Cooperative multi-catalyst systems for one-pot organic transformations

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One-pot co-catalyst systems are covered in this *tutorial review*. It is divided into three sections according to the reaction types: i) one catalyst performs a desired reaction as the second catalyst restores the first catalytic species back into its original state for the next catalytic cycles, ii) two catalysts carry out sequential organic transformations, in which the first step is carried out by one catalyst to afford certain intermediates being to be subjected to the second catalyst for the next step, and iii) cooperative catalytic actions on both substrates by suitable catalysts proceed in a substrate-selective manner followed by the subsequent coupling of the two activated adducts providing the desired products.

1 Introduction

Organometallic catalysts are traditionally designed and utilized to mediate, in most cases, a single step in a specific reaction. In contrast to the traditional one-catalyst one-reaction approach, some recent examples have illustrated that one-pot tandem reactions can be readily achieved by an exquisite combination of multiple catalysts. For example, sequential catalytic processes occur in one reaction vessel by the action of different metal species in a manner of either successive one-metal one-catalytic conversion or cooperative multi-catalytic one-process. The increasing demands for environmentally benign and economical synthetic processes necessitate the development of one-pot multiple catalytic transformations to provide desired products in most efficient ways.[1] It can be easily anticipated that this strategy would minimize production of waste and processing times. Realization and practice of the concept may be taken from Nature, in which numerous enzymes function by a synergistic cooperation of two or more active sites derived from each enzyme to result in one net transformation.[2] A series of specific biotransformations may be also achieved by the sequential and ingenious action of multiple enzymes in a designated order. In fact, an instructive example has been demonstrated in the *in vitro* synthesis of corrin from 5-aminolevulinic acid using 12 enzymes with an overall yield of 20% in a total 17 steps in a single flask.[3] Mimicking of the bio-system in artificial chemical catalysis would be a great interest for chemists not only in industry but also in academe. In this regard, extensive studies have been conducted on the preparation and utilization of multifunctional catalyst systems in organic synthesis. For example, catalysts that contain both Lewis acidic and basic sites have been elegantly utilized for the simultaneous activation of substrates and reagents, making possible multiple reactions in one-pot.[4] Despite the significant developments recently achieved, accurately predicting the binding mode and the interaction between substrates and catalysts is still in the early stages, and thus a more systematic design and synthesis of ambifunctional catalysts is still difficult.[5]

As shown in Scheme 1, the one-pot co-catalyst systems reviewed in this article are arbitrarily categorized into the following three general types. I) One catalyst performs a desired reaction as the second catalyst restores the first catalytic species back into its original state for the next catalytic cycles (eqn. (1)). II) Two catalysts perform sequential organic transformations (eqn. (2)), in which the first step is carried out by one catalyst to afford certain intermediates to be subjected to the second catalyst for the next step.[6] Alternatively, a single metal precursor alone permits

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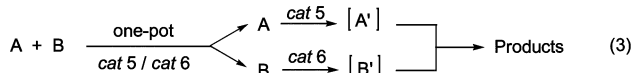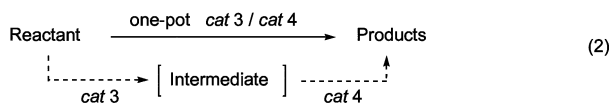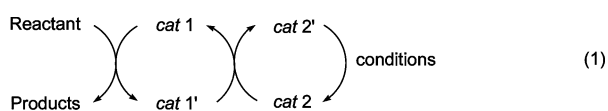
After receiving her BS in chemistry at Soongsil University (Seoul) in 1999, Youngim Na (born in 1975) finished her master degree in chemistry at Ewha Womans University under the supervision of Prof. Sukbok Chang in 2001. Currently, she is pursuing PhD in chemistry at KAIST under the same advisor. Her research is focused on catalysis with transition metals.

Hoon Han (born 1978) received his BS in chemistry at Sungkyunkwan University (Suwon) in 2001 and then he completed his MS at the same institute in Prof. Seungsoo Yoon's lab in 2003. Then he joined KAIST, where he is currently a PhD candidate working with Prof. Sukbok Chang.

Sukbok Chang (born in 1962) received his BS in chemistry from Korea University (Seoul) and MS degree from KAIST under the guidance of Prof. Sunggak Kim. He worked in a chemical company for 4 years in Korea. In 1996, he earned his PhD degree in chemistry at Harvard University working with Prof. Eric N. Jacobsen. After postdoctoral experience with Prof. Robert H. Grubbs at Caltech, he joined the faculty at Ewha Womans University in Seoul (1998). In 2002, he moved to KAIST, where he is now an associate professor in the chemistry department focusing on the developments of metal-based synthetic methodologies and molecular architectures.

(From right) Ji Min Lee, Youngim Na, Hoon Han and Sukbok Chang

Scheme 1 reaction equations:

Reactant / Products — cat 1 / cat 1' — cat 2' / cat 2 — conditions   (1)

$$Reactant \xrightarrow{\text{one-pot } cat\ 3\ /\ cat\ 4} Products \quad (2)$$

cat 3 ⟶ [Intermediate] ⟶ cat 4

$$A + B \xrightarrow[cat\ 5\ /\ cat\ 6]{\text{one-pot}} \begin{cases} A \xrightarrow{cat\ 5} [A'] \\ B \xrightarrow{cat\ 6} [B'] \end{cases} \longrightarrow Products \quad (3)$$

Scheme 1 Three types of the co-catalyst systems in organic transformations.

mechanistically distinct tandem catalytic reactions upon change of the reaction conditions, which alter the structure of the initial metal complexes into a new catalytic species that carries out subsequent catalytic processes to accomplish the net transformation. III) Cooperative catalytic actions on both substrates by suitable catalysts occur in a substrate-selective manner followed by the subsequent coupling of the two activated moieties providing the desired products (eqn. (3)). It is immediately anticipated that the key issue in co-catalytic procedures would be the compatibility of the second catalyst to the conditions of the first catalytic reaction. One catalytic cycle should not interrupt the subsequent or concurrent catalytic conversions. However, in reality, the reagents or catalysts may interfere with each other in several ways. For example, mismatched combination of reagents or catalysts can cause different reaction pathways. In addition, inhibition may occur through undesired interaction between ligands and catalysts.

This review covers studies of one-pot co-catalyst systems directed toward organic transformations and synthesis.[7] The activation of transition metal catalysts in olefin polymerization by the use of certain types of main group co-catalysts is not included herein.[8]

2 One-pot co-catalyst systems

2.1 Catalytic transformations assisted by the second catalysts (Type I, eqn (1))

One of the most widely known and classic examples of the co-catalyst system is the Wacker process, in which a bimetallic Pd/Cu catalyst system is used for the oxidation of alkenes in the presence of oxygen (Scheme 2).[9] This reaction has been developed as a highly efficient industrial method producing several million tons of acetaldehyde from ethylene annually.

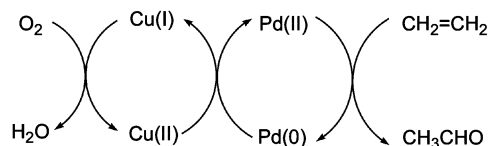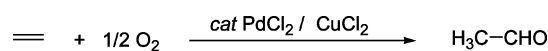$$\equiv\ +\ 1/2\ O_2 \xrightarrow{cat\ PdCl_2\ /\ CuCl_2} H_3C{-}CHO$$
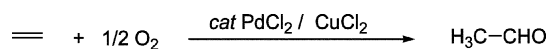
Scheme 2 Wacker-type oxidation with a Pd/Cu bimetallic catalyst system.

The transformation was actually derived from the procedures known as early as nineteenth century, in which regioselective oxidation of ethylene could be achieved using stoichiometric amounts of aqueous $PdCl_2$. A catalytic version was surmised to be possible with the introduction of the second catalyst that has the ability of reoxidizing palladium to maintain the catalytic cycle of the oxidation. Cupric chloride was successfully introduced for this purpose and it turned out that cuprous chloride resulting from this conversion could be readily returned to its original Cu(II) state by oxygen. The original procedure that uses a mixture of ethylene and oxygen has been modified into a more practical process, in which ethylene is reacted with an aqueous solution of palladium and cupric chloride under atmospheric air instead of pure oxygen (Scheme 3).

The catalytic cycles of the Wacker oxidation can be also presented in an analogy with biochemical catalysis (Scheme 4). The mechanistic details of the reaction have been extensively investi-
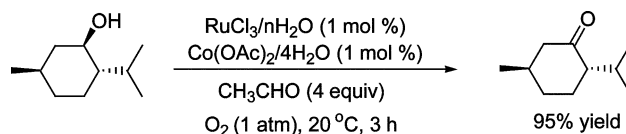
$$C_2H_4\ +\ PdCl_2\ +\ H_2O\ \longrightarrow\ CH_3CHO\ +\ 2\ HCl\ +\ Pd(0)$$
$$Pd(0)\ +\ 2\ CuCl_2\ \longrightarrow\ PdCl_2\ +\ 2\ CuCl$$
$$2\ CuCl\ +\ 2\ HCl\ +\ 1/2\ O_2\ \longrightarrow\ 2\ CuCl_2\ +\ H_2O$$

Scheme 3 Three basic catalytic steps in the modified Wacker process.

$$\equiv\ +\ 1/2\ O_2 \xrightarrow{cat\ PdCl_2\ /\ CuCl_2} H_3C{-}CHO$$

Catalytic cycle: O_2 / H_2O — Cu(I) / Cu(II) — Pd(II) / Pd(0) — $CH_2{=}CH_2$ / CH_3CHO

Scheme 4 Biomimetic catalytic cycles in the Wacker oxidation reaction.

gated on the basis of kinetic data, stereochemical outcomes, and isotope effects by several researchers including Stille[10] and Bäckvall.[11] It is currently accepted that coordination of an olefin and water to Pd(II) occurs first followed by attack of a free water molecule on the coordinated double bond. The hydroxypalladation step is generally regarded to proceed in a *trans*-fashion although there is speculation that the stereo-sense may be dependent on the concentrations of chloride ions and becomes *syn* at low [Cl⁻]. It was also observed that no deuterium is incorporated into acetaldehyde when the reaction is carried out in D_2O implying that β-elimination intermediates do not leave the coordination sphere of the palladium metal center until it rearranges itself into aldehyde by multiple insertion–elimination steps.
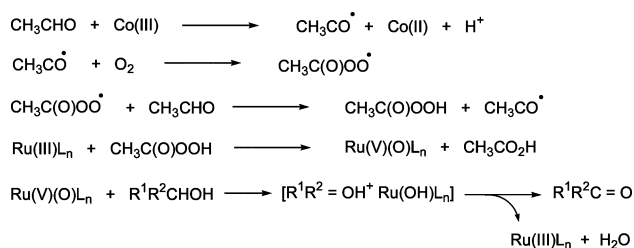
With the use of a Ru/Co bimetallic catalyst system, another example of using oxygen as an unlimited source of oxidant was illustrated by Murahashi *et al.* for the oxidation of alcohols at room temperature in the presence of an aldehyde (Scheme 5).[12] This was

Scheme 5: cyclohexanol derivative with OH →
reagents: RuCl₃/nH₂O (1 mol %); Co(OAc)₂/4H₂O (1 mol %); CH₃CHO (4 equiv); O₂ (1 atm), 20 °C, 3 h → cyclohexanone derivative, 95% yield

Scheme 5 Aerobic oxidation of alcohols with a bimetallic catalyst system of Ru/Co.

based on the earlier observations from the same group that *in situ* formed low-valent oxoruthenium complex can carry out specific oxidation of amines, amides, nitriles, and hydrocarbons. Further studies revealed that the active species are readily generated by the action of ruthenium precursors with molecular oxygen in the presence of aldehyde. Initial trials for the aerobic oxidation of alcohols in the presence of aldehydes were not successful with use of *in situ* generated oxoruthenium catalysts alone, presumably due to the fact that the formation of peracids is prevented by strong coordination of alcohol to the ruthenium metal center. This is now circumvented by the introduction of the second metal catalyst, $Co(OAc)_2$, making the oxidation of alcohols possible at room temperature with atmospheric pressure of O_2. The presumed role of the employed aldehyde in this bimetallic catalysts system is to accept hydrogen from the oxidation of alcohols, converting itself into a carboxylic acid.
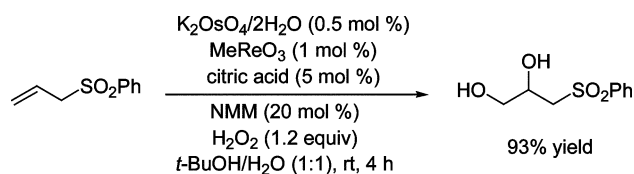
The authors proposed that the aerobic oxidation of alcohols by the bimetallic Ru/Co catalyst system proceeds by two sequential pathways: (i) formation of peracids by a Co-mediated radical chain reaction of aldehyde with molecular oxygen, and (ii) Ru-catalyzed oxidation of alcohols with the peracids thus formed (Scheme 6). In this pathway, ruthenium is believed to carry out the main oxidation reaction of alcohols with the help the cobalt co-catalyst that initiates a series of electron transfer steps starting from aldehyde. The

Scheme 6 Proposed pathway of the Murahashi's oxidation system.

Scheme 8 Triply catalytic dihydroxylation reaction of olefins by a bimetallic Os/Re system.

potential is mimicking electron-transfer processes occurring in biological systems.

A unique trifunctional heterogeneous catalyst system consisting of Pd, Os, and W species has been recently prepared and catalytic activity of that was examined by Choudary *et al.* for the tandem Heck olefination and asymmetric dihydroxylation reactions in one-pot (Scheme 9).[15] A trimetal catalyst system of Pd/Os/W was

reaction of an aldehyde with the cobalt(III) complex derived from a Co(II) precursor is assumed for the generation of an acyl radical, which reacts with atmospheric molecular oxygen affording an acylperoxy radical that subsequently abstracts hydrogen from the employed aldehyde to give a peracid and an acyl radical. Reaction of the used Ru(III) catalyst with the *in situ* generated peracid would generate Ru(III)OOCOR species which undergoes cleavage of the O–O bond providing an oxoruthenium(V) species. Abstraction of hydrogen from the alcohol substrates and subsequent electron transfer to the oxoruthenium intermediate would produce carbonyl compounds and water to complete the catalytic cycle.
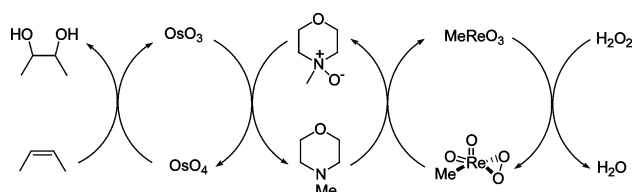
A novel bimetallic catalyst system of Os/Re has been utilized by Bäckvall *et al.* for dihydroxylation of various olefins (Scheme 7).[13]

Scheme 7 Dihydroxylation reactions of olefins by Os/Re/NMM/H$_2$O$_2$ system.

Even though hydrogen peroxide is generally considered as an attractive terminal oxidant because it is inexpensive and environmentally benign, its use in Os-catalyzed dihydroxylation of olefins is rather limited in some cases due to over-oxidation or non-selective manner. With the introduction of the second Re-catalyst as an electron transfer mediator into the original Os-catalyst system, the difficulties associated with the use of H$_2$O$_2$ could be circumvented in their most recent report. However, the employed methyltrioxorhenium (MTO) is unstable under the traditionally used oxidation conditions as the necessary presence of tertiary amine such as *N*-methylmorpholine (NMM) makes the reaction mixture basic. Addition of sub-stoichiometric amounts of citric acid to the Os/Re/NMM/H$_2$O$_2$ system finally resulted in significant improvements to meet the required efficiency of the transformation. The yield becomes low from the reactions in the absence of MTO indicating that although the direct reoxidation of Os by H$_2$O$_2$ is possible under the conditions, it is more effective to employ the triple catalytic system (Os/Re/NMM). A variety of electron-deficient olefins, poor substrates with the traditional Os catalyst systems, were converted into the corresponding diols in good to excellent yields with the help of Re co-catalyst. An asymmetric version of the same reaction was also successfully introduced by the same group, in which high enantioselectivities up to 99% ee were obtained in the presence of chiral alkaloid ligands.[14]
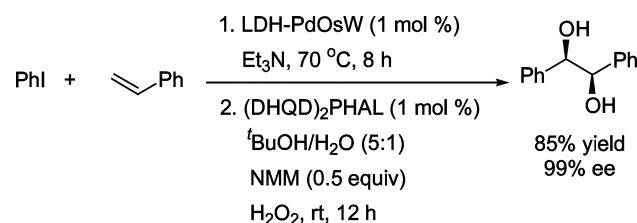
The proposed mechanism of the triple catalytic system of Os/MTO/NMM is depicted in Scheme 8. The rhenium peroxo species generated from MTO in the presence of H$_2$O$_2$ external oxidant recycles NMM to 4-methylmorpholine *N*-oxide (NMO), which in turn reoxidizes OsO$_3$ into OsO$_4$, active catalytic species for the dihydroxylation of olefins. In the presence of MTO, an intermediate NMO is easily generated and this in turn reoxidizes OsO$_3$ to OsO$_4$ for the next catalytic dihydroxylation cycle. Methyltrioxorhenium is thought to be the actual oxidizing species, which transfers one of its oxygen atoms to NMM, generating NMO fast in a mild reaction condition. The stepwise electron transfer with falling redox

Scheme 9 Tandem Heck–*N*-oxidation–AD reactions with trimetal heterogeneous catalyst system.

embedded into hexagonal layered double-hydroxides (LDHs) of which compositions are Mg$_{1-x}$Al$_x$(OH)$_2$(Cl)$_x$·zH$_2$O (x = 0.25). Ion-exchange technique was adapted for the synthesis of the heterogeneous three-catalyst system, LDH–[PdCl$_4$,OsO$_4$,WO$_4$], using LDH as an ion-exchanger and Na$_2$PdCl$_4$, K$_2$OsO$_4$, and Na$_2$WO$_4$ as the respective source of each metal. Spectroscopic data indicate the retention of the coordination geometries of the specific divalent anions anchored to the LDH matrix in their monomeric form. The multi-component catalyst system was designed for achieving tandem Heck coupling–asymmetric dihydroxylation (AD)–*N*-oxidation reactions in one-pot on the basis of the anticipated role of each component: Pd, Os, and W, respectively. It is truly remarkable to observe that, with the trifunctional catalyst, the designed tandem multiple reactions actually run with surprisingly high efficiency and excellent enantioselectivity. The Heck-olefination was run in solvent-free conditions and then H$_2$O$_2$ was added slowly over 12 h in the second step. The LDH-PdOsW and the chiral ligand are recovered almost quantitatively, and the metal matrix can be re-used over five recycles without loss of activity. They assume that whereas Os and W remain bound throughout the reaction, Pd leaches into solution during the reaction and is redeposited on the support after the reaction. The high ee values obtained in this study and X ray diffraction signify that the OsO$_4{}^{2-}$ ion is only present on the surface of the support.

A plausible mechanistic route for the tandem Heck coupling, asymmetric dihydroxylation, and *N*-oxidation mediated by the trifunctional catalyst composed of Pd, Os, and W is shown in Scheme 10. PdCl$_4$ precursor catalyzes the Heck coupling, followed by AD reaction with OsO$_4$. The peroxo species generated from tungstate and H$_2$O$_2$ rapidly recycle the *N*-methylmorpholine (NMM) to its *N*-oxide species (NMO), which in turn reoxidizes Os(VI) to Os(VIII). The continuous supply of NMO was ensured *in situ* through the oxidative cycle of NMM by H$_2$O$_2$. It is surprising that the efficiency and enantioselectivity using the heterogeneous trimetal catalyst system are highly comparable to those obtained when a mixture of three homogeneous precursors is employed simultaneously under otherwise identical conditions. The basicity of OH groups on the surface of LDH support makes the hydrolysis of the osmium monoglycolate intermediate accelerated with increased ee's in some cases, compared to those of homogeneous counterparts.[16] Although this reaction protocol may be regarded as
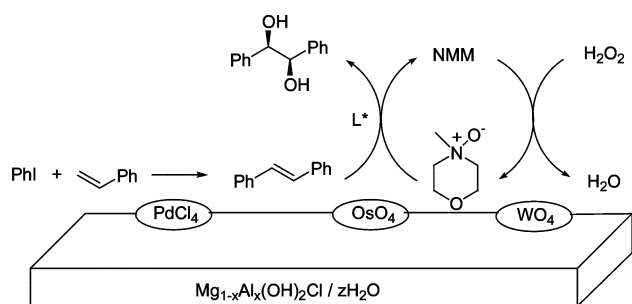
Scheme 10 A possible scheme for three tandem reactions in one-pot using LDH–PdOsW.

one of the most elegant examples closely mimicking biochemical catalysis, the origins of the observed extremely high enantiose-lectivity are not clearly understood considering the heterogeneous nature of the catalytic system.

## 2.2 Sequential catalytic reactions by compatible catalysts (Type II, eqn. (2))

A method for the activation of chloroarenes toward olefin arylation was reported by means of a bimetallic nickel and palladium co-catalyst system (Scheme 11).[17] Although both Ni and Pd catalysts
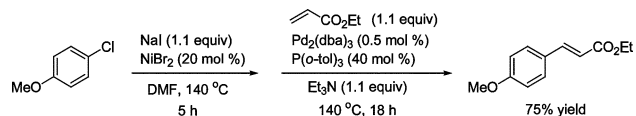
Scheme 11 Heck-type of olefination of chlorobenzene with a Ni/Pd co-catalyst system.

are required for the efficient transformation, the reaction is best performed in two separate one-pot stages. In contrast, combining the Ni and Pd components simultaneously results in a rather lower yield. It is surprising that the success of the reaction turned out to be dependent on the nickel-catalyzed conversion of small amounts (*ca.* 5%) of the starting chloroarene to the corresponding iodoarene *in situ*. It was claimed that the subsequent Pd-catalyzed Heck reaction consumes the *in situ* formed iodoarene thus driving the unfavorable exchange equilibrium toward product.

An electron transfer mechanism was proposed for the Ni-catalyzed halide exchange step in the reaction (Scheme 12). Under
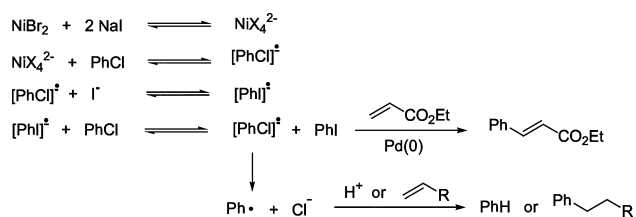
Scheme 12 Proposed routes for halide exchange and olefination reaction.

the reaction conditions, NiBr$_2$ is first converted to a tetrahedral polyhalo nickelate salt that transfers an electron to chloroarene giving a radical anion adduct, which is subjected subsequently to a halide exchange with I$^-$. As a result of the electron transfer process, free iodobenzene is generated *in situ* and it is coupled with activated olefin by the action of Pd catalyst. Formation of side products such as reduced adducts is attributed to a trap of the anionic intermediates by Et$_3$NH$^+$Cl$^-$ or excess olefin in solution. Experimental results that a radical scavenger suppresses the reaction and that *p*-nitrochlorobenzene does not undergo coupling may support the assumption on the mechanism.

An interesting co-catalyst system, composed of Wilkinson's rhodium(I) complex and palladium(II) acetate species, was utilized by Bankston *et al.* for efficient and selective intramolecular Heck olefination of a set of crotyl ethers (Scheme 13).[18] Although the same transformation can be also carried out with Pd(OAc)$_2$ catalyst
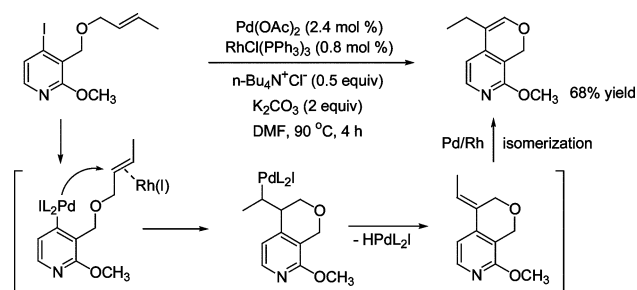
Scheme 13 Intramolecular Heck olefination reaction with Rh/Pd co-catalyst system.

alone, introduction of the second Rh(I) co-catalyst significantly improves the reaction rate, selectivity, and reproducibility under otherwise identical conditions. This shows one of the notable examples demonstrating beneficial effects offered by the simultaneous use of two different metals for interdependent cooperation in a specific reaction. Under the co-catalyst system consisting of Rh and Pd, the reaction was completed in 4 h affording *endo*-bicyclic ether as a major isomer with an *endo:exo* ratio as high as 29:1. In contrast, with the use of Pd catalyst alone under otherwise same conditions, it required 16–20 h to reach completion and selectivity for the *endo*-isomer became much lower (*endo:exo*, 3 ~ 8:1). Although detailed supporting evidence is not available, it is proposed that initial coordinative complex formation between rhodium(I) and crotyl ethers would enhance the rate of the Pd-catalyzed cyclization *via* 6-*exo-trig* route, and that subsequent isomerization of the initially formed *Z-exo* adduct into the final *endo*-isomeric product is also accelerated by the presence of the second Rh co-catalyst. It is also noteworthy that in the absence of palladium(II) species, rhodium(I) alone does not act as an isomerization agent, and it does not catalyze the intramolecular cyclization of the employed substrate as well. In addition, changing parameters such as concentration and temperature appeared to significantly affect the reaction rates and selectivity in the experiments involving the co-catalyst system. Although the exact role of the Wilkinson catalyst is not clear from the presented study, it does not seem to isomerize the allylic olefin before the cyclization, and its presence helps to provide a more reproducible outcome and a faster rate.

A combination of Pd and Rh catalysts has been used to carry out a one-pot Pauson–Khand reaction starting from propargyl malonate and allylic acetate (Scheme 14).[19] This includes two reactions: the
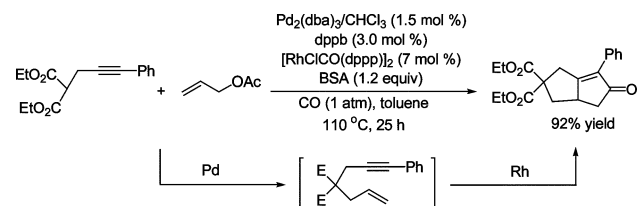

Scheme 14 Pauson–Khand type reaction by tandem catalysis of Pd and Rh.

first palladium-catalyzed allylation of alkynyl malonate to generate an enyne intermediate and the following rhodium-catalyzed cyclization in the presence of carbon monoxide. Because sodium propargyl malonate was not compatible as a nucleophile in the allylation with the employed catalysts, a method of *in situ* generation was taken by the use of bis-(trimethylsilyl)acetamide (BSA). It is interesting that the Lewis acidity of Rh(I) seems to influence significantly the Pd-catalyzed allylation efficiency. While [RhCl(CO)$_2$]$_2$ and [RhCl(CO)dppe] were not compatible with Pd(dba)$_2$/dppb, [RhCl(CO)(dppp)]$_2$ and [RhCl(CO)(dppb)]$_2$ turned out to be effective in combination of the Pd counterparts (dppe: 1,2-bis(diphenylphosphino)ethane, dppp: 1,3-bis(diphenyl-phosphino)propane, dppb: 1,4-bis(diphenylphosphino)butane). The optimized ratio of Rh(I)/Pd was 2–3/1, under which condition

the formation of unwanted side products was almost completely suppressed.

An alternative approach to the same Pauson–Khand cyclization reaction has been reported by Evans *et al*. A single metal catalyst, rhodium, was employed to facilitate both transformations in a tandem sequence, changing only the reaction temperature to modulate the catalytic activity for each step (Scheme 15).[20]
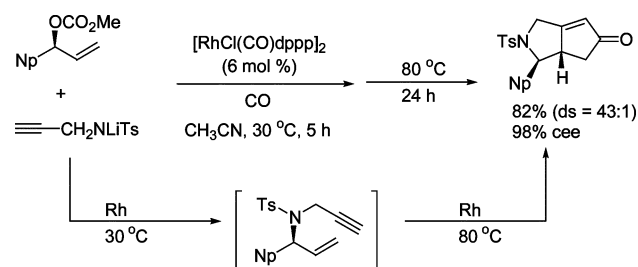
Scheme 15 Tandem allylic substitution and Pauson–Khand annulation with a single rhodium catalyst under different reaction temperatures.

Treatment of allylic carbonate with the sodium or lithium salt of carbon or heteroatom nucleophile and [RhCl(CO)dppp]$_2$ in acetonitrile at 30 °C, under an atmosphere of carbon monoxide, furnished enyne products highly favoring the secondary adduct. Subsequent annulation step was also achieved by the original rhodium precursor catalyst under the same conditions except for the reaction temperature being 80 °C. It is noteworthy that diastereoselectivity in the cyclization step was also high to excellent by the use of Rh catalyst. Selectivity in the annulation step is believed to be controlled by the steric size of the substituent at the C-2 position. In fact, an allylic carbonate having a very bulky group at C-2 position, 2-naphthyl substituent, produced azabicycles with excellent selectivity. Furthermore, the allylic amination is highly enantiospecific (98% ee) and proceeds with retention of absolute configuration with the catalysts system employed.

A bimetallic catalyst system of Pd/Co nanoparticles immobilized on silica support (PCNS) has been shown to be effective for a sequential allylic alkylation and Pauson–Khand annulation (Scheme 16).[21] It is interesting that the bimetallic nanoparticles
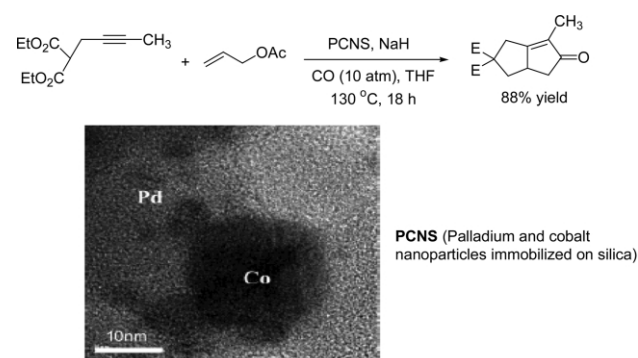

Scheme 16 Heterogeneous bimetallic catalysis for Pauson–Khand annulation.

were produced in the cluster-in-cluster structures. The sodium salt of the malonate nucleophile was prepared *in situ* using sodium hydride and annulation was best carried out at 130 °C under 10 atmosphere of carbon monoxide. In spite of the high surface-to-volume ratio of the nanoparticles, the re-usability of the PCNS (14.5 wt% of Co and 1 wt% of Pd) turned out to be notably limited, due to a significant leaching of palladium from the support in each cycle. Whether any synergistic effects between the two different metals species have been observed is not clear from this study, but it represents the first example of using immobilized bimetallic nanoparticles in two conceptually different catalytic reactions in one-pot processes.

Based on the approach shown above, Chung *et al*. have elegantly demonstrated the usefulness of the combination of cobalt and palladium catalysts in a three-step one-pot synthesis of fenestranes, mutually fused tetracyclic skeletons (Scheme 17).[22] Starting from
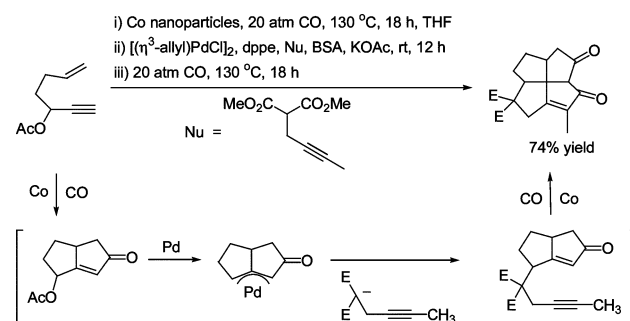
Scheme 17 Three-step one-pot synthesis of fenestranes.

an enyne and alkynyl malonate, it was designed that cobalt nanoparticle-catalyzed Pauson–Khand reactions are in action in two steps along with a Pd-catalyzed allylic alkylation in one step. The conversion is presumed to proceed *via* two different types of reactions in three steps; Co-catalyzed annulation of enynes with carbon monoxide in the first and third step, and Pd-catalyzed allylic alkylation in the middle step. The first and second steps were readily accomplished by using cobalt on charcoal and homogeneous Pd(II) catalysts, respectively. However, cobalt on charcoal turned out to be ineffective in the third step implying that cobalt on the charcoal system was damaged after the second step. In contrast, cobalt nanoparticles were tolerant of all the reaction conditions and effective for both the first and third Pauson–Khand reactions. This is a rare example of the combined use of transition metal nanoparticles and conventional homogeneous catalyst in a one-pot multiple-step reaction.

Uemura *et al*. have reported a co-catalyst system of ruthenium and platinum for three-step sequential processes to afford tri- and tetra-substituted furans and pyrroles in moderate to high yields starting from propargylic alcohols (Scheme 18).[23] A thiolate-
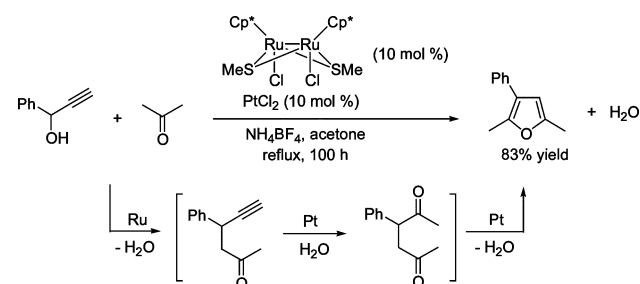
Scheme 18 Synthesis of furans *via* sequential catalysis by Ru/Pt.

bridged diruthenium complex, [Cp*RuCl(μ$_2$-SMeRuCp*Cl] (Cp* = η^5-C$_5$Me$_5$), initiates the first step of propargylic substitution with a ketone to give γ-ketoalkyne. Subsequent hydration of alkyne and dehydration of the resultant 1,4-diketone are presumed to be catalyzed by PtCl$_2$. Separately, the catalytic conversion of isolated γ-ketoalkyne into 1,4-diketone and furan was confirmed in the presence of PtCl$_2$. It is interesting to observe that co-existence of Ru and Pt catalysts promotes the conversion more smoothly when compared to the rate of the same reaction in the presence of a single Pt catalyst alone. This may demonstrate the synergistic effects of the co-catalytic system for a specific step although the individual step proceeds with a single catalytic species.[24]

An example of the use of two palladium catalysts in one-pot has been recently reported by Mascareñas *et al*. for the synthesis of oxabicyclic molecules *via* sequential ketone-alkyne cyclo-iso-merization and hydrogenation processes (Scheme 19).[25] The first step is presumed to proceed under kinetic control by co-ordination of electrophilic Pd(OAc)$_2$ catalyst to alkyne followed by *anti* attack of the carbonyl oxygen. It is interesting that the reaction is carried out in the presence of an H$_2$ atmosphere from the start and the
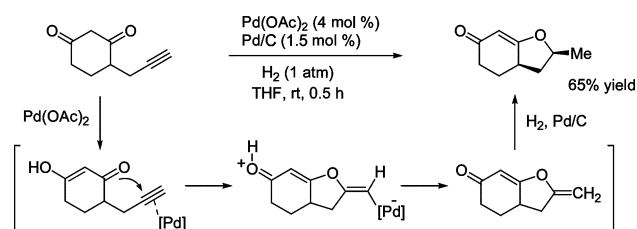
Scheme 19 Tandem cyclo-isomerization and hydrogenation of alkynyl diketones with a co-catalyst system of Pd(OAc)₂ and Pd/C.

reaction course is barely affected by the conditions. Moreover, noteworthy is that subsequent hydrogenation is carried out only by Pd/C even in the presence of Pd(OAc)₂ precursor catalyst in the reaction vessel.

Hayashi *et al.* have described an elegant strategy for the asymmetric synthesis of 1,2-diols from terminal alkynes by use of successive double hydrosilylation with Pt and Pd catalysts in one-pot followed by Tamao oxidation of the crude bis(silyl)ethanes (Scheme 20).[26] Because regioselectivity in the Pd-catalyzed
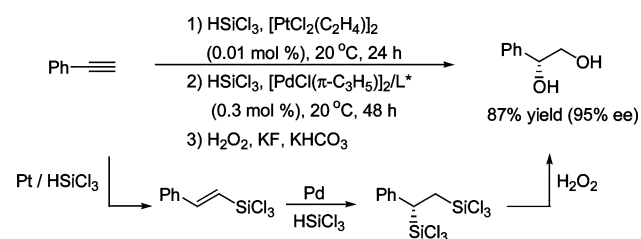
Scheme 20 Asymmetric synthesis of 1,2-diols from the successive double hydrosilylation of alkynes with Pt and Pd catalysts in one-pot.

hydrosilylation of terminal alkynes was low, Pt was employed as the first hydrosilylation catalyst generates (*E*)-vinylsilanes which are, without isolation, subjected to the subsequent Pd-catalyzed asymmetric hydrosilylation. With the Pt catalyst, the second hydrosilylation of vinyl silane intermediates does not occur under the reaction conditions. The asymmetric second hydrosilylation of alkenyl silanes was realized by use of a palladium catalyst with (*R*)-2-bis[3,5-bis(trifluoromethyl)phenyl]phosphino-1,1(-binaphthyl (L*) with a complete regioselectivity and high enantioselectivity. It is remarkable that when the conversion was initially tried with only a single Pd catalyst in the presence of the same chiral ligand, the desired diol product was obtained only in low yield (30%, 95% ee) along with the formation of a dimerization–hydrosilylation side adduct (60%). This again demonstrates the beneficial effects from the use of co-catalytic conditions instead of the more traditional single catalyst systems.

The titanium-catalyzed hydroamination of alkynes has been developed into as a versatile tool for the highly flexible synthesis of biologically interesting nitrogen-containing compounds. Expanding the synthetic protocol, Doye *et al.* designed a clever combination of a Ti-catalyzed hydroamination of alkynes with a Pd-catalyzed *N*-arylation of resultant imines affording a new method for the synthesis of indoles (Scheme 21).[27] This strategy
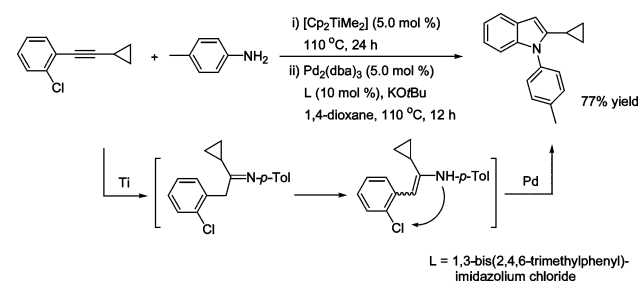

Scheme 21 One-pot procedure for the synthesis of indoles.

allows the successive formation of two C–N bonds during the one-pot procedure. It is assumed that under basic conditions, the imines,

which are regioselectively formed during the hydroamination of alkynes with [Cp₂TiMe₂] catalyst, are in equilibrium with the corresponding enamines. An *ortho*-chloro substituent in the aromatic ring would offer the possibility to convert the enamines into indoles by a [Pd₂(dba)₃]-catalyzed *N*-arylation/cyclization in the presence of a ligand, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (L). Since the enamines are removed from the equilibrium during the second part (cyclization cycle) of the one-pot procedure, it is expected to efficiently convert the imine intermediates into indole products.

While the ruthenium carbene complex L₂X₂Ru=CHR has found extensive use in olefin metathesis, it has also recently shown to be an effective pre-catalyst for mediating various mechanistically different reactions such as transfer radical polymerizations and olefin hydrogenations. It was already known that a ruthenium hydride complex RuHCl(H₂)L₂ is formed *in situ* upon introduction of H₂ following an olefin metathesis reaction using L₂Cl₂Ru=CHPh. The subsequent hydrogenation is believed to be catalyzed by the *in situ* generated ruthenium hydride, and the reaction is readily carried out in one-pot by simply elevating reaction temperatures under hydrogen atmosphere after olefin metathesis. Grubbs *et al.* have elegantly demonstrated that a more reactive *N*-heterocyclic ruthenium benzylidene is highly useful in performing one-pot three tandem catalytic reactions including ring-closing olefin metathesis (RCM) of dienes, transfer dehydrogenative oxidation of alcohols, and hydrogenation of olefins (Scheme 22).[28] The strategy was applied to a one-pot three-step synthesis of
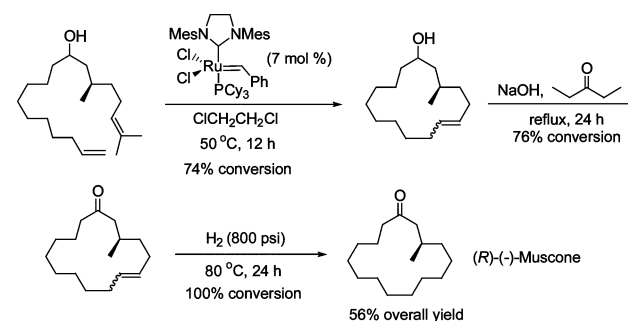
Scheme 22 One-pot three-step procedure of olefin metathesis, transfer dehydrogenation, and hydrogenation with a single-component Ru complex.

(*R*)-(−)-muscone, a natural product with a desirable fragrance. In this case, after the ring-closing metathesis (RCM) of a diolefinic alcohol, the transfer dehydrogenation of the resulting cycloalkenyl alcohol was carried out in the presence of 3-pentanone and NaOH. Subsequent hydrogenation of the olefinic ketone intermediate was presumed to proceed by *in situ* generated ruthenium hydride catalyst in excellent yield under mild conditions. The ruthenium catalyst in this protocol exhibits compatibility with many functional groups under the reduction conditions, which is not the case for many hydrogenation procedures.

Snapper *et al.* has presented additional example of a tandem protocol using a ruthenium carbene precursor for the synthesis of cyclic enol ethers, a major component among various bioactive compounds such as glycals, polyether antibiotics, and nucleoside antibiotics (Scheme 23).[29] This process provides cyclic enol ethers through Ru alkylidene-catalyzed ring closing metathesis (RCM) of acyclic dienes followed by olefin isomerization of the resulting RCM products in one-pot. It is interesting to note that while commercially available, unpurified ruthenium alkylidenes can affect the isomerization of generated double bonds, only purified ones possess the metathesis activity. The study indicates that the treatment of ruthenium alkylidene in CH₂Cl₂ with small amounts of H₂ leads to an olefin isomerization-active Ru catalyst, presumably a hydride derivative. Surprisingly, the tandem reactions are carried out under the atmosphere of N₂:H₂ (95:5) from the start suggesting that isomerization of cyclic allylic ethers into the corresponding
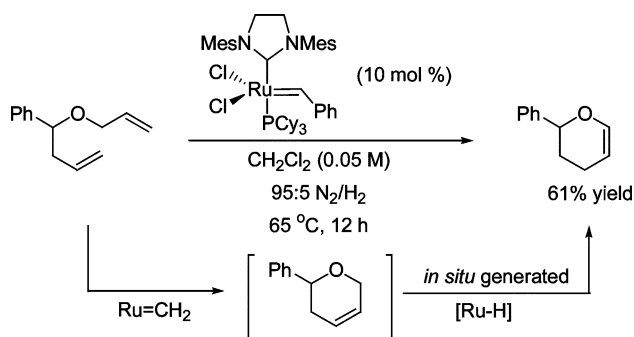
enols occurs with much slower rates compared to ring-closing metathesis. Despite the strong presumption that the ruthenium hydride is responsible for the olefin isomerization, characterization of the plausible species was unsuccessful by spectroscopic means. Because the preparation of vinyl ethers is not trivial in organic synthesis and, moreover, they are generally poor substrates for metathesis reactions with the ruthenium carbene catalysts, this user-friendly two-step approach would be an attractive route for the synthesis of cyclic enol ethers.

A different approach based on the tandem metathesis and hydrogenation sequence has been reported by Cossy *et al.* with the use of both ruthenium carbene and platinum catalysts simultaneously (Scheme 24).[30] This three-step one-pot procedure allows the
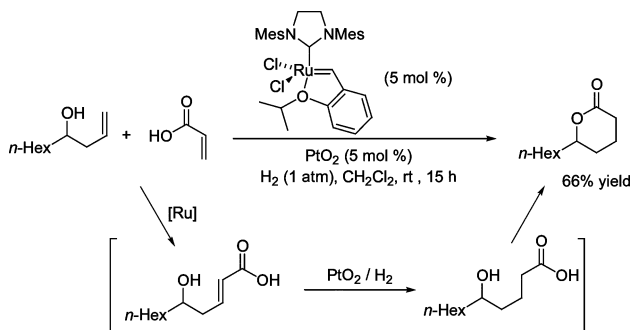
Scheme 24 Tandem cross-metathesis/hydrogenation/cyclization reactions by a simultaneous use of Ru and Pt catalyst.

facile synthesis of substituted lactones and lactols from acrylic acid and acrolein, respectively, in the presence of unsaturated alcohols. The co-catalytic system is so designed that the first step is accomplished with the tethered ruthenium carbene catalyst, and the subsequent hydrogenation is catalyzed by PtO$_2$ at room temperature under 1 atm of hydrogen. The two metal species show complete compatibility with each other under the reaction conditions. It is also noteworthy that the three-step reaction sequences are actually in the right order coincidentally to afford the desired products. In fact, the employed ruthenium carbene as well as PtO$_2$ do not catalyze the esterification of acids, ruling out an alternative sequence to lead to the same products: esterification–RCM–hydrogenation. However, it was observed that when a sterically hindered allylic alcohol is employed under the reaction conditions, the Pd-catalyzed hydrogenation is faster than the Ru-catalyzed cross-metathesis reaction.

Shibasaki *et al.* have recently shown that asymmetric epoxidation of α,β-unsaturated amides by chiral lanthanide catalysts can be efficiently combined with subsequent Pd-catalyzed epoxide opening process in one-pot to give β-aryl α-hydroxy amides in excellent yields and enantioselectivity (Scheme 25).[31] Epoxidation of unsaturated amides is readily performed with chiral lanthanide catalysts, Sm-(*S*)-BINOL-Ph$_3$PO in the presence of TBHP to afford α,β-epoxy amides. Upon completion of the epoxidation reaction, epoxide opening process is efficiently achieved with the use of Pd/
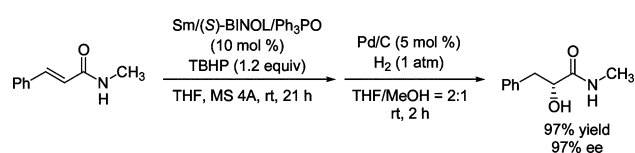
Scheme 25 One-pot sequential catalytic epoxidation and epoxide opening reactions.

C catalyst in THF and MeOH co-solvent. It is highly interesting that selectivity in epoxide opening is dependent on the components of the first step. When Pd/C was used alone, two side products, dehydroxylated adduct and α-oxoamide moiety, were also generated in about 8% from the reaction. In contrast, formation of the undesired molecules was almost completely suppressed when the reaction was carried out in the presence of all of the reagents for the first epoxidation. The authors suggest that beneficial modifications of the Pd catalyst are achieved by the Sm catalyst system of the first epoxidation reaction, producing a more suitable Pd catalytic system for the subsequent epoxide opening step.

## 2.3 Cooperative and concerted catalytic reactions (Type III, eqn. (3))

Coupling reactions between sp^2-carbon (pseudo)halides and terminal acetylenes have been developed as a highly useful and practical synthetic method for the introduction of alkynyl groups into arenes or alkenes with the use of Pd and Cu co-catalyst system, generally known as the Sonogashira reaction (Scheme 26).[32] In fact, this
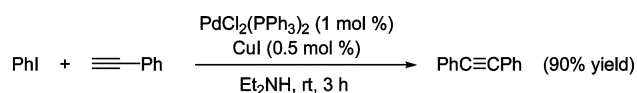
Scheme 26 Pd/Cu catalyzed alkynylation reaction.

catalytic route was derived from the previously known Castro-Stephens reaction, in which pre-prepared cuprous acetylides are coupled with aryl iodides in a stoichiometric reaction.[33] Although cuprous iodide is generally a copper catalyst of choice, choice of palladium counterpart is more flexible being (PPh$_3$)$_2$PdCl$_2$, (PPh$_3$)$_4$Pd, (dppe)PdCl$_2$, Pd(OAc)$_2$/PPh$_3$, (CH$_3$CN)$_2$Cl$_2$Pd/PPh$_3$, or Pd$_2$(dba)$_3$/AsPh$_3$ in the presence of secondary or tertiary alkyl amines. In any case, no catalytic substitution of acetylenes occurs at room temperature in the absence of cuprous iodide addressing the role of the copper co-catalyst for the conversion. Couplings between acetylenes and aryl iodides having electron-withdrawing groups *ortho* or *para* to the halide proceed even in the absence of copper co-catalyst, but only under more harsh conditions. This procedure has been shown to be particularly attractive and versatile because it usually offers, under mild reaction conditions, high product yields, good regio- and stereoselectivity, and excellent compatibility with many functional groups. Efficiency of the reactions has been extensively demonstrated in the area of organic synthesis, material sciences, and pharmaceutical and agricultural processes.

In the Sonogashira reaction, it seems likely that the palladium-catalyzed activation of aryl- and alkenyl (pseudo)halides is cooperatively coupled through a transmetallation transfer process with the catalytic route of *in situ* formation cuprous acetylides in the presence of amine (Scheme 27).[34] Although the exact structure of the catalytically active species and more precise role of copper catalyst still remain unclear, the reaction is assumed to follow the normal oxidative addition–reductive elimination steps common to Pd-catalyzed cross coupling reactions. The process is envisaged to involve palladium in zero oxidation state as [Pd(0)], [Pd(PPh$_3$)]$_2$, or anionic [Pd(0)(PPh$_3$)$_2$X]$^-$ being generated *in situ* from the Pd(II) pre-catalysts. The coordination of alkynyl triple bonds to copper salt would increase the acidity of acetylenic hydrogen enough to be deprotonated with such weak bases as diethylamine or triethylamine generating cuprous acetylide species. Details of the subsequent transmetallation transfer process of the acetylide group
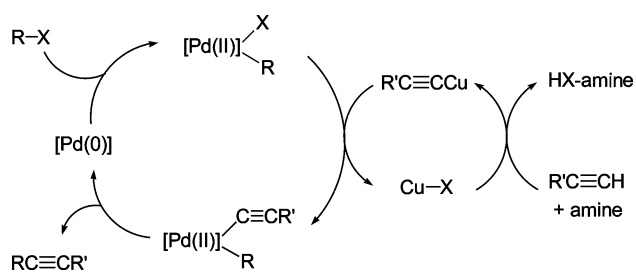
Scheme 27 Proposed co-catalytic routes in the Sonogashira reaction.

from copper to palladium moiety are not fully understood at the present stage. Reductive collapse of the alkynylpalladium(II) intermediates would afford the coupled products regenerating the active Pd(0) species. In this process, no acceleration was evidenced with the help of copper co-catalyst.

An elegant two-component catalyst system consisting of Rh and Pd metal species has been introduced by Ito *et al.* for the enantioselective allylic alkylation of activated nitriles (Scheme 28).[35] This is a rare example that the two catalysts activate their
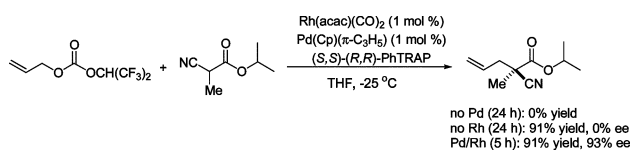
Scheme 28 Enantioselective allylic alkylation with the use of a two-catalyst system, Rh/Pd in the presence of a chiral ligand.

respective reactants in *a substrate-selective manner* and the resulting activated species react to afford coupled products in high enantioselectivity in the presence of a *trans*-chelating chiral phosphine ligand, (*S,S*)-(*R,R*)-2,2″-bis[(*R*)-1-(diphenylphosphi-no)ethyl]-1,1″-biferrocene (PhTRAP). It is a remarkable observation that this asymmetric Tsuji–Trost reaction shows high enantio-selectivity only in the presence of both Rh and Pd catalysts. The control experiment catalyzed only by the Pd catalyst proceeds more slowly, and the coupled product is racemic even in the presence of the same chiral ligand. In addition, no conversion is catalyzed by the Rh/L* alone in the absence of Pd catalyst. Therefore, it is assumed that the eminent enantioselectivity in the two-catalyst coupling reaction originates solely from the portion of Rh catalytic cycles and that the palladium-catalyzed routes have no effects on the degree of asymmetric induction. In fact, when a combination of preformed Rh/TRAP and Pd/L (L is an achiral ligand) is applied to the reaction conditions, the exactly same enantioselectivity (93% ee) was observed.

The authors suggest that a Rh(I)-coordinated α-cyano enolate complex is initially formed from Rh(acac)(CO)$_2$, a chiral phosphine ligand (L*; PhTRAP), and the cyano ester substrate, while π-allylpalladium(II) complex is generated by the decarboxylative oxidative addition of allyl carbonate to palladium(0) complex (Scheme 29). Subsequent nucleophilic attack of the Rh-enolate to
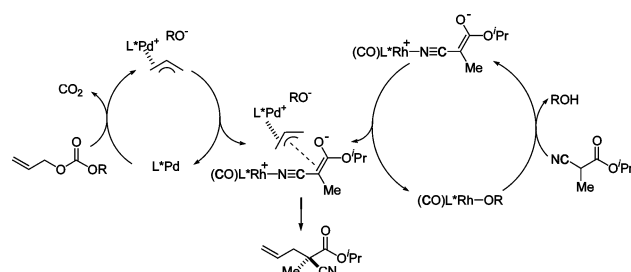

Scheme 29 Proposed cooperative catalytic pathway in the Ito Rh/Pd system.

the π-allylpalladium(II) adduct is assumed to occur enantiose-lectively to afford optically active product. At this step, the

palladium(0) is reproduced and alkoxide ion derived from carbon-ate becomes a ligand of the rhodium atom to form alkoxo rhodium(I) species. It is suggested that the catalytic system is completed by the proton exchange between alkoxo rhodium(I) complex and cyano ester, forming the α-cyano enolate intermediate and ROH. Although this represents a novel example of enantiose-lective cooperative two-catalyst systems, fully understanding the way the two metal intermediates interact, especially in terms of stereocontrol, is still at an early stage.

Maleczka, Jr. *et al.* have recently reported a significant example of a two-catalyst one-pot approach for achieving Stille coupling reactions that are catalytic in tin (Scheme 30).[36] The Stille reaction
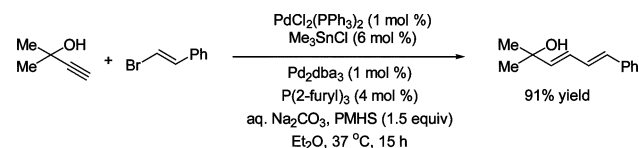
Scheme 30 Stille coupling reactions catalytic in tin with the use of two different Pd catalysts.

has been widely used as a reliable, efficient, and selective tool for the formation of C–C bonds in organic synthesis. However, one of main drawbacks in the reaction is that it requires stoichiometric amounts of organostannanes that are usually toxic, costly, unstable in some cases, and difficult to separate from the reaction mixture. Obviously, a way for relieving the "tin problem" would be the use of catalytic amount of tin in the coupling. With the use of alkynes as a precursor of vinylstannane, a novel co-catalytic system has been introduced for the new Stille reaction catalytic in tin by developing catalytic conditions for both hydrostannylation and subsequent couplings in one-pot. Syringe pump addition of 1.5 equiv of various Stille electrophiles to an ethereal mixture of an alkyne, aqueous Na$_2$CO$_3$, polymethylhydrosiloxane (PMHS), Pd$_2$dba$_3$ (1 mol%), trifurylphosphine, PdCl$_2$(PPh$_3$)$_2$ (1 mol%), and 0.06 equiv of Me$_3$SnCl over a period of 15 h at reflux temperature afforded the corresponding cross-coupled products in 75–91% displaying an average of ~ 15 tin turnovers. Choice of the tin turned out to be crucial for the efficiency of the coupling. For example, when sterically more demanding tributyltin chloride is used instead of the trimethyltin counterpart, the reaction is sluggish to afford lower product yields (48–72 h, 22–26% yield) representing 2–5 tin turnovers in this case. For optimal efficacy, the reaction is best run with α-trisubstituted alkynes so as to avoid regiochemical mixtures during the hydrostannylation step and beyond.

The basic strategy for the Stille coupling catalytic in tin is to find an optimal condition for achieving the catalytic hydrostannylation of alkyne precursors that are compatible with the subsequent Pd-catalyzed coupling between organoelectrophiles and the *in situ* formed vinylstannanes (Scheme 31).[37] The required hydrostannyla-
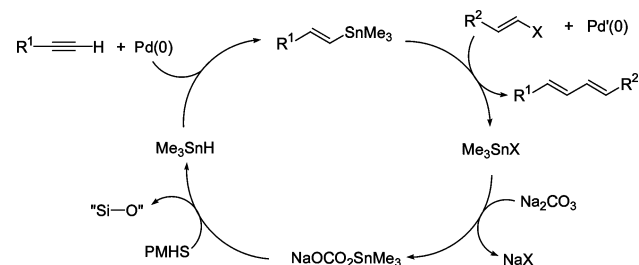

Scheme 31 Proposed double catalytic routes for the Stille couplings catalytic in tin.

tion of terminal alkynes is assumed to proceed by the action of a Pd catalyst with tin hydride that is generated *in situ* from a reaction of PMHS and tin carbonate, another proposed key intermediate in the catalytic cycle. Subsequently, vinyl tin adducts generated *in situ* couple with alkenyl halides by the Pd$_2$dba$_3$/P(2-furyl)$_3$ catalyst system to afford Stille products. The last step to complete the cycle

would be recycling the Me_3-SnX by-product back to Me_3SnH. Because PMHS does not directly reduce organotin halides to the corresponding hydrides, an indirect route is presumed in action *via* a tin carbonate intermediate. On the basis of the assumption, Na_2CO_3/PMHS turned out to be an ideal system for regenerating a tin hydride from a tin carbonate adduct in aqueous media. The exact structures of triorganotin carbonates, however, still remain a subject of debate. It is remarkable to note that the high efficiency was achieved in the present Stille reaction through balancing the opposite electronic environments between hydrostannylations (favor strong σ-donor ligands) and cross couplings (prefer weak σ-donor ligands). However, it is not clearly understood how the two employed Pd catalysts tell their individual missions apart for achieving the net couplings, if there are two separate catalytic cycles. Although the authors proposed a cooperative two-catalyst two-catalytic route in the reports, another possibility that the two added Pd complexes form *in situ* a single catalytically active adduct responsible for both hydrostannylation and cross couplings can not be completely ruled out at the present stage.

A bimetallic catalyst system consisting of Pd(0) and Cu(I) has been efficiently utilized by Yamamoto *et al.* in the coupling reaction of alkynylphenylisocyanates with allyl carbonates to provide substituted indoles (Scheme 32).[38] With the use of a single
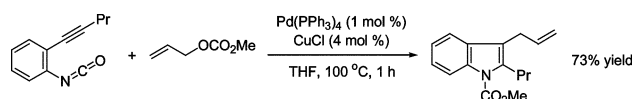
Scheme 32 Indole synthesis by a Pd/Cu co-catalyst system.

Pd catalyst in the absence of Cu species, *N*-allylated anilines are obtained exclusively instead of the cyclized indoles. While the addition of some copper(I) species such as CuCl and CuBr into the Pd catalyst system changes the synthetic route providing indoles in good yields, Cu(II) adducts do not show such effects at all. The reaction with bulky allyl carbonates also proceeds smoothly to give the corresponding indoles in good yield, and electronic variation on phenyl-substituted isocyanates has little effect on the efficiency of the reaction.

In the Pd and Cu cooperative catalytic system, the Cu(I) co-catalyst is assumed to act as a π-coordinative Lewis acid (Scheme 33).[39] Initially, the Pd(0) center reacts with allyl carbonates to give
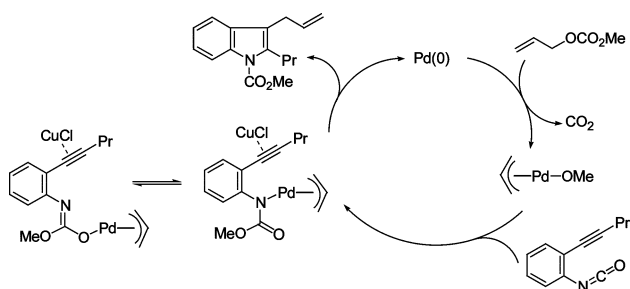
Scheme 33 A proposed route in the synthesis of indoles by a Pd/Cu bimetallic catalyst system.

the π-allylpalladium alkoxide complex with extrusion of CO_2. Then, the insertion of isocyanates into the π-allylpalladium species would form the π-allylpalladium intermediate that could be in equilibrium with the Pd–O bonded moiety. Insertion of the alkyne then occurs to form indole and the Pd(0) species is regenerated. The key step in this proposed mechanism is the insertion of the alkyne into the π-allylpalladium intermediates with the assistance of π-coordination of CuCl to the triple bond making it more reactive. However, an alternative mechanism still can not be ruled out, in which copper activates the nitrogen nucleophile and the triple bond coordinates to π-allylpalladium cationic species. Although it is not easy to single out the two possibilities, the observed effects of the additive copper co-catalyst is obvious, that no carboamination takes place at all in the absence of CuCl. More recently, a single catalyst

system of Na_2PdCl_4 or $PtCl_2$ has been shown by the same authors for the synthesis of indoles starting from alkynylisocyanates and alcohols instead of allyl carbonates as in the Pd/Cu bimetallic system. It is proposed that Pd(II) or Pt(II) catalyst exhibits a dual role acting as a Lewis acid to accelerate the addition of alcohols to isocyanates as well as a typical transition-metal catalyst to activate triple bond for subsequent cyclization.[40]

Lee *et al.* reported that allenylindium reagents generated *in situ* from the reaction of indium metal with propargyl bromides can be used in palladium-catalyzed cross coupling with organic electrophiles to afford allenes, polyallenes, bis(allenes) in excellent yields and high selectivities.[41] Although indium has to be employed in stoichiometric amounts, this represents one of elegant examples demonstrating high utility of the concept of cooperative metal systems in organic synthesis.

Recently, a new type of cooperative two-catalyst system has been introduced for the coupling reaction of a chelating formate with aryl and alkenyl (pseudo)halides (Scheme 34).[42] Whereas no
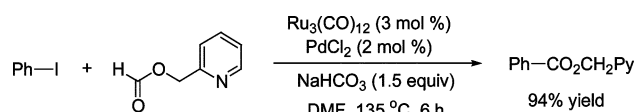
Scheme 34 Chelation-assisted alkoxycarbonylation of aryl halides with a Ru/Pd co-catalyst system.

coupled product was generated with the action of any single metal species alone (Ru, Rh, Pd, *etc.*), the net transformation was achieved only under the conditions that both Ru and Pd catalysts were used simultaneously. It is suggested that two catalytic processes are operational concurrently under the conditions; decarboxylation of pyridylmethyl formate by a Ru catalyst, and subsequent Pd-catalyzed alkoxycarbonylation of organic electrophiles. This is based on an independent experiment that a treatment of 2-pyridylmethyl formate with $Ru_3(CO)_{12}$ (5 mol%) results in complete decarbonylation within 1 h at the reaction temperature (DMF), generating 2-pyridinemethanol and CO in quantitative yields. The facile decarbonylation of 2-pyridylmethyl formate is believed to be chelation-driven by a coordination of Ru to pyridyl nitrogen atom of the formate. It is interesting that while $Ru_3(CO)_{12}$ was the only effective Ru species, a choice of Pd is more flexible and several Pd sources gave a rather similar efficiency for the coupling: $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(bda)_3$, or Pd/C. A large array of coupled products, 2-pyridylmethyl esters of aryl and alkenyl carboxylic acids, can be obtained in good to excellent yields with the use of the present two-catalyst protocol. One of the main advantages of this approach is claimed that it does not necessitate an external CO atmosphere compared to a Pd-catalyzed alkoxycarbonylation reaction, in which high pressure of CO is required to achieve high efficiency.

The reaction is presumed to proceed *via* two sequential catalytic cycles as shown in Scheme 35. When 2-pyridylmethyl formate was
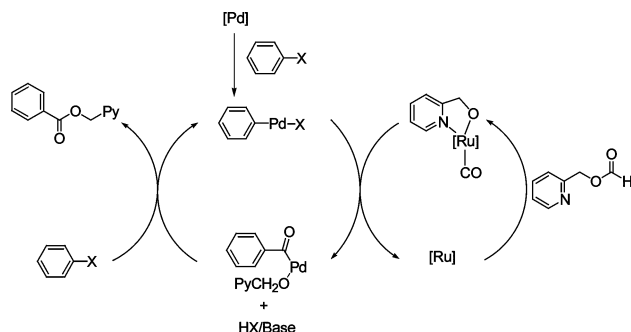
Scheme 35 Proposed mechanistic pathway for the Ru/Pd-catalyzed alkoxycarbonylation reaction.

treated with stoichiometric amount of $Ru_3(CO)_{12}$, a tri-ruthenium cluster coordinated with eight carbon monoxides and two mole-

cules of 2-pyridinemethanol was isolated and its structure was determined by a X-ray crystallographic analysis. The proposed mechanistic pathway is based on the observation that a coupled product is obtained albeit in moderate yield (43%) from the stoichiometric reaction of the isolated tri-ruthenium cluster with iodobenzene with the use of PdCl$_2$ catalyst (2 mol%) under CO atmosphere (1 atm). Transfer of 2-pyridinemethanol into the Pd-catalyzed alkoxycarbonylation cycles is assumed to be greatly accelerated by chelation of the intermediate with Ru. This leads to a presumption that the ruthenium catalyst has a dual role; decarbonylation of a chelating formate as well as transfer of the *in situ* generated carbinol to Pd catalytic cycles. The authors have also described a similar procedure for a cooperative aminocarboxylation of iodobenzene with a chelating formamide with the use of the same combination of Ru$_3$(CO)$_{12}$ and PdCl$_2$ catalyst.[43] With this approach, 2-pyridyl formamide and aryl iodides are readily coupled under the two-catalyst conditions to afford *N*-(2-pyridyl)benzamide adducts in moderate to good yields. It is also suggested that ruthenium catalyzes decarbonylation of *N*-(2-pyridyl)formamide to release carbon monoxide and 2-aminopyridine that are subsequently used in the Pd-catalyzed aminocarboxylation cycles, thus enabling the net transformation to be performed in the absence of external CO pressure.

With a similar approach as in the above case, Chung *et al.* employed 2-pyridylmethyl formate as a source of CO in the Pauson–Khand-type reaction using a heterobimetallic catalyst system of Ru/Co nanoparticles immobilized on charcoal (RuCNC, Scheme 36).[44] The cyclization product was also obtained in high
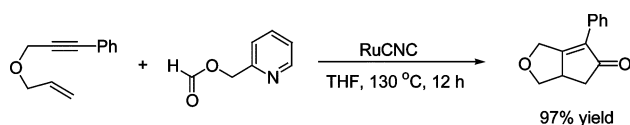
Scheme 36 Heterobimetallic catalyst system for Pauson–Khand-type reaction using a chelating formate as a CO source.

yield when the chelating formate was used with Ru$_3$(CO)$_{12}$ and cobalt nanoparticles in one-pot instead of RuCNC. However, no product was detected when either ruthenium carbonyl or colloidal cobalt nanoparticles were used as a single catalyst under otherwise identical conditions. Interestingly, when the Pauson–Khand reaction was tried in the presence of ruthenium nanoparticles under 20 atm CO, a considerable quantity of ruthenium metal was bled presumably due to the formation of stable ruthenium carbonyl complexes such as Ru$_3$(CO)$_{12}$. *In situ* generated CO from the Ru-catalyzed decarbonylation of 2-pyridylmethyl formate is presumed to insert into the subsequent cobalt-catalyzed carbonylative alkene-alkyne coupling cycles. However, it is still not clear whether the mechanistic route in the heterometallic cobalt-catalyzed cyclization is in a close resemblance to the homogenous catalysis. TEM images of RuCNC disclose the cluster-in-cluster structure, with mean sizes of 5 and 18 nm for ruthenium and cobalt particles, respectively. The bimetallic catalyst system is equally effective for both intra- and intermolecular Pauson–Khand reactions and easily reused up to five times without loss of catalytic activity. The observation that less than 0.1 ppm of both ruthenium and cobalt metal was leached from the support demonstrates the sturdiness of the catalyst system under the reaction conditions.[45]

3 Conclusions and outlook

Throughout this review, several representative examples of multiple catalytic one-pot systems are presented. The first type of reaction, in which a catalyst performs a desired reaction as the second catalyst reoxidizes the first catalyst for the next cycles, has been elegantly applied especially to the oxidation of olefins. It is further anticipated that, using the same strategy, efficient oxidative transformations of more diverse classes of substrates including alkynes would be possible with practical aspects. The illustrations where two catalysts perform sequential organic transformations in

a single vessel are significantly increasing in recent years. In many aspects, this approach of one-pot tandem catalysis demonstrates that it makes the processes more economical and time saving compared to the traditional one-catalyst one-reaction routes. In special cases, a single metal precursor carries out mechanistically different reaction steps in the same vessel upon change of reaction conditions. As the third type, some promising results have been revealed that both substrates are activated in a simultaneous/ cooperative manner by suitable catalysts followed by coupling of thus activated partners to generate the desired products. With the use of this approach, an increasing number of examples has demonstrated that it frequently offers opportunities not only for more efficient but also for entirely new transformations which cannot be achieved under any single catalyst conditions. Selectivities are additional significant benefits obtainable from the cooperative catalyst systems in some cases. Although the one-pot catalytic systems are state of the art having highly promising aspects, in practice they are still quite tricky since there are no definite rules for anticipating interaction, compatibility, and catalytic sequences between certain transition metal catalysts. Despite the fact that devising these one-pot reactions by multi catalysts relies heavily on either researchers' intuition or on a trial and error process, the *in situ* alignment of several distinct catalytic processes in a rather controlled manner, which is quite common in enzyme-catalyzed reaction sequences, would open up a new chapter in the area of catalysis not only for performing multiple step conversions in one-pot but also for developing totally new transformations on the basis of the co-operative roles of compatible metal species.

References

1 W. Keim, in *Transition Metals for Organic Synthesis*, ed. M Beller and C. Bolm, Wiley-VCH, Weinheim, 1998, **Vol. 1**, p. 14.
2 S. F. Mayer, W. Kroutil and K. Faber, *Chem. Soc. Rev.*, 2001, **30**, 332.
3 For a perspective review on the biosynthesis of corrin with multiple enzymes, see: A. I. Scott, *J. Org. Chem.*, 2003, **68**, 2529.
4 M. Shibasaki and N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187.
5 For a recent review on bimetallic catalysis by late transition metal complexes, see: E. K. van den Beuken and B. L. Feringa, *Tetrahedron*, 1998, **54**, 12985.
6 For a recent review on multi-catalyst systems consisting of one metal and multiple organic catalysts, see: V. K. Aggarwal and J. Richardson, *Chem. Commun.*, 2003, 2644.
7 For a recent review on the topic of ambifunctional cooperative catalysts, see: G. J. Rowlands, *Tetrahedron*, 2001, **57**, 1865.
8 For a review on the co-catalyst systems for metal-catalyzed olefin polymerizations, see: E. Y.-X. Chen and T. J. Marks, *Chem. Rev.*, 2000, **100**, 1391.
9 J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger and H. Kojer, *Angew. Chem.*, 1959, **71**, 176.
10 J. K. Stille and R. Divakaruni, *J. Am. Chem. Soc.*, 1978, **100**, 1303.
11 J. E. Bäckvall, B. Akermark and S. O. Ljunggren, *J. Am. Chem. Soc.*, 1979, **101**, 2411.
12 S.-I. Murahashi, T. Naota and N. Hirai, *J. Org. Chem.*, 1993, **58**, 7318.
13 A. H. Éll, A. Closson, H. Adolfssom and J.-E. Bäckvall, *Adv. Synth. Catal.*, 2003, **345**, 1012.
14 S. Y. Jonsson, H. Adolfsson and J.-E. Bäckvall, *Chem. Eur. J.*, 2003, **9**, 2783.
15 B. M. Choudary, N. S. Chowdari, S. Madhi and M. L. Kantam, *Angew. Chem., Int. Ed.,*, 2001, **40**, 4619.
16 B. M. Choudary, N. S. Chowdari, S. Madhi and M. L. Kantam, *J. Org. Chem.*, 2003, **68**, 1736.

17 J. J. Bozell and C. E. Vogt, *J. Am. Chem. Soc.*, 1988, **110**, 2655.

18 D. Bankston, F. Fang, E. Huie and S. Xie, *J. Org. Chem.*, 1999, **64**, 3461.

19 N. Jeong, S. D. Seo and J. Y. Shin, *J. Am. Chem. Soc.*, 2000, **122**, 10220.

20 P. A. Evans and J. E. Robinson, *J. Am. Chem. Soc.*, 2001, **123**, 4609.

21 K. H. Park, S. U. Son and Y. K. Chung, *Org. Lett.*, 2002, **4**, 4361.

22 S. U. Son, K. H. Park and Y. K. Chung, *J. Am. Chem. Soc.*, 2002, **124**, 6838.

23 Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. D. Milton, M. Hidai and S. Uemura, *Angew. Chem., Int. Ed.*, 2003, **42**, 2681.

24 Recently, Grigg *et al.* reported a diastereoselective Barbier-type cascade allylation of imines with allenes and aryl iodides using a palladium/indium combination: I. R. Cooper, R. Grigg, W. S. MacLachlan, M. Thornton-Pett and V. Sridharan, *Chem. Commun.*, 2002, 1372.

25 M. Gulías, J. R. Rodríguez, L. Castedo and J. L. Mascareñas, *Org. Lett.*, 2003, **5**, 1975.

26 T. Shimada, K. Mukaide, A. Shinohara, J. W. Han and T. Hayashi, *J. Am. Chem. Soc.*, 2002, **124**, 1584.

27 H. Siebeneicher, I. Bytschkov and S. Doye, *Angew. Chem., Int. Ed.*, 2003, **42**, 3042.

28 J. Louie, C. W. Bielawski and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 11312.

29 A. E. Sutton, B. A. Seigal, D. F. Finnegan and M. L. Snapper, *J. Am. Chem. Soc.*, 2002, **124**, 13390.

30 J. Cossy, F. Bargiggia and S. BouzBouz, *Org. Lett.*, 2003, **5**, 459.

31 T. Nemoto, H. Kakei, V. Gnanadesikan, S.-y. Tosaki, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2002, **124**, 14544.

32 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467.

33 C. E. Castro and R. D. Stephens, *J. Org. Chem.*, 1963, **28**, 2163.

34 K. Sonogashira, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, 2002, Wiley-Interscience, **Volume I**, Chapter III.2.8, pp. 493–529.

35 M. Sawamura, M. Sudoh and Y. Ito, *J. Am. Chem. Soc.*, 1996, **118**, 3309.

36 R. E. Maleczka, Jr., W. P. Gallagher and I. Terstiege, *J. Am. Chem. Soc.*, 2000, **122**, 384.

37 W. P. Gallagher, I. Terstiege and R. E. Maleczka, Jr., *J. Am. Chem. Soc.*, 2001, **123**, 3194.

38 S. Kamijo and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2002, **41**, 3230.

39 S. Kamijo and Y. Yamamoto, *J. Org. Chem.,*, 2003, **68**, 4764.

40 There is an excellent example for multi-catalyst systems including one metal and two organic catalysts in the addition of *in situ* generated diazos to carbonyl compounds: V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J.-L. Vasse and C. L. Winn, *J. Am. Chem. Soc.*, 2003, **125**, 10926.

41 K. Lee, D. Seomoon and P. H. Lee, *Angew. Chem., Int. Ed.*, 2002, **41**, 3901.

42 S. Ko, C. Lee, M.-G. Choi, Y. Na and S. Chang, *J. Org. Chem.*, 2003, **68**, 1607.

43 S. Ko, H. Han and S. Chang, *Org. Lett.*, 2003, **5**, 2687.

44 K. H. Park, S. U. Son and Y. K. Chung, *Chem. Commun.*, 2003, 1898.

45 For a recent example of hetero bi-(Cu/Pd) or trimetallic (Cu/Pd/Ru) nanocluster catalysts for Suzuki cross coupling reaction, see: M. B. Thathagar, J. Beckers and G. Rothenberg, *J. Am. Chem. Soc.*, 2002, **124**, 11858.