Co-operative effect of Lewis acids with transition metals for organic synthesis

Congyang Wang and Zhenfeng Xi*

Received 6th February 2007
First published as an Advance Article on the web 28th March 2007
DOI: 10.1039/b608694m

Transition metal-mediated or -catalyzed carbon–carbon bond or carbon–heteroatom bond forming reactions are among the most powerful tools in organic synthesis. In addition, Lewis acid-mediated or -catalyzed organic transformations are widely used. In this context, an effective combination of these two powerful protocols or an efficient cooperation of transition metals with Lewis acids should open a new era in synthetic chemistry. This *tutorial review* summarizes representative synthetic methodologies developed in the past decades employing this co-operative effect.

1. Introduction

For synthetic chemists, both transition metals and Lewis acids have long been two extremely powerful weapons. Transition metals (hereafter abbreviated as TM), can undergo many characteristic reactions with organic substrates including oxidative addition/reductive elimination through change of their oxidation states. A Lewis acid (hereafter abbreviated as LA), which normally does not change its oxidation state, is usually considered to activate unsaturated C-heteroatom bonds through σ-coordination (or *via* formation of adducts). Transition metal-mediated or -catalyzed carbon–carbon bond or carbon–heteroatom bond forming reactions are among the most powerful tools in organic synthesis. Meanwhile, Lewis acid-mediated or -catalyzed organic transformations are widely used. In most synthetic reactions, both unsaturated C–C bonds (π-coordination to TM and thus activated) and unsaturated C-heteroatom bonds such as carbonyl groups (σ-coordination to LA and thus activated) are integrated in one-pot. Thus, an effective combination of these two protocols or an efficient co-operation of transition metals with Lewis acids would be an exceptionally powerful tool in synthesis.

The concept of cooperation effect between TM and LA is briefly introduced in Scheme 1. Lewis acids may play a very important role in many types of transition metal mediated chemical bond forming reactions, mainly including (1) promoting reactivity (***type I***). The M–C bond in this category does not react or reacts very slowly with certain substrates

---

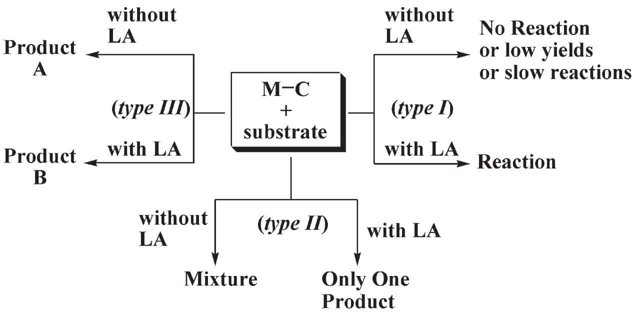
Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China. E-mail: zfxi@pku.edu.cn; Fax: (+86)-10-62759728

Congyang Wang

Congyang Wang was born in 1977 in Jiangsu Province, China. He received his BS degree from the Department of Chemistry, Nanjing University in 2000. Thereafter, he joined Professor Zhenfeng Xi's group at the College of Chemistry, Peking University as a PhD course student and obtained his PhD degree in 2005. He obtained the first-rank grant from the Postdoctorate Research Fund of China and is now a postdoctoral fellow in Prof. Xi's group. His research interests include organic synthesis and development of synthetic methods using organometallic compounds.

Zhenfeng Xi

Zhenfeng Xi was born in 1963 in Henan Province, China. He received his BS degree from Xiamen University in 1983, and his MS degree from Nanjing University, Zhengzhou University and the Henan Institute of Chemistry in 1989. He joined Professor Tamotsu Takahashi's group at the Institute for Molecular Sciences, Japan, as a PhD course student in 1993 and obtained a PhD degree in 1996. He took an Assistant Professor position at Hokkaido University, Japan, in 1997, after he worked as a postdoctoral research fellow with Professor Takahashi at Catalysis Research Center, Hokkaido University. In 1998, he joined the College of Chemistry at Peking University, where he is now a Professor. He has received several awards including the Outstanding Young Investigator award from the Qiu Shi Science & Technologies Foundation in 2000 and the Yaozeng Huang Organometallic Chemistry Award in 2004. He has been the holder of a Cheung Kong Professorship since 2002. Professor Xi's research interests include the development of synthetic methodologies based on selective cleavage of C–H, C–C and C–X bonds mediated by organometallic compounds, the development of organometallic reagents, studies of the mechanisms of reactions involving reactive organometallic intermediates, and the synthesis of functional structures.



Scheme 1 Possible effects of Lewis acids on reactions of organometallic compounds in terms of starting reagents and final products.

without Lewis acids. However, in the presence of Lewis acids, the reaction proceeds or speeds up. (2) Increasing the selectivity of the reaction (***type II***), and (3) changing the reaction direction (***type III***) from Product **A** (without LA) to Product **B** (with LA).

From the mechanistic point of view, LA and TM may cooperate in the following ways: (a) the LA activates organic substrates, for example, by forming adducts with carbonyl groups ($C{=}O \rightarrow LA$) mainly through σ-coordination, to generate more reactive electrophiles, which thus may be readily attacked by TM; (b) the LA activates TM or TM–organic substrate intermediates, for example, by abstracting halides from the TM to generate more reactive species, TM^{n+}; (3) the LA affects the stereo- or chemo-environment of the reactive intermediates *via* coordination to TM–organic substrate species. The LA may exhibit multiple functions in a single reaction process.

In fact, a number of excellent synthetic methods have been achieved by combining TM with LA, either in stoichiometric reactions or in catalytic reactions. Bi- or polymetallic catalyst systems have frequently appeared in the literature in recent years. Recently (2004), an excellent book entitled "Multimetallic Catalysts in Organic Synthesis" edited by Masakatsu Shibasaki and Yoshinori Yamamoto was published.[1] Some of the literature related to cooperative effects between TM and LA in catalytic reactions is also discussed in this book.

In this review, cooperation between LA and zirconocene-mediated reactions,[2] which are generally stoichiometric, will be introduced mainly as models to demonstrate the cooperative effects between LA and TM. Related reactions of bimetallic catalyst systems will also be addressed in order to show the catalytic version of the cooperative effect. The concept of a "Dual role catalyst" or "Dual role mediator", in which the same metal behaves as both TM and LA in one reaction process is introduced. Reactions that involve two or more metals but proceed *via* assured transmetallation are not included in this review. Classification of the literature has been done basically according to the explanation in Scheme 1.

2. Cooperation of LA with TM to make a reaction proceed or speed up

Many potentially useful organometallic intermediates do not react or react very slowly with most or certain substrates, due to low reactivity of either the organometallic intermediates or the substrates or both. For catalytic reactions, the catalyst or its precursor cannot initiate the catalytic cycle for similar reasons. Thus, by addition of LA to the reaction mixture, or by pre-treatment of a catalyst or its precursor, the cooperation of LA with TM may facilitate or speed up the otherwise unavailable reaction. In this section, we classify the literature into several groups according to the reaction mechanism. However, it should be pointed out that this classification is not precise, because LA in one reaction process may act towards substrates, TM and TM-substrate intermediates in several ways.

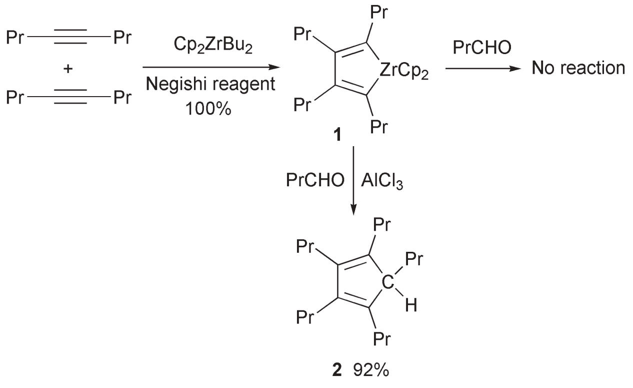
2.1 LA activates organic substrates

Selective cross-coupling of two identical or different alkynes on a low-valent zirconocene species (Cp_2Zr^{2+}) has been developed to generate their corresponding zirconacyclopentadiene derivatives or zirconaindene derivatives in high to quantitative yields.[2] However, due to the bulkiness of Cp ligands and low nucleophilicity of the Zr–C bonds, these potentially useful organometallic intermediates had been considered to be "dead-end" before Takahashi and co-workers developed transmetallation reactions using metal halides such as CuCl, $NiCl_2$, *etc.*[3]

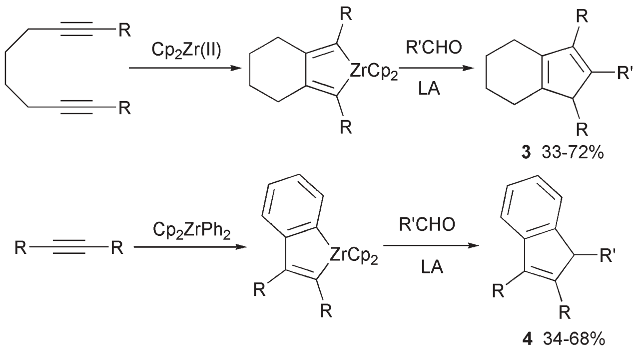
In 1998, we initiated a research project on LA-mediated reactions of zirconacycles including zirconacyclopentadienes. As demonstrated in Scheme 2, tetrapropylzirconacyclopentadiene **1**, formed *in situ* in quantitative yield using Negishi's method, does not react with aldehydes. Addition of $AlCl_3$ to the above reaction mixture caused an immediate formation of pentapropyl-substituted cyclopentadiene **2** in 92% yield.[4]

Various other Lewis acids such as $AlBr_3$, $AlEtCl_2$, BF_3, and $Sc(CF_3SO_3)_3$ are also effective for this deoxygenative cycloaddition of aldehydes with zirconacyclopentadienes. Both aromatic and aliphatic aldehydes can be used to prepare cyclopentadienes with various substituents. When a diyne is used, tetrahydroindene **3** derivatives can also be formed in high yields. A one-pot preparation of indene derivatives **4** from one benzyne, one alkyne, and one aldehyde can also be realized using a similar strategy (Scheme 3).

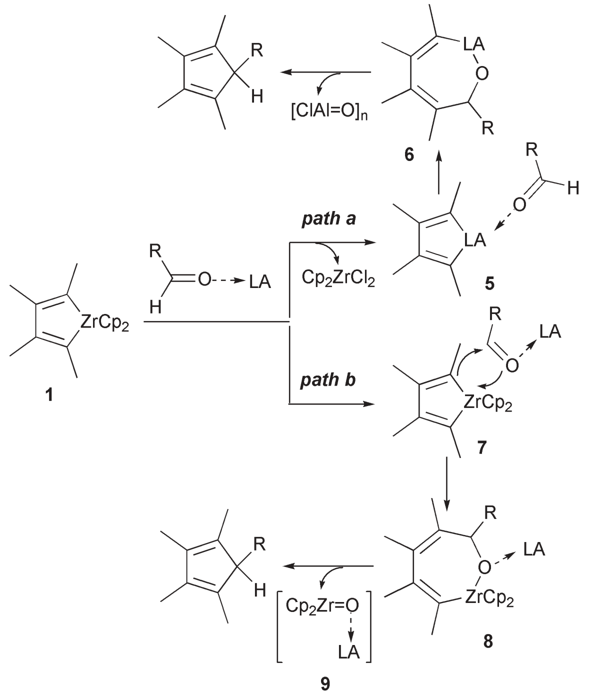
Two possible pathways are proposed for the reaction (Scheme 4). The adduct between a carbonyl group and the LA must be formed initially. In this way the carbonyl group is



Scheme 2 $AlCl_3$-mediated reaction of zirconacyclopentadienes with aldehydes.



Scheme 3 One-pot synthesis of tetrahydroindene and indene derivatives by the cooperation of zirconocene with LA.

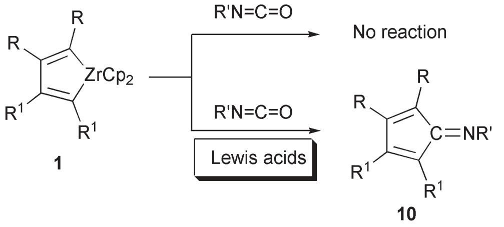


Scheme 4 Mechanism of LA-mediated reactions of zirconacyclopentadienes with aldehydes.

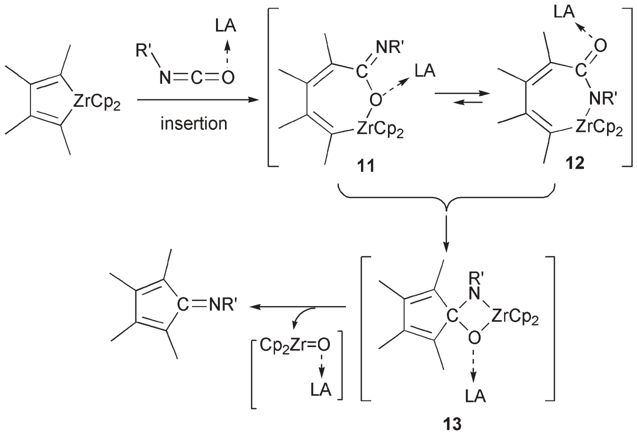
activated. In *pathway a*, transmetalation may take place to afford the intermediate **5**, such as aluminacyclopentadienes, followed by insertion of the activated carbonyl group into the Al–C bond to afford the oxo aluminium species **6**; On the other hand, the oxazirconacycle **8** was assumed to be formed *via* insertion of the activated carbonyl group into a Zr–C bond (*pathway b*), which finally afforded cyclopentadienes along with release of the adduct **9** of zirconocene oxide with LA.[5]

Further investigation showed that LA-promoted reactions of zirconacyclopentadienes **1** and isocyanates afforded multi-substituted iminocyclopentadiene derivatives **10** in good to excellent yields.[6] No reaction was observed when zirconacyclopentadienes **1** were treated with isocyanates without Lewis acids. As demonstrated in Scheme 5, after addition of $BF_3{\cdot}Et_2O$, reaction of zirconacyclopentadienes **1** with isocyanates took place smoothly to afford cyclopentadienylimines **10**.

A proposed reaction mechanism is given in Scheme 6, although a reaction path *via* transmetallation cannot be totally ruled out. The isocyanate molecule RN=C=O must be activated by LA through σ-coordination to LA. The Lewis acid-assisted insertion of isocyanate was proposed to take place firstly affording the intermediates **11** and **12**. The formation and metathesis of intermediate **13** is assumed to be a key process in this transformation.

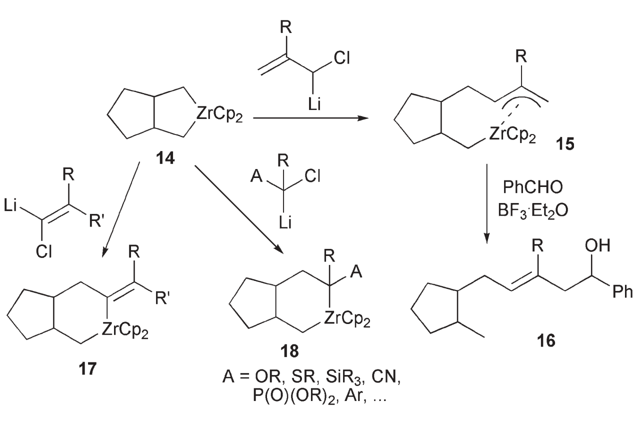


Scheme 5 Lewis acid-mediated reactions of zirconacyclopentadienes with isocyanates.

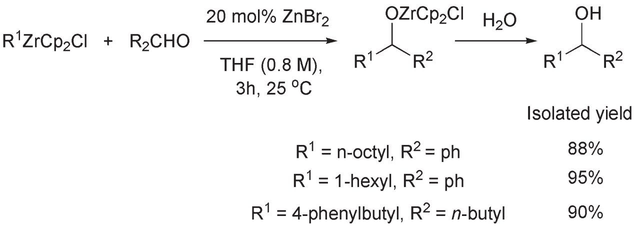


Scheme 6 Mechanism of LA-mediated reactions of zirconacyclopentadienes with isocyanates.

Whitby *et al.* reported the Lewis-acid promoted insertion reaction of aldehydes into zirconacycles which were obtained from the insertion of metal carbenoids (R^1R^2CLiX) into zirconacyclopenta(e)nes.[7] For instance, the insertion reaction of lithium chloroallylides into zirconacyclopentane **14** affords σ,η^3-zirconacycles **15**, which undergoes $BF_3{\cdot}Et_2O$-mediated reaction with aldehydes forming alcohol derivatives **16** (Scheme 7). Other carbenoids allowed the ring expansion to



Scheme 7 LA-promoted reactions of zirconacycles with aldehydes.



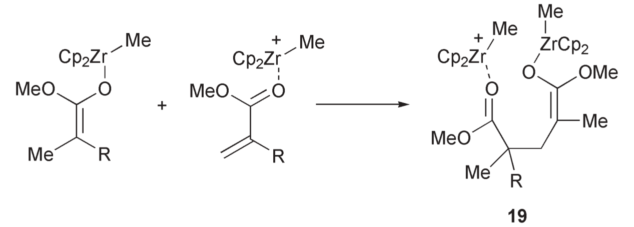
Scheme 8 $ZnBr_2$-catalyzed 1,2-addition reaction of organozirconocene chlorides with aldehydes.

afford the 6-membered zirconacycles **17** or **18**, which could also be further elaborated with aldehydes in the presence of Lewis acids.

Srebnik *et al.* demonstrated that the reaction of organozirconocene chlorides with aldehydes could be catalyzed by $ZnBr_2$ affording alcohols by hydrolysis in high yields (Scheme 8).[8] Carbonyl activation by $ZnBr_2$ followed by 1,2-addition of the alkylzirconocene was proposed to be the possible mechanism.

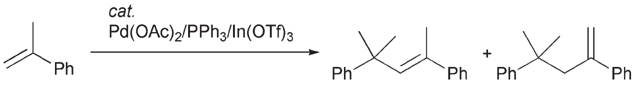
Group 4 metallocene initiators, usually as cationic species, have been widely used in polymerization. Collins and co-workers recently reported a new approach for the controlled synthesis of methacrylate polymers, using a cationic dinuclear zirconocene initiator **19** (Scheme 9).[9] The authors designed and generated *in situ* this cationic dinuclear enolate **19** based on the mechanistic study of their previous two-component initiator systems. This one-component initiator was found to be much more effective, probably because the rate-limiting intermolecular Michael addition reaction in the previous two-component initiator systems was changed to be intramolecular.

Lewis acids are known to activate alkynes and even simple alkenes, and can catalyze the Friedel–Crafts alkenylation of arenes. Shirakawa *et al.* found that a Pd/$In(OTf)_3$ bimetallic catalyst system was very effective for the dimerization of vinylarenes, compared with generally used cationic Pd(II) catalysts (Scheme 10).[10] In this reaction, $In(OTf)_3$ acts as an LA to activate vinylarenes to nucleophilic attack by palladium(0) complexes, affording oxidative adduct equivalents that accept insertion of another vinylarene (Scheme 11). This strategy may be applied for activation and utilization of various unreactive compounds.

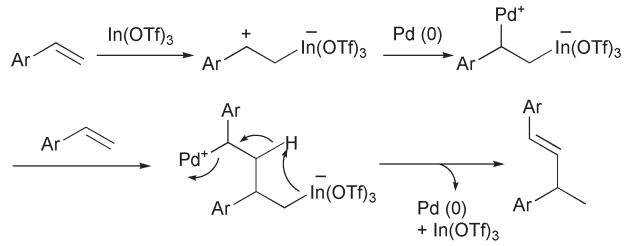


19

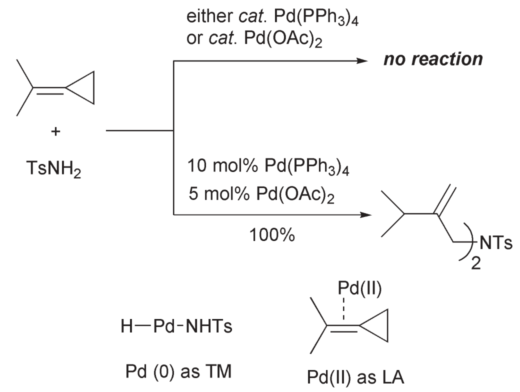
Scheme 9 Cationic dinuclear zirconocene enolates **19** as effective initiator for methacrylate polymerization.



Scheme 10 Palladium-catalyzed dimerization of vinylarenes using indium triflate as an effective co-catalyst.



Scheme 11 Cooperation between the Pd(0) catalyst and the Lewis acid catalyst $In(OTf)_3$.

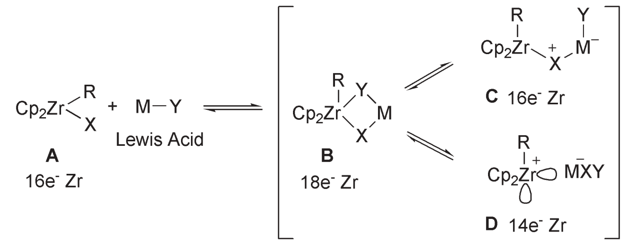


Scheme 12 Cooperation between the Pd(0) catalyst (TM) and the Pd(II) catalyst (LA).

Intermolecular hydroamination of methylenecyclopropane with sulfonamides was achieved by Shi *et al.* applying cooperation of Pd(0) and Pd(II) catalysts (Scheme 12).[11] The cooperation between these two catalysts is essential for realizing the ring-opening reaction with sulfonamides. The Pd(0) acts as TM to undergo an oxidative addition reaction affording a hydridopalladium amide species. On the other hand, the Pd(II) is proposed to serve as a weak Lewis acid, coordinating to the double bond of methylenecyclopropane. The coordination accelerates the hydropalladation step and the ring-opening of the cyclopropane moiety.

2.2 LA activates TM

Organozirconium compounds, such as alkyl- and alkenylzirconocene chlorides which are easily prepared through hydrozirconation of alkenes and alkynes respectively, have proved to be rather poor nucleophiles. Unlike organolithiums and Grignard reagents, they are generally very reluctant to participate in carbon–carbon bond-formation reactions except for carbonylation and acylation. There are several fundamentally different methods to solve the problem. One of the convenient approaches is to resort to organometallic transmetallation, which is not discussed in this review. Another approach is to seek help from a LA *via* activation of the organozirconium compounds such as by generating highly electrophilic cationic zirconocene derivatives and/or through activating the organic electrophilic reactants such as carbonyl compounds and epoxides, as described above. In some cases,

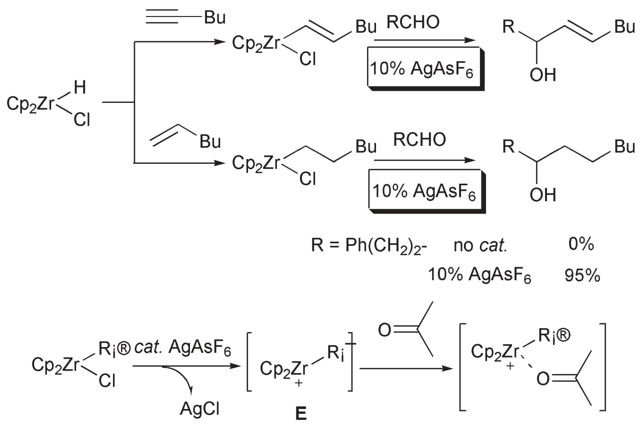


Scheme 13 Possible activated intermediates from organozirconium compounds and LA.

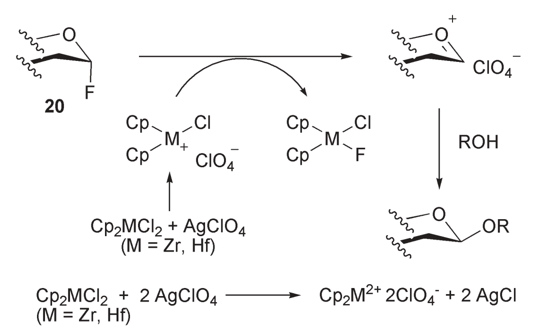
the success of reactions is attributed to the dual activating effect of LA on both organozirconium compounds and the substrates.

As depicted in Scheme 13, organozirconium compound **A** may interact with Lewis acids to form the stabilized intermediate **B**, which is an 18-electron-Zr doubly bridged saturated species. In principle, it may also generate the singly bridged 16-electron-Zr species **C**, which is more electrophilic than the original organozirconium **A**. In the extreme situation, polarization of the Zr–X bond may lead to its full ionization to form an ion pair **D**, which contains the 14-electron-Zr cationic species. Obviously, its electrophilicity is even higher than that of intermediate **C**. This kind of ''superelectrophile'' has also been implicated in the alkene polymerization processes.[2]

As mentioned above, hydrozirconation of alky(e)ne with the Schwartz reagent readily affords organozirconocene chlorides, which generally show poor reactivity toward carbonyl compounds. Suzuki *et al.* found that the reaction could be remarkably accelerated by employing a catalytic amount of $AgClO_4$ or $AgAsF_6$ (Scheme 14).[12] For example, *n*-hexylzirconocene chloride did not react with aldehyde at all even after a long reaction time. When employing $AgAsF_6$ as a catalyst, the reaction proceeded perfectly and afforded the corresponding alcohol in 95% yield.[13] The *in situ* generated cationic species **E** accounted for the enhancement of reactivity *via* the carbonyl activation.

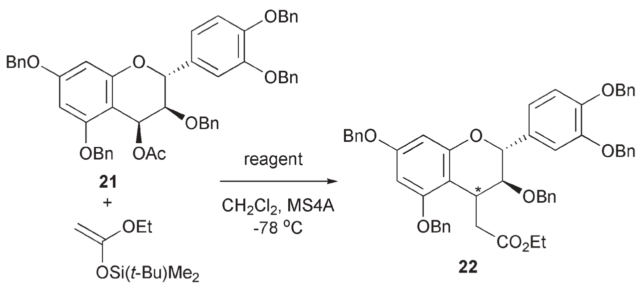


Scheme 14 Reactions of organozirconocene chlorides with aldehydes catalyzed by $AgAsF_6$.



Scheme 15 Reaction of glycosyl fluorides **20** with alcohol promoted by the Cp_2ZrCl_2–$AgClO_4$ system.

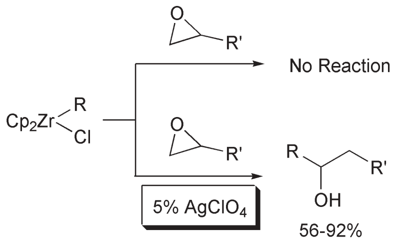
The same group also reported that Cp_2MCl_2–AgX (M = Ti, Zr, Hf; $X^- = ClO_4^-$, OTf^-) served as an efficient activator of glycosyl fluorides **20** or acetates in carbohydrate synthesis (Scheme 15). The high reactivity is attributed to the high electrophilicity of the cationic metallocene species. It could be further reinforced by generating the corresponding dicationic species (Scheme 15).[14] This cationic metallocene species also shows high efficiency for S_N1-type activation of the C(4) position of catechin derivative **21**, enabling selective substitution with various nucleophiles. Neither Cp_2ZrCl_2 nor $AgClO_4$ can work as a promoter alone. With the combination of Cp_2ZrCl_2 and $AgClO_4$, the reaction proceeded smoothly at −78 °C within 15 min, giving the product **22** in a high yield (Scheme 16).[15]



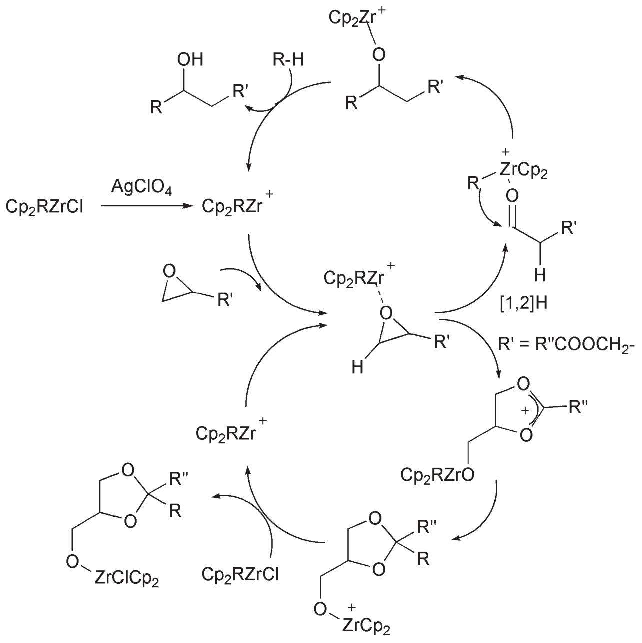
Reagent	Time (min)	Yield (%)
Cp_2ZrCl_2 (0.1)	15	n.r.
$AgClO_4$ (0.2)	15	n.r.
Cp_2ZrCl_2 (0.1), $AgClO_4$ (0.2)	15	85 (16:84)

Scheme 16 Reaction of catechin **21** with ketene silyl acetal promoted by the Cp_2ZrCl_2–$AgClO_4$ system.

Employing the same system, Wipf's group reported the reactions of organozirconocenes with epoxides resulting in the formation of chain-extended secondary alcohols (Scheme 17).[16] In the absence of $AgClO_4$, no reaction between epoxides and organozirconocenes was detected. In contrast, addition of



Scheme 17 $AgClO_4$-catalyzed reactions of organozirconocene chlorides with epoxides.

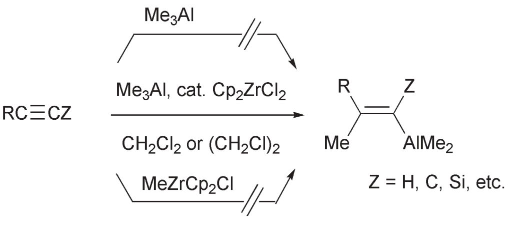


Scheme 18 Mechanism of the $AgClO_4$-catalyzed reactions of organozirconocene chlorides with epoxides.

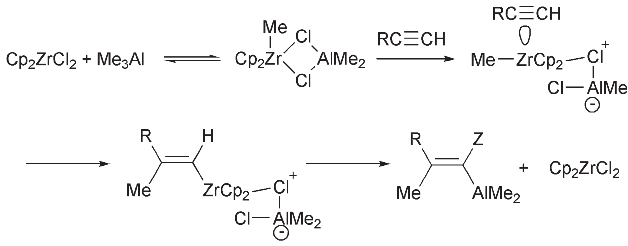
5 mol% of $AgClO_4$ to the reaction mixture led to a rapid formation of the secondary alcohols in 56–92% yields.

The mechanism may first involve the Ag(I)-induced chloride abstraction to generate the active species [Cp_2RZr^+]. Then it induced the epoxide opening, followed by a [1,2]H shift and nucleophilic attack on the resulting aldehyde (Scheme 18). When epoxy esters were used, synthetically useful dioxycarbenium intermediates were formed. At this stage, the R group was transferred from the zirconocene moiety followed by intermolecular chloride abstraction closing the catalytic cycle. This strategy was also applied for the synthesis of some functional molecules such as α-*C*-glycosides.[17]

In 1978, Negishi reported the reaction of the Cp_2ZrCl_2–$AlMe_3$ system with alkynes, which is not only quite general with respect to the alkyne structure but also catalytic in Zr.[18] Overall, it led to the carboalumination of an alkyne, which looks like a simple transmetallation process. Yet, neither $AlMe_3$ alone nor preformed $MeZrCp_2Cl$ without Al would react with alkyne under the same conditions, strongly suggesting a bimetallic mechanism for the crucial stage (Scheme 19).[2] Further study supported that the crucial reactive species might be the bimetallic $MeZrCp_2^{\delta+}$–$Cl^{\delta-}$–$AlMe_2Cl$, in which Zr is not only coordinatively unsaturated but also more positively polarized than in $MeZrCp_2Cl$ alone (Scheme 20).



Scheme 19 Zr-Catalyzed carboalumination of alkynes.

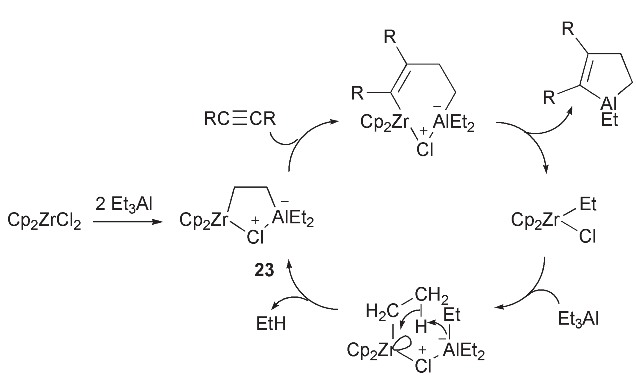


Scheme 20 Mechanism of the reaction of alkynes with Cp_2ZrCl_2–$AlMe_3$.

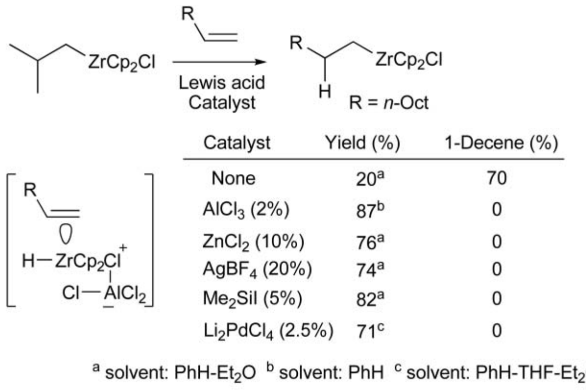
Indeed, this mode of activation by Lewis acid has been known in the Friedel–Crafts reaction and more pertinently in the Ziegler–Natta polymerization including the Kaminsky modification with zirconocene derivatives. Here, $AlMe_3$ shows dual effects, which is not only a Me group provider but a Lewis acid species. Following a similar strategy, Negishi's group developed the enantioselective carboalumination of alkenes under the influence of bulky chiral indene-containing zirconium complexes, especially $Cl_2Zr(NMI)_2$, where NMI is 1-neomenthylindenyl.[19]

As for the reaction of Cp_2ZrCl_2–$AlEt_3$ with alkynes, the mechanism is extremely complex. Judged by the patterns of D-incorporation results, the process may involve C–H bond activation of the Et group and probably formation of metallocyclopentenes or their equivalents (Scheme 21).[20] Although the mechanism needs to be further clarified, the crucial intermediate may involve bimetallic species **23**, where $AlEt_3$ has dual functions including an LA effect.

The same group also found that hydrogen transfer hydrozirconation of alkenes with alkylzirconocene chlorides, *e.g.*, *i*-$BuZrCp_2Cl$, could be significantly accelerated by catalytic amounts of a variety of Lewis acidic metal compounds, most notably $AlCl_3$, Me_3SiI, and Pd complexes, as indicated in Scheme 22.[21] Under otherwise identical conditions, uncatalyzed reaction of 1-decene with *i*-$BuZrCp_2Cl$ produced the desired hydrozirconation product in only 20% yield, with 70% of 1-decene remaining even after 15 h. The catalytic activity of $AlCl_3$ may be interpreted within the context of activation of *i*-$BuZrCp_2Cl$ by $AlCl_3$ through Zr–Cl–Al interaction to generate either *i*-$BuZrCp_2{}^+AlCl_4{}^-$ or *i*-$BuZrCp_2{}^{\delta+}$–$Cl^{\delta-}$–$AlCl_3$ which may be further converted to the corresponding zirconium hydrides as transient reactive species.



Scheme 21 Mechanism of the reaction of alkynes with Cp_2ZrCl_2–$AlEt_3$.



Catalyst	Yield (%)	1-Decene (%)
None	20[a]	70
AlCl$_3$ (2%)	87[b]	0
ZnCl$_2$ (10%)	76[a]	0
AgBF$_4$ (20%)	74[a]	0
Me$_2$SiI (5%)	82[a]	0
Li$_2$PdCl$_4$ (2.5%)	71[c]	0

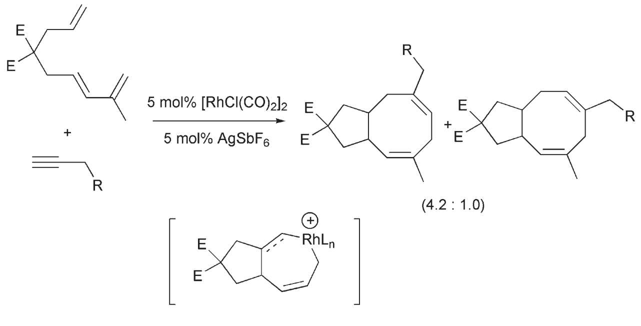
[a] solvent: PhH-Et$_2$O [b] solvent: PhH [c] solvent: PhH-THF-Et$_2$O

Scheme 22 Lewis acid-catalyzed hydrogen-transfer hydrozirconation of alkenes.

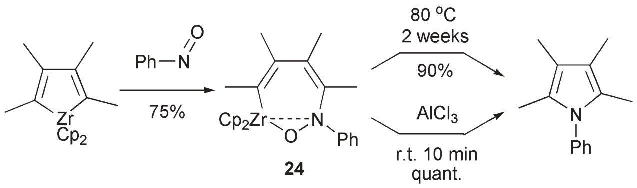
As discussed above, both a catalytic amount or a stoichiometric amount of LA can be used as a promoter to increase the reaction rate by abstracting halides from transition metals with the LA acting as a halide scavenge. This strategy has been applied in many synthetically useful late-transition-metal catalyzed reactions (TM as a catalyst). For example, in intramolecular [*n* + *m* + 2] cyclization reactions, the following bimetallic catalyst systems have been used: [Rh(CO)$_2$Cl]$_2$/AgOTf, [Rh(dppb)Cl]$_2$/AgSbF$_6$, [Rh(diphos)Cl]$_2$/AgSbF$_6$, [Rh(NBD)Cl]$_2$/AgSbF$_6$, RhCl(PPh$_3$)$_3$/AgOTf, Noyori's hydrogenation catalyst *trans*-RuCl$_2$[(*S*)-binap][(*S*,*S*)-dpen]/M$^+$, Pd(OAc)$_2$/AgNO$_3$, PdCl$_2$[(*R*)-binap]/AgOTf, [Rh(BICPO)-Cl]$_2$/AgSbF$_6$, CpRu(COD)Cl/In(OTf)$_3$, Ind(PPh$_3$)$_2$Cl/InCl$_3$, and so on. As one example shown in Scheme 23, a [4 + 2 + 2] cycloaddition reaction between 1,3-dienes, alkenes and alkynes forming cyclooctadienes was achieved using a [RhCl(CO)$_2$]$_2$/AgSbF$_6$ bimetallic catalyst system.[22] Without addition of AgSbF$_6$, the complex [RhCl(CO)$_2$]$_2$ could catalyze the reaction, but to afford only a small amount of products. The role of the Ag$^+$ additive is assumed, as commonly accepted, to be a chloride scavenger, removing the chloride ligand from the complex, freeing a vacant coordination site and forming a more reactive cationic Rh center.

2.3. LA activates TM–organic substrate intermediates

Tilley and co-workers reported that an LA can dramatically accelerate the transformation from the insertion intermediate **24** of nitrosobenzene to *N*-phenylpyrrole (Scheme 24).[23] The slow thermolysis of the intermediate **24** in benzene-*d*$_6$ at 80 °C occurred over *ca.* 2 weeks. When 1 equiv. of AlCl$_3$ was added to a benzene-*d*$_6$ solution of the intermediate at room temperature, the conversion to *N*-phenylpyrrole ocurred quantitatively within 10 min.



Scheme 23 Ag$^+$ promoted Rh-catalyzed [4 + 2 + 2] cycloaddtion reactions.

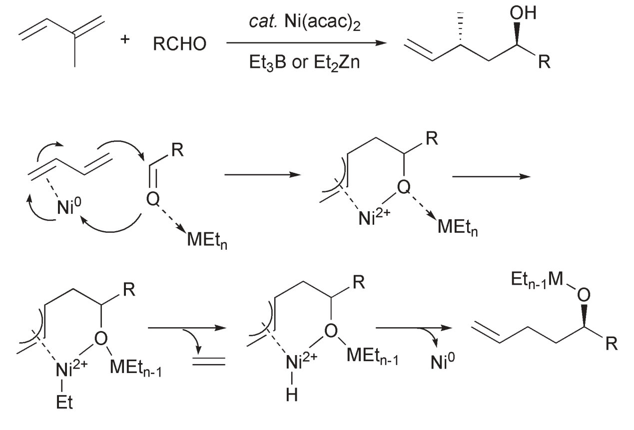


Scheme 24 AlCl$_3$-mediated reactions of zirconacyclopentadienes with PhNO.

Regio- and stereoselective intermolecular homoallylation of aldehydes and ketones with 1,3-dienes could be effectively catalyzed by a catalytic amount of Ni(acac)$_2$ and an excess of Et$_3$B or Et$_2$Zn, as reported by Tamaru *et al.*[24] The Et$_3$B or Et$_2$Zn behaved as a LA to activate carbonyl compounds and also as a reducing reagent to promote the homoallylation (or reductive coupling) of aldehydes with 1,3-dienes in the presence of a catalytic amount of Ni(acac)$_2$. The Ni/Et$_2$Zn combination was found to be particularly effective for the homoallylation of saturated aldehydes and ketones. These two catalyst systems, Ni/Et$_3$B and Ni/Et$_2$Zn, are complementary to each other. A proposed mechanism involves nucleophilic addition of diene–Ni(0) complexes to carbonyl compounds activated by coordination of Et$_3$B or Et$_2$Zn. Ethyl group migration from B or Zn to Ni affording a π-allylnickel intermediate, which was followed by β-hydrogen abstraction and reductive elimination (Scheme 25).

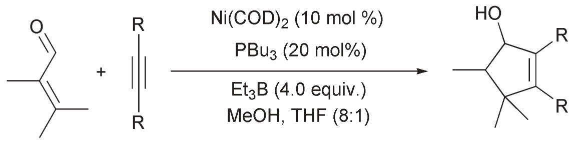
A catalytic intermolecular enal-alkyne [3 + 2] reductive cycloaddition has been recently realized by using 10 mol% of Ni(COD)$_2$ as catalyst in the presence of 4 equiv. of Et$_3$B. The Et$_3$B probably functions as a LA and also as a reducing agent (Scheme 26).[25] For this type of strategy, Ni/AlMe$_3$ system, Pd/Et$_3$B system have also been developed for synthetically useful reactions.

2.4 Dual role catalysts



Scheme 25 Et$_3$B or Et$_2$Zn acts both as a LA and a reducing agent in the Ni-catalyzed homoallylation of carbonyl compounds.

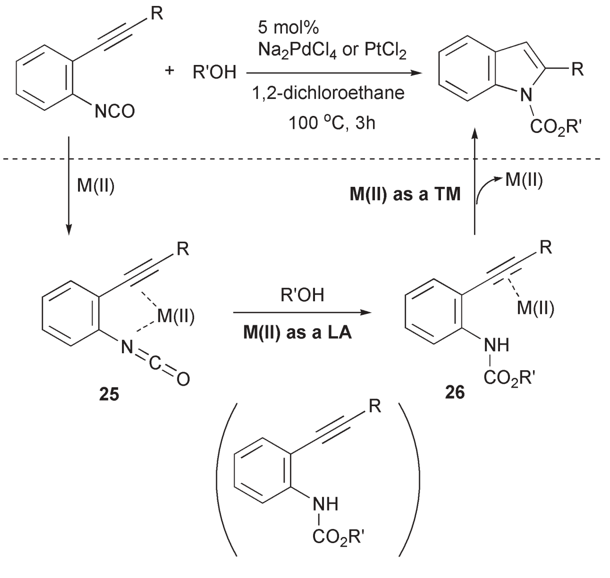
In the above-mentioned zirconocene-mediated reactions, it has been observed that in some cases the LA plays a dual role,



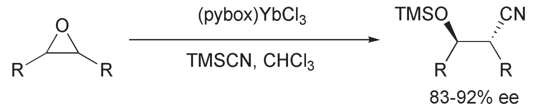
Scheme 26 Ni/Et$_3$B catalyst system for intermolecular enal-alkyne coupling leading to five-membered ring structures.

activating both the organozirconium compounds and the substrates. In catalytic reactions, it has been reported that a single organometallic compound or a simple metal halide plays the role of both TM and LA in the reaction process. An interesting example was reported by Yamamoto *et al.*, who showed that a single transition metal, Na_2PdCl_4 or $PtCl_2$, can act as a dual role catalyst to activate simultaneously isocyanates as a LA and alkyne as a TM (Scheme 27).[26] Indole derivatives were formed in high yields from the reaction of 2-(alkynyl)phenyl isocyanates and alcohols catalyzed by 5 mol% of Na_2PdCl_4 or $PtCl_2$. Further experiments to examine the catalysts as LA were also carried out. The reactions in the presence of a catalytic amount of Na_2PdCl_4 or $PtCl_2$ gave the corresponding carbamate in shorter reaction times compared with those of reactions without the catalysts. These results demonstrated that these metal halides act as dual role catalysts, which activate both π and σ-electrons simultaneously. A proposed mechanism based on a dual role catalyst is shown in Scheme 27. Firstly, both the alkynyl group (through π-coordination) and the isocyanate group (through σ-coordination) are coordinated to the catalyst M(II) forming **25** and are thus activated. Coordination of the Lewis acidic M(II) to the isocyanate makes the addition of the alcohol easier to afford the carbamate intermediate **26**. Successive amino-metalation (a normal step mediated by the typical TM nature of the catalyst) and regeneration of the catalyst M(II) gave the final indole.

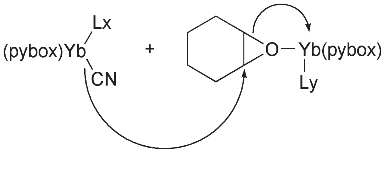
Lanthanide catalysts have also been reported to play dual roles. For example, in 2000, Jacobsen developed an enantioselective *meso*-epoxide opening with TMSCN catalyzed by (pybox)$YbCl_3$ complex (Scheme 28).[27] The authors found that the reaction shows a second-order kinetic dependence on catalyst concentration and a first-order dependence on epoxide concentration, which demonstrated a bimetallic mechanism involving simultaneous activation of epoxide and cyanide. The authors proposed that the catalyst acts a dual role of cyanide delivery agent and LA (Scheme 29).



Scheme 27 Dual role catalysts (**25**: dual activation mode) for the synthesis of indole derivatives.



Scheme 28 Catalytic asymmetric ring opening of *meso*-epoxide with TMSCN.

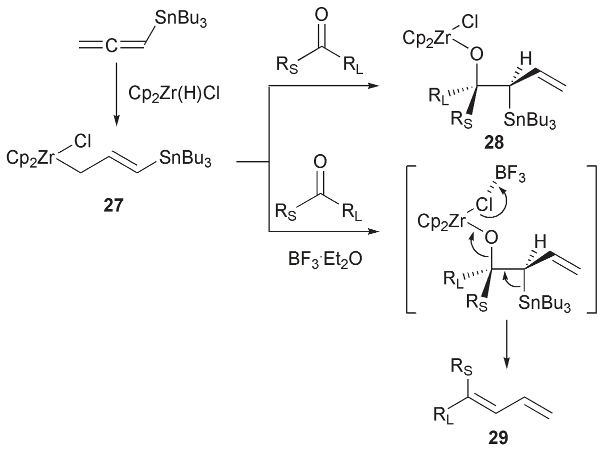


Scheme 29 A proposed bimetallic mechanism. Yb plays the dual role of cyanide delivery agent and LA.

We believe that similar types of catalysts may also behave as dual role catalysts in other reactions, but this has not yet been verified.

3. Cooperation of LA with TM to increase the selectivity

Suzuki *et al.* found that a LA could not only accelerate the reaction but also change the reaction pathway. For example, 1,3-(Sn,Zr)-bimetallic species **27**, which is available from the hydrozirconation of an allenylstannane, attacked carbonyl compounds to form the zirconocene alkoxide products **28**. When $BF_3{\cdot}Et_2O$ was added, 1,2-elimination took place and the 1,3-dienes **29** were furnished in high yields (Scheme 30: this transformation can be also considered as ***Type II***). The role of $BF_3{\cdot}Et_2O$ could be to polarize the Zr–Cl bond to trigger the C–O bond cleavage.[28]

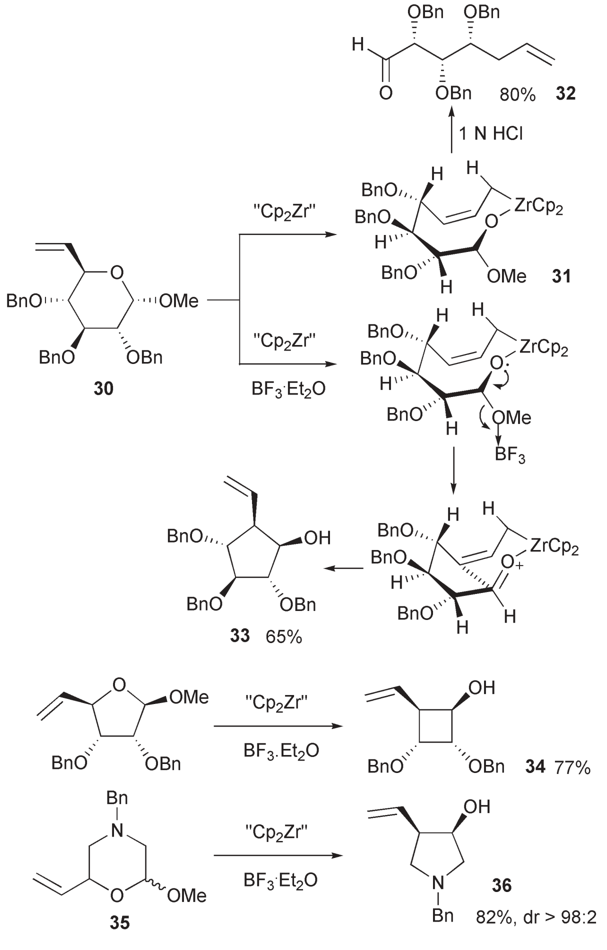


Scheme 30 $BF_3{\cdot}Et_2O$-selective addition–elimination reaction of organozirconocenes.

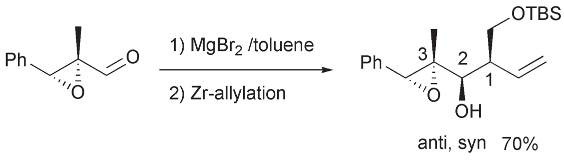
Taguchi *et al.*[29] and Paquette *et al.*[30] reported the "Cp_2Zr"-mediated highly stereoselective ring contraction of vinyl carbohydrate derivatives. 5-Vinylpyranoside **30** was converted to carbocycle **33** as a single isomer by sequential treatment with "Cp_2Zr" and $BF_3 \cdot Et_2O$ (Scheme 31). In the absence of $BF_3 \cdot Et_2O$, uncyclized aldehyde **32** was obtained after hydrolysis. It was assumed that $BF_3 \cdot Et_2O$ accelerated the elimination of the methoxyl group and changed the reaction from intermediate **31** to the final ring contraction product **33**. The strategy was also applicable to the synthesis of highly functionalized cyclobutane derivatives **34**. Vinylmorpholines **35** undergo similar ring contractions in the presence of "Cp_2Zr" and $BF_3 \cdot Et_2O$ affording optically pure pyrrolidines **36**.

In the synthesis of Myriaporone, Taylor *et al.* found that external Lewis acids influenced the stereoselectivity of Zr-allylation processes.[31] When epoxyaldehyde was pre-treated with magnesium bromide, subsequent Zr-allylation afforded a single diastereomeric addition product, namely the *anti*,*syn*-hydroxypropionate in 70% yield (Scheme 32). The preference to *syn*-1,2-stereochemistry was rationalized by proposing an acyclic transition state where the external Lewis acids obviated the need for internal Zr-activation of the aldehyde.

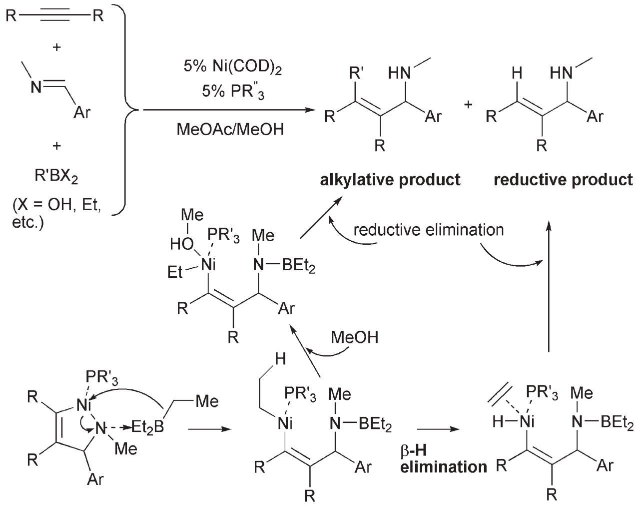
A catalytic three-component coupling of alkynes, imines, and organoboron reagents was reported by Patel and Jamison (Scheme 33).[32] Mechanistic studies revealed that methanol provided a substantial increase in yield, and also displayed high selectivity for alkylative coupling product over reductive coupling product.



Scheme 31 "Cp_2Zr"/$BF_3 \cdot Et_2O$-mediated stereoselective ring contraction of vinyl carbohydrates or morpholines.



Scheme 32 $MgBr_2$-mediated stereoselective Zr-allylation of epoxyaldehydes.

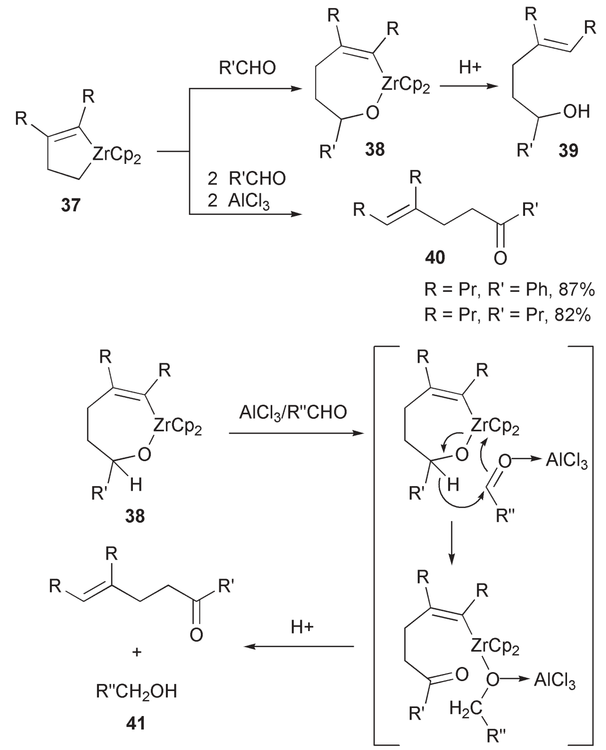


Scheme 33 Alkylative coupling and reductive coupling in catalytic three-component couplings.

4. Cooperation of LA with TM to generate different products from the same reactants

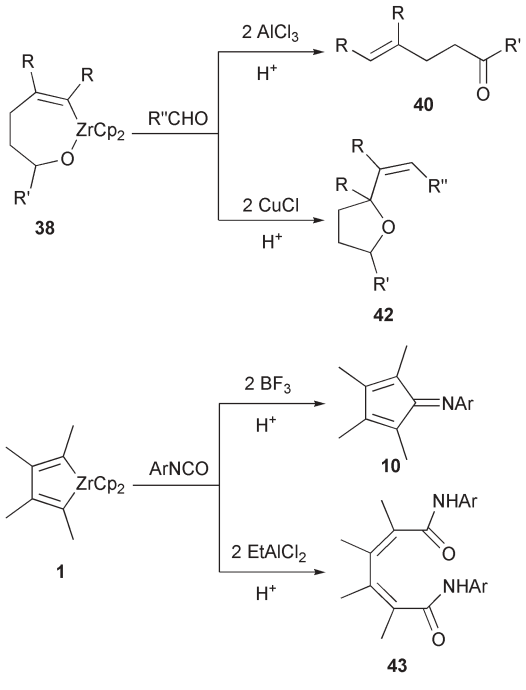
In addition to the above-mentioned cooperation of LA and TM, LA has been found to change the type of products formed from the same reactants. As part of our continuing interest in the combination of zirconocene-mediated carbon–carbon bond formation reactions and Lewis acid-promoted transformations, we investigated Lewis acid-mediated reactions of aldehydes with zirconacyclopentenes. Without Lewis acid, the insertion of aldehydes into zirconacyclopentenes **37** only affords seven-membered oxazirconacycles **38** which can be further transformed to alcohols **39** by subsequent hydrolysis (Scheme 34). However, homoallyl ketones **40**, instead of alcohols **39**, were formed in high yields in the presence of Lewis acids.[33] Besides freshly sublimed $AlCl_3$, other Lewis acids such as $AlBr_3$, $AlEtCl_2$, $FeCl_3$, and $SbCl_3$ also are effective for the above reactions. Further studies showed that a formal Oppenauer oxidation between oxazirconacycle **38** and LA–aldehyde adduct was the key step of this reaction.[34] This reaction represents the first example of ketone formation from three different components involving aldehydes, ethylene, and alkynes.

We also found that different products were selectively obtained in high yields when different Lewis acids were used.

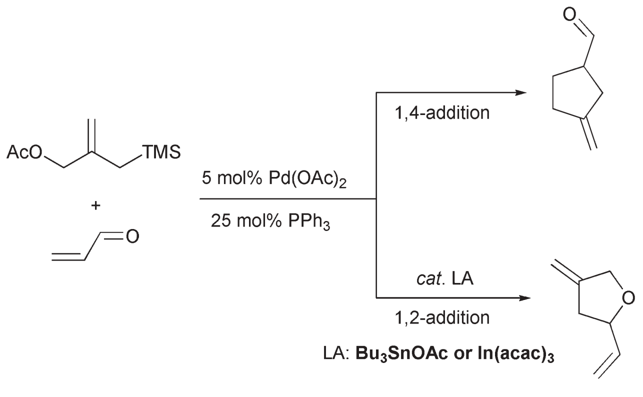


Scheme 34 Lewis acid-mediated reactions of aldehydes with zirconacyclopentenes affording homoallyl ketones.

For example, as shown in Scheme 35, homoallyl ketones **40** were formed in high yields in the presence of $AlCl_3$;[34] however, on the contrary, when CuCl was used as the LA, tetrahydrofuran derivatives **42** were obtained selectively.[35] For the reaction of zirconacyclopentadienes **1** with isocyanates in the presence of Lewis acids, either iminocyclopentadienes **10** or conjugated 1,6-bis-amides **43**, were obtained depending on the nature of Lewis acids used.[6]



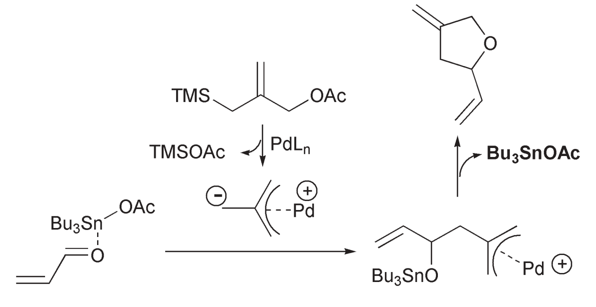
Scheme 35 Different LA affords different products.



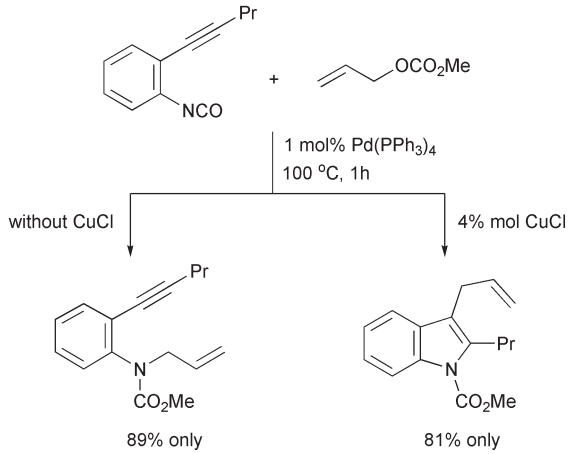
Scheme 36 A catalytic amount of Bu_3SnOAc or $In(acac)_3$ (LA) could alter the reaction course from 1,4-addition to 1,2-addition.

Control of 1,2-addition reactions and 1,4-addition reactions of nucleophiles with α,β-unsaturated carbonyl compounds represents a general challenge. The 1,4-addition has usually been observed when the Pd-trimethylenemethane (Pd–TMM) complex adds to α,β-unsaturated carbonyl compounds (Scheme 36). However, it has been found by Trost *et al.* that in the presence of Bu_3SnOAc or $In(acac)_3$ the 1,2-addition is realized.[36] Thus, the Pd–TMM complex adds to α,β-unsaturated carbonyl compounds including ynones in a 1,2-addition fashion to afford methylenetetrahydrofuran cycloadducts (Scheme 36). Possible roles of Sn and In additives have been proposed from consideration of both the rate of 1,2- *vs* 1,4-addition as well as the rate of ring closure (Scheme 37). The presence of an LA activated the carbonyl group by coordination prior to addition of the TMM–Pd complex, and stabilized the alkoxide anion generated after addition of the TMM–Pd complex to the carbonyl group. The LA was also proposed to promote the collapse of the zwitterions to the methylenetetrahydrofuran, as the counterion of the oxyanion was also found to be important.

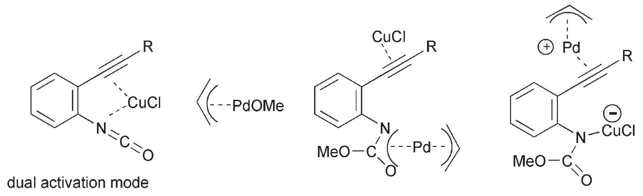
A new and efficient synthesis of 3-allyl-*N*-(alkoxycarbonyl)-indoles was realized from 2-(alkynyl)phenyl isocyanates and allyl carbonates using a bimetallic catalyst system, in which the CuCl acts as a LA to activate the isocyanate, and the Pd^0 acts as a TM catalyst for the formation of a π-allylpalladium alkoxide intermediate (Scheme 38), as reported by Kamijo and Yamamoto.[37] Without the addition of CuCl, the *N*-allylaniline



Scheme 37 A mechanistic proposal for the chemoselectivity switch catalyzed by $In(acac)_3$ or Bu_3SnOAc.



Scheme 38 Synthesis of 3-allyl-*N*-(alkoxycarbonyl)indoles under a bimetallic catalyst system (Pd–LA).



44 **45** **46**

Scheme 39 Proposed reaction intermediates.

was formed as the sole product, and the allylindoles were not obtained at all. However, in the presence of 4 mol% of CuCl, the allylindoles were obtained as the only product. Addition of CuCl changed the product of the reaction.

Three very important intermediates were proposed for this reaction (Scheme 39). Firstly, coordination of CuCl with 2-(alkynyl)phenyl isocyanates forms **44** (dual activation mode). In this way, the isocyanate group is activated and can react selectively with the π-allylpalladium alkoxide complex to afford probably a heteroatom containing bis-π-allylpalladium intermediate **45**. To reach the final product, the authors proposed that transmetallation between Pd and Cu would take place to product the intermediate **46**. The final cyclization step proceeded with the cooperative catalytic activity of Pd and Cu.

5. Conclusion and perspective

More and more synthetically useful methods and mechanistically interesting reactions have been reported in recent years employing the concept of cooperative effects between LA and TM. Not only stoichiometric reactions, but also catalytic versions of the cooperation effect have attracted much attention. This cooperative effect is also expressed by the increasing number of papers on multimetallic catalysts in organic synthesis.[1] As we introduced in Scheme 1, the cooperation between LA and TM may result in three major outputs in terms of starting materials and final products. Most of the relevant publications fall in the category of ***Type I***, that is, the cooperation makes an unavailable reaction proceed or speed up. This type of cooperative effect is obviously very important, because it makes unreactive organometallic intermediates and sluggish reactions more useful in practice. From a mechanistic point of view, the cooperative effect of LA with TM is mainly realized *via* LA activating organic substrates or TM or TM–organic substrate intermediates. Multiple functions of LA may exist in a single reaction process. Although some of the fundamental questions concerning the cooperation between LA and TM have been addressed, the mechanism of cooperation between LA and TM, especially in cases of multifunctional LA and TM in one reaction, is worthy of further investigation. We may also expect more studies on dual role catalysts, on the effect of LA towards the chemo- and stereo-environment surrounding TM–organic substrate intermediates, and on intentionally designed cooperative effects. We believe that an efficient co-operation of transition metals with Lewis acids should open a new era in synthetic chemistry.

Acknowledgements

Z. Xi thanks his past and present coworkers and students involved in this research group's long-term study on Cooperative Effect between Lewis Acids and Organometallic Compounds. Financial support from the Natural Science Foundation of China, the Major State Basic Research Development Program, the State Key Laboratory of Organometallic Chemistry, Dow Corning Corporation, and Peking University is gratefully acknowledged. The Cheung Kong Scholars Programme, Qiu Shi Science & Technologies Foundation, BASF, and Eli Lilly China are also gratefully acknowledged.

References

1 *Multimetallic Catalysts in Organic Synthesis*, ed. Masakatsu Shibasaki and Yoshinori Yamamoto, WILEY-VCH, Weinheim, 2004.
2 E. Negishi, *Dalton Trans.*, 2005, 827.
3 T. Takahashi, F. Y. Tsai, Y. Li, H. Wang, Y. Kondo, M. Yamanaka, K. Nakajima and M. Kotora, *J. Am. Chem. Soc.*, 2002, **124**, 5059.
4 Z. Xi and P. Li, *Angew. Chem., Int. Ed.*, 2000, **39**, 2950.
5 C. Zhao, P. Li, X. Cao and Z. Xi, *Chem.–Eur. J.*, 2002, **8**, 4292.
6 J. Lu, G. Mao, W. Zhang and Z. Xi, *Chem. Commun.*, 2005, 4848.
7 G. J. Gordon, T. Luker, M. W. Tuckett and R. J. Whitby, *Tetrahedron*, 2000, **56**, 2113.
8 B. Zheng and M. Srebnik, *J. Org. Chem.*, 1995, **60**, 3278.
9 G. Stojcevic, H. Kim, N. J. Taylor, T. B. Marder and S. Collins, *Angew. Chem., Int. Ed.*, 2004, **43**, 5523 and references therein.
10 T. Tsuchimoto, S. Kamiyama, R. Negoro, E. Shirakawa and Y. Kawakami, *Chem. Commun.*, 2003, 852.
11 M. Shi, Y. Chen and B. Xu, *Org. Lett.*, 2003, **5**, 1225.
12 For a review, see: K. Suzuki, *Pure Appl. Chem.*, 1994, **66**, 1557.
13 K. Suzuki, T. Hasegawa, T. Imai, H. Maeta and S. Ohba, *Tetrahedron*, 1995, **51**, 4483.
14 K. Suzuki, H. Maeta and T. Matsumoto, *Tetrahedron Lett.*, 1989, **30**, 4853.
15 K. Ohmori, K. Hatakeyama, H. Ohrui and K. Suzuki, *Tetrahedron*, 2004, **60**, 1365.
16 P. Wipf and W. Xu, *J. Org. Chem.*, 1993, **58**, 825.
17 P. Wipf, J. G. Pierce and N. Zhuang, *Org. Lett.*, 2005, **7**, 483.
18 D. E. van Horn and E. Negishi, *J. Am. Chem. Soc.*, 1978, **100**, 2252.
19 D. Y. Kondakov and E. Negishi, *J. Am. Chem. Soc.*, 1996, **118**, 1577.
20 E. Negishi, D. Y. Kondakov, D. Choueiry, K. Kasai and T. Takahashi, *J. Am. Chem. Soc.*, 1996, **118**, 9577.
21 H. Makabe and E. Negishi, *Eur. J. Org. Chem.*, 1999, 969.

22 P. A. Wender and J. P. Christy, *J. Am. Chem. Soc.*, 2006, **128**, 5354 and references therein.

23 M. Nakamoto and T. D. Tilley, *Organometallics*, 2001, **20**, 5515.

24 M. Kimura, H. Fujimatsu, A. Ezoe, K. Shibata, M. Shimizu, S. Matsumoto and Y. Tamaru, *Angew. Chem., Int. Ed.*, 1999, **38**, 397.

25 A. Herath and J. Montgomery, *J. Am. Chem. Soc.*, 2006, **128**, 14030 and references therein.

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

27 S. E. Schaus and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 1001.

28 K. Suzuki, T. Hasegawa, T. Imai, H. Maeta and S. Ohba, *Tetrahedron*, 1995, **51**, 4483.

29 H. Ito, Y. Ikeuchi, T. Taguchi, Y. Hanzawa and M. Shiro, *J. Am. Chem. Soc.*, 1994, **116**, 5469.

30 L. A. Paquette, I. H. Kim and N. Cuniere, *Org. Lett.*, 2003, **5**, 221.

31 R. E. Taylor, J. P. Ciavarri and B. R. Hearn, *Tetrahedron Lett.*, 1998, **39**, 9361.

32 S. J. Patel and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2003, **42**, 1364.

33 C. Zhao, T. Yu and Z. Xi, *Chem. Commun.*, 2002, 142.

34 C. Zhao, J. Yan and Z. Xi, *J. Org. Chem.*, 2003, **68**, 4355.

35 C. Zhao, J. Lu, Z. Li and Z. Xi, *Tetrahedron*, 2004, **60**, 1417.

36 B. M. Trost, S. Sharma and T. Schmidt, *J. Am. Chem. Soc.*, 1992, **114**, 7903.

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