

# Cooperative Catalysis for Organic Synthesis

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Metal catalysis has driven innovation in organic synthesis during the last half-century. An alternative to the traditional strategy of developing catalysts with a single metal center is the combined use of more than one metal complex and design of their cooperative action to achieve new synthetic transformations. With the rich chemistry of metal catalysis that has been developed over the last five decades, as well as recent advancements in organocatalysis and emerging photoredox catalysis, one can imagine that cooperativity of these known catalytic approaches could enable novel synthetic transformations that have been highly challenging via conventional single-site metal catalysis.

**METAL CATALYSIS IS** indispensable in contemporary organic synthesis for the production of useful substances, such as materials and drugs, for modern human life. Many useful metal-catalyzed organic reactions have enabled the cleavage and formation of covalent bonds, which is otherwise challenging, and led to innovation in organic synthesis through providing atom- and step-economical routes to target molecules. The potential of metal catalysts to further unveil novel chemical transformations is infinite because of the different reactivities of the metal elements of the periodic table and the diversity of ligands to finely tune the reactivity of the metal centers. Nevertheless, the development of totally new metal catalysts to allow novel and useful chemical reactions is often laborious.

Transition metal complexes show a variety of different types of reactions, such as oxidative addition, transmetalation, olefin insertion, reductive elimination, etc. The reactivity and selectivity of these elemental reactions depend heavily on the electronic and steric features of the metal complexes and can be precisely controlled by their formal oxidative states and the ligands binding to the metal centers. Consequently, a variety of single-metal-based catalysts bearing different transition metals

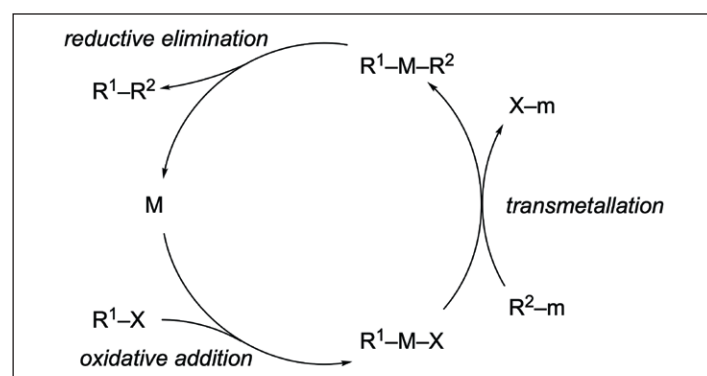
and ligands have been identified to achieve useful reactions such as cross-coupling, olefin metathesis, olefin/alkyne-functionalization, and oxidation/reduction reactions, among others. These catalytic reactions consist of various elemental reactions such as those mentioned above. For example, the catalytic cycle of Pd-catalyzed cross-coupling reactions can be expressed roughly via three steps: oxidative addition of an electrophile, transmetalation with a nucleophile, and C–C bond-forming reductive elimination (Scheme 1). Each step favors different electronic and steric characteristics with regard to the Pd center. The initial oxidative addition proceeds faster with electron-rich Pd species, and thus electron-donating ligands are favored to make the Pd center nucleophilic, whereas electrophilic Pd(II) undergoes transmetalation efficiently. Although the rate of the reductive elimination step does not usually affect the overall reaction rate, it can be accelerated by ligands with electron-withdrawing  $\pi$ -accepting nature. Accordingly, an optimum catalyst must have well-balanced electronic and steric characteristics to enable the overall catalytic cycle. This may limit the scope of electrophiles and nucleophiles that can participate in the cross-coupling reactions.

### Cooperative synergistic catalysis

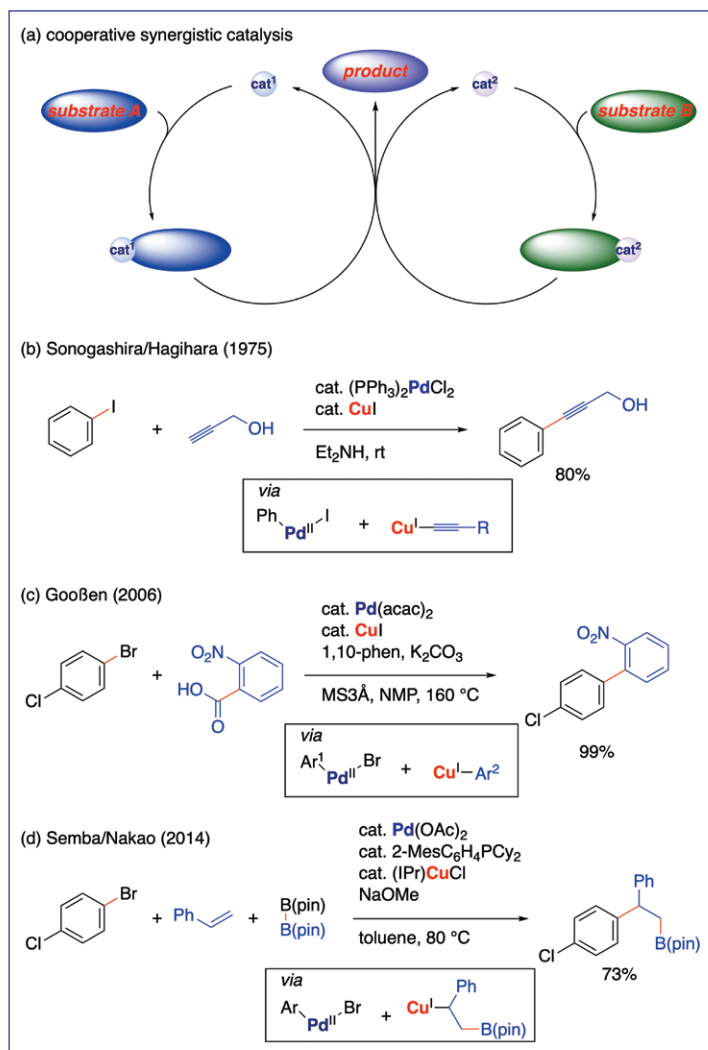
To avoid this dilemma and promote catalytic cycles requiring distinct electronic properties in each step, the use of two different metal catalysts can be considered.<sup>1</sup> One possible scenario is the use of a metal catalyst that activates electrophiles with another that preferentially reacts with nucleophiles. The thus-formed organometallic intermediates would react with each other to afford the products. This type of synergistic cooperative metal catalysis (Scheme 2a) has emerged as a powerful strategy to significantly expand the scope of cross-coupling reactions in recent years.<sup>2</sup> The pioneering contribution of this type of synergistic cooperative metal/metal catalysis for cross-coupling was reported in 1975 by Japanese chemists Sonogashira, Tohda, and Hagihara (Scheme 2b).<sup>3</sup> This reaction, which is now commonly called the Hagihara–Sonogashira coupling reaction, allows the coupling of organic halides and pseudo-halides with terminal alkynes via cooperative Pd/Cu catalysis. Pd(0) activates the organic halides through oxidative addition to give an electrophilic Pd(II) species, whereas Cu(I) reacts with terminal alkynes to generate Cu(I) acetylides as nucleophilic organometallic intermediates. These react with each other to give diorgano-Pd(II) intermediates that afford the product through C–C bond-forming reductive elimination. After 30 years, the scope of substrates for the Cu cycle was expanded to arenecarboxylic acids, which undergo decarboxylation to generate arylcopper nucleophiles. The decarboxylative coupling of carboxylic acids with organic electrophiles was established using cooperative Pd/Cu catalysis by Gooßen and coworkers (Scheme 2c).<sup>4</sup> The Cu(I) cycle was then further developed to accommodate multi-step transformations to generate organocopper nucleophiles. We demonstrated the first example of such a system by integrating the functionalization of alkenes in the Cu(I) cycle to develop an arylboration reaction (Scheme 2d).<sup>5</sup> This reaction can be useful to give highly functionalized organoboron compounds, which play versatile and important roles in modern organic synthesis.

Combinations of other transition metals for cooperative synergistic catalysis have also been reported. A pioneering example was reported by Sawamura, Sudoh, and Ito, who showed that the combination of Pd

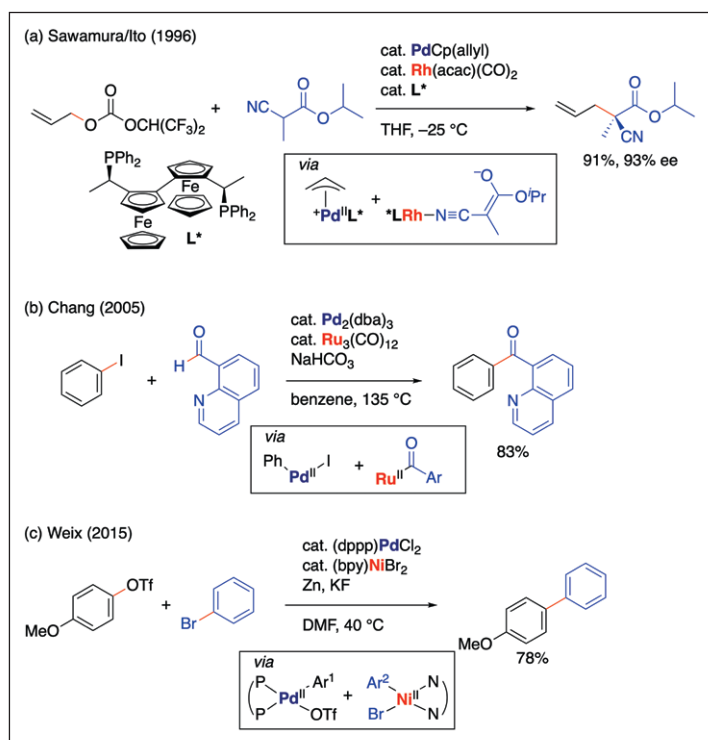
and Rh, both bearing chiral ligands, effectively catalyzed the allylation of  $\alpha$ -cyanoesters to construct quaternary carbon stereocenters (Scheme 3a).<sup>6</sup> It is essential for both metal catalysts to be optically pure to obtain high enantioselectivity in the allylation reaction. Catalytic C–H functionalization is one of the most important and extensively studied organic transformations in modern organic synthesis.<sup>7</sup> Cooperative synergistic catalysis involving C–H activation represents an ideal strategy to expand the scope of C–H functionalization, because metal complexes effective for C–H activation are not always competent for the subsequent functionalization events, in which the other metal catalyst could play a role in cooperative catalysis. Chang and coworkers reported a pioneering example using cooperative Pd/Ru catalysis (Scheme 3b).<sup>8</sup> The Ru cycle is likely responsible for the C–H activation, and a cross-coupling-type reaction proceeds on Pd. Another challenging and useful transformation in current synthetic organic chemistry is the so-called cross-electrophile coupling reaction,<sup>9</sup> in which two different electrophiles must be distinguished. Weix and coworkers demonstrated that cooperative synergistic Pd/Ni catalysis allowed the selective reductive cross-coupling of aryl halides and aryl triflates (Scheme 3c).<sup>10</sup>



**Scheme 1: A simplified single-metal-based catalytic cycle for cross-coupling reactions.**



**Scheme 2:** The concept behind cooperative synergistic catalysis, and examples of Pd/Cu catalysis.



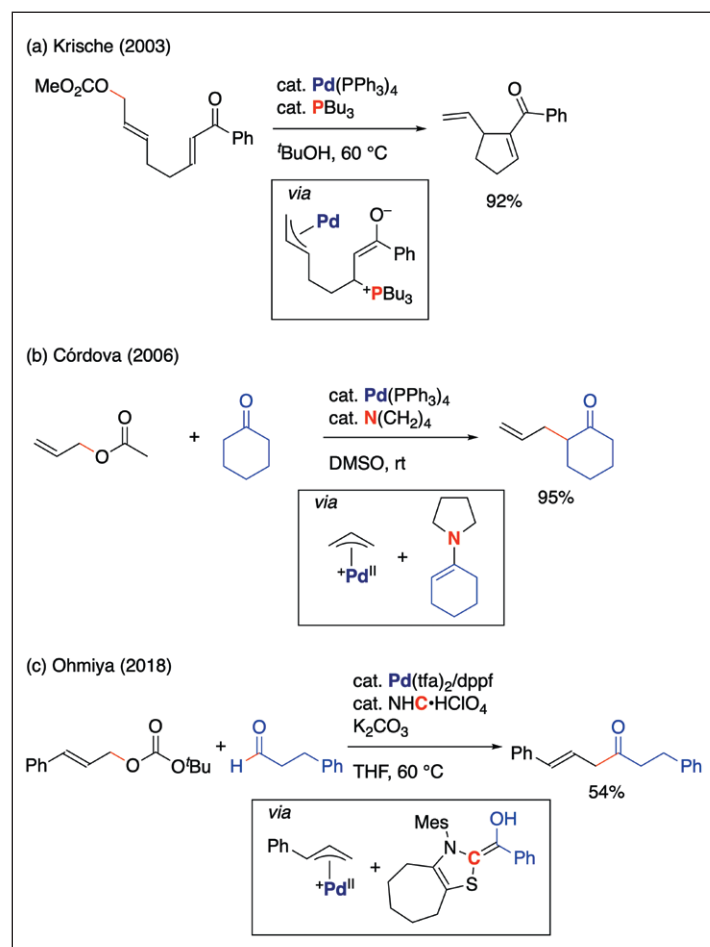
**Scheme 3:** Other examples of cooperative synergistic metal/metal catalysis.

Examples of cooperative metal/organo synergistic catalysis are also available as a result of the extensive studies on organocatalysis in the last two decades.<sup>11</sup> Krische reported an early example in which a nucleophilic phosphine catalyst was integrated into the intramolecular Pd-catalyzed allylic alkylation reaction (Scheme 4a).<sup>12</sup> An intermolecular variant employing an enamine catalyst was then reported by Córdova (Scheme 4b)<sup>13</sup>. More recently, carbene catalysts have been shown to participate in Pd chemistry to enable the allylic acylation reaction through the reaction of  $\pi$ -allylpalladium with the Breslow intermediate, as demonstrated by Ohmiya and coworkers (Scheme 4c)<sup>14</sup>.

Photoredox catalysis in organic synthesis has been developed significantly in the last ten years.<sup>15</sup> This strategy can also be successfully combined with transition metal catalysis to enable highly challenging cross-coupling-type transformations. Molander,<sup>16</sup> Doyle, and MacMillan<sup>17</sup> pioneered cooperative Ni/Ir photoredox catalysis to achieve novel cross-coupling-type reactions. For example, simple amino acids can participate in the Ni-catalyzed cross-coupling reaction through oxidative decarboxylation to generate radical species, which react with arylnickel intermediates to provide the products upon C–C bond-forming reductive elimination (Scheme 5). Although the proposed catalytic cycle does not involve reaction between two distinct organometallic intermediates, this particular type of cooperative catalysis has found to be highly general to overcome the limitations of cross-coupling chemistry.<sup>18</sup>

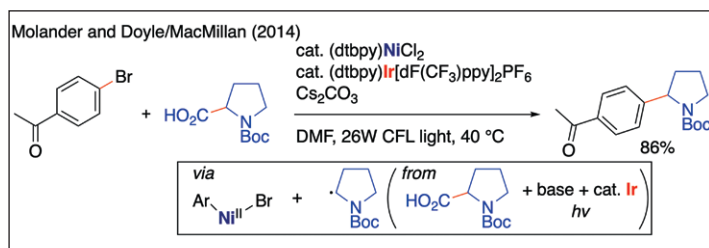
### Cooperative double activation catalysis

Another effective cooperative catalytic reaction is the use of two metal complexes that react with a single substrate (double activation) to promote bond-cleaving and/or -forming events that are inaccessible or sluggish using a conventional single metal catalyst (Scheme 6a).

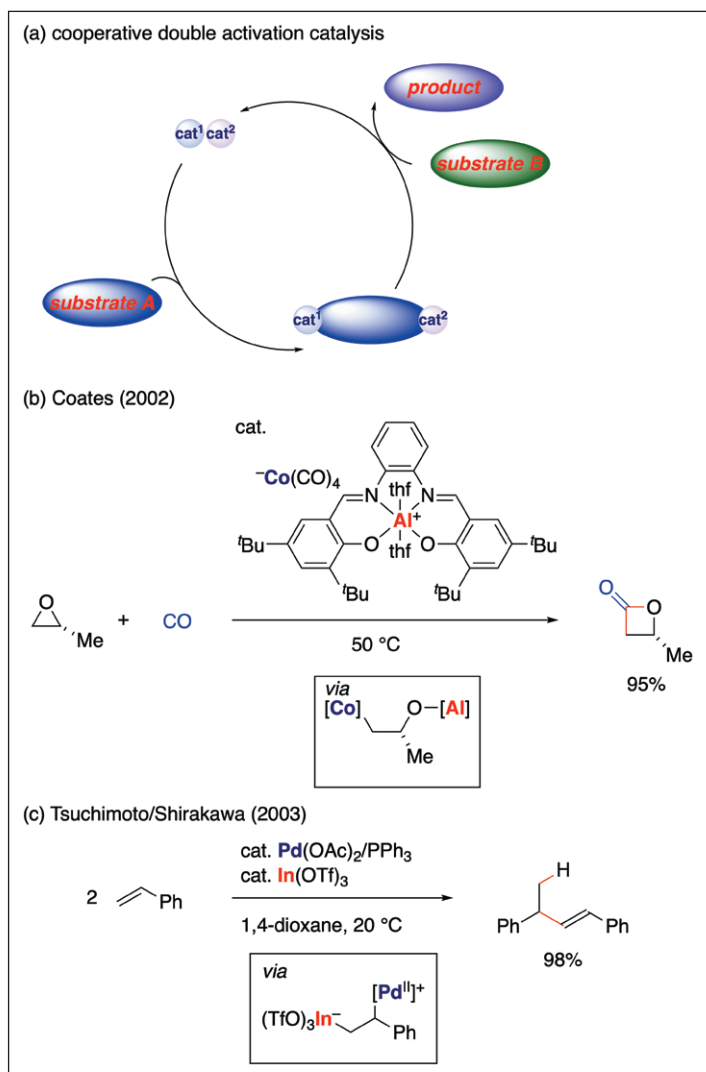


**Scheme 4:** Cooperative synergistic Pd/organo catalysis.

Combinations of Lewis-acidic metal catalysts and late transition metal catalysts have been established for cooperative double activation catalysis. Epoxides are highly versatile organic building blocks that are frequently used in organic synthesis. They have a Lewis-basic functionality that undergoes ring-opening reactions, often catalyzed by Lewis acids. Thus, the combination of Lewis acids and low-valent transition metal complexes can be envisaged for the development of novel ring-opening reactions of epoxides catalyzed uniquely via cooperative catalysis. The development of cooperative double activation catalysis for epoxides was pioneered by Coates and coworkers using an anionic cobalt catalyst bearing cationic aluminum as a Lewis-acidic counterion for the reaction of epoxides with carbon monoxide to give  $\beta$ -lactone products (Scheme 6b).<sup>19</sup> The epoxides form Lewis pairs with the cationic Al center and react with the nucleophilic anionic cobalt complex to give a metallacycle intermediate, in which CO insertion into the C–Co bond



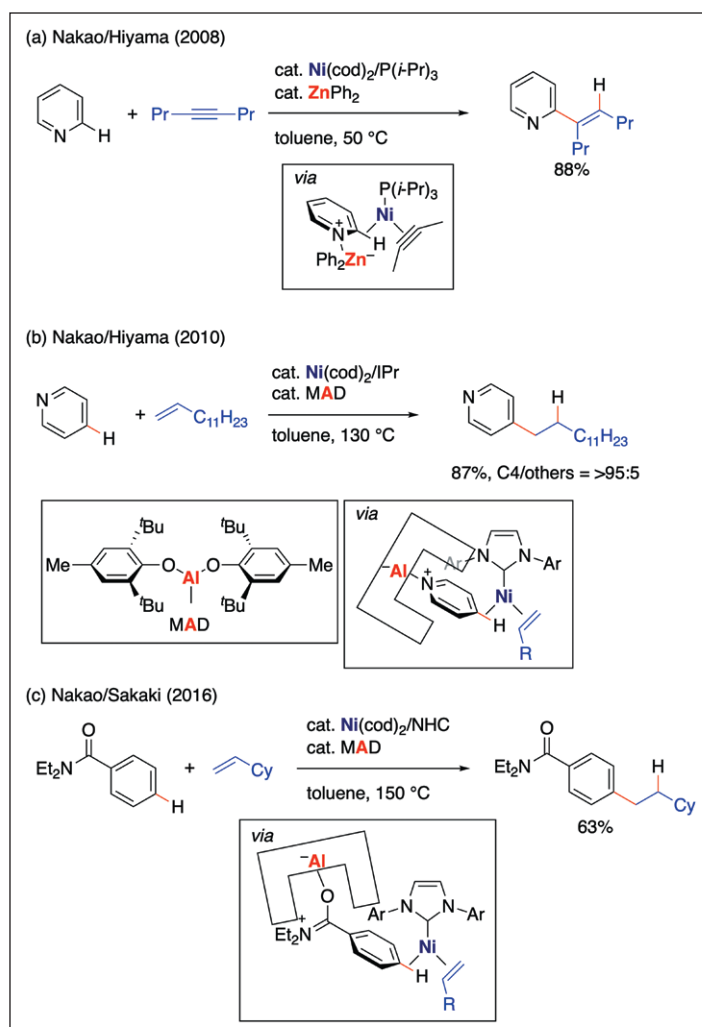
Scheme 5: Cooperative synergistic Ni/Ir photoredox catalysis.



Scheme 6: The concept behind cooperative double activation catalysis, and pioneering examples.

takes place. The lactone products are ejected to regenerate the cooperative catalyst system. Alkynes and alkenes can also serve as Lewis bases via their  $\pi$ -electrons. Some metal complexes are known to act as Lewis acids to form Lewis pairs with alkynes and alkenes, which in turn can act as electrophiles to react with electron-rich low-valent transition metal complexes. In an early example, the regioselective dimerization of styrene was reported by Tsuchimoto, Shirakawa, and coworkers using Pd/In as a cooperative double activation catalyst (Scheme 6c).<sup>20</sup> Styrene is likely activated by an In Lewis acid to act as an electrophile for the Pd(0) species; the subsequent carbopalladation reaction across another styrene gives an alkylpalladium intermediate, which undergoes  $\beta$ -hydride elimination to afford the dimerization products.

Cooperative double activation catalysis has proved to be effective for catalytic C–H functionalization. As an early example, we reported that cooperative Ni/Zn catalysis allowed C2-alkenylation of pyridine (Scheme 7a).<sup>21</sup> Pyridine coordinates to the Lewis-acidic Zn catalyst, and is then activated by the electron-rich Ni(0). Cooperative Ni/Al catalysis with bulky ligands was shown to be useful not only for the acceleration of the C–H functionalization, but also for controlling the site-selectivity. The steric repulsion between bulky Ni and Al catalysts likely induces the high C-4 selectivity of the alkylation reaction (Scheme 7b).<sup>22</sup> The Ni/Al catalysis was then applied to site-selective C–H functionalization of substituted benzenes. *Para*-selective alkylation of benzamides with alkenes was achieved using a similar bulky Ni/Al catalysis system (Scheme 7c).<sup>23</sup> Coordination of the Lewis-basic aminocarbonyl functionality to the bulky Al Lewis acid accelerates the rate and controls the *para*-selectivity of C–H activation by the bulky Ni catalyst. This is in stark contrast to



Scheme 7: Cooperative double activation Ni/Al catalysis for site-selective C–H alkenylation and alkylation.

conventional single metal catalysis, which commonly proceeds at the *ortho*-position through directed C–H metalation, in which the carbonyl groups bind to the metal catalyst to promote C–H activation at the proximal *ortho*-position.<sup>24</sup> Cooperative double activation catalysis thus offers unique opportunities for the promotion of C–H functionalization as well as control of the site-selectivity, which have been elusive by single-site catalysts.

The acceleration and the control of the *para*-selectivity of the bulky Ni/Al catalysis system for C–H functionalization reactions has been extended to other metal-catalyzed C–H functionalizations. Ir-catalyzed arene C–H borylation has been established, and its utility and reliability have been developed over the last three decades.<sup>25</sup> This is because the site-selectivity of the reaction can be controlled by steric factors in a highly predictable manner. For example, 1,3-di-substituted benzenes can be borylated selectively at the 5-position. However, controlling the site-selectivity can be difficult with certain arenes, such as mono-substituted and 1,2-di-substituted benzenes, because of the less-biased steric environments at the possible reaction sites; this issue has attracted great attention from synthetic organic chemists.<sup>26</sup> We revealed that cooperative Ir/Al catalysis could provide high *para*-selectivity for the C–H borylation of benzamides.<sup>27</sup> Again, the use of the bulky Al Lewis acid and an Ir catalyst bearing ligands with peripheral bulk was crucial (Scheme 8a). As in the case of cooperative Ni/Al catalysis, the Al catalysts play key roles in terms of steric repulsion and rate-acceleration to induce the *para*-selectivity through making the arene core electrophilic towards the Ir catalysts under much milder reaction conditions than those in single-center Ir catalysis. We could even achieve

*meta*-selectivity in the arene C–H borylation using a catalyst with tethered Ir and Al centers (Scheme 8b).<sup>28</sup> Notably, the benzene ring bearing the aminocarbonyl group was functionalized with high *meta*-selectivity exclusively over a phenyl substituent, which could also be borylated otherwise. The Ir/Lewis acid cooperative catalysis was also effective to achieve site-selective borylation of pyridine derivatives.

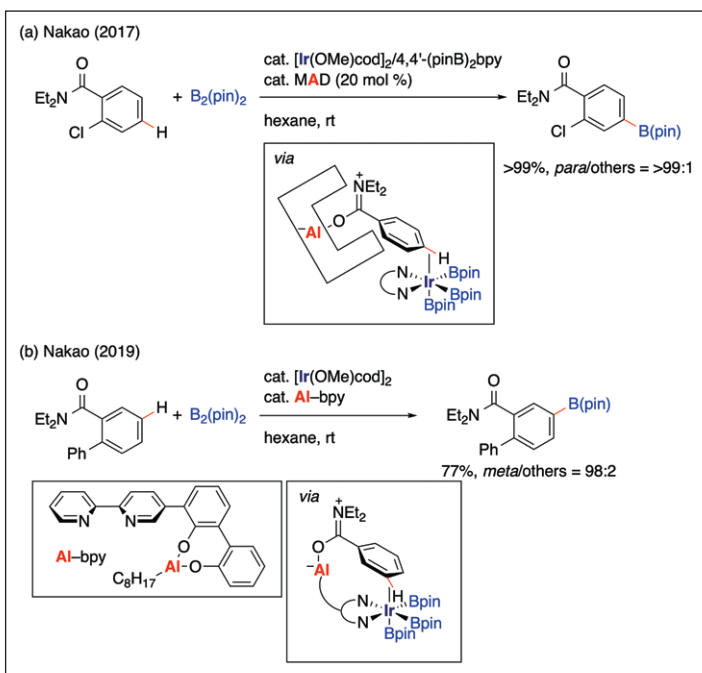
The activation and functionalization of C–C bonds have attracted great attention in organic synthesis recently, as they could enable innovative transformations.<sup>29</sup> The key to such transformations is the activation of the C–C bonds, which are commonly less kinetically and thermodynamically reactive. Successful and useful examples of C–C bond functionalization involving 3- and 4-membered compounds have been achieved via single site metal catalysts through the relief of ring strain as a major driving force to promote the C–C bond activation. Cooperative double activation catalysis has become a powerful strategy to expand the scope of C–C bond activation for organic synthesis.

The C–CN bonds of nitriles are thermodynamically stable, but can reportedly be activated and functionalized by several transition metal catalysts.<sup>30</sup> We expected that C–CN bond activation followed by the addition reaction of the organic and cyano fragments across unsaturated compounds, namely, the carbocyanation reaction, could be useful for organic synthesis, and initially performed the transformation using a single Ni catalyst. We then found that the scope of nitriles participating in this reaction could be significantly expanded using cooperative Ni/Al catalysis.<sup>31</sup> The cooperative double activation catalysis allows the activation of even acetonitrile to achieve the methylcyanation reaction (Scheme 9).<sup>32</sup> Experimental and theoretical studies revealed that the cyano group coordinated to the Al Lewis acid at the N atom, while the  $\pi$ -bond bound to the Ni catalyst to significantly lower the barrier of the oxidative addition of the C–CN bonds.

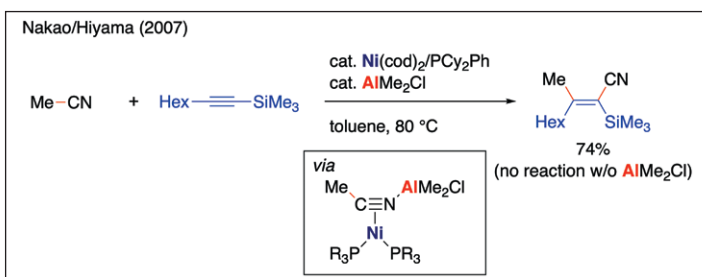
Cooperative transition metal/organic catalysis has also been developed to enable difficult C–H and C–C functionalizations that have been unavailable via single metal catalysts.<sup>33</sup> A pioneering work was reported by Jun in 1997, who demonstrated the hydroacylation of alkenes via cooperative Rh/2-aminopicoline catalysis through formyl C–H bond activation (Scheme 10a).<sup>34</sup> The amine catalyst reacts with aldehydes to give imines bearing a 3-methylpyridyl group, which serve as a coordinating directing group to bring the Rh catalyst close to the proximal formyl C–H bond, which undergoes oxidative addition to the Rh center. The ketone products are generated through the subsequent olefin insertion followed by C–C bond-forming reductive elimination. Hydroacylation via Rh catalysis alone has been limited to aldehyde and/or alkene substrates bearing a coordinating functional group to prevent unwanted decarbonylation through its intramolecular coordination to the Rh center. The cooperative Rh/2-aminopicoline system has recently been further developed to achieve the direct  $\alpha$ -alkylation of ketones with olefins (Scheme 10b).<sup>35</sup> In this reaction, the enamine species bearing the pyridyl directing group is likely responsible for the directed C–H activation at the Rh center. Jun's cooperative Rh/2-aminopicoline catalysis also effects the highly challenging catalytic C–C bond activation of ketones (Scheme 10c).<sup>36</sup> Temporarily formed imines bearing the directing pyridyl group undergo the oxidative addition of the proximal C–C bond to the Rh(I) center. The reaction of phenylethyl ketones with 1-alkenes proceeds to afford alkyl ketones and styrene through C–C bond activation followed by exchange of the alkyl groups through  $\beta$ -H elimination. Cooperative double activation catalysis has recently been applied to the ring-expansion reaction of cyclopentanones through sequential C–C and C(sp<sup>2</sup>)–H bond activation (Scheme 10d).<sup>37</sup>

## Conclusion

In conclusion, the principles and representative examples of cooperative metal catalysis have been introduced, with a particular focus on new reactions that are difficult to achieve using conventional single metal catalysis. Taking advantage of cooperative synergistic catalysis, the scope and versatility of cross-coupling-type transformations have been significantly improved via the generation of nucleophilic organometallic

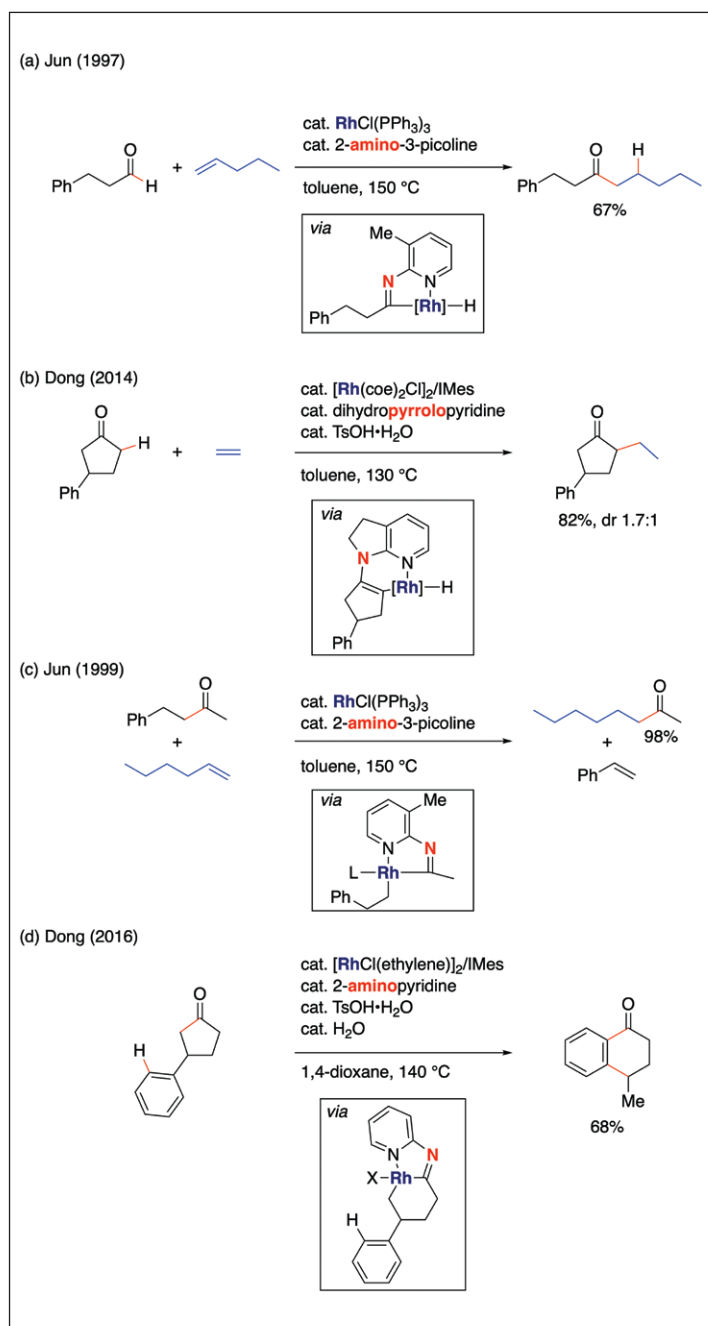


**Scheme 8:** Cooperative double activation Ir/Al catalysis for site-selective C–H borylation.



**Scheme 9:** Cooperative double activation Ni/Al catalysis for C–C functionalization.

intermediates via one catalytic cycle and their successful integration into the product-forming cycle, which operates using another metal. Synthetic transformations based on cooperative double activation catalysis have also been briefly surveyed. The combination of common Lewis acids and late transition metal catalysts is powerful, particularly for the functionalization of otherwise less-reactive C–H and C–C bonds. Steric repulsion or tethering between the transition metal and Lewis acid have also been utilized to control the site-selectivity of C–H functionalization. Cooperative catalysis can also incorporate organocatalysis to generate transient substrates bearing a directing group to coordinate to the metal complex, enabling selective bond activation/formation processes at the proximal site. Given the large variety of possible combinations of catalysis systems based on different principles that have been developed in organic synthesis during the last half century, cooperative catalysis should be a useful and promising strategy for synthetic chemists to design novel and efficient organic reactions, which are greatly needed to establish sustainable chemical processes



**Scheme 10:** Cooperative double activation Rh/organo catalysis for C–H and C–C functionalization.

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