Catalytic C–X (X = C and Heteroatom) Bond Formations Using Late-Transition Metal Complexes of N/O-Functionalized N-heterocyclic Carbenes

Prasenjit Ghosh

Abstract | Efficient construction of C–X (X = C and heteroatom) bonds in chemo- and regioselective fashion poses a perennial challenge in the world of organic synthesis, particularly in the context of drug discovery. Towards this end, the transition metals provide a viable solution, being adept in catalytic bond formation under amenable conditions. Our efforts in designing late-transition catalysts, based on N/O-functionalized N-heterocyclic carbenes, are discussed for a variety of synthetically useful organic transformations.

1. Introduction

An everyday challenge confronting the world of organic synthesis is in construction of C–X (X = C and heteroatom) bonds, and achieving that catalytically under amenable conditions thus has become very important.[1] Transition metals, in form of their organometallic compounds, construct such bonds with great ease under reasonably accessible laboratory conditions, and consequently their role in chemical catalysis has been in the focus of research in recent times.[2] Compared to the main group, *i.e.*, alkali or alkaline earth metals that are mainly involved in stoichiometric bond formations over and above of the handling issues pertaining to their high air and moisture sensitivities, the transition metals, particularly the ones residing at the later half of each row in the periodic table, often partake catalytic bond formations with reagents, which on many occasions, do so under less rigorous aerobic conditions. Consequently, the late-transition metals often enjoy a distinct advantage over the main group, alkali or the alkaline earth counterparts, and therefore interest in exploring the areas of late-transition metal mediated catalytic bond formation, which is of relevance to organic synthesis, remains sustained particularly to drug discovery.

NHCs or the N-heterocyclic carbenes are stable singlet carbenes of N-based heterocycles.

The N-heterocyclic carbenes (NHCs) have attracted attention lately, primarily for its new found success in homogeneous catalysis, with its role gaining prominence as the preferred "ligand of choice". The N-heterocyclic carbenes are increasingly seen as good "phosphine substitutes" leading to a large number of N-heterocyclic carbene analogs being synthesized for several of the existing phosphine based catalysts. In this context, we became interested in developing the transition metal chemistry of the N-heterocyclic carbenes, and of specific interest to us were the transition metal mediated coupling and addition reactions for their relevance to drug discovery. Thus in the current monograph our efforts in the area is briefly reviewed.

2. Results and Discussions

The C–C bond forming reactions are among the most common in organic synthesis, and of late

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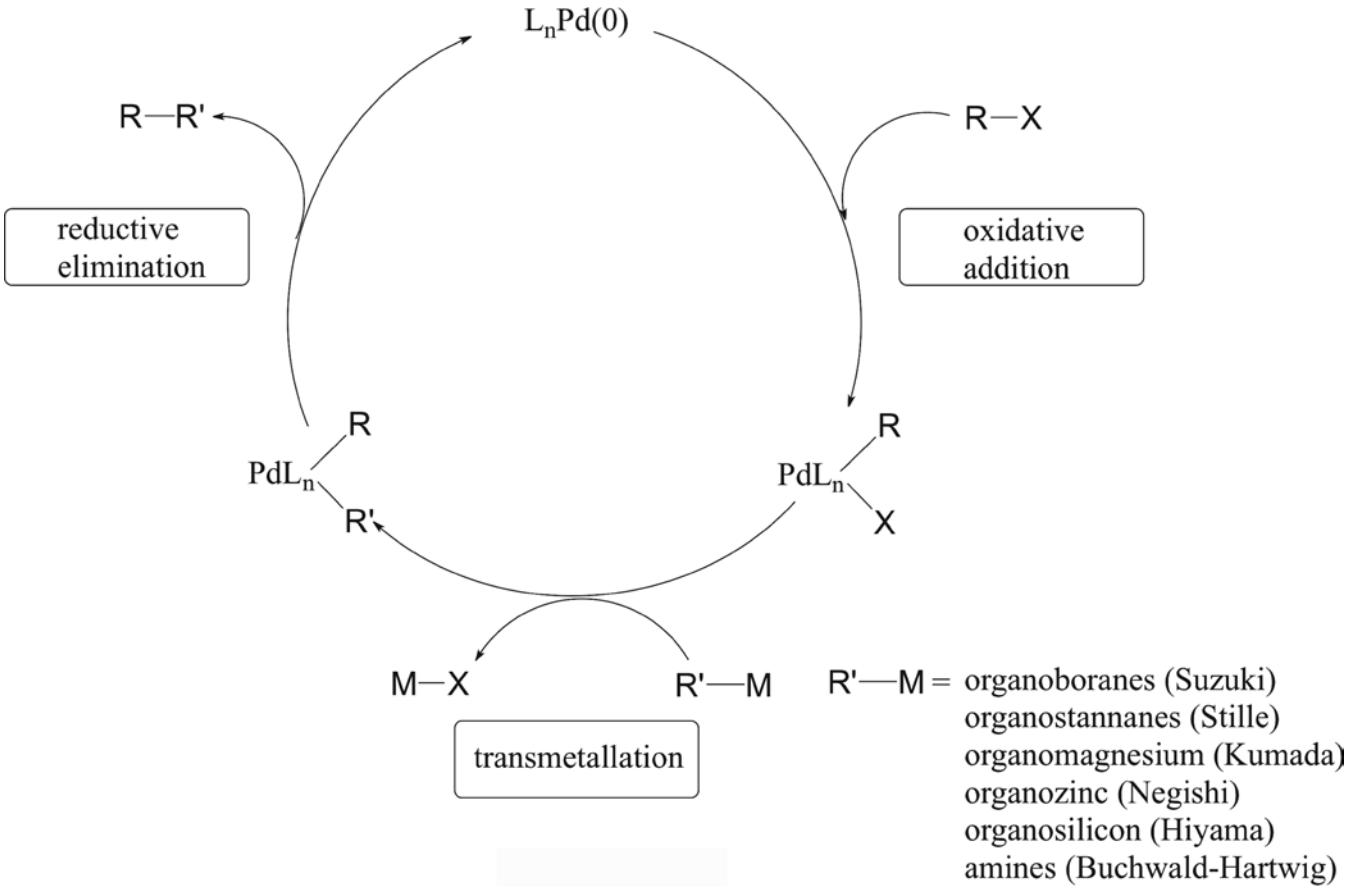
the area has been inundated with various named reactions, many of which are the palladium mediated ones involving a host of organic and organometallic nucleophiles with aryl halides (Equation 1). The rising popularity of these reactions lie in their generally being functional group tolerant and catalytic under amenable conditions. More interestingly so, these seemingly diverse coupling reactions proceed by a common mechanism involving a Pd(II)/(0) shuttle across three fundamental steps of the catalytic cycle, *i.e.*, an oxidative addition, a transmetallation and a reductive elimination, and thus provide with useful scope for a unified approach towards rational catalyst designing for the reaction (Scheme 1). Our efforts in exploring the catalytic potential of late-transition metal complexes of N-heterocyclic carbenes in a few of such reactions namely the Suzuki-Miyaura, Sonogashira and the Hiyama couplings, the base-free Michael addition, the

$$\mathrm{R{-}X} + \mathrm{R'{-}M} \xrightarrow{\mathrm{Pd}} \mathrm{R{-}R'} + \mathrm{M{-}X} \qquad (1)$$

R'—M = organoboranes (Suzuki)
organostannanes (Stille)
organomagnesium (Kumada)
organozinc (Negishi)
organosilicon (Hiyama)
amines (Buchwald-Hartwig)

Scheme 1:



hydroamination of alkynes and activated olefins, and in facile β-enaminone synthesis are described.

2.1. *Suzuki-Miyaura Coupling*

Suzuki-Miyaura reaction is a palladium catalyzed cross-coupling between an organoboronic acid and an aryl or vinyl halide.

With the award of the Nobel prize in 2010, the Suzuki-Miyaura C–C cross-coupling reaction is now duly recognized as one with a profound impact in the world of organic synthesis, particularly in a way the synthetic approaches are adopted today (Equation 2).[3] Because of functional group tolerance, together with non-toxicity of the boron reagents and high efficiency in exclusively yielding cross-coupled products, the Suzuki-Miyaura coupling has emerged as a resourceful synthetic protocol for use in organic syntheses these days.

Sonogashira reaction is a palladium catalyzed cross-coupling between a terminal alkyne and an aryl or vinyl halide.

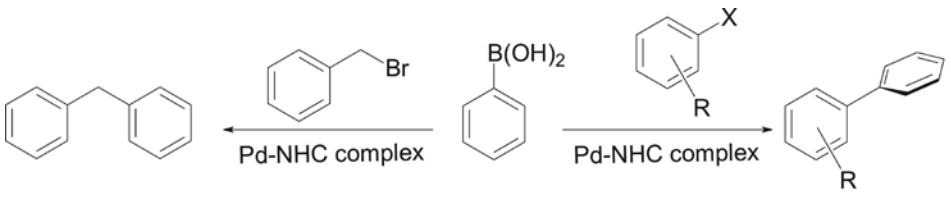
Since many of the coupling reactions proceed through a common mechanism, we became interested in probing the effect of electron density at the metal center on the catalysis. In particular, we rationalized that a metal complex with more electron-rich metal center would promote the oxidative addition step of the catalytic cycle, and based on this premise we sought to determine which of the two catalysts (*i*) the PEPPSI-themed (NHC) PdX_2(pyridine) (X = halide) (PEPPSI = Pyridine Enhanced Precatalyst Preparation, Stabilization and Initiation), containing one good σ-donating N-heterocyclic carbene ligand or (*ii*) catalyst of the type $(NHC)_2PdX_2$ (X = halide), containing two strongly σ-donating N-heterocyclic carbene ligands, would make a better catalyst for the coupling reaction. Though both types of the palladium complexes carried out efficient Suzuki-Miyaura C–C cross-coupling of aryl bromides and iodides with aryl boronic acid substrates, the $(NHC)_2PdX_2$ (**4**–**6**) containing two N-heterocyclic carbene ligands fared better than the PEPPSI-themed (NHC)PdX_2(pyridine) (**1**–**3**) complexes, containing one N-heterocyclic carbene ligand (Figure 1 and Equation 2).[4] Quite remarkably, for an activated substrate like *o*-bromobenzaldehyde, extremely high turnover number of up to 109,600 was observed for the $(NHC)_2PdX_2$ type pre-catalyst (**6**) for the coupling reaction with phenyl boronic acid.[4c]

Having verified our original hypothesis of electron rich $(NHC)_2PdX_2$ type pre-catalysts being better than the PEPPSI-themed (NHC) PdX_2(pyridine) complexes in the Suzuki-Miyaura coupling, we further setout to extend the same to other coupling reactions like the Sonogashira coupling.

2.2. *Sonogashira Coupling*

Lately, Sonogashira reaction has been gaining prominence for the construction of "enyne" and "arylyne" frameworks found in many important molecules of biological and commercial interests (Equation 3).[5] Like the "biphenyls" for the Suzuki-Miyaura coupling, the Sonogashira too provides a direct and simple approach to the "enyne" and "arylyne" scaffolds, thus contributing to the rising popularity of the reaction. In addition to palladium, the Sonogashira reaction often requires the presence of copper as a co-catalyst that not only makes the reaction air and moisture sensitive owing to the formation of organocopper reagents, but also yields homocoupled products by the so-called Glaser coupling under even slightly oxidizing environments.[6] Furthermore, the Sonogashira coupling often involves the use of amines as base that may raise environmental concerns. Against this backdrop, thus, the copper-free and amine-free Sonogashira couplings assume significance.

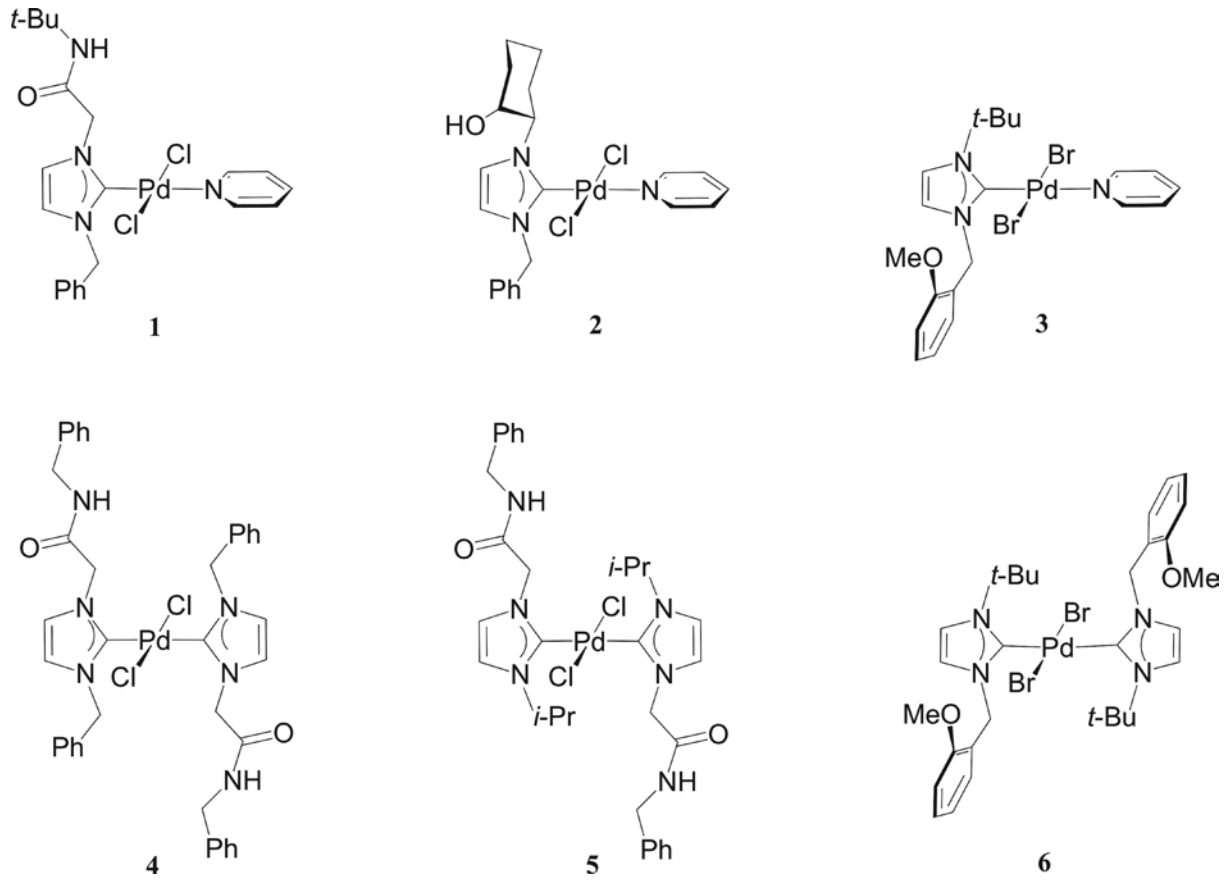
Several of the palladium N-heterocyclic carbene complexes efficiently performed the Sonogashira coupling of aryl bromides and iodides with terminal acetylenes under copper-free and amine-free conditions (Figures 2–4 and Equation 3). Here again, the more electron rich $(NHC)_2PdX_2$ type precatalyst (**16**–**17**) exhibited 2–3 fold better activity than the PEPPSI-themed (NHC)PdX_2(pyridine) ones (**18**–**19**), further confirming the original hypothesis of the electron rich metal center facilitating oxidative addition step and assistance in the coupling reaction.[7] Furthermore, among the PEPPSI themed precatalysts, the abnormal carbenes (**9**–**12**) were superior to the two representative normal N-heterocyclic carbene based precatalysts namely, [1-(2-hydroxycyclohexyl)-3-(benzyl)imidazol-2-ylidene]Pd(pyridine)Cl_2 (**2**) and [1-benzyl-3-

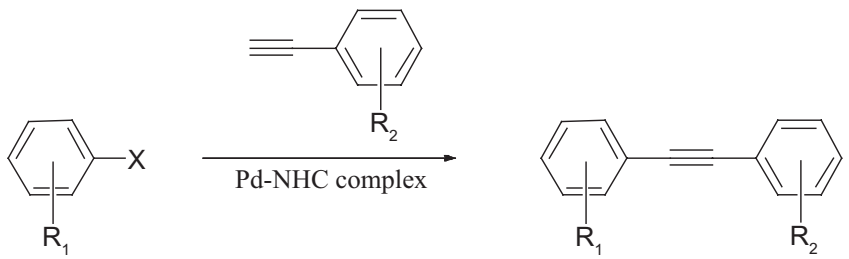


(2)

R = CHO, COMe, NO_2, Me, OMe, H
X = Br, I

Figure 1:





(3)

R_1 = H, COMe, OMe, Me, CHO, CN, NO_2
R_2 = H, NMe_2
X = Br, I

(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene] Pd(pyridine)Br_2 (**18**), and displayed substantial enhancement of the reaction yield of up to 64% for the aryl iodide substrates, and up to 69% for the aryl bromide substrates.

2.3. *Hiyama Coupling*

Hiyama coupling is emerging as one of the popular coupling methodologies alongside Suzuki-Miyaura and Stille reactions for constructing "biaryl" frameworks. It involves the coupling of aryl halide substrates with organosilicon reagents (Equation 4).[8] The Hiyama coupling enjoys certain distinct advantages like the use of cheap and non-toxic organosilicon nucleophiles in contrast to, for example, the Stille coupling that involves organotin reagents having toxicity issues associated with it. A major limitation of the Hiyama coupling, however lies with subdued nucleophilicities of the organosilicon reagents that arise out of small differences in electronegetivity between carbon and silicon atoms. The hurdle is overcome by

Hiyama reaction is a palladium catalyzed cross-coupling between an organosilane and an organic halide or a triflate.

Figure 2:

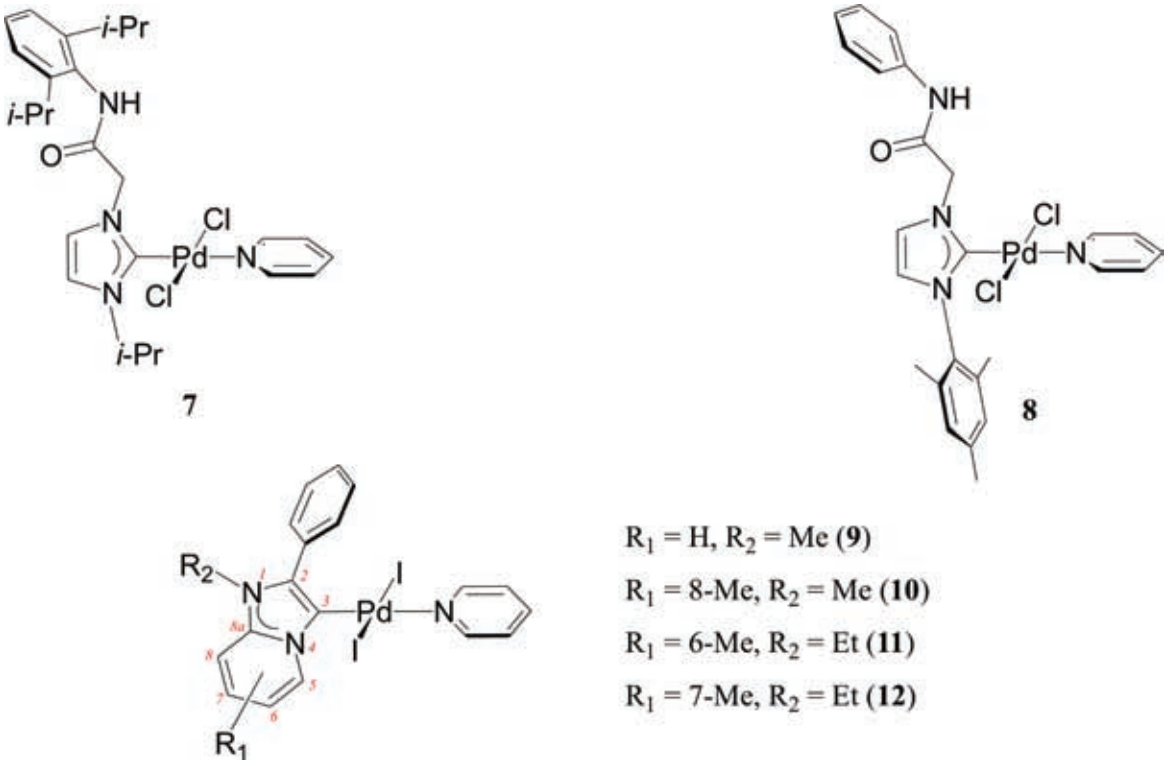
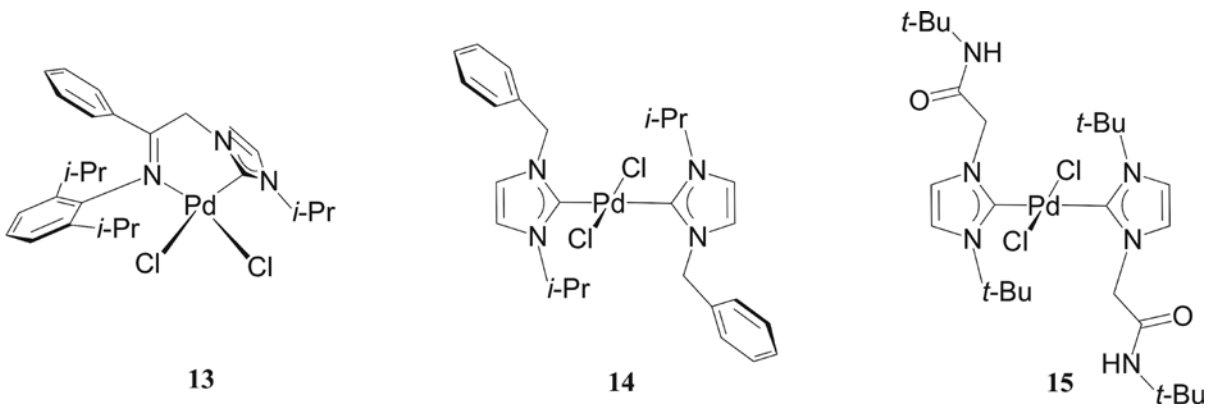


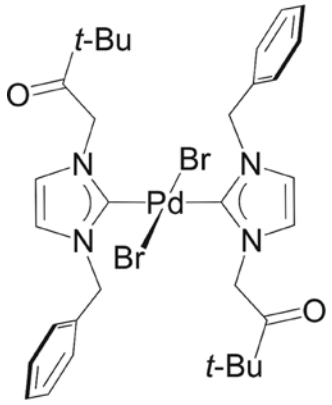
Figure 3:



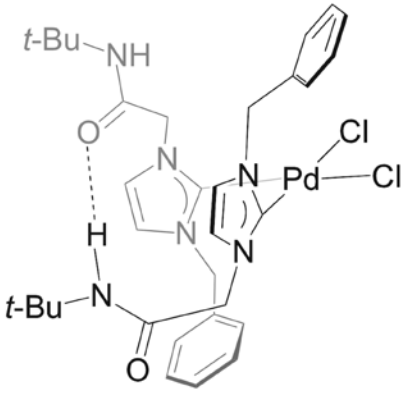
the addition of a base, namely a fluoride anion, which binds to the coordinatively unsaturated organosilicon reagent making it anionic, electron rich and more nucleophilic. As the use of fluoride as a base is hazardous to environment; the development of fluoride-free Hiyama coupling has thus become a foremost challenge in the area in recent times.

Quite remarkably, a series of PEPPSI themed (NHC)PdX_2(pyridine) complexes of imidazole (**20**–**23**) and 1,2,4-triazole (**24**–**25**) based N-heterocyclic carbenes performed the so-called

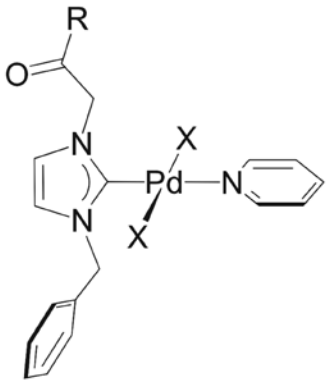
Figure 4:



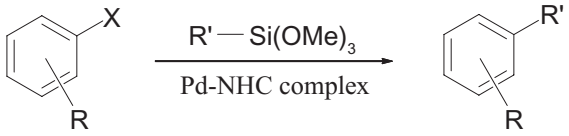
16 (*trans*)



17 (*cis*)



R = *t*-Bu, X = Br (**18**)
R = -NH(*t*-Bu), X = Cl (**19**)



(4)

R = COMe, NO_2, OMe, Me
R' = Ph, vinyl
X = I, Br, Cl

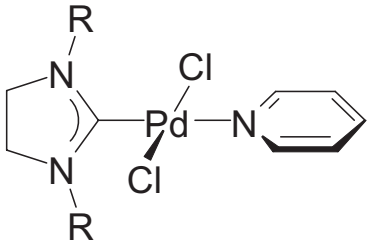
"fluoride-free" Hiyama coupling of the chloro, bromo and the iodo substrates with a host of organosilicon reagents employing hydroxide as a base (Figure 5 and Equation 4).[9] Interestingly, an enhancement of the product yield of up to 91% for the C4–C5 saturated imidazole complexes (**20**–**23**) and up to 84% for the triazole complexes (**24**–**25**) were observed relative to the control experiment performed with $PdCl_2$ under analogous conditions.

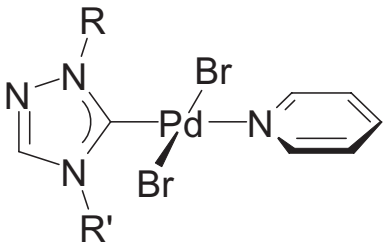
2.4. *Base-free Michael addition reaction*

Michael addition is a nucleophilic addition of a carbanion or another nucleophile to α, β-unsaturated carbonyl compound.

A time-tested conventional methodology for C–C bond formation is the Michael reaction involving conjugate addition of various nucleophiles to activated ethylene compounds in the presence of a Brønsted base.[10] A key issue associated with the Michael addition arises from the presence of the base, it promotes a variety of unwanted side reactions like the aldol cyclization, retro-Claisen type decomposition, ester solvolysis, hetero-Diels-Alder dimerization, Knoevenagel reaction, etc., and thereby undermining the yield of the desired Michael addition product.[11] In this regard, various strategies have been adopted ranging from the use of milder base to basic zeolites, or alumina to phase-transfer catalysts and solid-phase catalysts. Among the approaches taken, an ingenious approach involves employing of bifunctional catalysts for achieving base-free condition of the Michael addition. Specifically, the use of an external base, which leads to unwanted side reactions, is avoided by using bifunctional catalysts containing both acidic and basic sites incorporated within the metal complex. Further elaborating the concept, we rationalized that designing of bifunctional catalysts stabilized over N-heterocyclic carbene ligand, containing a metal chelating N/O-functionalized sidearm, would result in superior activity since the N-heterocyclic carbenes are known to be catalytically active, and thus we setout to design nickel complexes of chelating amido-functionalized N-heterocyclic carbene ligands.

Figure 5:





R = 2,6-*i*-$Pr_2C_6H_3$ (**20**)
R = 2,6-$Et_2C_6H_3$ (**21**)
R = 2,4,6-$Me_3C_6H_2$ (**22**)
R = 2,6-$Me_2C_6H_2$ (**23**)

R = *i*-Pr, R' = CH_2Ph (**24**)
R = CH_2CONHt-Bu, R' = CH_2Ph (**25**)

Hydroamination of alkyne and activated olefin is an addition of an N-H bond across a C=C or C≡C bond of an alkene or alkyne.

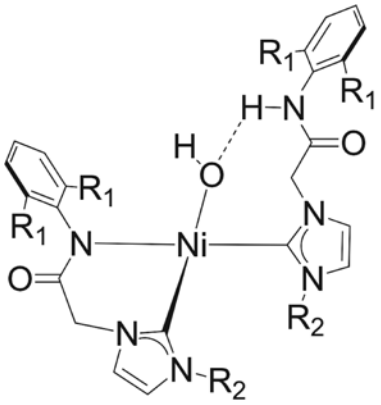
Significantly enough, nickel complexes (**26–34**) performed the base-free Michael addition of β-dicarbonyl, β-ketoester, β-diester and α-cyanoester compounds with α,β-unsaturated carbonyl compounds in air at ambient temperature (Figure 6 and Equations 5 and 6).[12] Higher rates of conversions were observed for the cyclic 5-membered ethyl-2-oxocyclopentanecarboxylate and 2-acetylcyclopentanone substrates than that for the 6-membered ethyl-2-cyclohexanone carboxylate and the acyclic cyanoethyl acetate substrates.

A possible mechanism for a representative cyclic β-dicarbonyl compound with an activated ethylene compound is proposed to proceed through an intermediate (**I**), which reacts with the cyclic β-dicarbonyl compound resulting in its deprotonation (Scheme 2). Subsequent binding of the anionic substrate to the metal along with the concomitant protonation of the one of the amido-sidearm of a NHC ligand leads to the de-chelation of the NHC ligand resulting in the intermediate (**II**). The intermediate (**II**) then reacts with an activated olefinic substrate to give the intermediate (**IV**) *via* a proposed transition state (**III**). The last step involves deprotonation of the amido-N site of the NHC ligand followed by re-chelation to the metal center to generate back the starting intermediate (**I**) along with the protonation, and subsequent elimination of the Michael addition product. The successful catalysis by (**26–34**) of the base-free Michael addition under ambient condition further lends credence to the rationale of designing bifunctional catalysts for the reaction.

2.5. *Hydroamination of alkynes and activated olefins*

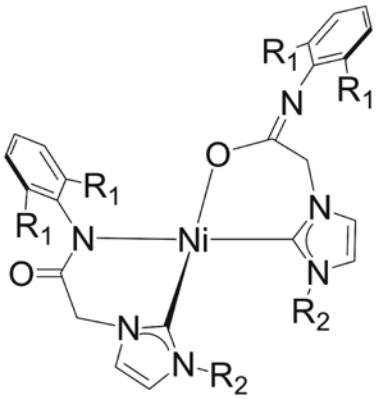
Being atom economic and hence highly sought after, the hydroamination reactions of unsaturated substrates like that of the alkynes and olefins, result in C–N bond formation, thus giving access to a large body of nitrogen containing compounds.[13] The reasons like the amines being cheap and readily available, and also the fact that no waste product is formed in the reaction, together make hydroamination a popular reaction. Though an attractive option, hydroamination poses certain operational challenges like the reaction being nearly thermoneutral owing to both the reacting substrates, *i.e.,* the amine and the alkyne or the olefin, being electron rich entities having less propensities to mutually react. Furthermore, between alkyne and olefin hydroaminations, the former is more facile by virtue of being sterically less demanding and also due to the fact that its π-bond is *ca.* 70 kcal/mol weaker than that in olefins.[14] The transition metals provide an all important solution by resorting to various activation pathways involving either the amine or the alkyne and olefinic substrates. Depending upon the type of metal used, the hydroamination reaction may be air-sensitive, like that with the lanthanides, alkali metal and the early-transition metals, whereas the late-transition metals being less oxophilic are less sensitive to air and moisture. Our efforts have been toward understanding the utility of various 1st–3rd row late-transition metals in the hydroamination reactions of alkynes and the activated olefinic substrates. More specifically, our

Figure 6:



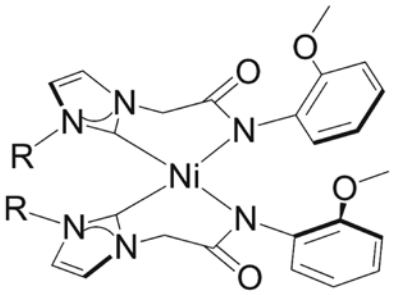
R_1 = *i*-Pr, R_2 = *i*-Pr (**26**)

R_1 = *i*-Pr, R_2 = CH_2Ph (**27**)

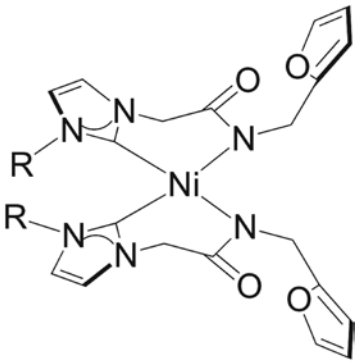


R_1 = Et, R_2 = CH_2Ph (**28**)

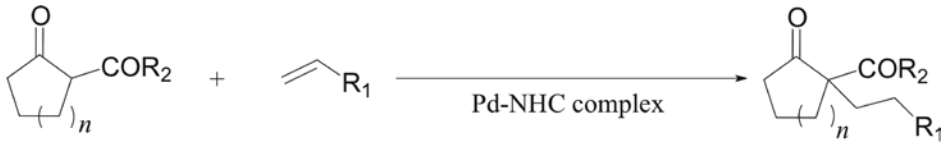
R_1 = Me, R_2 = CH_2Ph (**29**)



R = Me (**30**), *i*-Pr (**31**), CH_2Ph (**32**)



R = Me (**33**), CH_2Ph (**34**)

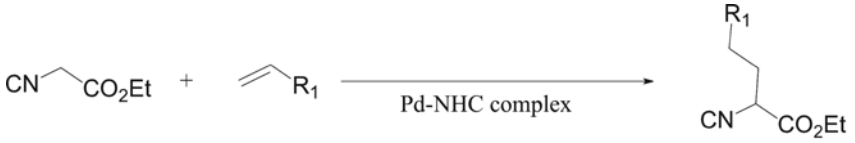


(5)

R_1 = COMe, CO_2Me, CO_2Et, CO_2t-Bu, CN

R_2 = Me, OEt

n = 1, 2



(6)

R_1 = COMe, CO_2Me, CO_2Et, CN

Scheme 2:

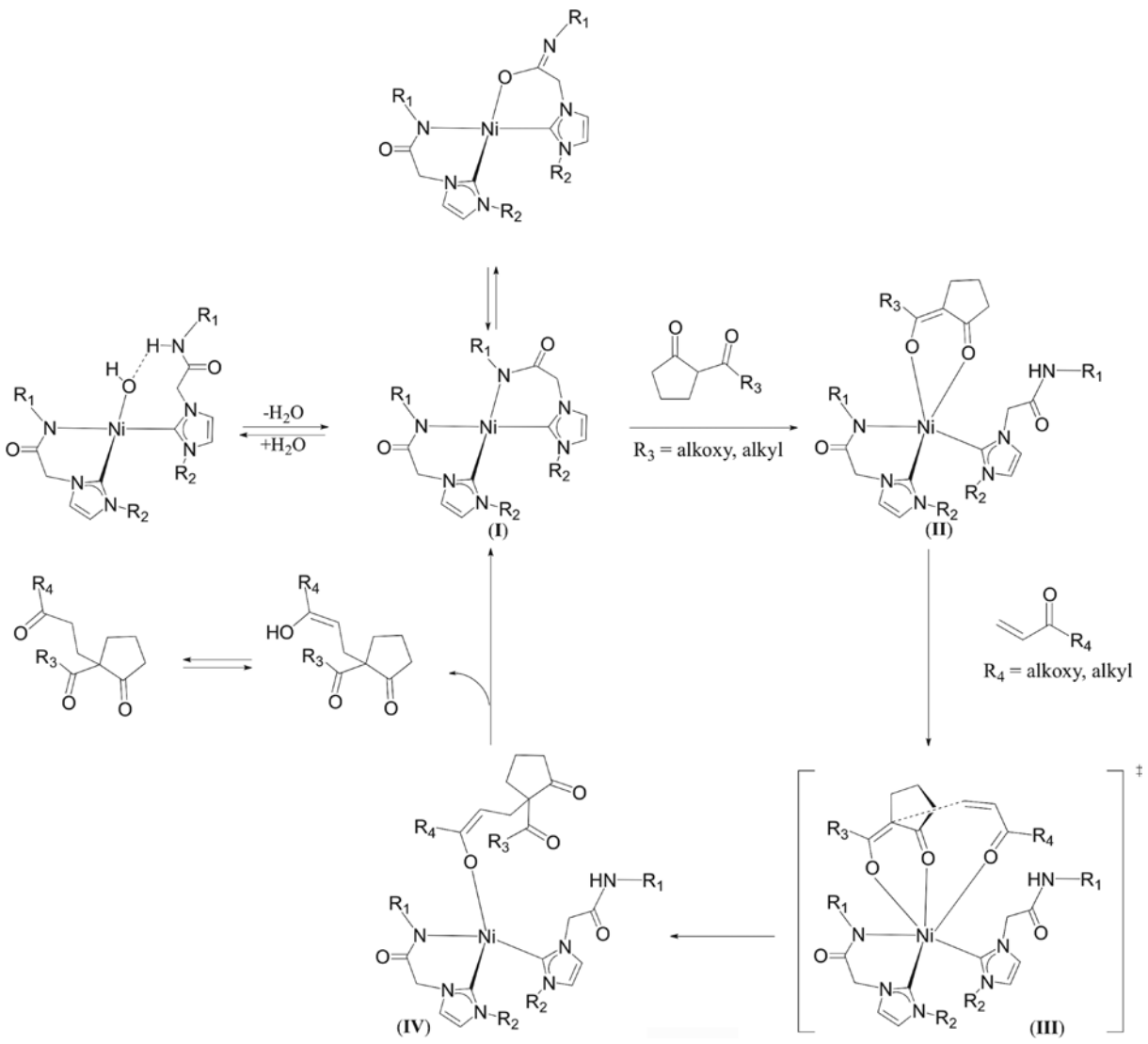
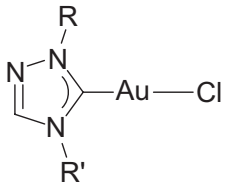


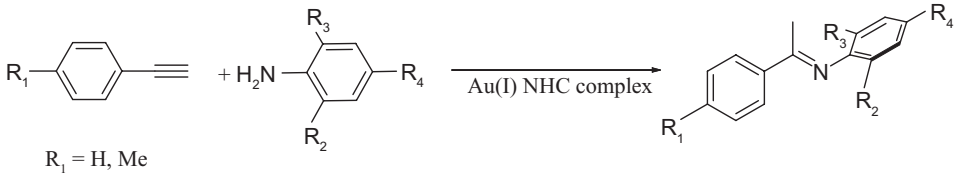
Figure 7:



R = CH_2CO*t*-Bu, R' = CH_2Ph (**35**)
R = CH_2CONH*t*-Bu, R' = CH_2Ph (**36**)
R = CH_2CO*t*-Bu, R' = CH_2CO*t*-Bu (**37**)
R = $C_6H_{10}OH$, R' = CH_2Ph (**38**)

studies on the application of gold N-heterocyclic carbene complexes in the hydroamination of alkyne and the applications of nickel and palladium complexes in the hydroamination of activated olefin substrates are outlined below.

Significantly enough, the gold(I) complexes (**35–38**) efficiently carried out the intermolecular hydroamination reaction of terminal alkynes like phenylacetylene and 4-ethynyl toluene, with *o*/*p*-substituted aryl amines such as, 2-methylaniline, 2,6- dimethylaniline, mesitylaniline, 2,6-diethylaniline, and 2,6-di-*i*-propylaniline in air (Figure 7 and Equation 7).[15] Moreover, the hydroamination reaction performed with the silver analogs showed subdued conversions thereby highlighting the role of gold in catalysis. The



(7)

R_1 = H, Me
R_2 = H, Me, Et, *i*-Pr
R_3 = Me, Et, *i*-Pr
R_4 = H, Me

Scheme 3:

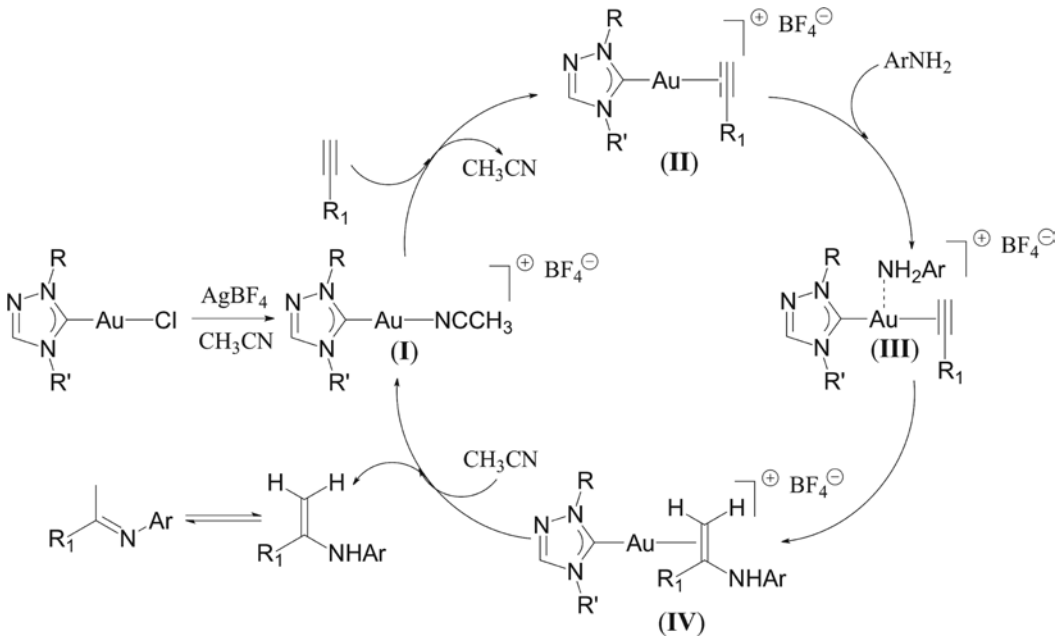
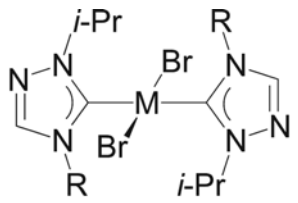


Figure 8:



R = CH_2CH_3, M = Ni (**39**)
R = CH_2CH_3, M = Pd (**40**)
R = $CH_2CH{=}CH_2$, M = Ni (**41**)
R = $CH_2CH{=}CH_2$, M = Pd (**42**)

regiochemistry of the reaction, as established by product isolation and subsequent characterization, showed Markovnikov type N-H addition across the alkyne substrates.

One proposed mechanism (Scheme 3) involves a solvent coordinated active species [(NHC)Au(CH_3CN)]BF_4 (**I**), formed from the precatalyst (**35–38**) by treatment with $AgBF_4$ in acetonitrile and accompanied by the precipitation of AgCl. Reaction of the active species (**I**) with terminal alkyne (RCCH) yields an alkyne coordinated species [(NHC)Au(alkyne)]BF_4 (**II**), which on reaction with an arylamine results in the intermediate (**III**), [(NHC)Au(amine)(alkyne)]BF_4. The species (**III**) then undergoes Markovnikov type hydroamination of the coordinated alkyne to give enamine coordinated species [(NHC)Au(enamine)]BF_4 (**IV**). The species (**IV**) finally yields the desired ketimine product through

(8)

X = CN, COOR (R = Me, Et, *t*-Bu)

Scheme 4:

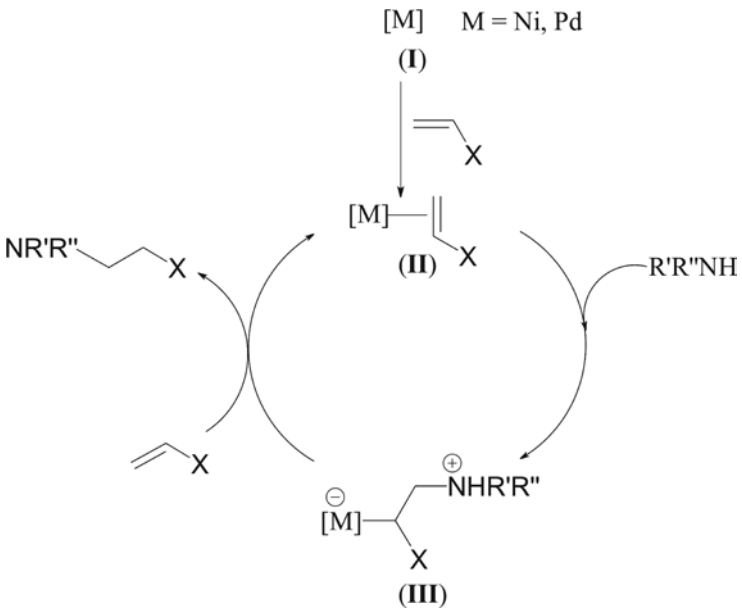
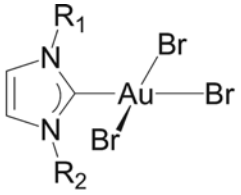


Figure 9:



R_1 = *i*-Pr, R_2 = CH_2Ph (**43**)

R_1 = mesityl, R_2 = CH_2Ph (**44**)

R_1 = *i*-Pr, R_2 = CH_2CO *t*-Bu (**45**)

R_1 = *t*-Bu, R_2 = CH_2CO *t*-Bu (**46**)

tautomerism along with the regeneration of active species (**I**).

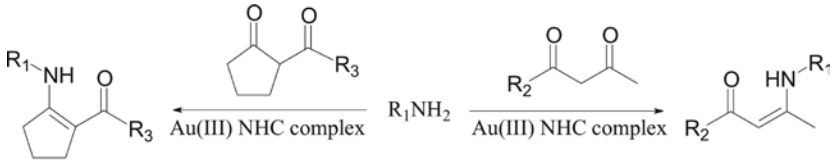
Similarly, the nickel (**39** and **41**) and palladium (**40** and **42**) complexes were moderately active for hydroamination reaction of activated olefins like acrylonitrile, methyl acrylate, ethyl acrylate and *t*-butyl acrylate with a variety of secondary amines, namely morpholine, piperidine, pyrrolidine and diethylamine, at room temperature in 1 hour of the reaction time (Figure 8 and Equation 8).[16] The regiochemistry of the hydroamination reaction, as established from product isolation and characterization, was found to be anti-Markovnikov type N–H addition across the activated olefinic substrates. Significantly, the nickel (**39** and **41**) complexes were more effective than the palladium (**40** and **42**) counterparts owing to greater Lewis acidity of the former.

Yet another proposed mechanism involves an olefin activation step, in which the olefin coordinates to the active species (**I**) yielding an olefin coordinated intermediate (**II**) (Scheme 4). Subsequent attack by a secondary amine at the less substituted side of (**II**) would yield a metal bound 2-aminoalkyl intermediate (**III**) *via* an anti-Markovnikov addition. The last step involves the elimination of the hydroaminated product by protonolysis of the metal bound 2-aminoalkyl intermediate (**III**) in the presence of an olefin, and an alongside regeneration of the olefin coordinated intermediate (**II**).

2.6. *β-Enaminone Synthesis*

β-Enaminones and β-enaminoesters, ubiquitous in numerous biologically active compounds that exhibit anticonvulsant, anti-inflammatory and anticancer properties, represent an important class of target molecules in the world of organic synthesis.[17] They display interesting properties of nucleophilicity of enamines as well as electrophilicity of the enone functionalities, and as a consequence, the development of high yielding processes towards their synthesis remains a formidable challenge in the area. A common protocol involving condensation of 1,3-dicarbonyl compounds with amines suffers from the need for separation of water from the reaction mixture. Tedious procedures like the azeotropic separation of water from the reaction performed in aromatic solvents, or the use of molecular sieves or a dehydrating agents or Lewis acids, are often involved.[18] We became interested in developing facile synthetic protocol using transition metals for the β-enaminone and β-enaminoester syntheses and in this context we sought to explore

β-Enaminones are compounds having adjacent keto and enamine moieties.



(9)

R_1 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu
R_2 = Me, Ph
R_3 = Me, OEt

the utility of gold(III) complexes of N-heterocyclic carbenes.

Significantly enough, all the gold(III) complexes used (**43**–**46**) performed efficient β-enaminones synthesis from the condensation of 1,3-dicarbonyl compounds like acetylacetone, benzoylacetone, 2-acetylcyclopentanone, and ethyl-2-oxocyclopentanecarboxylate, with primary aliphatic amines namely methylamine, ethylamine, *n*-propylamine, *i*-propylamine, and *n*-butylamine, at room temperature in 6 hours (Figure 9 and Equation 9).[19] The gold(III) complexes (**43**–**46**) exhibited better activity than the corresponding gold(I) counterparts under analogous conditions, thus highlighting the importance of the electrophilicity of the metal center in the catalysis.

3. Conclusions

In summary, N-heterocyclic carbene transition metal complexes have great potential in homogeneous catalysis including the catalytic C–X (X = C and heteroatom) bond formations. The late-transition metal catalysts based on Ni, Pd and Au, as demonstrated by our study, are efficient in carrying out a host of such reactions namely the Suzuki-Miyaura, the Sonogashira and the Hiyama cross-couplings, the base-free Michael addition, the hydroamination of terminal alkynes and activated olefinic substrates and the efficient synthesis of β-enaminones from the condensation of 1,3-dicarbonyl compounds with primary amines.

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References

1. a. Koser, G. F. *C-Heteroatom-bond Forming Reactions;* Springer: Berlin, **2003**.
   b. Coates, R. M.; Denmark, S. E. *Handbook of Reagents for Organic Synthesis: Reagents, Auxiliaries and Catalysts for C-C Bond Formation;* Wiley-Interscience: New York, **1999**.
2. a. Hartwig, J. F. *Nature* **2008**, *455*, 314–322.
   b. Singh, B. K.; Kaval, N.; Tomar, S.; Van der Eycken, E.; Parmar, V. S. *Org. Process Res. Dev*. **2008**, *12*, 468–474.
   c. Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174–238.
   d. Beletskaya, I. P. *Pure Appl. Chem*. **2005**, *77*, 2021–2027.
   e. Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev*. **2000**, *100*, 3187–3204.
   f. Hegedus, L. S. *Coord. Chem. Rev*. **1998**, *168*, 49–175.
3. a. Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147–168.
   b. Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457–2483.
   c. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett*. **1979**, *20*, 3437–3440.
4. a. Kumar, S.; Shaikh, M. M.; Ghosh, P. *J. Organomet. Chem*. **2009**, *694*, 4162–4169.
   b. Ray, L.; Shaikh, M. M.; Ghosh, P. *Dalton Trans*. **2007**, 4546–4555.
   c. Ray, L.; Shaikh, M. M.; Ghosh, P. *Organometallics* **2007**, *26*, 958–964.
5. a. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467–4470.
   b. Cassar, L. *J. Organomet. Chem*. **1975**, *93*, 253–257.
   c. Dieck, H. A.; Heck, F. R. *J. Organomet. Chem*. **1975**, *93*, 259–263.
6. a. Chinchilla, R.; Nájera, C. *Chem. Rev*. **2007**, *107*, 874–922.
   b. Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed*. **2007**, *46*, 834–871.
   c. Negishi, E.; Anastasia, L. *Chem. Rev*. **2003**, *103*, 1979–2017.
   d. Sonogashira, K. *J. Organomet. Chem*. **2002**, *653*, 46–49.
   e. Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed*. **2000**, *39*, 2632–2657.
7. a. John, A.; Shaikh. M. M.; Ghosh, P. *Dalton Trans*. **2009**, 10581–10591.
   b. Samantaray, M. K.; Shaikh, M. M.; Ghosh, P. *J. Organomet. Chem.* **2009**, *694*, 3477–3486.
   c. Ray, L.; Barman, S.; Shaikh, M. M.; Ghosh. P. *Chem. Eur. J*. **2008**, *14*, 6646–6655.
8. a. Hiyama, T. *J. Organomet. Chem*. **2002**, *653*, 58–61.
   b. Itami, K.; Mitsudo, K.; Nokami, T.; Kamei, T.; Koike, T.; Yoshida, J. *J. Organomet. Chem.* **2002**, *653*, 105–113.
   c. Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull*. **2002**, *50*, 1531–1541.
9. Dash, C.; Shaikh, M. M.; Ghosh, P. *Eur. J. Inorg. Chem*. **2009**, 1608–1618.
10. a. Oare, D. A.; Heathcock, C. H. *Top. Stereochem*. **1989**, *19*, 227–407.
    b. Bergmann, E. D. ; Ginsburg, D.; Pappo, R. *Org. React*. **1959**, *10*, 179–555.
11. Christoffers, J. *Eur. J. Org. Chem*. **1998**, 1259–1266.
12. a. Ray, S.; Shaikh. M. M.; Ghosh, P. *Eur. J. Inorg. Chem*. **2009**, 1932–1941.
    b. Samantaray, M. K.; Shaikh, M. M.; Ghosh, P. *Organometallics* **2009**, *28*, 2267–2275.
13. a. Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420.
    b. Pohlki, F.; Doye, S. *Chem. Soc. Rev*. **2003**, *32*, 104–114.
    c. Müller, T. E.; Beller, M. *Chem. Rev*. **1998**, *98*, 675–703.

14. Straub, T.; Haskel, A.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017–5035.
15. Dash, C.; Shaikh, M. M.; Butcher, R. J.; Ghosh, P. *Inorg. Chem*. **2010**, *49*, 4972–4983.
16. Dash, C.; Shaikh, M. M.; Butcher, R. J.; Ghosh, P. *Dalton Trans*. **2010**, *39*, 2515–2524.
17. a. Palmieri, G.; Cimarelli, C. *Arkivoc* **2006**, *vi*, 104–126.
    b. Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463–8480.
    c. Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem*. **1999**, *71*, 979–988.
    d. Greenhill, J. V. *Chem. Soc. Rev*. **1977**, *6*, 277–294.
18. a. Lin, J.; Zhang, L.-F. *Monatshefte für Chemie* **2007**, *138*, 77–81.
    b. Khodaei, M. M.; Khosropour, A. R.; Kookhazadeh, M. *Synlett.* **2004**, 1980–1984.
    c. Gao, Y.; Zhang, Q.; Xu, J. *Synth. Commun*. **2004**, *34*, 909–916.
    d. Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett*. **1995**, *36*, 2937–2940.
    e. Taguchi, K.; Westheimer, F. H. *J. Org. Chem*. **1971**, *36*, 1570–1572.
    f. Martin, D. F.; Janusonis, G. A.; Martin, B. B. *J. Am. Chem. Soc*. **1961**, *83*, 73–75.
19. Samantray, M. K.; Dash, C.; Shaikh, M. M.; Pang, K.; Butcher, R. J.; Ghosh, P. *Inorg. Chem*. **2011**, *50*, 1840–1848.

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