**.

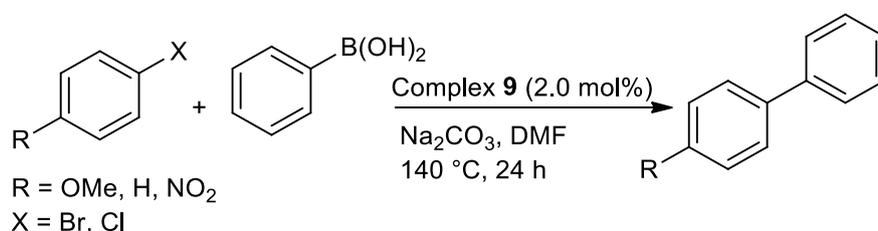
Bidentate complexes **3** and **4** prepared and characterised by Paul et al., and described above in relation to their catalytic activity in the Heck reaction (Figure 1), were also examined for their possible use in the Suzuki–Miyaura reaction [95,102]. The coupling of phenylboronic acid with *p*-bromoacetophenone, *p*-bromobenzaldehyde, or *p*-bromobenzonitrile was investigated using both the mono-ligand complex **3** containing PPh<sub>3</sub> as a supporting ligand and the bis-ligand phosphane-free

complex **4** (Scheme 12). Relatively mild conditions were used (ethanol-toluene or PEG solvent, NaOH as base, temperature 95–110 °C) and very high TONs (100,000) and TOFs (up to 11,111 h<sup>-1</sup>) were recorded for the former complex while lower, but still high, TONs (up to 8,800) and TOFs (up to 733 h<sup>-1</sup>) were recorded in the latter case. The mono-ligand complexes showed tolerance to water although the best results were obtained in dry conditions. The reaction involving *p*-bromoacetophenone using the mono-ligand complex **3** was even successful at 25 °C giving a conversion of 99%, TON of 100,000, and TOF of 5,000 h<sup>-1</sup>.



**Scheme 12.** Suzuki reaction of aryl bromides with phenylboronic acid catalysed by complex **3**.

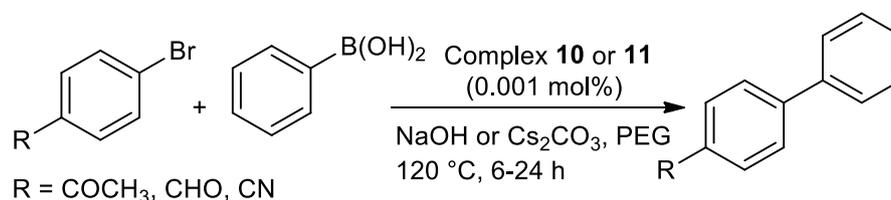
The phosphane-free complex **9** was reported by Castiñeiras et al. (Figure 2) [103]. The tridentate coordination of the dianionic ligand derived from 5-acetylbarbituric-4*N*-dimethylthiosemicarbazone was confirmed by XRD crystallography. In the reaction between phenylboronic acid and bromobenzene, *p*-bromoanisole, *p*-bromonitrobenzene and the corresponding chloro-derivatives, conversions of between 46 and 78% were observed for the aryl bromides, while somewhat lower values from 21 to 32% were found for the chlorides (Scheme 13). The authors postulated that, since the ligand is dianionic, the mechanism involves initial oxidative addition of the aryl halide and cycling between palladium +2 and +4 oxidation states as had previously been proposed for other Pd catalysts possessing pincer ligands, rather than via the 0 and +2 states [104,105]. However, it should be noted that it is now generally accepted that cross-couplings catalysed by cyclometallated Pd(II) complexes proceed via a Pd(II) to Pd(0) pathway and that Pd(0) species are the active catalysts [57].



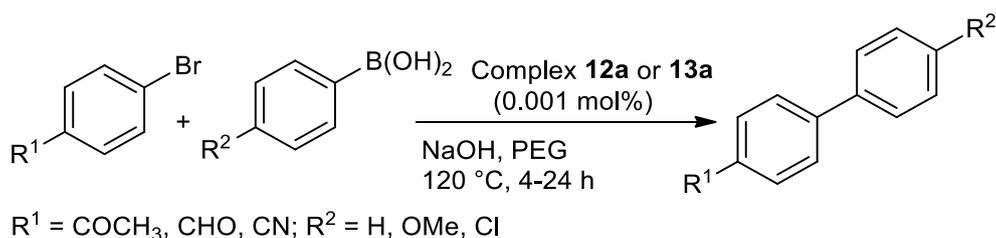
**Scheme 13.** Suzuki reaction of aryl halides with phenylboronic acid catalysed by complex **9**.

In 2012 the group of Bhattacharya reported new thiosemicarbazone complexes (**10**, **11**) of palladium with 1-nitroso-2-naphtholate or quinolin-8-olate supporting ligands (Figure 2) [106]. The thiosemicarbazone ligands were derivatives of benzaldehyde with a range of para-substituents in order to investigate their effect on catalytic activity. The complexes contain two 5-membered rings and only the configuration where the two nitrogens are trans to each other was observed. Catalysis of the Suzuki–Miyaura reaction by complexes **10** and **11** was studied, with optimisation of certain parameters being carried out with phenylboronic acid and *p*-bromoacetophenone as substrates. Using catalyst loadings of 0.001 mol%, 100% conversions were obtained after 24 h in PEG at 120 °C using either NaOH or Cs<sub>2</sub>CO<sub>3</sub> as base (Scheme 14). Under these conditions, TONs of up to 100,000 and TOFs of up to 16,667 h<sup>-1</sup> were recorded. Reduction of the loading to 0.0001 mol% gave slightly lower conversions as did replacement of *p*-bromoacetophenone with the less reactive *p*-bromobenzaldehyde or *p*-bromobenzonitrile. Other halo-derivatives were also examined and, as expected, *p*-iodoacetophenone also gave 100% conversion while *p*-chloroacetophenone required a higher loading of 0.1 mol% to achieve a similar result. Interestingly, low but significant yields, 10–12%,

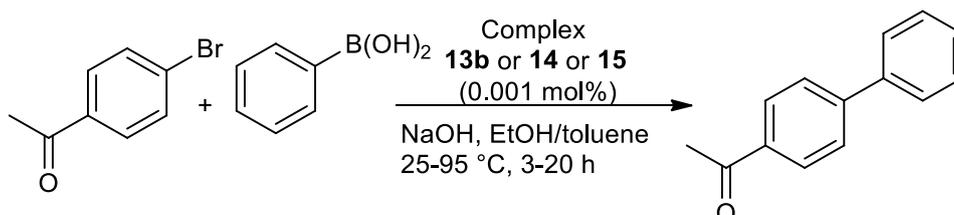
of the product of coupling *p*-fluoroacetophenone with phenylboronic acid were observed with 1 mol% catalyst loading. Although no specific studies of the likely mechanism were described, the authors favoured a process involving initial formation of a zerovalent Pd species, in which the protonated thiosemicarbazone and *N,O*-donor ligands remain coordinated, followed by oxidative addition of the aryl halide. If indeed the active species is as proposed, it could be of interest to determine if it remains active for reuse in repeated cycles. In an attempt to produce analogous complexes with 2-picolinic acid as the supporting ligand, Dutta and Bhattacharya, instead of the expected mono-ligand complexes, obtained the bis-ligand complexes **12** with a rare *cis*-configuration and also a second product which was postulated to be a polymeric bridged complex containing a tridentate cyclometallated ligand (Figure 2) [107]. This was confirmed by cleavage of the bridges by triphenylphosphine to give the mononuclear complexes of the type **13a** whose structures were also confirmed by X-ray crystallography. The two sets of complexes were examined for their potential as catalysts for the Suzuki–Miyaura reaction for a range of aryl halides and substituted phenylboronic acids (Scheme 15). Very good conversions were observed for most of the reactions with aryl iodides and bromides under relatively mild conditions (PEG as solvent, 120 °C, NaOH as base, 1–8 h) and catalyst loadings of 0.001 mol%, while aryl chlorides required higher catalyst loadings of 0.1 mol% to achieve comparable results. The *p*-methoxyphenyl and *p*-chlorophenylboronic acids reacted more sluggishly than phenylboronic acid itself. Of the two sets of complexes, the mono-ligand complexes gave somewhat superior results and this was attributed to the presence of the triphenylphosphine supporting ligand. For both sets of complexes, no additional ligand was needed and the authors argue that this implies that the ligands in the pre-catalyst do not dissociate and that they stabilize the intermediate Pd(0) species. The same research group has also reported further examples of the mono-ligand cyclometallated complex with PPh<sub>3</sub> supporting ligand (complexes **13b**, **14**, **15**). These were prepared by a slightly different route and, together with a non-cyclometallated complex containing a bidentate thiosemicarbazone ligand as well as PPh<sub>3</sub>, were examined for their activity in the coupling of *p*-haloacetophenones with phenylboronic acid (Scheme 16) [108]. Results similar to those given above were obtained, the cyclometallated complexes giving the better results. Notably, coupling of the fluoro-derivative could also be achieved with these catalysts. Analogous cyclometallated palladium complexes **16** based on 3,4-dichloroacetophenone thiosemicarbazone have also been reported by Yan et al. [109]. These complexes were screened for their activity in the Suzuki–Miyaura reaction and the most promising of the four, a dinuclear complex with a 1,1'-bis(diphenylphosphino)ferrocene bridging supporting ligand, was used for further study. Reactions were carried out for 24–48 h in air or argon, using DMF as a solvent, K<sub>3</sub>PO<sub>4</sub> as base and a temperature of 130 °C, using a range of aryl bromides and chlorides and various aryl boronic acids (Scheme 17). Substitution on the boronic acid had no major effect except for 2-methoxyphenyl boronic acid, which gave lower yields, possibly because of steric effects. The aryl bromides all gave moderately good to excellent yields while the chlorides, as expected, gave lower conversions except for *p*-nitrochlorobenzene.



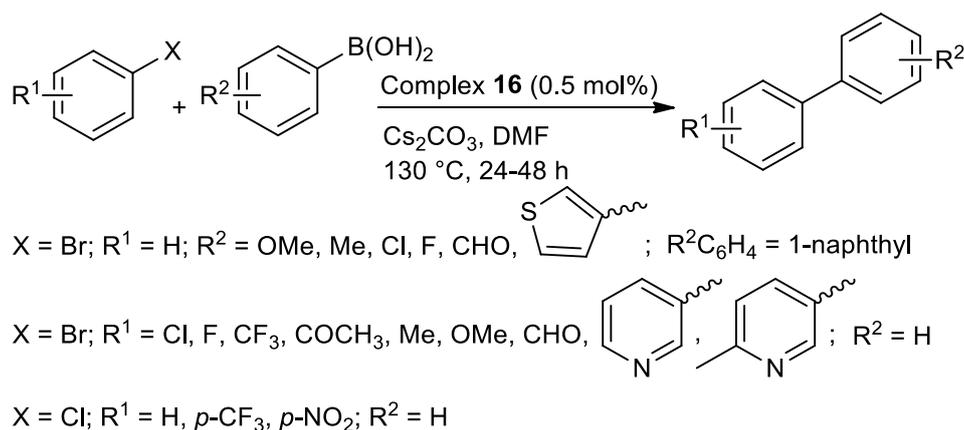
**Scheme 14.** Suzuki reaction of aryl bromides with phenylboronic acid catalysed by complex **10** or **11**.



**Scheme 15.** Suzuki reaction of aryl bromides with substituted phenylboronic acids catalysed by complex **12a** or **13a**.

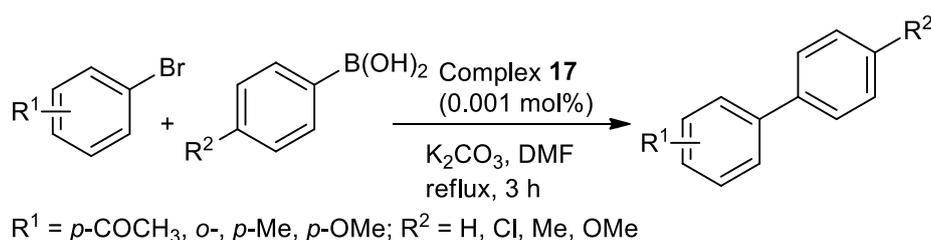


**Scheme 16.** Suzuki reaction of *p*-bromo-acetophenone with phenylboronic acid catalysed by complex **13b**, **14** or **15**.

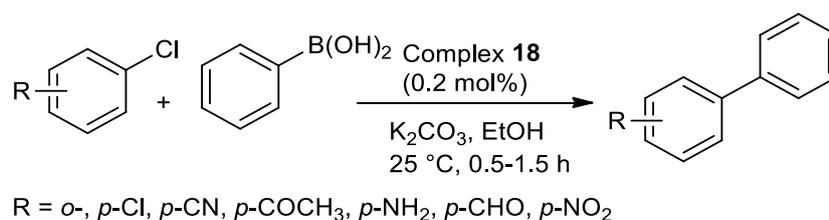


**Scheme 17.** Suzuki reaction of aryl halides with substituted phenylboronic acids catalysed by complex **16**.

The complex **17** was reported by Pandiarajan et al. (Figure 3) [110]. The dianionic ligand binds through S, N, and O donors and the complex is air and moisture stable. It catalysed the Suzuki–Miyaura reaction in refluxing DMF with  $\text{K}_2\text{CO}_3$  base with very good conversions after 3 h for a number of aryl bromides and boronic acids (Scheme 18). Coupling of *p*-iodoacetophenone was also achieved with excellent conversion while with the analogous chloro-derivative moderate yields of product were obtained after 12 h. In the same year, another phosphane supported thiosemicarbazone palladium complex, **18**, was reported by Verma et al. (Figure 3) [111]. The thiosemicarbazone in this case is derived from a sugar aldehyde and the complex from the analogous semicarbazone was also prepared. These ligands were shown by structural studies to bind to the metal in a bidentate manner. The authors were particularly interested in the catalytic activity of these complexes in the coupling of aryl chlorides with boronic acids and found that this could be achieved in good to excellent yields at ambient temperatures using a catalyst loading of 0.2 mol% in EtOH, with  $\text{K}_2\text{CO}_3$  as base and reaction times of just 30–90 min (Scheme 19). At lower catalyst loadings, however, the reaction times were much longer and yields were also reduced. The authors were able to demonstrate that the catalysts retained their activity after five cycles.

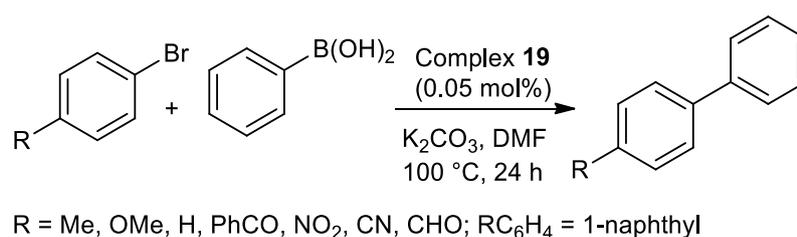


**Scheme 18.** Suzuki reaction of aryl bromides with substituted phenylboronic acids catalysed by complex 17.



**Scheme 19.** Suzuki reaction of aryl chlorides with phenylboronic acid catalysed by complex 18.

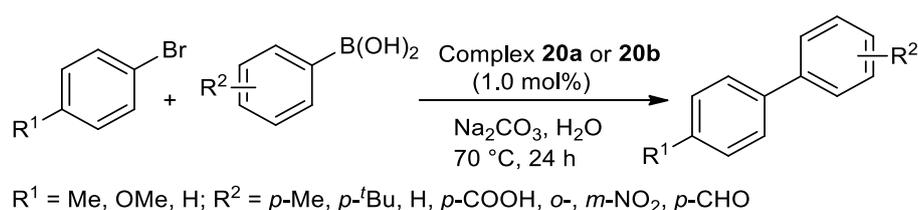
In an attempt to develop a phosphane-free catalyst, the group of Kostas synthesised a binuclear palladium complex **19** with a ligand derived from  $\beta$ -D-glucopyranosyl-thiosemicarbazone (Figure 3) [112]. The complex was characterised spectroscopically and investigated as a potential catalyst for the Suzuki–Miyaura reaction between aryl bromides and phenyl boronic acid (Scheme 20). After 24 h at 100 °C in DMF and with  $\text{K}_2\text{CO}_3$  as base, good to excellent conversions were obtained using a 0.05 mol% catalyst loading. Aryl chlorides, however, gave rather poor conversions. Tests were carried out in order to determine the nature of the catalyst and it was concluded that the active species was heterogeneous and possibly composed of Pd(0) nanoparticles. The complexes used in this study and in the study mentioned in the previous paragraph [111] are of additional interest in that they employ chiral ligands. Although in these studies, possible applications in asymmetric catalysis were not explored, the amenability of thiosemicarbazone ligands to functionalisation with chiral groups could provide a promising avenue for future work.



**Scheme 20.** Suzuki reaction of aryl bromides with phenylboronic acid catalysed by complex 19.

The use of aqueous media for carrying out catalytic reactions has many attractions and in 2017, Matsinha et al. reported the synthesis of two water-soluble palladium complexes **20a** and **20b** containing sulfonated-thiosemicarbazone ligands (Figure 3) [113]. In both complexes, the ligand is tridentate, and the vacant position is occupied by a tertiary phosphine ( $\text{PPh}_3$  in **20a** and 1,3,5-triaza-7-phosphaadamantane in **20b**). The complexes displayed good stability in water. Catalytic coupling of a range of aryl bromides with aryl boronic acids was investigated in water at 70 °C using  $\text{Na}_2\text{CO}_3$  as base and TBAB (tetrabutylammonium bromide) as a phase-transfer mediator (Scheme 21). Satisfactory results were obtained, although it should be noted that rather long reaction times (24 h) and higher catalyst loadings (1 mol%) were employed than were usual for reactions in non-aqueous media. An investigation into the reusability of the catalysts indicated that activity drops off quite

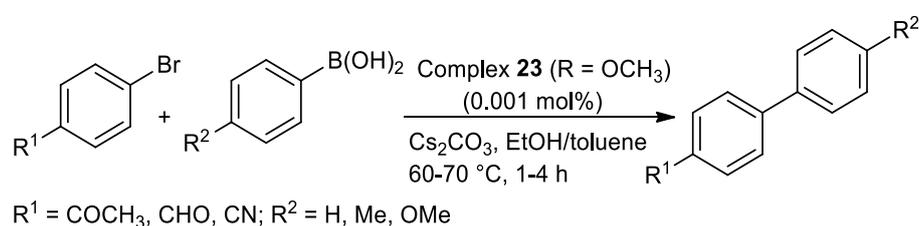
rapidly and that during the fourth cycle activity was low. The authors speculate that this could be due either to leaching of the active catalyst during the extraction step or to partial decomposition of the active species. However, the possibility that the catalyst was the precursor to a heterogeneous system which then degraded quickly was ruled out by the authors, since the mercury drop test for such cases failed to affect the catalytic activity to any significant extent. An aqueous media was also employed by Baruah et al. for the complex **21** (Figure 3) [114]. In this case, the supporting ligand is imidazole and the thiosemicarbazone adopts bidentate coordination as a monoanion. After a number of optimisation runs, the authors examined the coupling of a range of aryl halides and aryl boronic acids using this complex as a precatalyst. Ambient temperatures were employed with  $K_2CO_3$  as the base and a catalyst loading of 1.18 mol%. For most of the aryl bromides, good conversions were achieved after 2–6 h, while the aryl chlorides examined needed an elevated temperature (60 °C) and longer reaction times for comparable results. The complex itself was not soluble in water and was used as a suspension and it was suspected that the actual catalyst could be a Pd(0) species. Support for this came from a mercury drop test, which inhibited catalytic activity. The activity of the catalyst falls off in subsequent cycles but no significant leaching of palladium was observed. The catalyst isolated after a first cycle was therefore examined by TEM, SEM-EDX, and XRD and was determined to consist of Pd(0) nanoparticles which are presumed to be formed by dissociation of the ligands from the initial complex during the reaction. SEM-EDX examination of these nanoparticles indicated that they are possibly stabilized by surface thiosemicarbazone ligands. They were found to have an initial size of 1.5–2.0 nm, but after successive runs they aggregated to larger particles with lower activity.



**Scheme 21.** Aqueous Suzuki reaction of aryl bromides with substituted phenylboronic acids catalysed by complex **20a** or **20b**.

Dharani et al. reported a series of palladium complexes **22** derived from 3-acetyl-7-methoxy-2*H*-chromen-2-one thiosemicarbazones (Figure 3) [115]. Three of the products (**22a–c**) proved to be tetranuclear complexes in which ligands are bonded via S, N, and C, cyclometallation having taken place by activation of the ortho-C–H bond. The palladium atoms are connected via thiolate bridges. The fourth complex, with phenyl substitution on the terminal nitrogen of the thiosemicarbazide, was the mononuclear species **22d**. All of the complexes were screened for activity as catalysts for the Suzuki–Miyaura reaction and one them (**22b**) was chosen for further study. Using a 0.125 mol% loading of the complex, EtOH–H<sub>2</sub>O as solvent,  $K_2CO_3$  as base, and a temperature of 70 °C, good conversions were obtained for the coupling of phenyl boronic acid with a range of aryl halides including chloroquinolines. The results were found to compare well with those obtained for other tetranuclear palladium complexes in aqueous conditions. The catalyst isolated from the reaction could be used up to four more times with only partial loss of activity. In further cycles, however, a 50% loss of activity occurred. A mechanism was proposed involving initial cleavage of the tetranuclear complex into a mononuclear species followed by a Pd(II)–Pd(IV) oxidative addition/elimination sequence. The fall-off in activity in fifth and successive cycles was ascribed to the gradual aggregation of the mononuclear species to form less active nanoparticles, evidence for which was obtained by powder X-ray diffraction studies. More recently, Bakir et al. have reported similar tetranuclear complexes derived from di-thienyl ketone thiosemicarbazone [116]. These were screened for their possible use as precatalysts in the Suzuki–Miyaura reaction but the results were only moderate. This was ascribed by the authors to be at least partly due to the polymeric nature and insolubility of the complex.

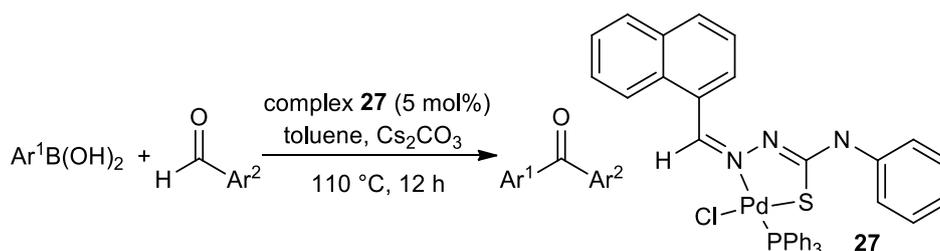
Cationic complexes **23** of the type  $[\text{Pd}(\text{dppe})\text{L}]\text{NO}_3$  ( $\text{dppe} = 1,2\text{-bis}(\text{diphenylphosphino})\text{ethane}$ ), where L is a bidentate thiosemicarbazone ligand derived from a *p*-substituted benzaldehyde were prepared by Thapa et al., and structurally characterised, confirming the formation of *N,S*-chelated 5-membered rings (Figure 4) [117]. The authors hypothesised that, in view of the previously observed improvements in catalytic efficiency due to the presence of phosphine supporting ligands, the use of a diphosphine could potentially enhance this even further. Indeed, compared with other analogous complexes prepared by these workers [95], superior results were seen. Good conversions with high TONs (up to 980,000) and TOFs (up to  $326,667\text{ h}^{-1}$ ) were observed for a number of aryl iodides and bromides at  $95\text{ }^\circ\text{C}$  in EtOH-toluene with  $\text{Cs}_2\text{CO}_3$  as base and catalyst loadings of 0.001–0.0001 mol% (Scheme 22). Chlorides also engaged quite readily in the coupling reaction with somewhat higher catalyst loadings and slightly modified conditions, while aryl fluorides could also be coupled with the unsubstituted phenyl boronic acid at  $130\text{ }^\circ\text{C}$  in PEG using  $\text{NaO}^t\text{Bu}$  as base and with a 1 mol% catalyst loading.



**Scheme 22.** Suzuki reaction of aryl bromides with substituted phenylboronic acids catalysed by complex **23**.

Catalysis of the Suzuki–Miyaura reaction by nickel complexes has attracted attention in recent years due to the greater accessibility of nickel and also its greater activity in certain cases. Thiosemicarbazone complexes of nickel, however, have been much less investigated than their palladium counterparts. In 2011, Datta et al. reported the synthesis of mono- and dinuclear nickel complexes **24** and **25**, respectively, derived from salicylaldehyde, 2-hydroxyacetophenone and 2-hydroxynaphthaldehyde thiosemicarbazones with bipyridine or terpyridine supporting ligands (Figure 4) [118]. The tridentate ligands are bonded via N, S, and O donors and the dinuclear complexes are bridged via thiolate and phenolate groups. The complexes were examined for their activity in the Suzuki–Miyaura reaction for some aryl bromides and iodides with phenyl boronic acid. Relatively good activity was observed although it was much less than that shown by similar palladium complexes. Similar *O,N,S*-bonded nickel complexes **26** derived from 9,10-phenanthrenequinone thiosemicarbazone, 9,10-phenanthrenequinone *N*-methylthiosemicarbazone and 9,10-phenanthrenequinone *N*-phenylthiosemicarbazone have also been reported by Anitha et al., but these complexes gave only rather moderate results for Suzuki–Miyaura couplings [119].

Although it is not a normal Suzuki–Miyaura reaction, we may also mention here the application of the palladium thiosemicarbazonato complex **27** as a catalyst for the synthesis of diaryl ketones via the C–C coupling reaction between aryl aldehydes and aryl boronic acids reported by Prabhu and Ramesh (Scheme 23) [120]. Optimal conditions were found to be  $110\text{ }^\circ\text{C}$  in toluene in the presence of  $\text{Cs}_2\text{O}_3$  and using 5 mol% of the complex. The scope of the reaction was demonstrated by the synthesis of diaryl ketones from the reaction of a wide variety of aromatic and heteroaromatic aldehydes with phenyl boronic acid as well as from the reaction of a selection of aryl boronic acids with benzaldehyde. Satisfactory to excellent isolated yields were obtained.



**Scheme 23.** Synthesis of diaryl ketones by carbon–carbon coupling reaction between aryl aldehydes and aryl boronic acids.

Table 2 summarises representative conditions and yields for Suzuki–Miyaura reactions catalysed by thiosemicarbazone complexes.

**Table 2.** Suzuki–Miyaura reactions catalysed by thiosemicarbazone complexes: representative conditions and yields <sup>1</sup>.

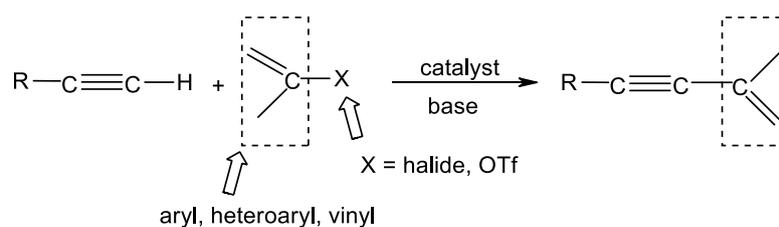
Metal	T (°C)	Solvent	Time (h)	Ligand <sup>2</sup>	Base	Catalyst (mol%)	Yield (%)	Ref.
Pd	100	DMF/H <sub>2</sub> O	24	O,N,S	Na <sub>2</sub> CO <sub>3</sub>	0.1	40–88	[16]
Pd	100–157	DMF/H <sub>2</sub> O	0.25–1	O,N,S	Na <sub>2</sub> CO <sub>3</sub>	0.001–0.1	25–85	[100] <sup>3</sup>
Pd	25–95	EtOH/toluene	9–20	N,S	NaOH	0.001	>99	[102]
Pd	140	DMF	24	O,N,S	K <sub>2</sub> CO <sub>3</sub>	2.0	46–78	[103]
Pd	120	PEG	6–24	N,S	NaOH or Cs <sub>2</sub> CO <sub>3</sub>	0.001	100	[106]
Pd	120	PEG	6–24	N,S	NaOH	0.001	65–100	[107]
Pd	120	PEG	4–24	C,N,S	NaOH	0.001	71–100	[107]
Pd	25–95	EtOH/toluene	9–20	N,S	NaOH	0.001	98–100	[108]
Pd	25–95	EtOH/toluene	3–14	C,N,S	NaOH	0.001	100	[108]
Pd	130	DMF	24–48	C,N,S	K <sub>3</sub> PO <sub>4</sub>	0.5	31–99	[109]
Pd	reflux	DMF	3	O,N,S	K <sub>2</sub> CO <sub>3</sub>	0.001	78–99	[110]
Pd	25	EtOH	0.5–1.5	N,S	K <sub>2</sub> CO <sub>3</sub>	0.2	76–98	[111] <sup>4</sup>
Pd	100	DMF	24	N,S	K <sub>2</sub> CO <sub>3</sub>	0.05	60–99	[112]
Pd	70	H <sub>2</sub> O	24	O,N,S	Na <sub>2</sub> CO <sub>3</sub>	1.0	25–98	[113]
Pd	28	H <sub>2</sub> O	2–12	N,S	K <sub>2</sub> CO <sub>3</sub>	1.18	65–90	[114]
Pd	60–70	EtOH/H <sub>2</sub> O	1–4	C,N,S	K <sub>2</sub> CO <sub>3</sub>	0.125	51–99	[115]
Pd	95	EtOH/toluene	6–8	N,S	Cs <sub>2</sub> CO <sub>3</sub>	0.001	79–100	[117]
Ni	140	DMF	24	O,N,S	Cs <sub>2</sub> CO <sub>3</sub>	2.0	40–99	[118]
Ni	90	DMA	7	O,N,S	K <sub>2</sub> CO <sub>3</sub>	1.0	28–64	[119]
Pd	110	toluene	12	N,S	Cs <sub>2</sub> CO <sub>3</sub>	5.0	62–97	[120] <sup>5</sup>

<sup>1</sup> conditions refer to reactions involving aryl bromides and phenyl or aryl boronic acids. <sup>2</sup> ligand donor atoms.

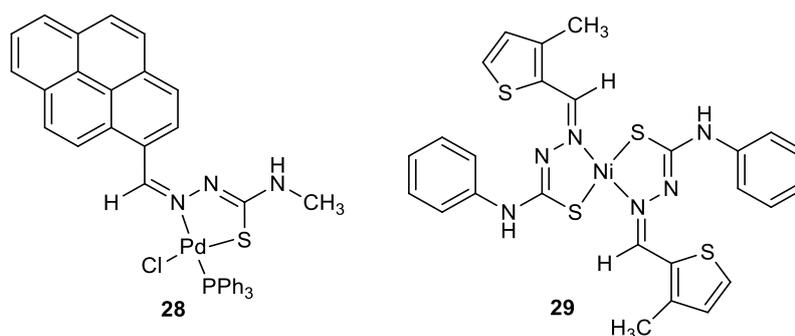
<sup>3</sup> microwave irradiation <sup>4</sup> aryl chlorides were used. <sup>5</sup> Aryl aldehydes used instead of aryl halides.

### 2.3. Sonogashira and Related Reactions

Since the first report by Sonogashira in 1975 [121], the metal complex-catalysed coupling of terminal alkynes with haloorganics has developed into an essential tool for the synthetic organic chemist (Scheme 24) [1,5,9]. Palladium or copper complexes are generally employed to facilitate this reaction and some very efficient systems have been reported for a wide variety of halides. Reports of the use of thiosemicarbazone complexes for this reaction have appeared only relatively recently. Representative metal complexes are shown in Figure 5; see also Figures 1, 3 and 4.



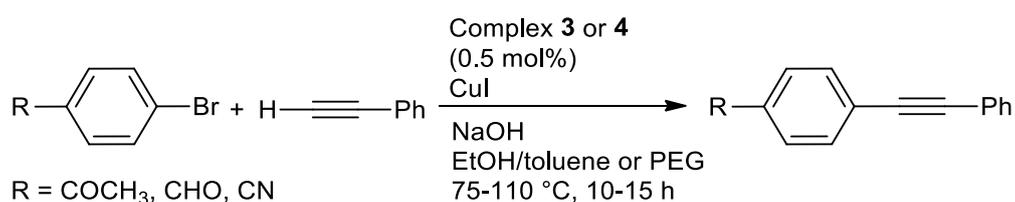
**Scheme 24.** Sonogashira reaction.



**Figure 5.** Representative metal complexes of thiosemicarbazones as catalysts for the Sonogashira reaction.

Reports of the use of thiosemicarbazone complexes for this reaction have appeared only relatively recently. The few studies that have been made concern Pd and Ni complexes and are often subsidiary to studies of other coupling reactions. Thus there have been no significant studies on the nature of the active species in these reactions or of other features which may confer advantages over previously reported complexes.

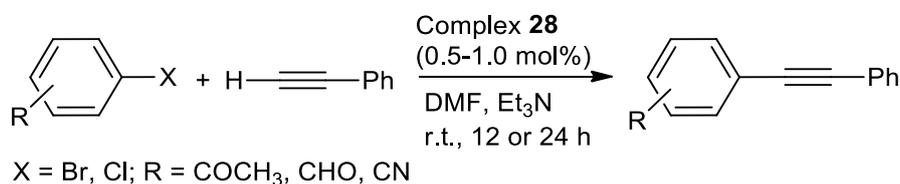
In 2011, Paul et al. in their study described above in connection with the use of thiosemicarbazone complexes of palladium in the Mizoroki–Heck or Suzuki–Miyaura couplings also examined their application to the Sonogashira reaction (see complexes 3 and 4 in Figure 1) [95]. Moderate to good conversions were obtained for the coupling of a limited number of aryl bromides with phenyl acetylene using either toluene-ethanol or PEG as solvent in the presence of Cu(I) and NaOH at 75–110 °C (Scheme 25). Catalyst loadings of 0.5 mol% were employed giving TONs of up to 200 and TOFs of up to 20 h<sup>-1</sup>.



**Scheme 25.** Sonogashira reaction of aryl bromides with phenylacetylene catalysed by complex 3 or 4.

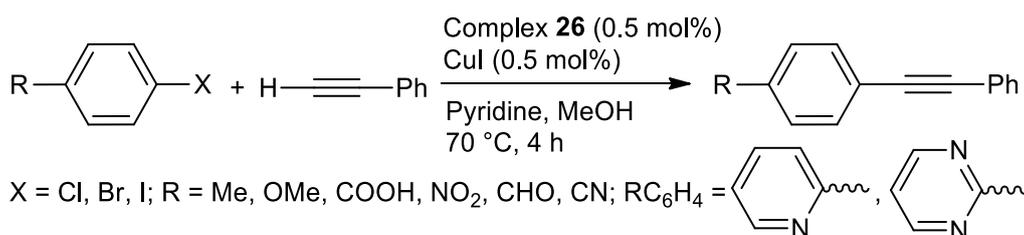
In addition to the Suzuki–Miyaura reaction, Verma et al. also applied their carbohydrate derived thiosemicarbazone Pd complex 18, shown in Figure 3, to the Sonogashira reaction between phenylacetylene and chlorobenzene, *p*-nitrobromobenzene or iodobenzene in triethylamine at 80 °C [111]. Moderate conversions of about 65% were obtained with 0.5 mol% catalyst loadings. In order to avoid the use of copper compounds in the Sonogashira reaction, a number of attempts have been made to develop complexes that are active under copper-free conditions. The first instance of a such a catalyst containing a thiosemicarbazone ligand was reported by Prabhu and Pal who synthesised a pyrenealdehyde thiosemicarbazone palladium complex 28 (Figure 5) containing a Ph<sub>3</sub>P supporting ligand [122]. Single crystal X-ray diffraction indicated bidentate *N,S*-coordination of the ligand. The complex is air stable and was shown to catalyse the Sonogashira reaction between

phenylacetylene and a range of aryl chlorides and bromides at room temperature in DMF/Et<sub>3</sub>N using a 0.5 or 1 mol% catalyst loading (Scheme 26). Moderate to very good conversions were obtained after 12 h (for the bromides) or 24 h (for the chlorides).

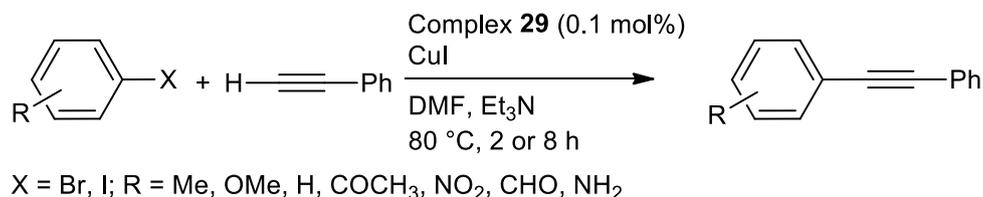


**Scheme 26.** Copper-free Sonogashira reaction of aryl halides with phenylacetylene catalysed by complex 28.

The octahedral nickel complexes **26** (Figure 4) prepared by Anitha et al. derived from 9,10-phenanthrenequinone thiosemicarbazone, 9,10-phenanthrenequinone *N*-methylthiosemi carbazone and 9,10-phenanthrenequinone *N*-phenylthiosemicarbazone described briefly above in connection with the Suzuki–Miyaura reaction were also examined for their activity in the Sonogashira reaction of phenyl acetylene with aryl halides [119]. Using catalyst loadings of 0.5 mol%, they were found to give good to very good conversions after 4 h in MeOH and in the presence of Cu(I) and pyridine (Scheme 27). Heteroaromatic chlorides also entered into the reaction as did ortho-substituted aromatics, albeit in lower yields. The authors concluded that steric effects in the ligands play a more important role than electronic effects in the catalytic activity of the complexes. Very good conversions were observed by Prabhu and Ramesh with a square-planar nickel complex NiL<sub>2</sub> (**29**) (Figure 5) where ligand L is derived from the reaction of 4-phenyl-3-thiosemicarbazide with 3-methyl-thiophene-2-carboxaldehyde [123]. The structure was confirmed by X-ray diffraction studies. Very promising results were obtained in the reaction of a range of aryl bromides and iodides with phenyl acetylene in the presence of the nickel complex together with Cu(I) in Et<sub>3</sub>N at 80 °C (Scheme 28). Very good yields of the coupled products (79–99%) with good TONs were obtained after 2 h in the case of iodides (TONs of up to 1980 and TOFs of up to 990 h<sup>-1</sup>) or 8 h in the case of the bromides (TONs of up to 990 and TOFs of up to 124 h<sup>-1</sup>). Aryl halides with ortho-substitution also coupled readily.



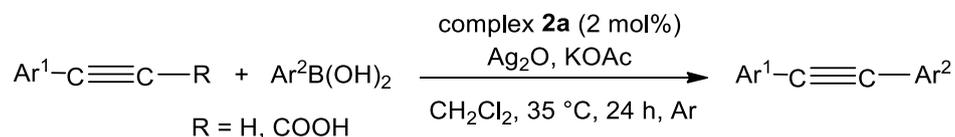
**Scheme 27.** Sonogashira reaction of aryl halides with phenylacetylene catalysed by Ni complexes **26**.



**Scheme 28.** Sonogashira reaction of aryl halides with phenylacetylene catalysed by Ni complex **29**.

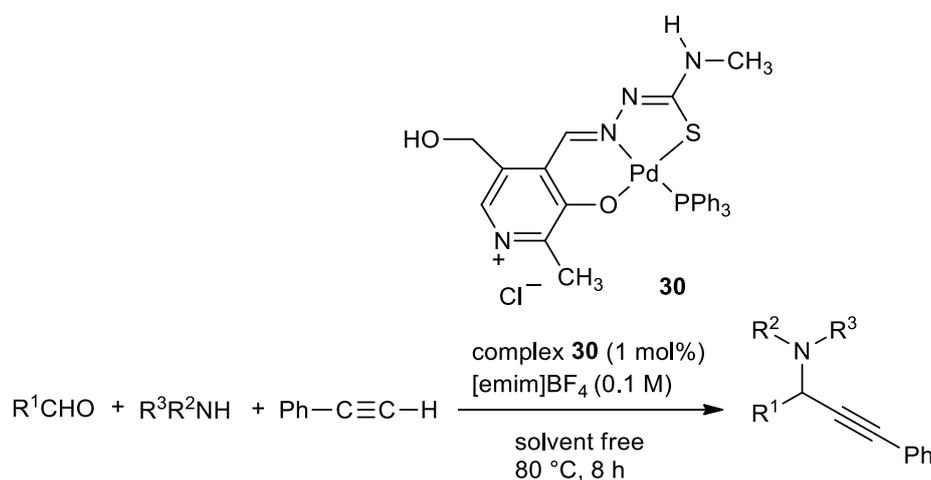
It is also appropriate to mention here a reaction related to the Sonogashira reaction, which involves coupling between aryl boronic acids with alkynes or alkynyl carboxylic acids (Scheme 29) reported by Lu et al. [124] using tridentate salicylaldiminato-thiosemicarbazone palladium catalysts **2** (Figure 1), which had previously been shown to catalyze the Mizoroki–Heck coupling [94]. The best yield was

obtained by complex **2a**. Using mild conditions ( $\text{CH}_2\text{Cl}_2$ , KOAc,  $\text{Ag}_2\text{O}$ , 24 h, under argon) and a 2 mol% catalyst loading very good yields of coupled products were obtained except where steric hindrance was present (in the case of 1-naphthyl boronic acid and ortho-substituted aryl boronic acids) as well as for 2-pyridyl boronic acid. When carboxylic acids are used, decarboxylation occurs before coupling.



**Scheme 29.** Alkynylation coupling reaction between alkynes or alkynyl carboxylic acids and arylboronic acids.

Additionally related to coupling reactions involving alkynes is the A3 coupling reaction, which is particularly useful in asymmetric synthesis [125]. This is a three-component reaction with an aldehyde, an amine and a terminal alkyne as the substrates. The reaction has been shown to be catalysed by a number of transition metal systems, including the thiosemicarbazone complex  $[\text{Pd}(\text{PPh}_3)\text{L}]$  **30** where L is a dianionic tridentate O,N,S-coordinating ligand derived from pyridoxal thiosemicarbazone or pyridoxal N-methylthiosemicarbazone as reported by Manikandan et al. (Scheme 30) [126]. In this case an ionic liquid,  $[\text{emim}]\text{BF}_4$  (emim = 1-ethyl-3-methylimidazolium) was used as the reaction medium. After optimisation runs, a number of substrates were subjected to the reaction at  $80^\circ\text{C}$ , 8 h reaction time with a 1 mol% catalyst loading. Phenyl acetylene was used as the terminal alkyne together with a range of aromatic or heteroaromatic aldehydes, formaldehyde or cyclohexyl carboxaldehyde and piperidine, morpholine, pyrrolidine or diethylamine as the amine component. In all cases, very good yields of the coupled products were obtained. Importantly, the catalyst could be recovered readily and retained its activity for at least five further cycles.



**Scheme 30.** A3 coupling reaction for the synthesis of propargylamines.

Sonogashira-type reactions catalysed by thiosemicarbazone complexes are summarised in Table 3.

**Table 3.** Sonogashira reactions catalysed by thiosemicarbazone complexes: representative conditions and yields <sup>1</sup>.

Metal	T (°C)	Solvent	Time (h)	Ligand <sup>2</sup>	Base	Catalyst (mol%)	Yield (%)	Ref.
Pd	75–110	EtOH/toluene or PEG	10–15	N,S	NaOH	0.5	68–99	[95]
Pd	80	Et <sub>3</sub> N	8	N,S	Et <sub>3</sub> N	0.5	65	[111]
Pd	rt	DMF	12	N,S	Et <sub>3</sub> N	0.5	67–99	[122]
Ni	70	MeOH	4	O,N,S	pyridine	0.5	55–85	[119]
Ni	80	DMF	8	N,S	Et <sub>3</sub> N	0.1	79–99	[123]
Pd	35	CH <sub>2</sub> Cl <sub>2</sub>	24	O,N,S	KOAc	2.0	30–99	[124] <sup>3</sup>

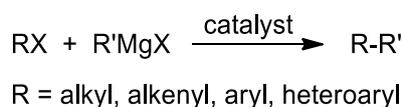
<sup>1</sup> conditions refer to reactions involving aryl bromides and phenylacetylene. <sup>2</sup> ligand donor atoms. <sup>3</sup> reaction between arylboronic acids and phenylacetylene.

#### 2.4. Kumada–Tamao–Corriu Reaction

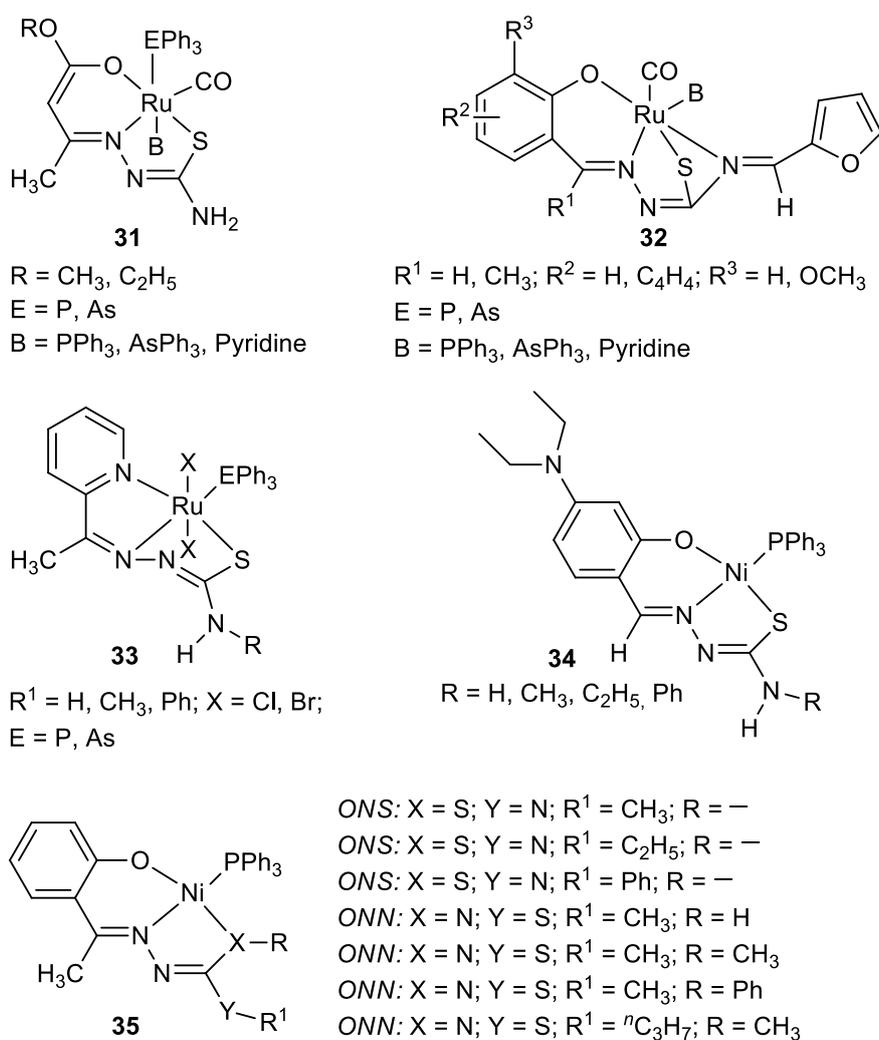
The use of organometallic reagents to form carbon–carbon bonds is a standard procedure in organic synthesis but there are still many instances where the simple stoichiometric reaction is unsuccessful for one or more reasons. A number of transition metal catalysts have been developed for specific cases such as the Negishi coupling of organozinc reagents with aryl or alkenyl halides [127], or the related Kumada–Tamao–Corriu reaction involving the analogous coupling with Grignard reagents (Scheme 31) [8]. There are a number examples of the latter involving thiosemicarbazone complexes although the majority of the reports describe only one instance of a coupling of an aryl bromide and aryl magnesium bromide and thus do not permit a good assessment of wider applicability (Figure 6). Thus, there are accounts of ruthenium complexes derived from thiosemicarbazones. The mixed ligand complexes of Ru(II) **31**, [RuCO(EPh<sub>3</sub>)<sub>2</sub>L] and [RuCO(PPh<sub>3</sub>)(py)L] (where E = P or As and L is a dibasic tridentate ligand derived from the condensation of ethylacetoacetate or methylacetoacetate and thiosemicarbazide) catalysed the coupling of PhMgBr and PhBr as reported by Thilagavathi et al. [64]. Using a 200:1 substrate to catalyst ratio, rather low conversions were reported. Analogous complexes derived from chalcone thiosemicarbazone gave similar results [128]. Somewhat better yields were reported by Raja et al. for the complexes **32** [RuCO(EPh<sub>3</sub>)L] and [RuCO(py)L], where L is a tetracoordinated dianionic ligand derived from the reaction of 2-hydroxyaryl aldehyde, thiosemicarbazide and furfuraldehyde [62]. The coupling of PhMgBr with *p*-bromoanisole catalysed by a Ru(III) complexes **33** containing a monoanionic 2-acetylpyridine thiosemicarbazone ligand has also been reported by Manikandan et al. [81]. A 300:1 substrate to catalyst ratio was used and conversions of 28–48% were obtained.

Priyarega et al. reported nickel thiosemicarbazone complexes **34** with Ph<sub>3</sub>P supporting ligand that catalyse the formation of biphenyl in good yield [129]. From the experimental data, it is stated that a large amount (0.05 mol) of complex is used for 0.01 mol of PhBr but presumably this is a typographical error with the correct amount of complex to be probably 0.05 mmol. Güveli et al. have prepared a series of thiosemicarbazone complexes **35** derived from *o*-hydroxyacetophenone in which either *O,N,S*- or *O,N,N*-tridentate coordination is observed [130]. In addition to structural and computational studies, the authors also examined the coupling of PhMgBr with PhBr in the presence of these compounds. The *ONN*-complexes gave higher yields compared to the *ONS*-complexes and this was ascribed to the larger size of the S atom and also to the higher charge on the metal. A range of aryl halides were employed by Anitha et al. in their study of Ni(II) complexes containing *O,N,S*-tricoordinating thiosemicarbazone ligands, which have also been described above as catalysts for the Suzuki–Miyaura and Sonogashira reactions (see complexes **26** in Figure 4) [119]. Moderate to excellent yields of biaryls were obtained under mild conditions (Et<sub>2</sub>O, 4 h) and with catalyst loadings of 0.2 mol% (Scheme 32). TONs of up to 93 and TOFs of up to 2 h<sup>−1</sup> were recorded. Reactions for aryl halides with electron withdrawing substituents were found to give slightly higher yields than those with electron-donating

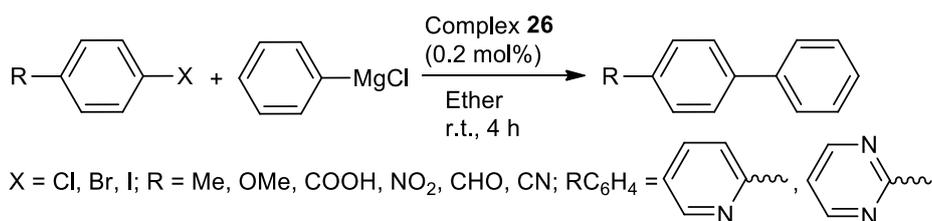
substituents, while ortho-substituted aryls gave lower yields. Overall, their catalytic efficiency was found to compare favorably with previously reported catalysts.



**Scheme 31.** Kumada–Tamao–Corriu reaction.



**Figure 6.** Representative metal complexes of thiosemicarbazones as catalysts for the Kumada–Tamao–Corriu reaction.

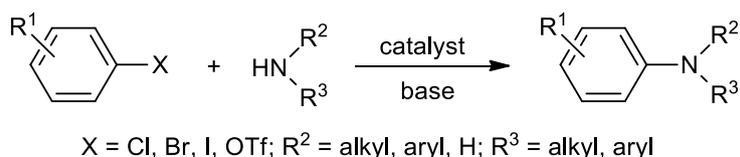


**Scheme 32.** Kumada–Tamao–Corriu reaction of aryl halides with phenylmagnesium chloride catalysed by Ni complexes **26**.

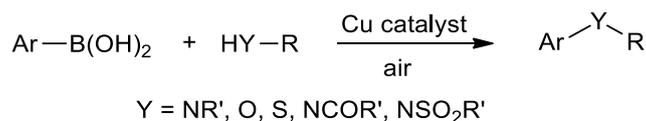
### 3. Carbon–Heteroatom Coupling Reactions

Although the majority of the work on metal complex catalysed coupling reactions concerns the formation of carbon–carbon bonds, carbon–heteroatom coupling reactions have also been widely studied. These predominantly concern the formation of carbon–nitrogen bonds for systems where non-catalysed coupling is not possible or very difficult. Reactions in this category include the Pd-catalysed arylation of amines (the Buchwald–Hartwig coupling shown in Scheme 33) [131,132], the Pd-catalysed formation of C–N, C–O or C–S bonds using aryl boronic acids and suitable heteroatom derivatives (the Chan–Lam coupling shown in Scheme 34) [133,134], and also the metal-catalysed Ullmann reaction (Scheme 35) [135,136]. Representative metal complexes catalyzed carbon–heteroatom coupling reactions are shown in Figure 7; see also in Figures 2 and 4.

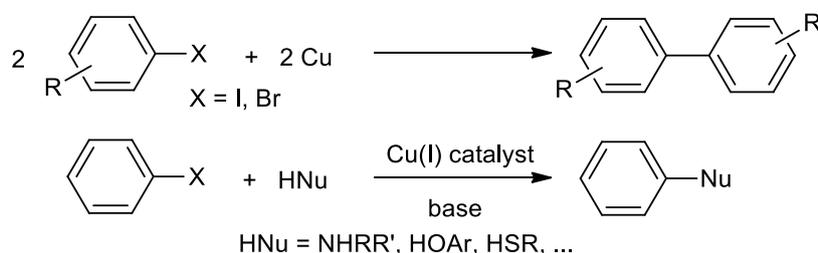
A number of thiosemicarbazone complexes of palladium have been screened as potential catalysts for C–N coupling reactions. Many of these have also been investigated as catalysts for C–C couplings and have therefore been described above in the relevant sections. Thus, the mixed-ligand benzaldehyde thiosemicarbazone Pd-complexes **10**, **11**, **12**, and **13a** (Figure 2) prepared by Dutta et al., described previously [106,107], are also active catalysts for the Buchwald–Hartwig arylation of primary and secondary amines (Scheme 36). The addition of the hindered XPhos ligand (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) was required for good activity and it was presumed that it was necessary to stabilize the active species, the other ligands having been displaced. Although somewhat higher catalyst loadings were found to be necessary for the C–N couplings than were used in the Suzuki–Miyaura reaction, catalytic efficiency was comparable to other palladium complexes under similar conditions. Very good results were also obtained under slightly milder conditions when the same group employed the cyclopalladated complexes **13b**, **14**, and **15** (Figure 2) for the coupling of selected aryl halides with aniline, providing TONs of 10,000 and TOFs of up to 833 h<sup>-1</sup> (Scheme 37) [108]. A much broader range of aryl halides were used by Prabhu and Ramesh in their study of the catalytic activity of the complex **36** (Figure 7), [PdBr(PPh<sub>3</sub>)L], where L is a bidentate chelating monoanionic ligand derived from 1-naphthaldehyde thiosemicarbazone [137]. Good to excellent results were obtained under relatively mild conditions (2-BuOH as solvent, K<sub>2</sub>CO<sub>3</sub> as base, 100 °C, N<sub>2</sub> atmosphere, 24 h) using a 500:1 of substrate to complex molar ratio for the coupling of aromatic and heteroaromatic bromides with cyclic secondary amines (Scheme 38). Dibromides could also be successfully coupled with the same secondary amines under similar conditions. The coupling of aryl chlorides took place using slightly longer reaction times (30 h) and with somewhat lower conversions. It was found that the catalyst could be used twice without any detectable loss of activity but that gradual loss of activity was observed for subsequent cycles. Apart from the aforementioned monophosphine complexes, a recent study reports the synthesis of a cationic Pd thiosemicarbazone complex **23** (R = OCH<sub>3</sub>; see in Figure 4) containing a diphosphine which, apart from catalysing the Suzuki–Miyaura reaction (see above) was also found to be effective in the Buchwald–Hartwig arylation [117]. Aryl bromides and iodides gave good conversions in the reaction with primary or secondary amines in either dioxane at 100 °C or PEG at 150 °C with low catalyst loadings (0.01 mol%) in the presence of NaOBu<sup>t</sup>. Aryl chlorides, however, generally gave poor yields.



**Scheme 33.** Buchwald–Hartwig reaction.



Scheme 34. Chan-Lam coupling.



Scheme 35. Classic Ullmann reaction (top) and Ullmann-type reaction (bottom).

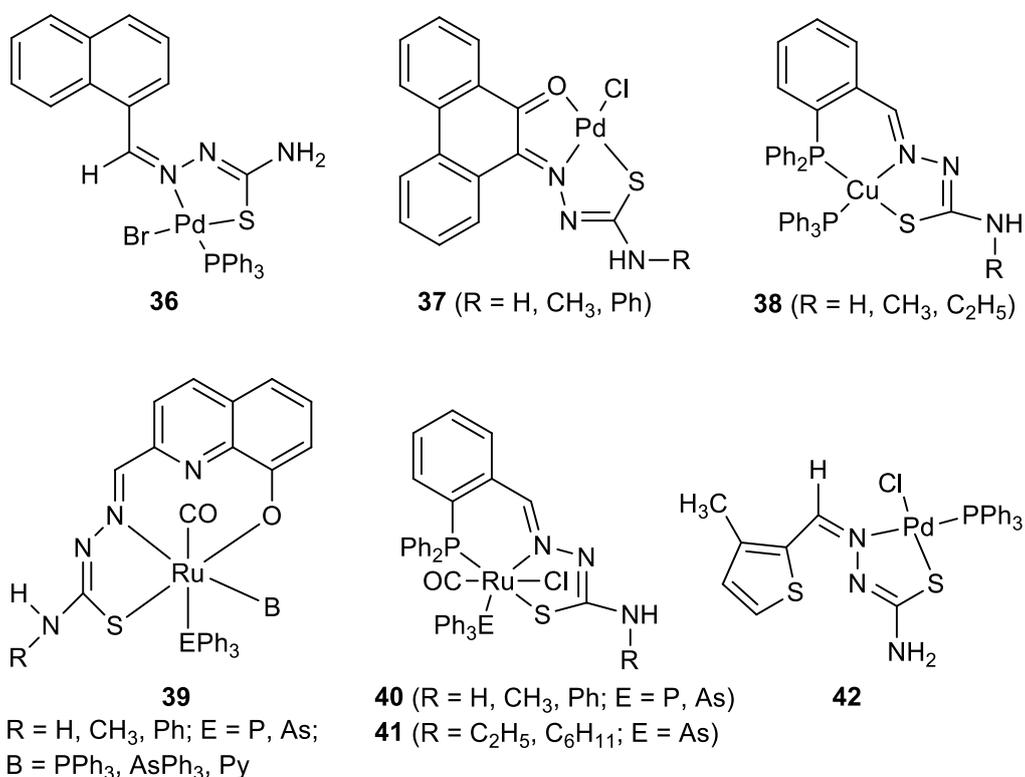
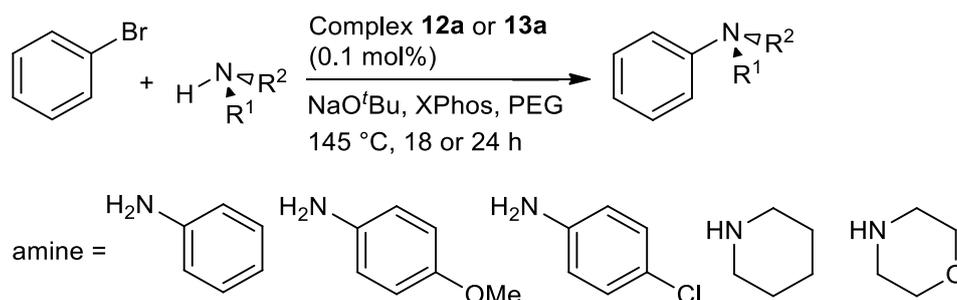
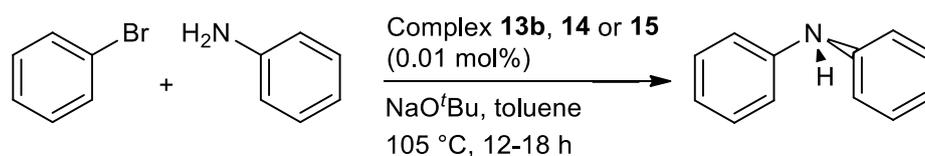


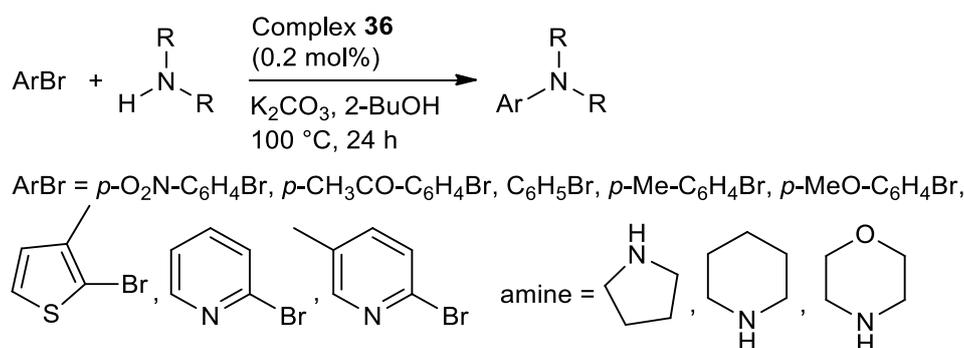
Figure 7. Representative metal complexes of thiosemicarbazones as catalysts for carbon-heteroatom coupling reactions.



Scheme 36. Buchwald-Hartwig arylation of primary and secondary amines catalysed by complexes 12a or 13a.



**Scheme 37.** Buchwald–Hartwig reaction of phenyl bromide with aniline catalysed by complexes **13b**, **14**, or **15**.



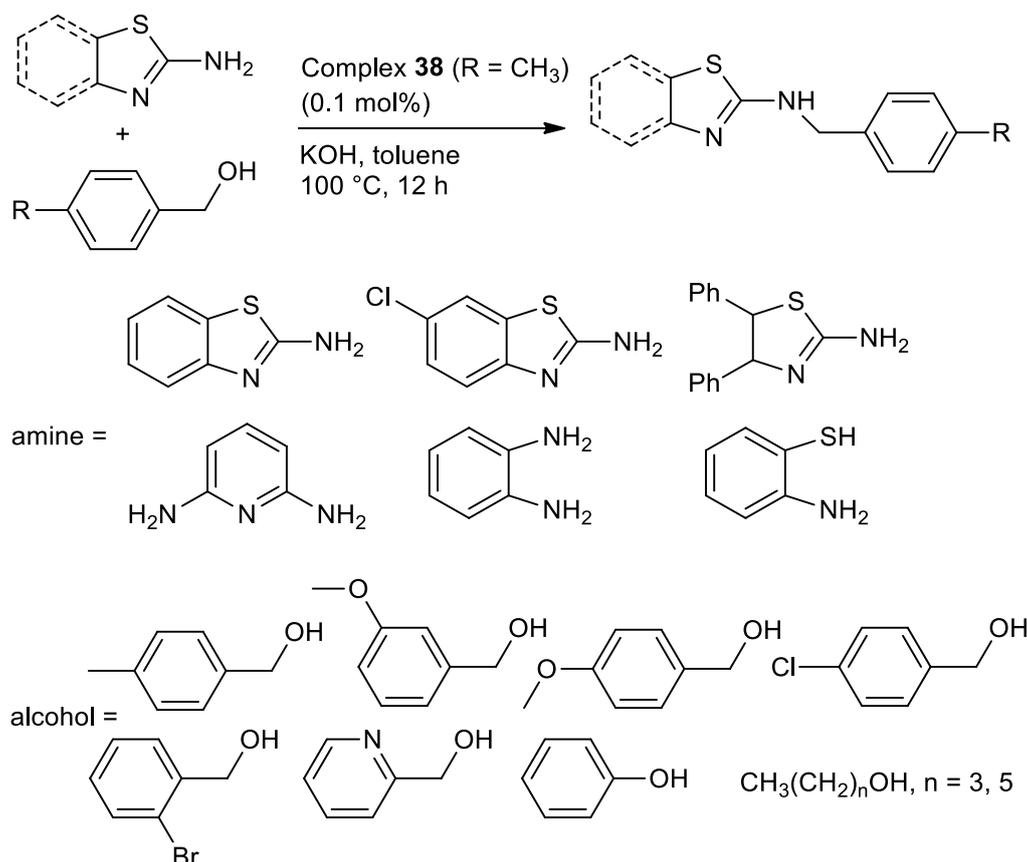
**Scheme 38.** Buchwald–Hartwig reaction of aryl- and heteroaryl bromides with cyclic secondary amines catalysed by complex **36**.

*N*-arylation of heterocycles can be achieved by using a palladium catalyst derived from 9,10-phenanthrenequinone thiosemicarbazones **37** (Figure 7) as well as the corresponding semicarbazone as reported by Anitha et al. [138]. The ligand in these complexes is tridentate monoanionic and the most efficient one in initial screening experiments was that derived from phenanthrenequinone *N*-methylthiosemicarbazone. A range of aromatic and heteroaromatic chlorides, bromides and iodides were employed for coupling with imidazole in DMSO at 110 °C in the presence of KOH and 0.75 mol% of the complex. Moderate to very good yields were obtained, and it was shown that the reaction had the potential to be extended to other related heterocycles. Due to the fact that the best solvent for the reaction was DMSO, the authors favour a Pd(II)/Pd(IV) mechanistic oxidative addition pathway over a Pd(0)/Pd(II) one.

Copper complexes are also known to catalyse C–N coupling reactions. These are often Cu(I) complexes but the first instance of a thiosemicarbazone copper complex catalysed C–N coupling involves the Cu(II) oxidation state as reported by Shan et al. [139]. The use of copper compounds in this oxidation state offers some advantages since they are generally more convenient to handle. The catalytic procedure involved in situ complex formation from CuCl<sub>2</sub> (10 mol%) and excess ligand, 3-methoxy, 4-hydroxybenzaldehyde thiosemicarbazone in the presence of K<sub>2</sub>CO<sub>3</sub> together with the appropriate substrates in DMF at 110 °C. Under these conditions, moderate to good yields of coupled products were obtained from the reaction of imidazole or benzimidazole with aryl bromides or iodides. The use of Cu(I) instead of CuCl<sub>2</sub> gave inferior results under the same conditions and the authors speculate that the reaction proceeds via a Cu(II)/Cu(IV) oxidative-addition pathway which is favoured by the stabilisation of the copper intermediate by the electron-rich ligand and the consequent decrease in the oxidation potential. Another instance of Cu(II) catalysed *N*-arylation was also recently reported by Gogoi et al. [140]. This involves a Chan-Lam coupling of a number of aryl or heteroaryl boronic acids with aniline or with *N*-containing heterocycles. Here again the complex was formed in situ, in this case from Cu(OAc)<sub>2</sub> and 2,5-dimethoxy benzaldehyde-4-phenylthiosemicarbazide; use of the preformed complex gave inferior results. Moderate to very good yields were obtained under mild conditions (room temperature, aqueous DMF as solvent, Et<sub>3</sub>N as base, 10 mol% catalyst loading) which compare very favorably with previously reported results for similar systems.

*N*-alkylation of amines by means of alkyl alcohols can be catalysed by Cu(I) complexes and this has been demonstrated for complexes **38** (Figure 7) containing 2-(2-(diphenylphosphino) benzyldiene)

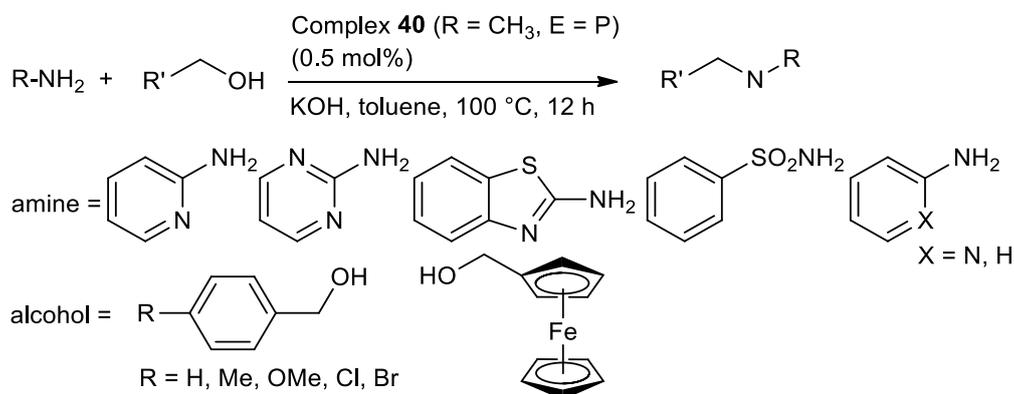
thiosemicarbazone ligands by Ramachandran et al. (Scheme 39) [141]. In these complexes, the ligand is bound to the metal through P, N and S. A range of substituted benzyl alcohols were employed together with a number substituted aminobenzothiazoles as well as 1-amino-diphenylthiazole, benzimidazole and 2,6-diaminopyridine. *n*-Butanol and *n*-hexanol were also successfully used as the alkylating agent. The conditions used involved a catalyst loading of 0.1 mol%, KOH as base, toluene as solvent and heating to 100 °C for 12 h. Good to excellent yields, TONs of up to 990 and TOFs of up to 83 h<sup>-1</sup> were obtained, in particular for complex in which R is the CH<sub>3</sub> group.



**Scheme 39.** N-alkylation of amines with various alcohols catalysed by Cu complex 38 (R = CH<sub>3</sub>).

Several reports have also appeared from the group of Viswanathamurthi and co-workers concerning C–N coupling reactions catalysed by ruthenium complexes [74,142–145]. The initial report briefly describes the benzylation of aniline catalysed by ruthenium hydroxyquinoline–thiosemicarbazone complexes 39 (Figure 7) at 100 °C under nitrogen in the presence of KOBu<sup>t</sup>. Good conversions were obtained using a 1000:1 substrate to catalyst molar ratio [74]. Subsequent reports from this group describe XRD structurally characterised complexes containing tridentate *P,N,S*-chelating thiosemicarbazone derivatives of 2-diphenylphosphino benzaldehyde as ligands in which the effect of terminal *N*-substitution is examined. Thus, the complexes [RuCl(CO)(EPh<sub>3</sub>)L] (40) (Figure 7), where E = P, As and L = 2-(2-(diphenylphosphino)benzylidene)-*N*-R-thiosemicarbazone (R = H, CH<sub>3</sub> or Ph) were prepared and their catalytic activity studied for the *N*-alkylation of heteroaromatic amines by alcohols [142]. Optimisation experiments indicated that the complex containing the 2-(2-(diphenylphosphino)benzylidene)-*N*-methylthiosemicarbazone was found to give the best results, with a 0.5 mol% catalyst loading in the presence of KOH in toluene at 100 °C for 12 h (Scheme 40). Good to very good yields were obtained for the alkylation using *p*-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OH or ferrocenylCH<sub>2</sub>OH and primary amines such as aniline, 2-aminopyridine 2-aminobenzothiazole while dialkylation of 2,6-diaminopyridine

could also be affected. In addition to straightforward alkylations, when 2-nitropyridine was employed as substrate initial reduction to the primary amine and subsequent alkylation could be achieved, while for aminobenzene ortho-substituted with NH<sub>2</sub>, OH or SH, the alkylation reaction with primary alcohols gave good yields of 2-substituted heterocyclic products, viz. benzazoles, benzoxazoles, or benzothiazoles. In a subsequent report, comparable catalytic activity was demonstrated for complexes of the type [RuCl(CO)(AsPh<sub>3</sub>)(L)] (**41**) where L = 2-(2-(diphenylphosphino)benzylidene)-*N*-ethyl-thiosemi carbazone or 2-(2-(diphenylphosphino)benzylidene)-*N*-cyclohexyl-thiosemicarbazone (Figure 7) [143]. The authors propose that the mechanism for the reaction is via a so-called “borrowed hydrogen” pathway, whereby the alcohol is catalytically dehydrogenated to the corresponding aldehyde, which then condenses with the amine to give an intermediate imine, which is subsequently hydrogenated by the catalyst. A further series of ruthenium complexes, bearing the 2-(2-(diphenylphosphino)benzylidene)-*N*-ethyl-thiosemicarbazone ligand, L, were prepared, namely [RuCl(CO)(PPh<sub>3</sub>)L], [RuH(CO)(PPh<sub>3</sub>)<sub>2</sub>L], [RuCl(PPh<sub>3</sub>)<sub>2</sub>L], [RuCl(dmsO)<sub>2</sub>L], and [RuL<sub>2</sub>] [144]. Of these complexes, the last one showed little or no catalytic activity while the first three complexes showed the best results and were studied in more detail. Using conditions comparable with those in the previous studies, and with similar substrates, the complexes were found to give good to excellent conversions. *N*-Alkylation of sulfonamides was also very successful. We may also mention here that the complex [RuL<sub>2</sub>], where L is the monoanionic ligand derived from 2-(2-(diphenylphosphino)benzylidene)-*N*-phenylthiosemicarbazone, has also been screened for its catalytic activity in the *N*-alkylation of primary amines [145]. In this investigation, the complex proved to be inferior to other semicarbazone complexes that were examined and was not subjected to further detailed study.



**Scheme 40.** *N*-alkylation of (hetero)aromatic amine/amides with alcohols catalysed by Ru complex **40** (R = CH<sub>3</sub>, E = P).

Apart from the above C–N coupling reactions, there has also been one report by Suganthi et al. of C–O coupling catalysed by a thiosemicarbazone complex [146]. Thus the coupling of *p*-cresol with a number of aryl halides containing electron-withdrawing or electron-donating groups could be effected, with moderate to very good yields, in DMF at 80 °C after 12 h in an inert atmosphere using a 1 mol% loading of the catalyst [PdCl(PPh<sub>3</sub>)L] (**42**), where L is the bidentate *N,S*-chelating ligand derived from the deprotonation of 3-methyl-thiophene-2-carboxaldehyde thiosemicarbazone (Figure 7).

Published results of the use of thiosemicarbazone complexes as described above for C-heteroatom coupling reactions are summarised in Table 4.

**Table 4.** Carbon–heteroatom coupling reactions catalysed by thiosemicarbazone complexes: representative conditions and yields.

Metal	Substrates	T (°C)	Solvent	Time (h)	Ligand <sup>1</sup>	Base	Catalyst (mol%)	Yield (%)	Ref.
Pd	ArBr + 2 <sup>ary</sup> amine	145	PEG	24	N,S	NaOBU <sup>t</sup>	1.0	50–62	[106]
Pd	ArBr + 1 <sup>ary</sup> /2 <sup>ary</sup> amine	145	PEG	24	N,S	NaOBU <sup>t</sup>	0.1	100	[107]
Pd	ArBr + 1 <sup>ary</sup> /2 <sup>ary</sup> amine	145	PEG	18	C,N,S	NaOBU <sup>t</sup>	0.1	100	[107]
Pd	ArBr + aniline	105	toluene	12–18	C,N,S	NaOBU <sup>t</sup>	0.01	100	[108]
Pd	(het)ArBr + 2 <sup>ary</sup> amine	100	2-BuOH	24	N,S	K <sub>2</sub> CO <sub>3</sub>	0.2	77–99	[137]
Pd	(het)ArBr + N-heterocycle	110	DMSO	10	O,N,S	KOH	0.75	75–90	[138]
Cu	ArBr + N-heterocycle	110	DMF	24	O,N,S	K <sub>2</sub> CO <sub>3</sub>	10.0	42–56	[139]
Cu	(het)ArB(OH) <sub>2</sub> + aniline	r.t.	DMF/H <sub>2</sub> O	14–18	N,S	Et <sub>3</sub> N	10.0	74–95	[140]
Cu	(het)ArB(OH) <sub>2</sub> + N-heterocycle	r.t.	DMF/H <sub>2</sub> O	18–24	N,S	Et <sub>3</sub> N	10.0	70–94	[140]
Cu	RCH <sub>2</sub> OH + 1 <sup>ary</sup> amine	100	toluene	12	P,N,S	KOH	0.1–0.2	89–99	[141]
Ru	RCH <sub>2</sub> OH + aniline	100	none	6	O,N,S	KOBU <sup>t</sup>	1.0	61–86	[74]
Ru	RCH <sub>2</sub> OH + 1 <sup>ary</sup> amine	100	toluene	12–24	P,N,S	KOH	0.5–1.0	45–99	[142]
Ru	RCH <sub>2</sub> OH + 1 <sup>ary</sup> amine	100	toluene	12	P,N,S	KOH	0.5	79–98	[143]
Ru	RCH <sub>2</sub> OH + 1 <sup>ary</sup> amine	100	toluene	12	P,N,S	KOH	0.5	59–98	[144]
Ru	RCH <sub>2</sub> OH + sulfonamide	120	toluene	12	P,N,S	KOH	0.5	21–99	[144]
Pd	ArBr/ArI + <i>p</i> -cresol	80	DMF	12	N,S	K <sub>2</sub> CO <sub>3</sub>	1.0	62–94	[146]

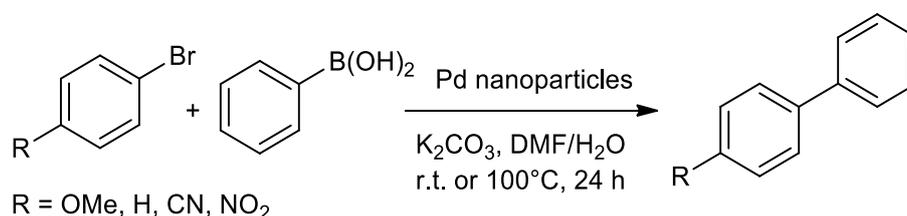
<sup>1</sup> ligand donor atoms.

#### 4. Immobilised and Heterogeneous Catalysts

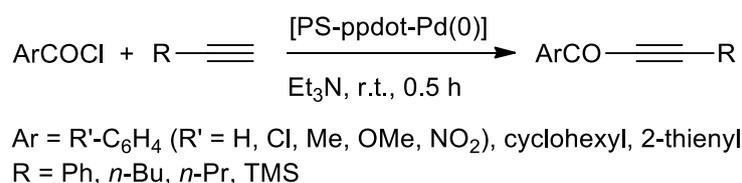
Recovery of catalysts after use is an important factor for consideration for all reactions which involve transition metal complexes. Not only it is important because of the often high cost of the catalysts themselves, but it is also important to minimise contamination of the products. This becomes particularly significant when scale-up of a reaction is being planned. For these reasons, a great deal of effort has been made to develop heterogeneous analogues of homogeneous catalytic reactions in which, the catalyst can be reclaimed by straightforward separation procedures although, attractive as it may seem, this is not always without its disadvantages [147], and special consideration must be given to the stability of the catalysts and to leaching phenomena [87]. In the case of thiosemicarbazone complexes, there have been a number of attempts to develop such systems for coupling reactions. By reduction of K<sub>2</sub>PdCl<sub>4</sub> with hydrazine hydrate in the presence of pyridine-2-carbaldehyde thiosemicarbazone as stabilizer of the nanoparticles, Kostas, Kovala-Demertzi, and co-workers were able to prepare nanoparticles which were characterized by XRD and SEM [148]. They were active catalysts for the Suzuki–Miyaura reaction of phenyl boronic acid with aryl bromides (Scheme 41). Best results were obtained for *p*-bromonitrobenzene and *p*-bromobenzonitrile, which gave excellent conversions in DMF/H<sub>2</sub>O at 100 °C with 0.1% *w/w* catalyst loading and with K<sub>2</sub>CO<sub>3</sub> as base. Higher catalyst loadings (1% *w/w*) were required for good yields from the coupling reactions with bromobenzene and *p*-bromoanisole, as well as for reactions at room temperature, which only gave good yields with *p*-BrC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> and *p*-BrC<sub>6</sub>H<sub>4</sub>CN. These thiosemicarbazone-derivatized nanoparticles were found to be more efficient catalysts than the homogeneous catalyst Pd(PPh<sub>3</sub>)<sub>4</sub> under identical reaction conditions. The catalyst could be recovered but was progressively less active in successive cycles.

Bakherad et al. have reported a polystyrene supported complex of palladium with a 1-phenyl-1,2-propanedione-2-oxime thiosemicarbazone ligand [149]. By attaching the ligand to the polystyrene and then reaction with PdCl<sub>2</sub>(PhCN)<sub>2</sub> followed by reduction with hydrazine hydrate, a Pd(0) species was obtained which was evaluated for its catalytic activity in the acylation of terminal alkynes. Under optimized solvent-free conditions, namely using 1 mol% catalyst with Et<sub>3</sub>N as base, excellent conversions (97–99%) were obtained after 30 min in air at room temperature for a range of aromatic acyl chlorides as well as cyclohexyl carboxylic acid chloride with phenylacetylene, pent-1-yne, hex-1-yne,

and  $\text{Me}_3\text{SiC}\equiv\text{CH}$  (Scheme 42). The catalyst could be recovered by centrifugation and was reused several times with only a slight decrease in activity.



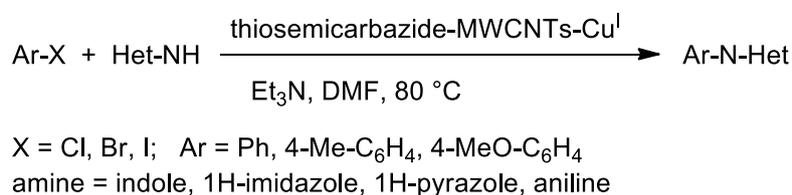
**Scheme 41.** Suzuki reaction of aryl bromides with phenylboronic acid catalysed by thiosemicarbazone-derivatised Pd nanoparticles.



**Scheme 42.** Copper- and solvent-free Sonogashira reaction of acid chlorides with terminal alkynes catalysed by 1-phenyl-1,2-propanedione-2-oxime thiosemicarbazone-functionalized polystyrene resin-supported Pd(0) complex [PS-pdot-Pd(0)].

Suzuki–Miyaura coupling of various aryl halides with alkenyl boronic acid has been achieved using a Pd(II) thiosemicarbazone complex tethered to a silica support [150]. Aryl halides were coupled with *trans*-2-phenylvinyl boronic acid in DMF/H<sub>2</sub>O in the presence of K<sub>2</sub>CO<sub>3</sub> and catalyst (25 mg per mmol of ArX), under microwave irradiation at 110 °C for 25 min. The reaction was selective for the formation of *E*-stilbenes and the catalyst was readily recovered by filtration. The catalyst could be used for at least six consecutive trials without loss of activity. Absence of palladium in the liquid phase after filtration suggested that no leaching of the catalyst had occurred during the reaction.

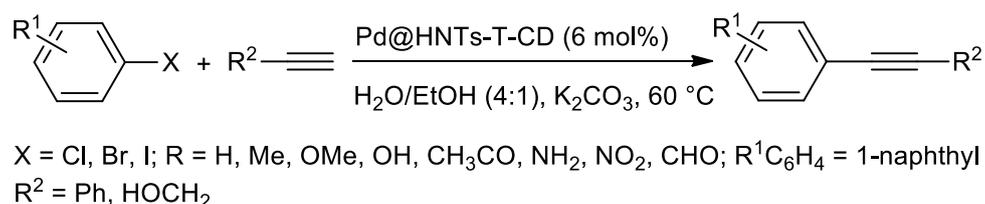
Veisi et al. have used multi-walled carbon nanotubes to which thiosemicarbazide has been grafted to form supported Cu(I) complexes that are able to catalyse the Ullmann coupling of indole, amines or imidazoles with aryl halides [151]. The coupling reactions were optimally carried out in DMF/Et<sub>3</sub>N at 80 °C using a substrate:Cu ratio of 50/1 and reaction times ranging from 1–3 h for ArI, 3–6 h for ArBr and 12–24 h for ArCl (Scheme 43). Good to excellent yields (65–98%) were reported. The catalyst could be recovered by centrifugation and, in studies of the coupling of PhI with indole, was found to be reusable five times with marginal loss of activity. The filtrate from the reaction was found to be inactive, indicating that no leaching of active complex from the supported complexes had occurred.



**Scheme 43.** Ullmann coupling of indole, amines, or imidazoles with aryl halides catalysed by thiosemicarbazide-multi-walled carbon nanotubes-Cu<sup>I</sup> nanocatalyst.

Halloysite is a form of natural clay that can be modified by the attachment of a variety of functionalities. Sadjadi has reported the conjugation of tosylated cyclodextrin to thiosemicarbazide functionalized halloysite, which in turn was used to immobilize Pd nanoparticles [152]. This immobilized system was then examined for its activity in the Sonogashira and Mizoroki–Heck reactions. In the former case, a range of aryl halides were coupled with phenylacetylene or propargyl

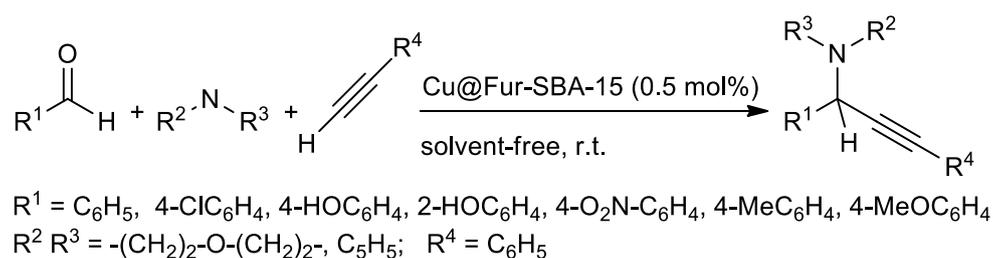
alcohol in water/EtOH at 60 °C, in the presence of K<sub>2</sub>CO<sub>3</sub> using 6 mol% Pd catalyst loading (Scheme 44). The activities followed the usual trend with iodides requiring the shortest reaction times (1.5–3.5 h) and giving the best conversions (83–95%) and chlorides requiring the longest reaction times (*ca.* 5 h) and giving moderate conversions (*ca.* 50%). In an examination of the recyclability of the catalyst, it was recovered and reused thirteen times in a typical reaction. The first four runs showed comparable activity but subsequent runs showed a gradual reduction such that from an original 95% conversion the final run gave 69%. In order to obtain more insight into the nature of the catalyst, the authors examined the recycled material by SEM, TEM and FT-IR. They found that there were no major observable differences after four cycles but thereafter there were indications of morphological changes due to agglomeration although the basic structure of the material was maintained. This agglomeration together with a limited amount of leaching that was also detected was presumed to be the cause of the gradual decrease in activity. The immobilised system was also demonstrated to be an active catalyst for the Mizoroki–Heck coupling of iodobenzene with styrene but a systematic examination of the scope of the reaction was not performed. Halloysite has also been functionalized with (3-chloropropyl) trimethoxysilane and subsequently reacted with thiosemicarbazide and furfural and then with Cu(OAc)<sub>2</sub> to provide an immobilized copper species [153]. Using ultrasonic irradiation, this system was active in the A3 coupling reactions of aldehydes, phenyl acetylene, and amines for synthesis of corresponding propargylamines. Very good conversions were obtained at room temperature within 30 min. The catalyst was readily recovered and after four runs showed little loss in activity. No leaching was detected and the catalyst reclaimed after successive runs and examination by FTIR, TEM, XRD, SEM, and EDX indicated it to be essentially unchanged.



**Scheme 44.** Sonogashira reaction of aryl halides with terminal alkynes catalysed by Pd nanoparticles immobilized on tosylated cyclodextrin-thiosemicarbazide-functionalized-halloysite nanotubes (Pd@HNTs-T-CD).

Finally, there have recently been reports on the use of thiosemicarbazide modified mesoporous silica materials in the immobilization of potential catalysts. Sadjadi et al. have prepared such a system, which consists of furfural thiosemicarbazone tethered through the terminal nitrogen to the mesoporous SBA-15 [154]. Reaction with copper acetate produced a system which, similar to that described above, was an active A3 coupling catalyst at ambient temperatures. Using a catalyst loading of 0.5 mol%, and under solvent-free conditions, very good yields of products, TONs of up to 190, and TOFs of up to 13 min<sup>-1</sup> were obtained within 40 min or less for the coupling of a variety of aryl aldehydes, phenyl acetylene, and morpholine or piperidine (Scheme 45). The reusability of the catalyst was also confirmed for four cycles. A similar copper system derived from the mesoporous material SBA-16 was used for C–S arylation reactions as reported by Ghodsinia et al. [155]. Coupling of aryl halides with elemental sulfur or thiourea provide symmetrical diaryl sulfides in generally very good yields. A catalyst loading of 1.3 mol% was used under solvent-free conditions in the presence of KOH. The yields in the reaction increased according to the aryl halide, ArX used, in the order Cl < Br < I. A study of the reusability of the catalyst indicated only a gradual loss of activity after seven runs. An array of techniques were employed to investigate the catalyst and it was found that the structural integrity of the material was maintained after successive runs. In addition, no significant leaching was detected. It was suggested that the loss of activity that had been observed was due to the partial saturation during the reaction process of the mesochannels containing the catalytic active sites. A very recent paper by Ahmadi et al. describes a magnetic mesoporous silica-Fe<sub>3</sub>O<sub>4</sub> nanocomposite

functionalised with a Pd thiosemicarbazone complex [156]. The material was investigated for its catalytic activity in the Suzuki–Miyaura reaction. Optimal conditions were found to be DMF as solvent and a temperature of 120 °C. The preferred base was K<sub>2</sub>CO<sub>3</sub> (1.2 mmol) and a 0.18 mol% (based on Pd) catalyst loading was used. A variety of aryl halides were examined in the reaction with phenyl boronic acid. With the exception of the hindered ortho-bromotoluene, all the halides used gave very good to excellent yields in short reaction times (60 min or less). After the catalytic run, the catalyst could be extracted using an external magnet. After washing and drying, the catalyst was reused and it was shown that it could be recycled for five times without significant decrease in the catalytic activity. Leaching was negligible and FT-IR and XRD indicated the structure of the catalyst to be unchanged after each cycle.



**Scheme 45.** A3 coupling reaction for the synthesis of propargylamines catalysed by Cu species immobilized on functionalized mesoporous SBA-15 with thiosemicarbazide and furfural (Cu@Fur-SBA-15).

## 5. Future Prospects

It is clear that thiosemicarbazone complexes are promising catalysts for a number of applications. Phosphane-free thiosemicarbazone complexes as well as the analogous complexes with additional *P*-ligands as catalysts for cross-coupling reactions have received much attention during the last fifteen years. The fact that the ligands are relatively readily accessible and that the complexes formed show good stability make them popular subjects for investigation. Up until now, there have been relatively few reports concerning the nature of the species formed during the reactions using these complexes. More research into aspects such as the formation of nanoparticles, aggregation and deaggregation phenomena, leaching effects, the role of the ligands with different metals etc. is needed for the development of systems with general applicability. Undoubtedly, there will be increasing attention paid to areas such as catalyst immobilisation and to complexes that are active under mild, preferably aerobic conditions. The potential for applying these complexes in solvent-free or aqueous systems is also clear. An additional area where developments may be expected is that of asymmetric catalysis. Up until now there appear to be no reports of thiosemicarbazone complexes having been investigated for this purpose but chiral thiosemicarbazone ligands have certainly been prepared and it remains to be seen whether their complexes can show the appropriate selectivity.

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