ACCOUNTS
of chemical research

Metal–Organic Cooperative Catalysis in C–H and C–C Bond Activation and Its Concurrent Recovery

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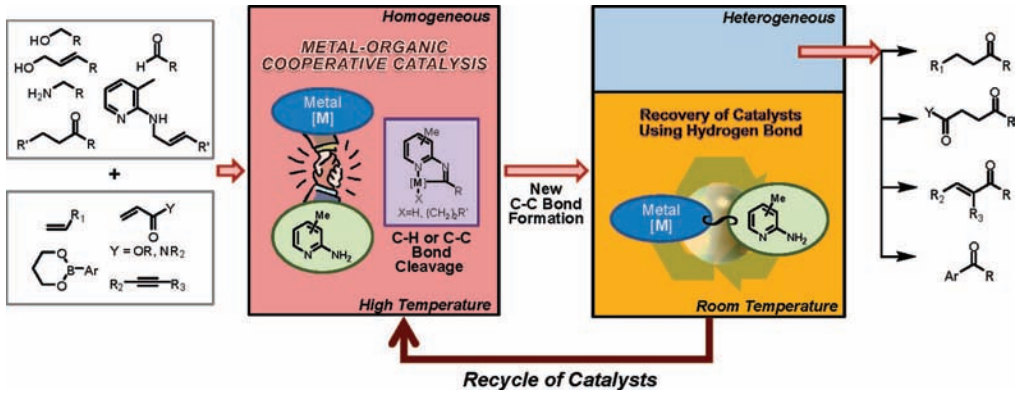
RECEIVED ON MAY 30, 2007

CONSPECTUS



The development of an efficient catalytic activation (cleavage) system for C–H and C–C bonds is an important challenge in organic synthesis, because these bonds comprise a variety of organic molecules such as natural products, petroleum oils, and polymers on the earth. Among many elegant approaches utilizing transition metals to activate C–H and C–C bonds facilely, chelation-assisted protocols based on the coordinating ability of an organic moiety have attracted great attention, though they have often suffered from the need for an intact coordinating group in a substrate.

In this Account, we describe our entire efforts to activate C–H or C–C bonds adjacent to carbonyl groups by employing a new concept of metal–organic cooperative catalysis (MOCC), which enables the temporal installation of a 2-aminopyridyl group into common aldehydes or ketones in a catalytic way. Consequently, a series of new catalytic reactions such as alcohol hydroacylation, oxo-ester synthesis, C–C triple bond cleavage, hydrative dimerization of alkynes, and skeletal rearrangements of cyclic ketones was realized through MOCC. In particular, in the quest for an optimized MOCC system composed of a Wilkinson's catalyst $(Ph_3P)_3RhCl$ and an organic catalyst (2-amino-3-picoline), surprising efficiency enhancements could be achieved when benzoic acid and aniline were introduced as promoters for the aldimine formation process. Furthermore, a notable accomplishment of C–C bond activation has been made using 2-amino-3-picoline as a temporary chelating auxiliary in the reactions of unstrained ketones with various terminal olefins and Wilkinson's catalyst. In the case of seven-membered cyclic ketones, an interesting ring contraction to five- or six-membered ones takes place through skeletal rearrangements initiated by the C–C bond activation of MOCC.

On the other hand, the fundamental advances of these catalytic systems into recyclable processes could be achieved by immobilizing both metal and organic components using a hydrogen-bonded self-assembled system as a catalyst support. This catalyst-recovery system provides a homogeneous phase at high temperature during the reaction and a heterogeneous phase at room temperature after the reaction. The product could be separated conveniently from the self-assembly support system by decanting the upper layer. The immobilized catalysts of both 2-aminopyridine and rhodium metal species sustained high catalytic activity for up to the eight catalytic reactions.

In conclusion, the successful incorporation of an organocatalytic cycle into a transition metal catalyzed reaction led us to find MOCC for C–H and C–C bond activation. In addition, the hydrogen-bonded self-assembled support has been developed for an efficient and effective recovery system of homogeneous catalysts and could be successful in immobilizing both metal and organic catalysts.

Published on the Web 02/02/2008 www.pubs.acs.org/acr
10.1021/ar700133y CCC: $40.75

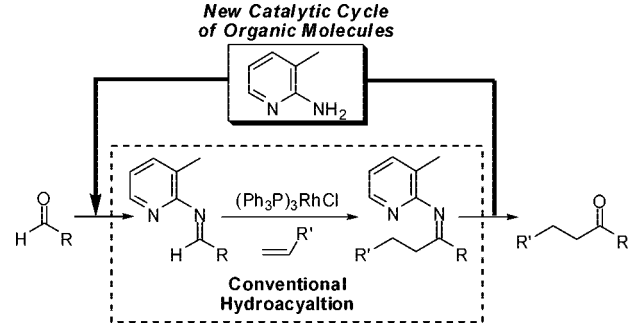
Introduction

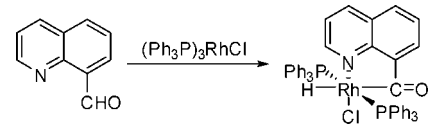
Among the many elegant examples of transition metal catalyzed activation of C–H and C–C bonds,[1] chelation-assisted protocols have recently attracted increasing attention in organometallic chemistry. Directed metalation processes have been demonstrated by valuable applications in organic synthesis, showing remarkable efficiency and chemoselectivity.[2] In general, a chelation-assisted protocol facilitates the formation of either the kinetically or thermodynamically favored five- or six-membered metallacycle; a prepositioned coordinating group induces spatial proximity between the C–H or C–C bonds and the transition metal center.[1,2] Despite the magnificent usefulness in activating otherwise stable C–H and C–C bonds, a major drawback of the chelation-assisted protocol is the need for a coordination group in a substrate. As a consequence, this introduces the necessity of additional steps to remove the coordinating groups, and the method often suffers from limitations in employing noncoordinating or weakly coordinating substrates. In particular, the C–H bond activation process of aldehydes, a key step of hydroacylation of olefins, can be seriously hampered by the lack of a strong coordinating group in a substrate leading to more critical problems such as decarbonylation (Scheme 1).[3]

Because the principal challenge associated with the C–H bond cleavage of an aldehyde involves suppressing the decarbonylation process of the acyl–metal hydride species, some catalyst systems under a high pressure of carbon monoxide or ethylene gases have been devised to stabilize acyl–metal hydride species.[4] However, these systems are not general and efficient due to the harshness of the reaction conditions and limitation of the olefins that can be used.

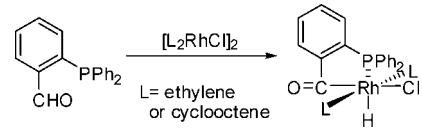
An alternative approach to stabilize the acyl–metal hydride species was inspired by the isolation of cyclometalated complexes derived from 8-quinolinecarboxaldehyde[5] (eq 1) and 2-(diphenylphosphanyl)benzaldehyde[6] (eq 2), which were a milestone of chelation-assisted hydroacylation. Although it is apparent that these aldehydes were very effective in avoiding decarbonylation, their structures are too specific to apply for common aldehydes.

SCHEME 2





(1)

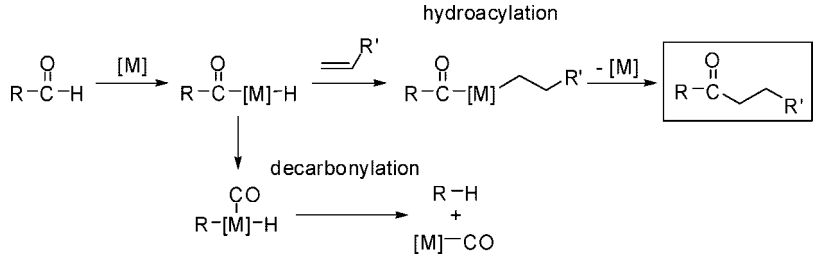


(2)

The turning point of general chelation-assisted hydroacylation was realized from the example of hydroacylation using aldimine made up of 2-amino-3-picoline (**1**) and benzaldehyde.[7] There is a very important consideration in our focus on a metal–organic cooperative catalysis (MOCC). For instance, if incorporation of a new catalytic cycle of aldimine formation into the conventional hydroacylation of aldimine is possible, we anticipated that a general and decarbonylation-free hydroacylation of olefins with a variety of aldehydes could be devised (Scheme 2).

Fascinated by the concept of MOCC, we have investigated a catalytic system consisting of a transition metal and an organic catalyst as a new chelation-assisted hydroacylation protocol. In the quest for an optimized system composed of a Wilkinson's catalyst, $(Ph_3P)_3RhCl$ (**2**) and **1**, we found that common aldehydes can be successfully applied in this transformation.[8] In addition, surprising efficiency enhancements could be achieved when benzoic acid and aniline were introduced

SCHEME 1



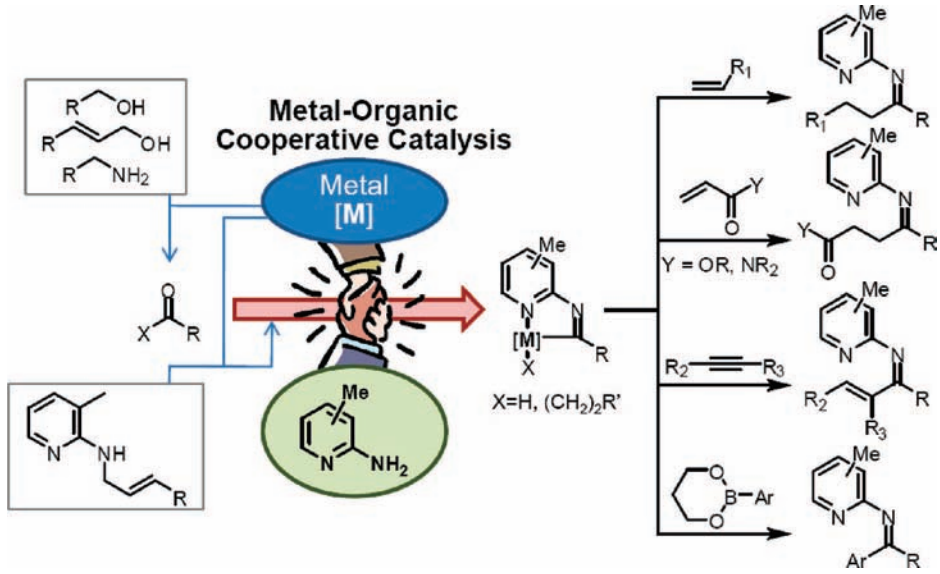


FIGURE 1. MOCC in C−H and C−C bond activation.

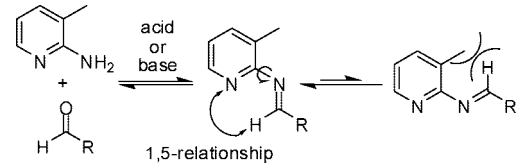
as promoters for the aldimine formation process.[9] Based on the remarkable reactivity and applicability of the metal−organic cooperative system in hydroacylation, a series of new catalytic reactions involving C−H and C−C bond activation can be realized (Figure 1).

In this Account, we summarize our ongoing research on chelation-assisted catalytic C−H and C−C bond activation operating under a MOCC system. We discuss how each organic catalyst affects each reaction from a mechanistic viewpoint and what kinds of substrate can be successfully applied in the catalytic process. In addition, recent efforts for the fundamental advances of these catalytic systems into recyclable processes by immobilizing both metal and organic components using a hydrogen-bonded self-assembled system as a catalyst support are described.

Catalytic Effects of 2-Amino-3-picoline and Its Derivatives in C−H and C−C Bond Activation

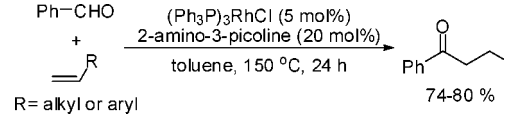
In applying an imine-forming reaction to the conventional hydroacylation, the chemical nature of condensation between aldehydes and primary amines implies some intriguing points to be considered. First, the rate of imine-forming reactions can be accelerated by acid or base catalysis. Second, otherwise unperturbed by external conditions, the condensation process is in equilibrium between reactants (aldehydes and amines) and products (imines), that is to say, reversible. Third, ketimine is more susceptible toward hydrolysis than aldimine. Since a ketone is the final product and its concentration increases throughout the reaction, this fact is helpful to make the catalytic cycle of **1** more efficient.

Considering these features together, a 2-aminopyridine-like molecule is a good candidate for our design of a metal−organic cooperative catalytic system. It is noteworthy that the position of the methyl group on the pyridine ring is exquisite in the cyclometalation process because the adjacent 3-positioned methyl group makes free rotation of the imine group rather difficult. The resulting geometrical bias also facilitates the cleavage of the imino C−H bond through decreasing the distance between the catalyst and the C−H bond (eq 3).



(3)

Hydroacylation with Aldehydes. From the cyclometalation model of aldimine, we examined **1** as a chelation-directing organic catalyst under in situ conditions in order to directly employ an aldehyde substrate for hydroacylation.[8a] When the reaction of benzaldehyde and olefins was carried out for 24 h at 150 °C in the presence of **2** and **1**, the corresponding ketones were obtained in fairly good yields (eq 4).



(4)

The mechanism of the reaction is depicted in Scheme 3.

Initially, benzaldehyde condenses with **1** to form the aldimine, which then undergoes pyridine group coordination to **2** accompanied by the C−H bond cleavage. The resulting acylrhodium(III) hydride species reacts successively with olefins causing the olefin insertion into the metal−hydride bond

SCHEME 3

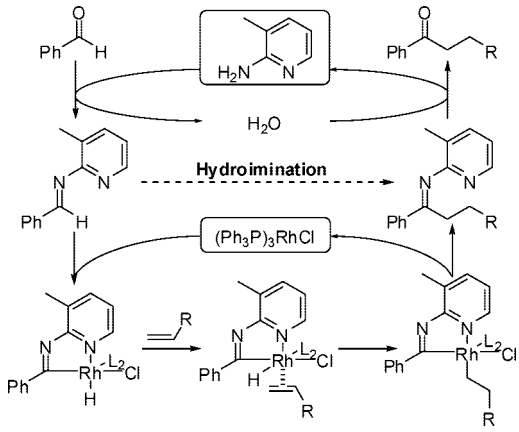
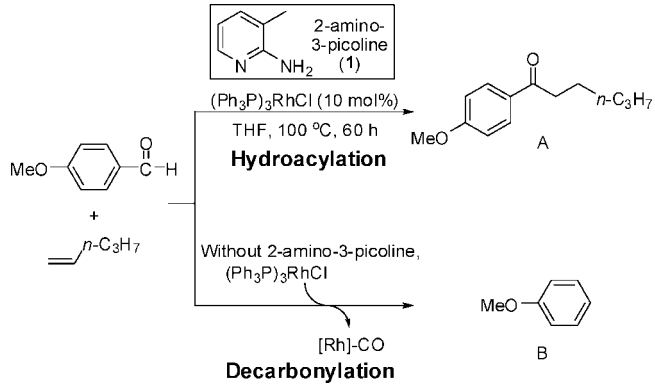


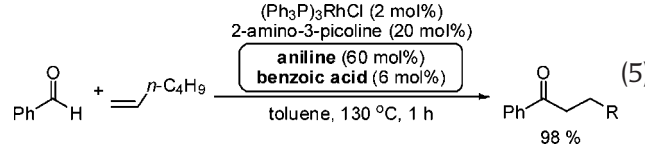
TABLE 1. Effects of **1** in Hydroacylation of Olefin with Aldehyde



entry	amount of 2-amino-3-picoline (mol %)	A/B	isolated yield of A (%)
1	0	0/100	0
2	10	58/42	14
3	20	85/15	57
4	50	85/15	70
5	70	90/10	80
6	100	93/7	83

(hydrometalation), which finally affords ketimine via reductive elimination. In this reaction, **1** is a chelation-directing organic catalyst, which can be temporarily installed on the aldehyde and uninstalled from ketimine by hydrolysis after hydroimination. Control experiments again revealed that the presence of **1** is essential in this reaction because, in the absence of **1**, no hydroacylation took place but the rapid decarbonylation prevailed. In addition, the concentration of **1** also affected the bifurcated reaction pathway, hydroacylation and decarbonylation (Table 1).[8a]

This observation is very important in terms of the kinetic aspects of the entire reaction because the concentration effect of **1** strongly implies that the imine condensation process should be a rate-determining step. Indeed, the use of organic auxiliaries, which can shift the equilibrium point of the imine condensation reaction, could dramatically improve the efficiency of hydroacylation (eq 5).[9]

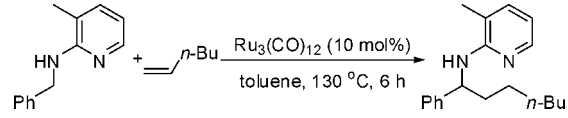


(5)

For instance, the transimination by aniline as well as the acid catalysis of benzoic acid turned out to be effective in accelerating the condensation step between an aldehyde and **1**. The mechanism of this acceleration is illustrated in Scheme 4.

First, an aldehyde condenses with a more reactive aniline to form aldimine, and the subsequent transimination with **1** generates the chelating aldimine;[10] both processes can be catalyzed under acidic conditions. The highly enhanced reactivity of this catalyst system implies that the indirect condensation of an aldehyde with **1** by transimination is a more efficient process than the direct condensation of an aldehyde and **1**.[11] It is worth mentioning that the hydroacylation of 1-alkenes with aldehydes can be considerably enhanced under microwave irradiation by stabilizing a polar intermediate.[12]

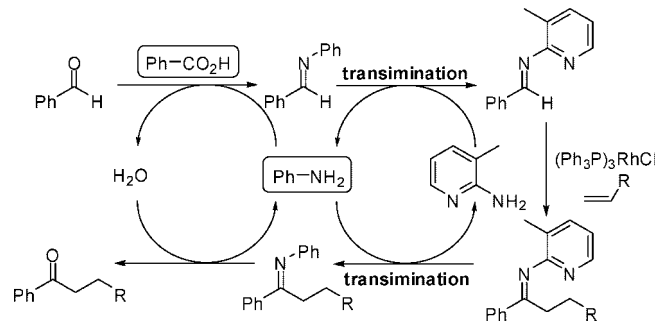
In general, C–H bond activation reactions are mainly centered on the sp^2 C–H bond and not on the sp^3 C–H bond, probably due to the better thermodynamic stability of the metal–sp^2 carbon bond compared with that of the metal–sp^3 carbon bond. Among the limited examples,[2g] the catalytic addition of a benzylic sp^3 C–H bond to various alkenes with benzylamine bearing the 3-methyl-2-pyridyl group is an interesting one showing the usefulness of the chelation-assisted cyclometalation strategy (eq 6).[13]



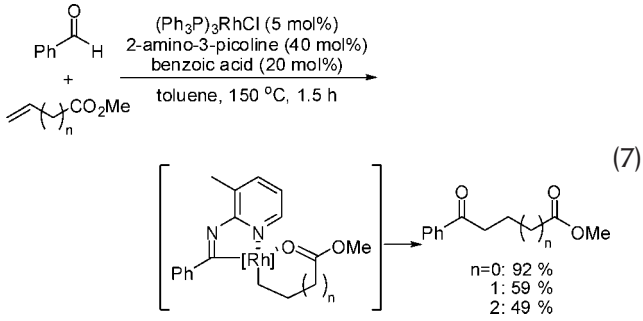
(6)

A challenging variant of the intermolecular hydroacylation involves the application of functionalized olefins as hydro-

SCHEME 4

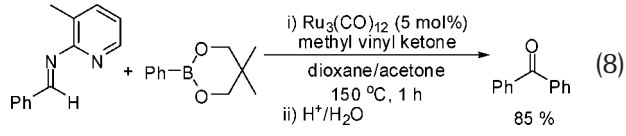


metalation partners. Most of the olefins used in the intermolecular hydroacylation are relatively simple molecules such as 1-alkenes or vinylsilanes. Although there have been some attempts to apply functionalized olefins including the use of methyl acrylate,[14] 1,6-hexadien-3-ol,[15] and 1,5-hexadiene,[16] more systematic variations of the functionalized olefinic substrates were still limited. However, under the same MOCC protocols, the synthesis of various oxo acids via the reaction of aldehydes with ω-alkenoic acid derivatives is a notable exception (eq 7).[17]



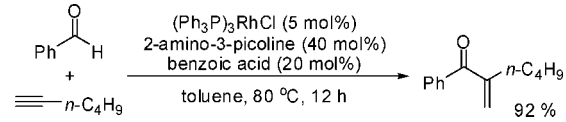
(7)

When methyl acrylate ($n = 0$), methyl 3-butenoate ($n = 1$), and methyl 4-pentenoate ($n = 2$) were used in this chelation-assisted hydroacylation reaction instead of a simple 1-alkene under identical reaction conditions, the corresponding γ-oxo, δ-oxo, and ϵ-oxo esters were isolated with 92%, 59%, and 49% yields, respectively. Such a broad scope for olefinic substrates can be extended to polymeric substrates such as polybutadiene.[18] On the other hand, a direct method for the synthesis of a diaryl ketone from an aldehyde (or corresponding imine) has hardly been developed.[19] In order to synthesize diaryl ketones using the **1**-based cyclometalation strategy, aryl boronates were applied instead of an alkene.[20] For example, when the reaction of aldimine with phenyl boronate was carried out in an acetone/dioxane mixture in the presence of $Ru_3(CO)_{12}$, benzophenone was isolated after hydrolysis of the resulting ketimine (eq 8).



(8)

Alkynes are also a challenging substrate for intermolecular hydroacylation because the hydrometalation step of alkynes may produce several regio- and stereoisomers. However, contrary to our expectation, the reaction of benzaldehyde and 1-hexyne in the presence of the cocatalyst system consisting of **2**, **1**, and benzoic acid in toluene at 80 °C for 12 h exclusively affords the branched α,β-enone in a 92% yield (eq 9).[21] The observed regioselectivity cannot be explained well by the hydrometalation mechanism, because the branched α,β-enone should originate from the most sterically demanding approach of the alkyne to the metal–hydride bond. The pronounced results of alkyne hydroacylation suggest that other mechanistic scenarios, such as a carbometalation pathway, may be involved in this reaction.



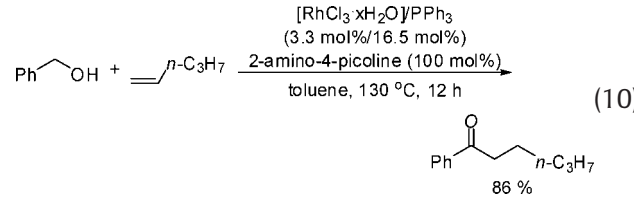
(9)

Such possibility of carbometalation during alkyne hydroacylation was also observed in chelation-assisted hydrative dimerization of 1-alkyne.[22] When the reaction of 1-octyne with H_2O was performed without aldehyde in the presence of **1** and **2**, branched and linear α,β-unsaturated enones were obtained in a 78:22 ratio (Scheme 5).

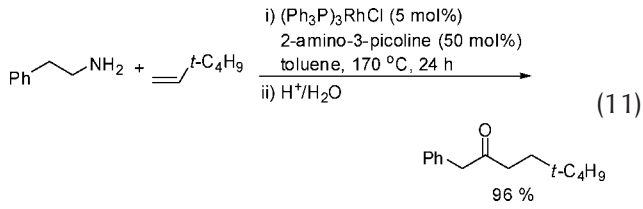
Interestingly, 1-alkyne is not only a substrate for hydroacylation but also a precursor of the aldehyde in this reaction. The catalyst **2** reacts with 1-alkyne to form the alkylidene complex, followed by the N–H addition of **1** with a chelation, double bond migration, and hydride abstraction to yield the identical intermediate in the chelation-assisted hydroacylation of the aldehyde.

Hydroacylation with Alcohols and Amines. Primary alcohols and amines including allylic ones can be utilized in situ as aldehyde precursors through an oxidation reaction by transfer hydrogenation and transition metal catalyzed isomerization, respectively (Scheme 6).

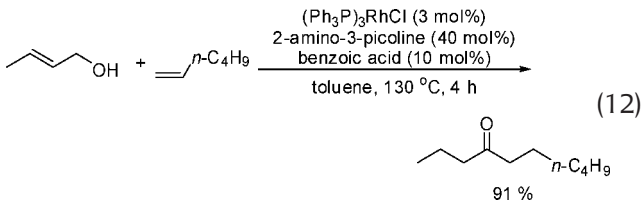
In the transfer hydrogenation case, the reaction of benzyl alcohol with excess olefin afforded the corresponding ketone in good yield in the presence of a Rh complex and 2-amino-4-picoline (**3**) (eq 10).[23] The overall reaction takes place by two consecutive reactions, dehydrogenation and hydroacylation. The primary alcohol was dehydrogenated by a rhodium(I)-catalyzed transfer hydrogenation to generate an aldehyde. The resulting aldehyde reacts with **3** and undergoes the chelation-assisted hydroacylation. Primary amines also experience similar reaction pathways except that transimination should be involved (eq 11).[24] The allyl alcohol isomerizes to an aldehyde and enters the same MOCC (eq 12).[25]



(10)



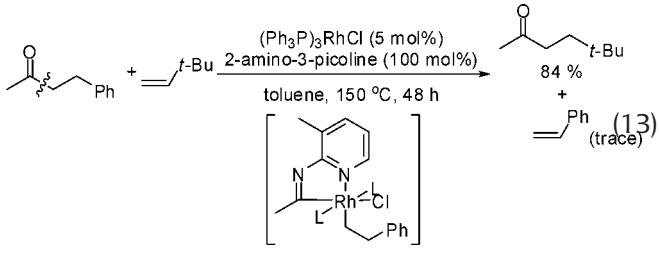
(11)



(12)

Carbon–Carbon Bond Activation. Once we had realized the metal–organic cooperative chelation-assisted hydroacylation of aldehydes, we noticed the possibility that the same protocols could be applied to C–C bond activation of common ketones. Since our MOCC method can also provide the special driving forces through chelation assistance, it seemed to be reasonable that the generation of stable metal complexes could be achieved by lowering the energy state of the C–C bond cleaved complexes (Scheme 7). In addition, the representative stoichiometric examples of this strategy showing the activation of the α-C–C bond of the carbonyl group in 8-quinolinyl alkyl ketone also supported our expectation.[26] If a carbonyl group has β-hydrogens, this C–C bond cleavage reaction could be converted to a catalytic reaction under pressure of ethylene gas.[27]

A notable accomplishment of C–C bond activation in unstrained simple ketones has been realized using **1** as a temporary chelating auxiliary.[28] For example, when benzylacetone reacts with excess *tert*-butylethylene, under a MOCC system of **2** and **1**, an alkyl group exchanged ketone and a trace of styrene could be observed (eq 13).

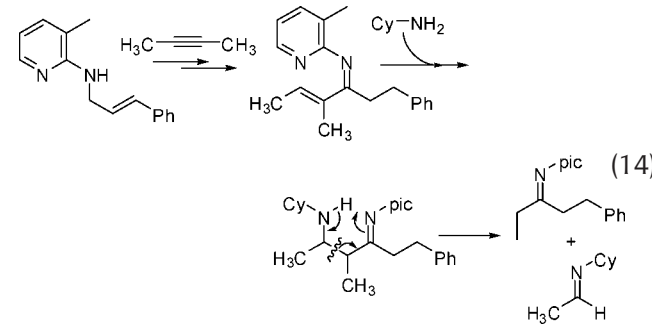


(13)

Similar to the case of hydroacylation of an aldehyde, the first step should be the formation of ketimine by the condensation of a ketone and **1** (Scheme 8). The C–C bond of ketimine is cleaved by the Rh(I) complex to generate an (iminoacyl)rhodium(III) phenethyl accompanied by β-hydrogen elimination giving an (iminoacyl)rhodium(III) hydride and styrene. The hydrometalation of *tert*-butylethylene with Rh–H and the subsequent reductive elimination yield ketimine. When the alkyl group exchanged ketimine is hydrolyzed by H_2O formed during the initial condensation step, the final ketone can be obtained in a free form with regeneration of **1**. Since the whole reaction lies in thermodynamic equilibrium, the polymerization of styrene drives the forward reaction.

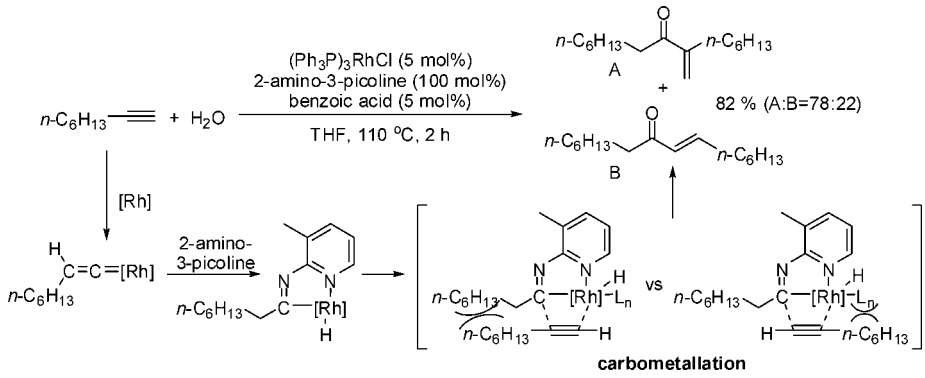
As in the case of primary alcohol hydroacylation, secondary alcohols can also be applied to the C–C bond activation through in situ transfer hydrogenation.[29] Among the examples utilizing the in situ isomerization process, allylamines provide some merits from a substrate standpoint. For instance, aliphatic aldehydes are not good substrates in the metal–organic cooperative hydroacylation because they usually produce aminals, not desirable imines, during the reaction with **1**.[7,8a] The formation of aminal considerably reduces the efficiency of the whole reaction. However, the existence of the double bond migration process of allylamines in the presence of transition metal complexes provides another chance for the application of aldimines of the aliphatic aldehydes. In addition, the resulting aldimines with aliphatic alkyl group can undergo both C–H and C–C bond activation by the Rh(I) catalyst (Scheme 9).[30] Thus, allylamine can be regarded as a masked form of formaldehyde. This approach was successfully applied to the synthesis of symmetrical dialkyl ketone and cyclic ketones using 1-alkenes and dienes, respectively (Scheme 10a,b).[31]

A further application of allylamine is a C–C triple bond cleavage. Although the C–C triple bond of alkynes is one of the strongest bonds in organic molecules, it can be efficiently cleaved when the **1**-based hydroacylation of alkyne is combined with an appropriate organic promoter such as cyclohexylamine (Scheme 10c).[32] In this transformation, the C–C triple bond of the alkyne is initially transformed into a C–C double bond through hydroacylation of the alkyne. The resulting α,β-unsaturated imine undergoes a subsequent retro-Mannich reaction with a cyclohexylamine leading to the formation of the C–C bond cleavage products, aldimines and enamines (eq 14).

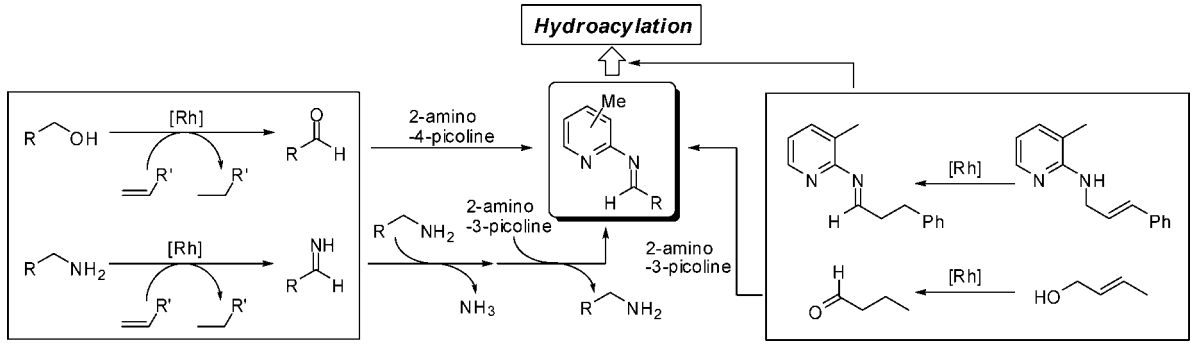


(14)

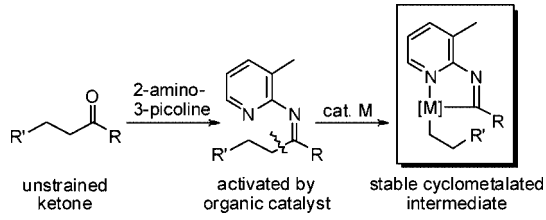
SCHEME 5



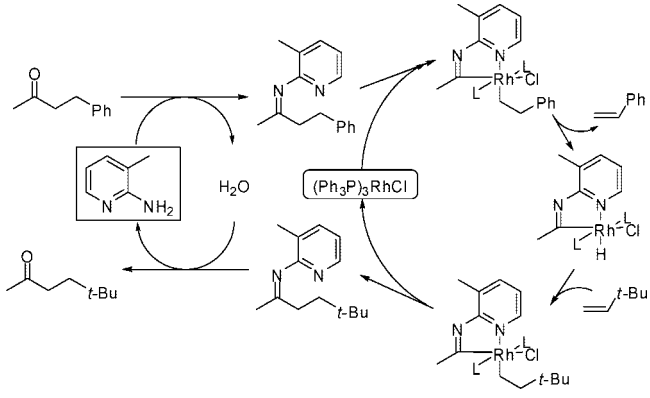
SCHEME 6



SCHEME 7

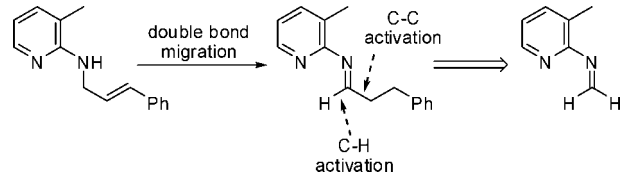


SCHEME 8



Furthermore, not only allylamine, but also common aldehydes such as acetaldehyde could be applied to this hydroacylation-triggered C–C triple bond cleavage. Since an aldehyde can be regenerated through the fragmentation of an α,β-unsaturated ketone and the subsequent reaction with the remaining alkyne, a serial cleavage of an alkyne induced by a small amount of external aldehyde could be possible. Utilizing the propagation nature of these methods, the ring-opening oligomerization of cycloalkyne was achieved (Scheme 11).[33] This protocol can be also applied directly to the cleavage of the C–C double bond of α,β-unsaturated ketones.[34]

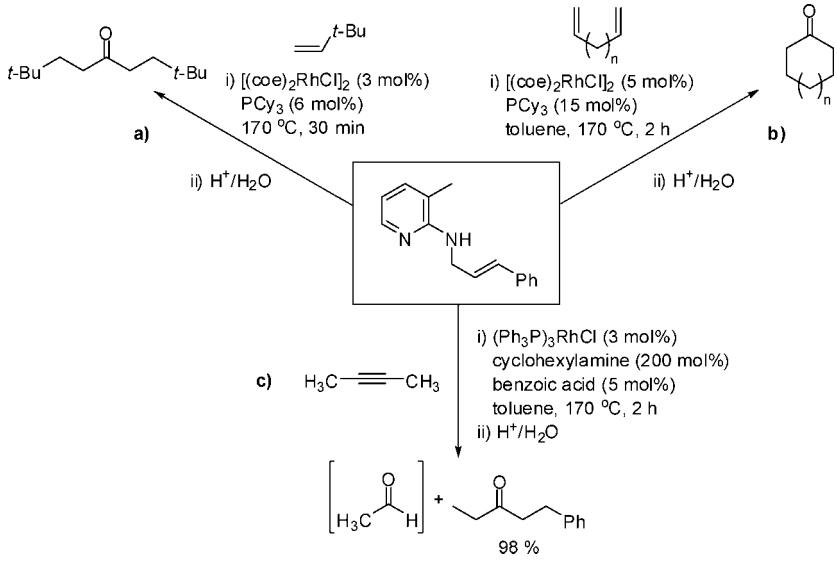
SCHEME 9



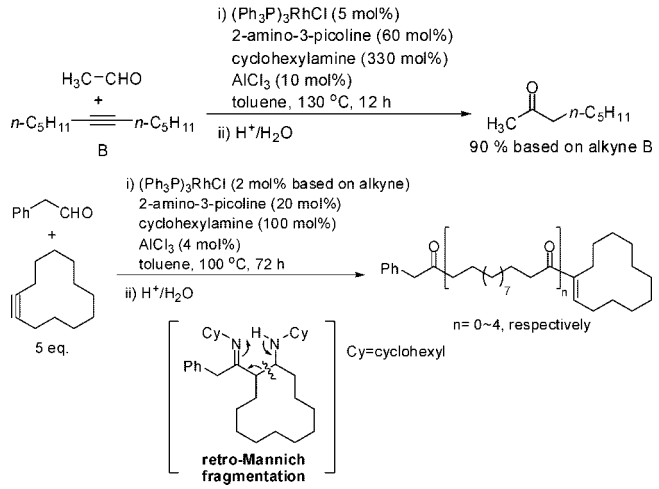
The C–C bond cleaving ability of cocatalyst system of **2** and **1** showed an interesting example of the skeletal rearrangement of a cyclic ketone or its imine.[35] When cycloheptanoketimine was reacted with the Rh(I) complex in the absence of an external olefin, a mixture of the ring-contracted cycloalkanones was obtained after hydrolysis (Scheme 12).

Starting with C–C bond cleavage of ketimine by the Rh(I) complex and subsequent β-hydrogen elimination, the intramolecular hydride insertion takes place. The resulting (iminoacyl)rhodium(III) alkyl intermediate is transformed

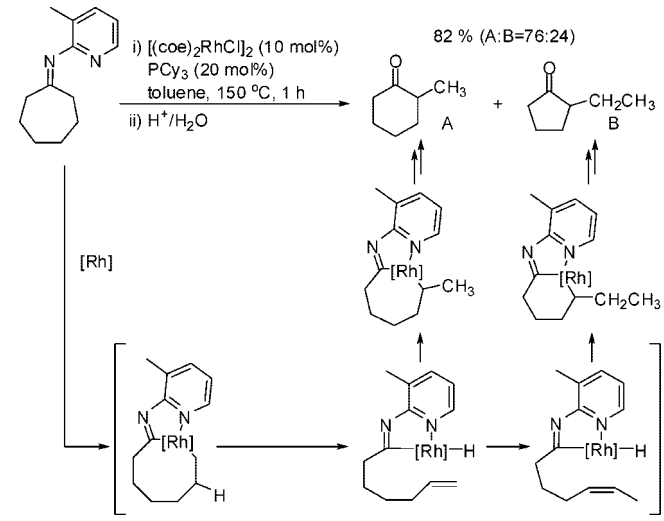
SCHEME 10



SCHEME 11



SCHEME 12



into a six- or five-membered ring ketimine through reductive elimination.

Hydrogen-Bonded Self-Assemblies as a Metal–Organic Catalyst Recovering Support

The challenges to recover catalysts from a homogeneous reaction always have encountered paradoxical situations such that the catalysts should have considerable inhomogeneity to be cleanly separated from the homogeneous phase. The more inhomogeneity the catalysts have, the more heterogeneous the reaction becomes. As a result, the original efficiency or selectivity of the reaction in a homogeneous state often has been significantly impaired. Such trends were also found in our earlier efforts to recover the rhodium catalysts from hydroacylation reactions using polystyrene-based phosphanes.[36] The solubility of polystyrene was not sufficient to make a reaction ideally homogeneous.

Among the physical aspects that govern the nature of the separation processes, we noticed hydrogen bonding as a solubility-regulating interaction because the strength of an intermolecular hydrogen bond can be easily diminished by the application of heat.

Biphasic Solvent System Based on the Phenol and 4,4′-Dipyridyl Hydrogen-Bonding Couple. Based on the fact that phenol and 4,4′-dipyridyl form a hydrogen-bonding complex,[37] a mixed solvent system was conceived as a reaction medium for the hydroacylation of primary alcohols.[38] Interestingly, this solvent system forms two immiscible phases with hydrocarbons such as alkane or olefin at room temperature. Because a strong hydrogen-bonding network is hardly

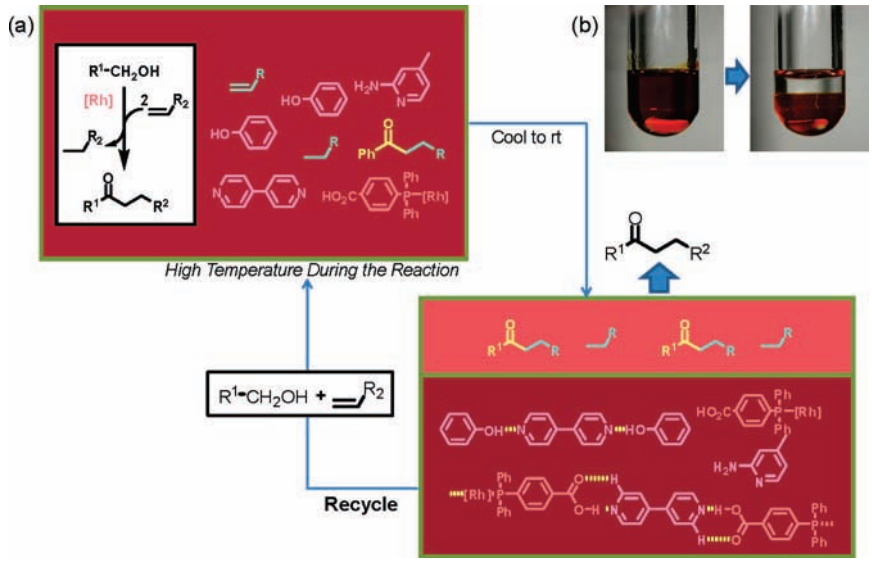
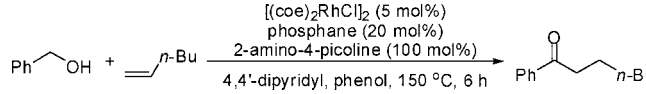


FIGURE 2. (a) A biphasic system using hydrogen-bonding solvent and a schematic diagram of the recycling of the catalysts for chelation-assisted hydroacylation with primary alcohol and (b) a phase separation of the reaction mixture consisting of benzyl alcohol, 1-decene, $[(C_8H_{14})_2RhCl]_2$, 4-PBA, **3**, phenol, and 4,4′-dipyridyl after cooling.

TABLE 2. Recycling of the Catalysts for Hydroacylation of Olefin with Alcohol



			isolated yield of ketone (%)						
entry	phosphane	additive	1st	2nd	3rd	4th	5th	6th	7th
1	4-PBA		88	96	92	95	91	94	96
2	PPh_3	$PhCO_2H$ (20 mol%)	93	34	28	12			
3[a]	4-PBA		94	56	61	43	29		

[a] The reaction was performed in the absence of phenol.

established at high temperature, these two phases combine into one phase upon heating (Figure 2a).

During the high temperature reaction, the ketone reaction product as well as the reactants and catalysts can completely form a homogeneous mixture. After the reaction, along with the cooling of the reaction mixture to room temperature, hydrogen bonding is reestablished and the single phase turns into the initial two phases (Figure 2b). Because the polar components of the reaction mainly condense in the lower phenol and 4,4′-dipyridyl phase while the nonpolar components are largely partitioned into the upper nonpolar hydrocarbon phase, the product of hydroacylation, ketones, can be separated by a simple decanting procedure. In addition, by employment of 4-diphenylphosphanylbenzoic acid as an external ligand, the rhodium catalysts also can be left in the polar phase through a hydrogen-bonding interaction between the carboxylic acid groups and 4,4′-dipyridyls (Figure 2a).

The control experiments revealed that both phenol and 4-diphenylphophanylbenzoic acid are essential to sustain a consistent reactivity of the reaction throughout repeated recycling (Table 2).

Although this biphasic system showed a remarkable ability to recover the rhodium catalysts (*ave.* 0.015% leaching of the initial Rh over two recycles), the continuous slight leaching of the organic catalyst, **3**, was inevitable.

Barbiturate and Triaminopyrimidine Based Hydrogen-Bonding Couple. The finding that the hydrogen-bonding based approach can be applied to the C–H bond activation reaction without a loss of reactivity exemplifies a new possibility in designing of a novel catalyst-recovery system. One important principle for such a purpose was that a catalyst-immobilization support should provide sufficient homogeneity to maximize the collision rate between the catalyst and substrate during the reaction but become nearly heterogeneous through a highly cross-linked interaction after the reaction. To achieve this goal, a multiple point interaction of hydrogen bonding was thought to be desirable. Among the many examples of multiple hydrogen-bonding pairs, the barbiturate (BA) and 2,4,6-triaminopyrimidine (TP) based system

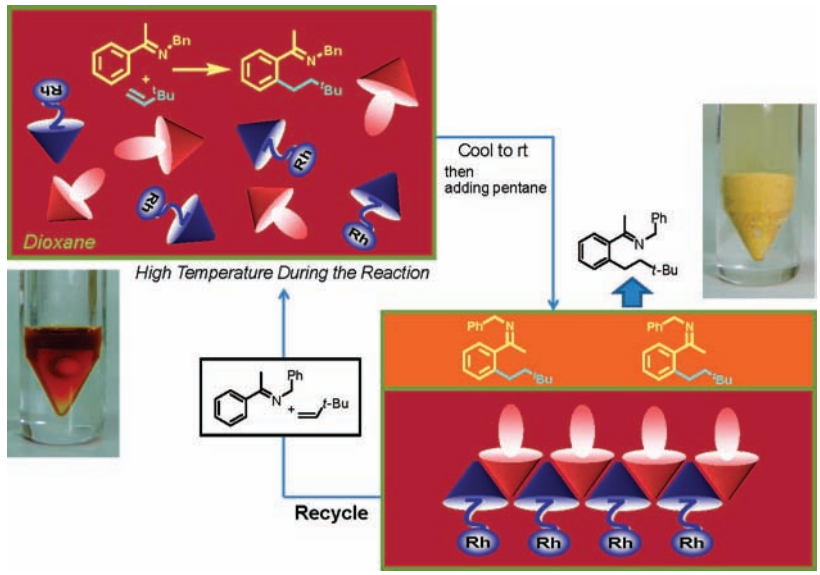


FIGURE 3. Schematic illustration of the recycling of metal catalyst.

SCHEME 13

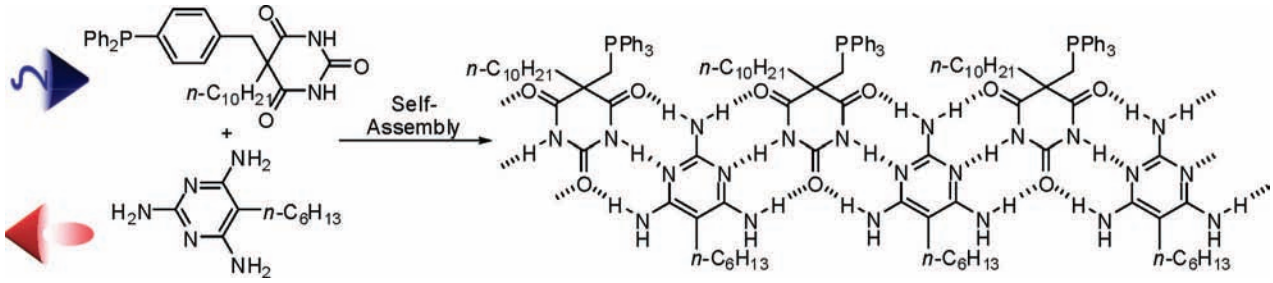
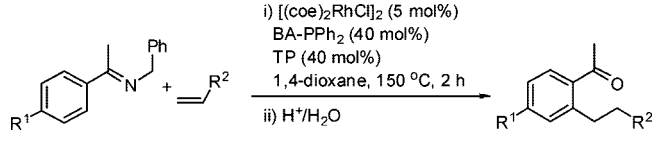


TABLE 3. Recycling of the Metal Catalysts for Orthoalkylation of Imine with Olefin



			isolated yield of ortho-alkylated product (%)							
entry	R^1	R^2	1st	2nd	3rd	4th	5th	6th	7th	8th
1	H	*t*Bu	87	91	94	97	95	92	89	86
2	MeO		85	90	89	85	88	87	84	87
3	CF_3		92	95	94	97	93	93	89	91
4	H	*n*Bu	68	73	77	76	76	74	79	75

was suitable because it is known to form large and stable supramolecular assemblies through six hydrogen-bonding interactions per molecule.[39] Furthermore, this system can be derivatized simply and systematically. Thus, we expected that the introduction of a phosphanyl group on BA should lead to supramolecular assemblies (Scheme 13), which could serve as a catalyst support and a ligand for the transition metals, simultaneously.

To verify our initial concept of self-assembly support, we applied the BA-PPh_2 and TP self-assembly system to the benzylimine-assisted orthoalkylation[2e] as a model system of rhodium-catalyst immobilization. The schematic explanation of the recycle experiments is depicted in Figure 3.

During the reaction, the solution became homogeneous at the high reaction temperature, but a pale yellow solid precipitate was observed at room temperature upon addition of *n*-pentane after the reaction. The solid precipitate corresponds to the hydrogen-bonded self-assembly of BA-PPh_2 and TP, including the Rh(I) metal with the phosphorus coordination of BA-PPh_2. The separated liquid phase upon addition of *n*-pentane contained very small amounts of rhodium metal (estimated by ICP-MS as 0.024%, 0.009%, and 0.012% leaching over three cycles), but almost the entire orthoalkylated imine product remained in the solution phase. Therefore, the catalysts could be recovered from the product very efficiently. Besides the feasibility of catalyst recovery, this system also showed remarkable reactivity for the repeated uses of transition-metal catalyst (Table 3). The catalytic results are comparable to the original homogeneous version.[40]

On the other hand, in application of the hydrogen-bonding support system to the chelation-assisted hydroacylation,

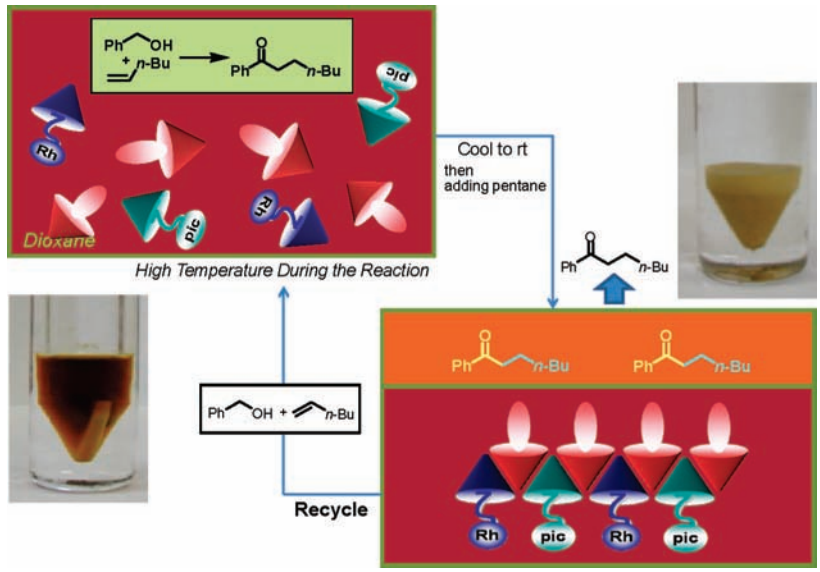
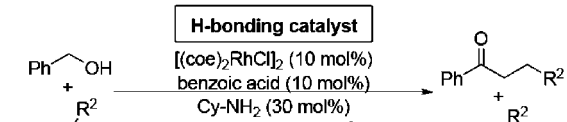
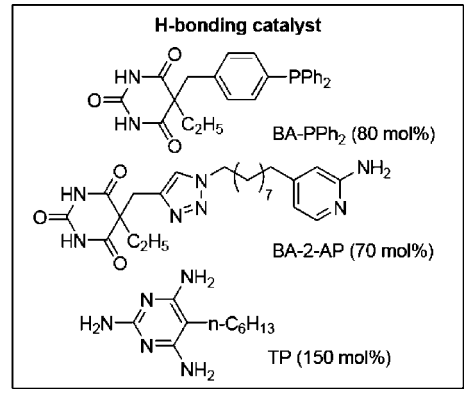


FIGURE 4. Schematic illustration of the recycling of both metal and organic catalysts.

TABLE 4. Recycling of both Metal and Organic Catalysts for Hydroacylation of Olefin with Alcohol



		isolated yield of product (%)							
entry	R^2	1st	2nd	3rd	4th	5th	6th	7th	8th
1	n-C_4H_9	95	88	94	87	82	89	81	91
2	$SiMe_3$	92	91	77	90	84	93	85	91



immobilization of **1**, an organic catalyst, was a formidable problem as observed in the case of the phenol and 4,4′-dipyridyl system. However, inspired by the BA-PPh_2 and TP system, we expected that a 2-aminopyridin-4-yl group as a chelation auxiliary would be incorporated into the BA backbone leading to the formation of a hydrogen-bonded self-assembly with TP.

Important improvements were found regarding the immobilization of the 2-aminopyridine catalysts.[41] For example, BA-2-AP stayed in the lower solid phase assembled with TP (the reaction mixture became homogeneous at the high reaction temperature), while the product ketone and other catalysts [$(Ph_3P)_3RhCl$, Cy-NH_2, and benzoic acid] could be separated from the self-assembled solid phase by washing with *n*-pentane. It is noteworthy that only the targeted (tagged by BA) organic catalyst remained and, most importantly, the separation efficiency of the product is nearly perfect. The remaining BA-2-AP and TP were recycled for subsequent reactions with an addition of substrates and other catalysts for up to 10 catalytic reactions while maintaining a very high efficiency.

To recycle both organic and transition metal catalysts, PPh_3 in the reaction can be replaced by BA-PPh_2, a triphenylphosphane bearing a barbiturate moiety. Considering the hydrogen-bonding pattern of BA and TP, the ratio of BA species (BA-PPh_2 and BA-2-AP) and TP was adjusted to 1:1 to form a complete supramolecular hydrogen-bonded network (Figure 4).

We observed that this catalytic system was also homogeneous at high temperature and heterogeneous at room temperature. As was the case in the above examples, the ketone product could be separated from the self-assembled support system by decanting the upper layer. The remaining immobilized catalysts (BA-2-AP and BA-PPh_2-Rh species) could afford the product ketones in very high yields for up to eight catalytic reactions (Table 4).[41]

Concluding Remarks

The successful incorporation of an organocatalytic cycle into a transition metal catalyzed reaction led us to find MOCC for C−H and C−C bond activation. As a result, a very efficient and general hydroacylation method could be achieved through gradual understandings of each catalytic cycle involving the metal and organic components. Upon application of the metal−organic cooperative protocol to C−H and C−C bond activation, a series of new catalytic reactions such as alcohol hydroacylation, oxo-ester synthesis, C−C triple bond cleavage, hydrative dimerization of alkynes, skeletal rearrangements of cyclic ketones, and so on could also be devised. In addition, the hydrogen-bonded self-assembled support has been developed for an efficient and effective recovery system of homogeneous catalysts and could be successful in immobilizing both rhodium and 2-aminopyridine species in MOCC reactions. To expand the scope of this new catalysis and recovery system for C−H and C−C bond activation into other undiscovered transformations, various efforts are being undertaken in our laboratory.

The author thanks the talented researchers who are listed as coauthors of the publications emanating from his laboratories. This work was supported by a Korean Research Foundation Grant (MOEHRD) funded by the Korean Government (KRF-2005-201-C00024) and the Center for Bioactive Molecular Hybrids (CBMH). J.-W.P. acknowledges the fellowship of the BK21 program from the Ministry of Education and Human Resource Development.

BIOGRAPHICAL INFORMATION

Young Jun Park was born in 1971. He received his B.S., M.S., and Ph.D. degrees in chemistry from Yonsei University in 1995, 1997, and 2003, respectively. He worked as a postdoctoral associate in the Department of Chemistry and the Center for Bioactive Molecular Hybrid at Yonsei University under the guidance of Professor Chul-Ho Jun.

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Chul-Ho Jun was born in 1953. He graduated from Department of Chemistry of Yonsei University in 1976. He received his Ph.D. degree from Brown University in 1986 on C−C bond activation by organometallic compounds. From 1991 to 1992, he held a postdoctoral fellowship at Yale University. Starting in 1976, he worked as a research scientist at the Agency for Defense Development in Korea. In 1993, he moved to Yonsei University as an Associate Professor, and then, in 1995, he was promoted to full Professor. He was one of the directors of the National Research Laboratory of Korea (2000−2005). He spent his sabbatical stay at Department of Chemistry of Harvard University in 2003. His research interests are design and synthetic approach of the transition metal catalyzed C−H and C−C bond activation and application to the recyclable catalysis and syntheses of organic−inorganic hybrid.

FOOTNOTES

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