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Temporary or removable directing groups enable activation of unstrained C–C bonds

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Abstract

Carbon–carbon (C–C) bonds constitute basic skeletons in most organic molecules. One can imagine that selective manipulation of C–C bonds would provide a direct approach to edit or alter molecular scaffolds but has been an ongoing challenge. Due to the kinetic inertness of C–C bonds, the common strategies of activating these bonds by transition metals rely on either the use of highly strained substrates or the assistance of a permanent directing group (DG), in which strain relief or formation of stable metallocycles becomes the driving force. To allow more common and less strained compounds utilized as substrates for C–C activation, the use of temporary and removable DGs has emerged as an attractive strategy in the past two decades. A variety of C–C bonds in unstrained or less strained organic molecules now can be converted to more reactive metal–carbon bonds, and further downstream transformations have led to diverse synthetic methods. This review highlights the development of catalytic approaches that can activate unstrained C–C bonds enabled by temporary or removable DGs. The content is mainly divided based on the nature of the DGs: temporary and removable. Applications of these methods in syntheses of natural products or bioactive molecules are also discussed.

Introduction

Carbon–carbon (C–C) bonds are ubiquitously found in organic compounds, and normally constitute molecular backbones. If efficient and selective methods can be realized for manipulation of a specific C–C bond in a complex structure, tools would be unlocked for directly editing skeletons of biologically important compounds. On the other hand, merging activation of C–C bonds in simpler chemicals with various coupling processes can provide a rapid and unconventional approach to access more valuable scaffolds.^{1–9} While attractive, catalytic C–C bond activation, i.e. conversion of a C–C bond to a C–M (M: metal) bond, has been a significant and ongoing challenge, largely due to that C–C bonds are generally thermodynamically stable and kinetically inert. They are strong bonds and often shielded by hydrogens or other substituents that are on the “surface” of molecules.

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Competing interests statement

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Traditionally, two strategies have been frequently used to activate C–C bonds by transition metal catalysts.¹⁰ The first one is capitalized on the relief of ring strain as a driving force.^{11–16} In this context, three- and four-membered ring substrates have been employed to realize a wide range of synthetically useful methods through ring-opening reactions (FIG. 1A). Compared to unstrained systems, strained C–C bonds are generally weaker in terms of bond-dissociation energy, and more bended from their internuclear axis, which makes these bonds more suitable to coordinate with transition metals. To tackle the less exposed and stronger unstrained C–C bonds, the use of a directing group (DG) is another common strategy to promote interactions with catalysts through proximity effect.^{1–9} The use of a permanently attached DG in C–C activation can be dated back to 1980s, when Suggs demonstrated the first directed activation of ketone α -C–C bonds assisted by a quinoline moiety.^{17,18} The role of DGs is critical in these reactions, as a suitable DG can not only determine which C–C bond to be activated but also lower the activation energy by forming a stable metallocycle (FIG. 1B). It is noteworthy that C–C activation in these strategies can proceed via either an oxidative addition³ (intermediates **1** and **3**) or β -carbon elimination¹⁹ (intermediates **2** and **4**) pathway.

While the strain-driven and permanent DG-based strategies continue shaping the field of C–C activation, the scope of substrates has nevertheless been restricted to highly strained molecules or special types of compounds. To address this shortcoming, an emerging approach is the use of temporary or removable DGs (FIG. 1C).^{7,20–23} When DGs can be conveniently installed to and removed from a substrate, more common and less strained substrates are permitted for C–C activation reactions. As a general mechanistic consideration, two scenarios are possible. In the case of temporary DGs (^TDGs), the DG is installed onto the substrate via a reversible reaction and effectively promotes the key reaction, which then is removed *in situ* to release the product. In an ideal circumstance, a temporary DG can be used as a co-catalyst. In an alternative scenario, stoichiometric DGs are required as the DG installation is generally either irreversible or not compatible with the key reaction. These DGs can be removed to release products through two pathways. In **path a**, the removable DG (^RDG) is cleaved as a leaving fragment *during* the C–C bond activation process, and the remaining part of the substrate continues to undergo further transformations. In **path b**, the ^RDG moiety is removed *after* the C–C bond activation through simple operations; often, this type of ^RDG could be recycled.

This article is inspired by a number of excellent reviews and book chapters in this field.^{1–9} Here, the focus is given to the recent advance on activation of unstrained C–C bonds enabled by temporary or removable DGs, as well as their applications in the syntheses of natural products or bioactive molecules. The main part of the review is divided into two sections according to different kinds of DGs. In each section, the content is organized based on the types of transformations.

C–C activation using temporary DGs

While temporary DGs are frequently employed in C–H activation reactions, their use in C–C activation has been much less developed and primarily limited to ketone substrates.⁹ Compared to other substrates, ketone α C–C bonds are generally weaker and more polar. In

addition, the electrophilic carbonyl moiety can serve as a convenient handle for reversibly installing an imine-type DG,⁷ which makes ketones privileged substrates for catalytic C–C activation using a temporary DG strategy.

Olefin extrusion/reinsertion.

In 1999, Jun and Lee pioneered the use of 2-aminopyridine derivatives as temporary DGs for activating α -C–C bonds in unstrained ketones.²⁴ It was found that, in the presence of a catalytic amount of Wilkinson's catalyst and 2-amino-3-picoline (**DG-1**), simple acyclic ketone **11** can react with 1-hexene to produce a formally alkyl-swapped ketone **12** in an excellent yield (FIG. 2A). Mechanistically, **DG-1** first condenses with the ketone substrate (**11**) to give ketimine **13**, which can promote a pyridine-directed oxidative addition of Rh into the α -C–C bond. The resulting rhodacycle **14** then undergoes β -hydrogen elimination to extrude styrene and hydride insertion into the added olefin (i.e. 1-hexene) to give a new rhodacycle **16**. Finally, C–C reductive elimination followed by ketimine hydrolysis produces the ketone product (**12**) and regenerates the rhodium catalyst and **DG-1**. Note that the rhodium-hydride species **15** is also a key intermediate in a typical 2-aminopyridine-assisted hydroacylation reaction,^{25–27} thus the ketone substrate can be considered as an aldehyde equivalent by extruding a molecule of olefin via C–C activation. Typically, linear aliphatic ketones with β -hydrogens were employed as substrates. A large excess of olefins and the strong tendency of polymerization of styrene are considered as the driving force of this reaction. Taking advantage of the reversible imine formation, only a catalytic amount of the temporary DG was required to achieve this formal alkyl exchange of simple ketones. Later, Jun and coworkers found that this reaction can finish within 5 min through microwave irradiation under solvent-free conditions, wherein the addition of cyclohexylamine as a cocatalyst can dramatically improve the reaction efficiency.²⁸

Apart from simple ketones, *sec*-alcohols were also found to be suitable substrates for the formal alkyl-exchange reaction via C–C activation.²⁹ The transformation involves an initial transfer hydrogenation³⁰ catalyzed by a rhodium complex to form the corresponding ketone **11**. The addition of a catalytic amount of K₂CO₃ can largely accelerate this transfer hydrogenation process. With the help of **DG-1**, C–C activation of ketone **11** then takes place, followed by the same olefin extrusion and reinsertion to deliver the desired product **18** in excellent yield. In this reaction, the terminal olefin plays two roles, serving as both a hydrogen acceptor and a coupling partner (FIG. 2Ba). Compared to linear substrates, the reactivity of cycloalkanols largely depended on the ring size. While cyclohexanol showed almost no reactivity, with enlarging the ring size of cycloalkanol substrates the yields of the coupling products increased significantly. Such a trend is similar to those observed in the C–C bond activation of cycloketimines (*vide infra*). Both mono- (**19**) and bis-activation products (**20**) were observed, in which the latter were the major products in these reactions (FIG. 2Bb). In addition, Jun and coworkers developed the use of primary amines as the substrates in the formal alkyl exchange reactions.³¹ Mechanistically, a similar transfer hydrogenation occurs to generate the corresponding imine from the primary amine, which can then react with **DG-1** to give the pyridine-imine intermediate (**24**). At this point, a sequence of pyridine-assisted C–H and C–C activation could take place to give ketone **23**, which was produced in moderate yields. Alternatively, intermediate **25** can directly undergo

hydrolysis without C–C activation to deliver ketone **22**, which was observed as a minor product in this reaction (FIG. 2C).

Intramolecular C–H activation.

C–C bond activation of less strained five- or six-membered rings has been a significant challenge, as the reverse process, i.e. forming five- or six-membered rings, is typically more favorable.³² In 2016, Dong, Liu and coworkers discovered a general and catalytic approach to activate α C–C bonds of cyclopentanones (FIG. 3A).³³ One key was to couple the thermodynamically unfavored C–C bond activation with a more favorable downstream process, such as a C–H arylation reaction. The catalytic system includes a rhodium pre-catalyst, an NHC (*N*-heterocyclic carbene) ligand and an amino-pyridine temporary DG. The NHC ligand, i.e. IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), was crucial for this transformation and simple 2-amino-pyridine (**DG-2**) was found much more efficient than **DG-1**, which represent some differences from Jun's system (FIG. 2). 3-Aryl-cyclopentanone **26** was employed as the substrate, which underwent a skeleton-rearrangement to produce two aromatic ketones **27** and **28**.

The reaction mechanism was investigated through a combination of computational and experimental efforts. The DFT study showed that, after forming ketimine **29**, the directed C–C oxidative addition (**30**) is a reversible and uphill step. The following intramolecular C–H activation with the aryl group gave a rhodium-bridged bicyclic intermediate (**31**); the subsequent C–C reductive elimination afforded the rearrangement products. The major product (α -tetralone **27**) came from activation of the proximal (C1–C2) bond, while the minor product (1-indanone **28**) was generated from the activation of the distal (C1–C5) bond. The formation of a more stable aromatic ketone from an aliphatic ketone accounts for the thermodynamic driving force of this transformation.

This unusual C–C/C–H-bond rearrangement method provided a unique and deconstructive approach to access chiral α -tetralone derivatives. For example, α -tetralone (*R*)-**32** was previously prepared in 6 steps³⁴ and shown to be the key intermediate in the syntheses of erogorgiaene,^{35,36} (*R*)-ar-himachalene³⁴ and (–)-heliophenanthrone.³⁷ Combining the Hayashi–Miyaura reaction³⁸ and this method, only two steps are needed to access the enantio-enriched α -tetralone **32**, which consequently shortens the synthetic routes of these natural products by four steps (FIG. 3B). Dong and co-workers further demonstrated the utility of this reaction in the asymmetric total syntheses of a series of di- and sesqui-terpenoids, including (–)-microthecaline A, (–)-leubeanol, (+)-pseudopteroxazole, (+)-*seco*-pseudopteroxazole, pseudopterosin A–F and G–J aglycones, and (+)-heritonin in 4 to 9 steps.³⁹ Compared to the previous syntheses of these natural products, this C–C/C–H-bond rearrangement method enabled rapid construction of the polysubstituted tetrahydronaphthalene skeleton in an enantioselective manner (FIG. 3C). In addition, improvement of this method has been found by using phosphoric acids in place of TsOH for some problematic substrates. Recently, the same group used this method in the asymmetric synthesis of 1-tetralones bearing a remote quaternary stereocenter via a combination with Pd-catalyzed asymmetric 1,4-addition.⁴⁰

By carefully tuning the catalytic system, a combination of IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as the ligand and 2-amino-6-picoline (**DG-3**) as the temporary DG can change the site-selectivity during the C–C activation of ring-fused cyclopentanones (FIG. 3D).⁴¹ Under the new conditions, ring-fused cyclopentanone **33** was converted to spiro-indanone **34** in excellent yield through almost exclusive cleavage of the distal C–C bond. It was proposed that both the bulky IPr ligand and the 6-methyl group in **DG-3** would have steric repulsion with the aryl moiety in **33** when activating the proximal C–C bond. Notably, apart from ring-fused cyclopentanones, initial success on the distal selective C–C activation of regular cyclopentanones was also achieved.

The C–C/C–H activation mode can also be applied to the activation of cyclohexanones, although the reaction efficiency was moderate (FIG. 3E).³³ Giving that cyclohexanones are less strained and therefore more challenging substrates for C–C activation than cyclopentanones, a forcing condition with one equivalent of **DG-3** in the presence of molecule sieves (pushing the imine formation step) was developed. As expected, the C–C bond cleavage occurred exclusively at the distal (C1–C6) position to produce 1-indanone as the product, as formation of the alternative seven-membered ketone product was thermodynamically unfavored.

Intermolecular cross-couplings.

Transition-metal-catalyzed cross couplings represent one of the most important reactions in modern organic synthesis.⁴² Through developing new C–C activation methods, the scope of electrophiles that can undergo cross couplings has been extended to less polar compounds. Previously, ketones with high ring strain⁴³ or a permanent DG^{44,45} were used as electrophiles in Suzuki–Miyaura coupling (SMC) reactions. By employing the temporary-DG strategy, Dong and coworkers developed the SMC reactions of simple unstrained ketones with arylboronates via cleavage of the α C–C bonds of ketones (FIG 4A).^{46–48} A more electron-rich NHC ligand (^{Me}IMes, 1,3-bis(2,4,6-trimethylphenyl)imidazol-4,5-dimethyl-2-ylidene) was used to promote oxidative addition, and ethyl crotonate was anticipated to serve as a π acid to accelerate the reductive elimination (from **39** to **40**).⁴⁹ Water was employed as the proton source. Considering the stability and reactivity of arylboronates derived from different diols, 1,3-propanediol-driven ones turned out to be the optimal for this transformation. As the leaving group is a basic carbon moiety, additional base was not required. Instead, one equivalent of water was used to provide the proton source as well as to balance the boron residue after transmetallation.

Under these conditions, cyclopentanone reacted with arylboronate **36** to produce the corresponding linear aromatic ketone in 67% yield. Other ketones, such as 1-indanones, acetophenones, acetone and aliphatic methyl ketones, were also competent substrates. Notably, the electronic property of the aryl ketone substrates has a large influence on their reactivity: those bearing electron-deficient substituents showed higher reactivity and up to 76% yield was obtained with 4,6-difluoro-1-indanone. The C(aryl)–C(carbonyl) α bonds were exclusively cleaved for aryl ketone substrates, and no carbonyl-directed *ortho* C–H arylation⁵⁰ was observed. Aliphatic methyl ketones, e.g. **11**, also reacted albeit with decreased reactivity, slightly favoring cleavage at the less sterically hindered side. Other

types of ketones were almost inactive, likely due to their low reactivity toward imine formation, which is the step to install the ^TDG.

The mechanism of this ketone-SMC reaction was proposed to proceed via a C–C oxidative addition/transmetallation pathway through forming intermediate **39**, which then undergoes C(sp²)–C(sp²) reductive elimination and protonation of the alkyl-Rh species (**40**) to afford the product and regenerate the catalyst. The order between C–C oxidative addition and transmetallation step was unclear at this stage (FIG 4B).

“Cut-and-sew”.

The aforementioned reactions break one C–C bond in substrates and form only one new C–C bond in products. In contrast, the “cut-and-sew” chemistry represents a transformation that breaks one C–C bond in substrates and then inserts an unsaturated unit in-between the two carbon terminus, therefore forming two new C–C (or one C–C and one C–X) bonds in products. It typically involves three processes: C–C oxidative addition, migratory insertion of an unsaturated unit and C–C reductive elimination.⁵ While the “cut-and-sew” reactions with highly strained substrates or ketones bearing a permanent DG have been well established,^{5,51,52} the use of regular ketones for such a transformation was not reported until 2018. Compared to Jun’s olefin extrusion/insertion reaction, the challenge for “cut-and-sew” was how to inhibit the undesired β-hydrogen elimination process. Dong and co-workers found that bulky NHC ligands can effectively inhibit the β-hydrogen elimination and/or promote olefin insertion. First, they showed that an intramolecular “cut-and-sew” transformation via the ^TDG strategy could be realized (FIG 5A).⁵³ IMes was found to be the optimal ligand; as a comparison, Wilkinson’s catalyst (RhCl(PPh₃)₃) only led to fragmentation via β-hydrogen elimination. Supported by a ¹³C-labelling study, the mechanism of this reaction was proposed to involve the formation of a rhodium species **42** via pyridine-assisted C–C oxidative addition, followed by olefin migratory insertion and C–C reductive elimination. A drawback of the system is that the substrate scope was limited to methyl ketones with a biaryl scaffold. The driving force of this “cut-and-sew” transformation comes from breaking a C–C σ-bond and a C–C π-bond to form two new C–C σ-bonds, as σ-bonds are typically stronger than π-bonds.

Later, the same group developed an intermolecular “cut-and-sew” reaction between 1-indanones and ethylene gas, which represents a two-carbon homologation process to give 7-membered rings (FIG. 5B).⁵⁴ The reaction showed tolerance of diverse functional groups and substitution patterns on 1-indanones. It also worked well on larger scales with good recycling yield of the ^TDG (**DG-1**). The use of other unstrained ketones or non-ethylene olefins was not fruitful with the current catalyst system. Given that many 1-indanones are commercially available, this (5+2) reaction provides an atom economical and rapid protocol to access functionalized benzocycloheptenones, which are important synthetic intermediates to several bioactive compounds but nontrivial to prepare via other approaches. For examples, benzocycloheptenones **44a-c**, synthesized in a single step from commercially available 1-indanones **43a-c** and ethylene via this intermolecular “cut-and-sew” strategy, were the key precursors for anti-obesity agent **45**, ALK (anaplastic lymphoma kinase) inhibitor **46** and

NMDA (*N*-methyl-D-aspartate) receptor **47**, which previously required significantly longer synthetic routes with low overall yields (FIG 5C).^{55–57}

C–C activation using removable DGs

Besides the temporary DG-based strategy, the use of removable DGs has its own merits. Compared to the reversible formation of DGs *in situ*, the preinstalled DGs are generally more robust and allow more challenging substrates to react. In this section, more diverse unstrained or low strained substrates can undergo C–C activation enabled by removable DGs. The content is divided according to how DGs are removed in the reaction.

DGs removed via post-chemical transformations.

As discussed in the above section, 2-aminopyridine derivatives are very useful and efficient temporary DGs for the activation of unstrained C–C bonds in ketones or molecules that can be isomerized to ketones, and the key is the reversible formation of a ketimine intermediate that can facilitate the C–C bond oxidative addition. For ketones that are difficult to form the corresponding ketimines with 2-aminopyridine derivatives *in situ*, it would be beneficial to install the DG first in a separate step. In 2001, Jun and coworkers systematically investigated the rhodium-catalyzed C–C activation of cycloalkanones via preforming the corresponding ketimines with 2-amino-3-picoline.⁵⁸ The imine substrates **48** can undergo C–C activation and subsequent coupling with alkenes to produce two ring-opening products **19** and **20** after hydrolysis. These products came from the mono- and di-C–C activation of the corresponding ketimines, respectively, favoring the di-C–C activation product **20**, which is a symmetrical ketone. The combination of [Rh(*coe*)₂Cl]₂ (chlorobis(cyclooctene)rhodium(I) dimer) and PCy₃ (tricyclohexylphosphine) was the optimal catalyst system. Cyclic ketimines with medium to large ring sizes (ring size: 7, 8, 10, 12, 15) generally worked smoothly, producing the corresponding ring-opening products in good yields. However, reactivity of cyclopentanone and cyclohexanone-derived imines were low, giving 9% and 5% yields, respectively (FIG 6Aa).

The reason for this intriguing reactivity difference among cyclic ketimines with different ring sizes was elusive. Jun and coworkers provided a speculation that this trend was governed by how easy the formation of the rhodacyclic intermediate (like **51**) via C–C oxidative addition, as medium-to large-sized rings are more flexible and easy to meet the conformation requirement when forming the rhodacyclic intermediate. However, suggested by the recent studies, an alternative explanation of this trend could come from reactivity of the resulting rhodacyclic intermediate towards downstream transformations. For example, DFT calculations have revealed that C–C oxidative addition in the cyclopentanone-derived imine exhibits a low activation barrier (ca. 10 kcal/mol) and is completely reversible.³³ One can imagine that rhodacycles derived from cyclopentanone or cyclohexanone ketimine should be more stable than those from larger rings, and therefore more reluctant to undergo further transformations, e.g. β -hydrogen elimination.

When the reaction of ketimines was carried out in the absence of alkenes, a skeletal rearrangement was observed (FIG 6Ab). Generally, the reactivity of the skeletal rearrangement was lower than that in the ring-opening reaction with 1-hexene. Again,

the reaction efficiency largely depended on the ring size of the substrates. Cycloheptanone-derived ketimine **48a** was the most efficient substrate in this transformation, providing the ring-contracted products **49** and **50** in good yields with a ratio of 76:24. Mechanistically, imine **48a** first undergoes oxidative addition to give rhodacycle **51**, which is followed by a β -hydrogen elimination process to form rhodium-hydride species **52**. An intramolecular olefin reinsertion gives a new rhodacycle **53** and the subsequent reductive elimination delivers the cyclohexanone isomer **49** after imine hydrolysis. A further ring contraction could take place from intermediate **53** to give the five-membered product **50**. For comparison, cyclohexanone and cyclooctanone-derived ketimines showed low reactivity, while other cyclic ketimines showed no reactivity towards the skeletal rearrangement.

The same group later disclosed that 2-amino-3-picoline-derived allylic amines were also competent substrates for C–C activation.⁵⁹ Using a similar catalytic system, allylic amine **55** could react with a terminal olefin to afford two types of linear aliphatic ketones **22** and **23** (FIG 6B). The reaction was proposed to first proceed via formation of aldimine **56** through isomerization of the allylic amine; a following pyridine-assisted hydroiminoacylation, containing a sequence of aldimine C–H activation, olefin insertion and reductive elimination, gives ketone product **22** after hydrolysis. Through further C–C activation and coupling with another molecule of the terminal olefin, symmetrical linear ketone **23** was eventually produced. Of note that the same rhodium complex was efficient to catalyze all the steps including allylic amine isomerization, C–H activation and C–C activation. Moreover, the same group reported the use of dienes in place of olefins as the coupling partner to react with allylic amines, providing a new access to various cycloalkanones.⁶⁰ In this case, the allylic amine served as a masked formaldehyde to provide a one-carbon unit. All 1,3-, 1,4- and 1,5-dienes were efficiently coupled to afford cycloalkanones in a ring-size of five to seven. Many factors could affect the ring-size of the products, including the type of dienes, the regioselectivity of the olefin migratory insertion step and/or the skeletal rearrangement (FIG 6Ca). For example, the reaction of 1,5-hexdiene with allylic amine **55** can deliver three cycloalkanones including cycloheptanone **57**, 2-methyl-cyclohexanone **49** and 2-ethyl-cyclopentanone **50** (FIG 6Cb). Mechanistically, the reaction starts with isomerization of the allyl amine to aldimine **56**, which then undergoes intermolecular hydroiminoacylation with one alkene in the diene. The subsequent C–C activation and β -hydrogen elimination extrudes styrene. The resulting rhodium-hydride species **52** could be considered as the same intermediate proposed in the prior skeletal rearrangement reaction shown in FIG 6A. Thus, through the intramolecular Rh–H migratory insertion and β -hydrogen elimination, rhodacycles **51**, **53** and **54** could be formed analogously, leading to cycloalkanones **57**, **49** and **50**, respectively (FIG 6Cc).

Apart from imine-type DGs, phosphinites can also serve as a promising class of temporary or removable DGs due to the reversibility of forming P–O bonds.^{61–63} For example, the use of phosphinite as a temporary DG has been demonstrated in the *ortho*-C–H activation of phenols by Lewis^{61,62} and Bedford⁶³. On the other hand, activation of unstrained C–C bonds was majorly focused on more polarized substrates, such as ketone or imine α -C–C bonds.⁶⁴ To broaden the scope of unstrained C–C bonds that can be activated in a catalytic manner, Dong and coworkers developed the use of phosphinites as removable DGs

in the rhodium-catalyzed activation of unstrained aryl–aryl bonds in 2,2'-biphenols (FIG 7).⁶⁵ The challenges in the activation of aryl–aryl bonds^{66,67} are two-fold: kinetically, the interaction between an aryl–aryl moiety and a transition metal center is difficult due to electronic (an nonpolar aryl–aryl bond lacks a low-lying anti-orbital) and steric (an aryl–aryl moiety existing in a twisted conformation is hard to access) effects;⁶⁸ thermodynamically, an aryl–aryl bond, with a bond-dissociation energy of more than 110 kcal/mol, is much stronger than a typical C–C bond.

Through installing a phosphinite group on each arene, the chelation effect pushes the electron-rich rhodium center close to the aryl–aryl σ bond, and the formation of two relatively stable rhodacycles after C–C oxidative addition can alleviate the energy required to cleave the strong aryl–aryl bond. As shown in a gram-scale reaction, hydrogenolysis of bisphosphinite **58** gave the mono-phenol **59** in a high yield using a low catalyst loading (FIG 7Aa). Up to 298 turnover number (TON) of rhodium could be achieved using $\text{RhH}(\text{PPh}_3)_4$ as the precatalyst. The substituents at 3,3'-positions were crucial for the high efficiency, presumably due to suppression of a competing *ortho*-C–H bond activation. Such a limitation was not observed in their recent work on a ruthenium-catalyzed activation of aryl–aryl bonds using pyridines as permanent DGs.⁶⁹ Note that the transformation could be conducted in a one-pot two-step manner directly from free 2,2'-biphenols, although the yield was decreased to some extent (FIG 7Ab). When the C–C activation process was completed, the phosphinite DG could be removed conveniently by adding silica gel; on a larger scale, *i*-Pr₂PCl can be easily recycled by treatment with dry HCl, which could be re-used to install the phosphinite DG (FIG 7Ac). Taking advantage of this new mode of activation, the syntheses of 2,3,4-trisubstituted phenols as well as the preliminary success on breaking the aryl–aryl moieties in lignin models were demonstrated. The reaction mechanism has been explored via both experimental and computational studies. It was proposed that the rhodium-bisphosphinite complex **62** first reacts with hydrogen to form a rhodium(I)–hydride species **63**, which serves as the key intermediate to cleave the aryl–aryl bond to form diaryl rhodium(III)–hydride intermediate **64**. A sequence of C–H bond reductive elimination, hydrogen oxidative addition and another C–H bond reductive elimination completes the catalytic cycle (FIG 7B).

On the other hand, heterocycles such as pyridine^{70–74} and quinoline^{44,45,51,52} derivatives have been frequently used as DGs in the activation of unstrained C–C bonds. Compared to imine or phosphinite-type DGs that are easily removable by hydrolysis, heterocycle-based DGs were generally considered to be stable and only a few of them can be removed via simple post-chemical transformations. In 2018, Hao, Xu and coworkers developed a nickel-catalyzed ketone decarbonylation^{75,76} via chelation-assisted C–C bond activation.⁷⁷ The 2-benzoyl indole substrate (**66**) bearing a pyrimidine DG was converted to 2-phenyl indole **67** in excellent yield, catalyzed by $\text{Ni}(\text{cod})_2$ (bis(1,5-cyclooctadiene)nickel) and a NHC ligand. DFT calculations suggested that the decarbonylation reaction proceeds via oxidative addition of Ni(0) to the C(indole)–C(carbonyl) bond (**69**), followed by carbonyl extrusion and C–C reductive elimination. The pyrimidine DG can be easily removed under basic conditions,⁷⁸ providing free indole **68** in good yield (FIG 8A).

Such indole-derived substrates can also undergo deacylative cross-coupling reactions. In 2018, Wei and coworkers reported a rhodium(III)-catalyzed SMC reaction of 2-aryl indoles with aryl pinacol boronates, producing 2-aryl indole **67** as the coupling product.⁷⁹ Similarly, pyrimidine served as the DG and can be facilely removed under basic conditions (FIG 8Ba). The C–C bond cleavage was proposed to be triggered by an acetate-mediated nucleophilic addition to the coordinated ketone, followed by β -carbon (2-indoyl) elimination, to form rhodacycle **71**. Subsequent transmetallation and C–C reductive elimination afford the coupling product. A mixed anhydride is generated in this process, which then reacts with methanol to give the corresponding methyl ester. Later, a similar reaction mode was applied in a Hiyama-type reaction of 2-aryl indoles with aryl silicon reagents by the same research group.⁸⁰

In addition, Zhou and coworkers reported a rhodium(I)-catalyzed SMC reaction between 2-benzoyl pyridine *N*-oxides and arylboronic acids.⁸¹ The *N*-oxide moiety acts as a DG to assist the C(aryl)–C(carbonyl) bond activation (**72**), and can be removed via simple treatment with PBr₃ (FIG 8Bb). This method could be applied in the synthesis of an antitumor agent **73**. Very recently, the same group reported a similar transformation using amides as the substrate, in which the amide α -aryl–acyl bonds were cleaved and coupled with arylboronic acids to achieve a formal benzamide transarylation.⁸² One key to the success of this reaction was the design of the suitable removable DG. In this context, the bulky aryl substituent on the nitrogen makes the *trans*-conformation of the amide moiety more favorable, which consequently makes the pyridine group pointing towards the aryl–carbonyl bond. The amide DG was transformable; as shown in the synthesis of an antitumor reagent, the DG was replaced by an amine to give a new amide under basic conditions (FIG 8Bc).⁸³

Beyond activation of carbonyl compounds, Kakiuchi and coworkers developed a novel rhodium(III)-catalyzed alkenylation of allylbenzenes via the C(aryl)–C(allyl) bond activation.⁸⁴ Nitrogen-containing heterocycles including pyridine and pyrazole were efficient DGs to assist the C–C activation. When pyrazole was used as the DG, it could be removed in 2 steps giving an *ortho*-alkenyl aniline in good yield. Their mechanistic studies indicated that the C–C activation is promoted by a Rh(III)–hydride (generated from EtOH)-mediated olefin migratory insertion followed by a β -carbon elimination process. The resulting aryl rhodium species **75** can undergo olefin exchange and a Heck-like pathway to deliver the alkenylation product (FIG 8C). Very recently, the same group applied this hydrometallation/ β -carbon elimination strategy to the catalytic activation of C(aryl)–C(alkenyl) bonds in styrene derivatives under similar reaction conditions.⁸⁵

Furthermore, using pyrazole as the DG, Ackermann and coworkers reported that an inexpensive manganese complex is capable of activating C(aryl)–C(alkyl) bonds in tertiary and secondary alcohols.⁸⁶ The reaction proceeded through a directed β -carbon elimination process to release a molecule of ketone, and the generated aryl manganese intermediate then reacts with a series of unsaturated components, including allylic carbonates, alkynes and α,β -unsaturated carbonyls to produce the corresponding allylation, alkenylation and alkylation products, respectively. These reactions could be conducted using water as solvent

without any additives. Similarly, the pyrazole DG could be removed in two steps to provide functionalized anilines (FIG 8D).

DGs removed in the catalytic cycle.

Sometime, after C–C cleavage, the DG-containing fragment is not involved in the final products. In this situation, although the DG cannot be reversibly installed (thus different from temporary DGs), it is formally removed during the catalytic cycle of the C–C activation reaction. As one such example, in 2019 Dong, Liu and coworkers disclosed an aromatization-promoted C–C bond activation strategy^{87–91} that provides an alternative approach to activate and functionalize unstrained ketones (FIG 9).⁹² This strategy was first demonstrated in the deacetylation of methyl ketones. For example, the acetyl moiety in linear ketone **76** was replaced by hydrogen to give compound **77** in good yield using 2-hydrazinyl-4-methylpyridine (**DG-4**), 1,3-diene and an iridium-bisphosphine catalyst (FIG 9A). Detailed mechanistic studies revealed that the reaction starts with forming hydrazone **79** from the ketone and **DG-4**, which then undergoes a [3+2] cycloaddition⁹³ with 1,3-diene followed by double bond migration to generate a pre-aromatic intermediate **80**. A chelation-assisted N–H bond oxidative addition (**81**) followed by an aromatization-promoted C–C bond cleavage generates an alkyl–iridium or alkyl radical species, in which the latter can be converted to the former via radical recombination. Finally, C–H bond reductive elimination produced the deacetylation product **77** and release pyrazole **78** that contains the DG.⁹⁴ It should be noted that the site-selectivity of this transformation was excellent favoring the cleavage of the more substituted sides, i.e. C(alkyl)–C(carbonyl) bond over C(methyl)–C(carbonyl) bond. Besides methyl ketones, other linear ketones were also effective substrates.

In addition to simple deacetylation, the alkyl fragment generated via the C–C activation process could be trapped by excess 1,3-butadiene when **L2** was used as the ligand, producing C–C bond forming intermediate **81**. Simple ozonolysis transformed **81** to aldehyde **82**, and the overall process can be regarded as a formal 1,2-oxo-migration (FIG 9B). In addition, the alkyl fragment could also be trapped by a more substituted diene, i.e. 2,3-dimethyl-1,3-butadiene, when it was added in excess along with 1,3-butadiene. A similar ozonolysis treatment produced a one-carbon homologated ketone **83** in good yield (FIG 9C). Compared to other ketone homologation approaches,⁹⁵ this method avoids use of sensitive carbenoids and provides high site-selectivity (at the more substituted side). Moreover, this C–C activation mode also offers a unique way to access functionalized pyrazoles, a common pharmacophore found in numerous approved drugs,⁹⁶ particularly when using cyclic ketones as substrates. Notably, the pyridine moiety could be facilely removed using SmI₂ (FIG 9D). Thus, when pyrazoles become the desired products, the reaction mode then falls into the first category of removable DG-promoted C–C activation.

In 2019, García-López, Lautens, and coworkers reported a directed and palladium-mediated activation of unstrained C(alkyl)–C(alkyl) bonds in linear amides.⁹⁷ While this is not a catalytic reaction and uses stoichiometric palladium, it is nevertheless included here as an exception due to its novel reaction mode. This reaction employed 8-aminoquinoline-derived aliphatic amides (**85**) as the substrate, which reacted with 1 equiv. of Pd(OAc)₂, 1 equiv.

of K_2CO_3 and an excess amount of a diazo compound to afford the β C–C cleavage product (**86**). Mechanistically, it was proposed that a directed $\text{C}(\text{sp}^3)\text{--H}$ bond activation first delivers a five-membered palladacycle **87** that can then react with the diazo compound via a carbene migratory insertion⁹⁸ to give a six-membered palladacycle **88**. Interestingly, instead of a commonly observed β -hydrogen elimination, **88** underwent an unexpected β -carbon elimination process to give the olefin product (**86**) and a tentatively assigned palladacycle **89**.⁹⁹ As the isolated palladium complex **89** was not able to initiate this reaction, a stoichiometry amount of $\text{Pd}(\text{OAc})_2$ was therefore required to achieve this transformation (FIG 10). Nevertheless, the unique reactivity could provide new perspectives towards future development of activation of unstrained $\text{C}(\text{alkyl})\text{--C}(\text{alkyl})$ bonds.

Summary and perspective

In summary, strategies of using temporary or removable DGs for activating unstrained C–C bonds have been extensively developed in the past two decades. The scope of unstrained substrates that can be activated and functionalized has been broadened to a great extent. Beyond more polar $\text{C}(\text{carbonyl})\text{--C}$ and $\text{C}(\text{iminy})\text{--C}$ bonds, cleavage of less polar $\text{C}(\text{aryl})\text{--C}(\text{aryl})$ and $\text{C}(\text{aryl})\text{--C}(\text{allyl})$ bonds has also been achieved recently using removable DGs. Compared with the use of permanent DGs, the C–C activation methods promoted by temporary or removable DGs start to receive attentions for complex molecule synthesis or other synthetic applications. The resulting versatile metal–carbon bonds after C–C bond activation can participate in diverse downstream transformations, including olefin extrusion/reinsertion, intramolecular C–H activation, “cut-and-sew” reactions and various intermolecular cross-couplings, which offers new perspectives of using C–C bonds as functional handles to introduce molecular complexity.

Despite the remarkable advancement in this field, catalytic activation of unstrained C–C bonds still exhibits several grand challenges to be addressed. First, while the temporary DG strategy is more desirable from the prospects of saving steps and enabling catalytic DGs, the current scope of substrates is nevertheless limited to only a few types of ketones. The origin of such a problem comes from the difficulty of installing temporary DGs. The current use of aminopyridines is not efficient to form imine-type DGs, as they are not as nucleophilic as regular amines. Thus, only more reactive, less sterically hindered ketones are suitable for such a strategy. To enable a broadly useful temporary DG strategy, the efficiency for the DG installation process needs to be significantly improved, which could be benefited from designing new condensation reagents/conditions, new C–C activation modes, or new types of ^TDGs besides imines. The ultimate goal is to allow activation and subsequent functionalization of C–C bonds in diverse and common substrates, beyond a subset of ketones, using temporary DG strategies. In addition, most of the known C–C activation methods rely on expensive noble metal catalysts, particularly rhodium. It could be an attractive direction to realize general and synthetically useful earth-abundant metal-catalyzed activation of unstrained C–C bonds, which has been rare in literature to date. The challenge is due to that oxidative addition with first-row transition metals are typically more difficult than second- and third-row metals. It is, therefore, anticipated that addressing this issue would require more powerful ligands that can provide new capabilities to first-row metals. Moreover, another main limitation of the current C–C activation methods could be

seen from relatively high catalyst loadings, high reaction temperature and long reaction time. The discovery of more efficient catalyst systems could likely be accelerated by better understanding of reaction mechanism, which is often aided by modern computational chemistry. Through overcoming these grand challenges, it is our expectation that C–C activation reactions could ultimately be found in chemists' toolbox for precise molecular editing in the future.

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Glossary terms

Directing group (DG)

a substituent on a molecule that can coordinate to metals and direct the metal to the proximity of the reaction site

Oxidative addition

a process in which a metal is inserted into a covalent bond and the oxidation state and coordination number of the metal are both increased by two

Ring strain

a type of ground-state destabilization in ring systems that arises from distorted bond angles (Baeyer strain), torsional eclipsing interactions (Pitzer strain) and interactions of substituents on non-adjacent atoms (transannular strain)

β -Carbon elimination

a process in which a carbon substituent β to the metal center is cleaved to form a metal–carbon species and the corresponding unsaturated unit

β -Hydrogen elimination

a process in which a hydrogen atom β to the metal center is cleaved to form a metal–hydride species and the corresponding unsaturated unit

Migratory insertion

a process in which an anionic ligand and a neutral ligand in a metal complex combine intramolecularly to generate a new coordinated anionic ligand

Transmetallation

a process in which a ligand is transferred from one metal center to another

References

1. Dong G (ed.) C–C Bond Activation. Vol. 346 of Top. Curr. Chem. (Springer, 2014).
2. Chen F, Wang T & Jiao N Recent advances in transition-metal-catalyzed functionalization of unstrained carbon–carbon bonds. Chem. Rev. 114, 8613–8661 (2014). [PubMed: 25062400]
3. Souillart L & Cramer N Catalytic C–C bond activations via oxidative addition to transition metals. Chem. Rev. 115, 9410–9464 (2015). [PubMed: 26044343]

4. Murakami M (ed.) Cleavage of carbon-carbon single bonds by transition metals. (Wiley-VCH Verlag GmbH & Co. KGaA, 2015).
5. Chen P, Billett B & Tsukamoto T & Dong G “Cut and sew” transformations via transition-metal-catalyzed carbon-carbon bond activation. *ACS Catal.* 7, 1340–1360 (2017). [PubMed: 29062586]
6. Nairoukh Z, Cormier M & Marek I Merging C–H and C–C bond cleavage in organic synthesis. *Nat. Rev. Chem* 1, 1–16 (2017).
7. Kim D-S, Park W-J & Jun C-H Metal-organic cooperative catalysis in C–H and C–C bond activation. *Chem. Rev.* 117, 8977–9015 (2017). [PubMed: 28060495]
8. Song F, Gou T, Wang B-Q & Shi Z-J Catalytic activations of unstrained C–C bond involving organometallic intermediates. *Chem. Soc. Rev.* 47, 7078–97115 (2018). [PubMed: 30112546]
9. Deng L & Dong G Carbon-carbon bond activation of ketones. *Trends in Chem.* 2, 183–198 (2020).
10. Rusina A & Vilek AA Formation of Rh(I)-carbonyl complex by the reaction with some non-alcoholic, oxygen-containing solvents. *Nature* 206, 295–296 (1965).
11. Rubin M, Rubina M & Gevorgyan V Transition metal chemistry of cyclopropenes and cyclopropanes. *Chem. Rev.* 107, 3117–3179 (2007). [PubMed: 17622181]
12. Jiao L & Yu Z-X Vinylcyclopropane derivatives in transition-metal-catalyzed cycloadditions for the synthesis of carbocyclic compounds. *J. Org. Chem.* 78, 6842–6848 (2013). [PubMed: 23758406]
13. Seiser T, Saget T, Tran DN & Cramer N Cyclobutanes in catalysis. *Angew. Chem. Int. Ed.* 50, 7740–7752 (2011).
14. Chen P & Dong G Cyclobutenones and benzocyclobutenones: versatile synthons in organic synthesis. *Chem. Eur. J.* 22, 18290–18315 (2016). [PubMed: 27620805]
15. Mack DJ & Njardarson JT Recent advances in the metal-catalyzed ring expansions of three- and four-membered rings. *ACS Catal.* 3, 272–286 (2013).
16. Fumagalli G, Stanton S & Bower JF Recent methodologies that exploit C–C single-bond cleavage of strained ring systems by transition metal complexes. *Chem. Rev.* 117, 9404–9432 (2017). [PubMed: 28075115]
17. Suggs JW & Cox SD Directed cleavage of sp^2 - sp carbon-carbon bonds *J. Organomet. Chem.* 221, 199–201 (1981). (Demonstrates the first use of DGs in C–C bond activation.)
18. Suggs JW & Jun C-H Directed cleavage of carbon-carbon bonds by transition metals: the α -bonds of ketones. *J. Am. Chem. Soc.* 106, 3054–3056 (1984).
19. Miura M & Satoh T Catalytic processes involving β -carbon elimination. *Top. Organomet. Chem.* 14, 1–20 (2005).
20. Rousseau G & Breit B Removable directing groups in organic synthesis and catalysis. *Angew. Chem. Int. Ed.* 50, 2450–2494 (2011).
21. Bhattacharya T, Pimparkar S & Maiti D Combining transition metals and transient directing groups for C–H functionalizations. *RSC Adv.* 8, 19456–19464 (2018).
22. Gandeepan P & Ackermann L Transient directing groups for transformative C–H activation by synergistic metal catalysis. *Chem* 4, 199–222 (2018).
23. Rej S & Chatani N Rhodium-catalyzed $C(sp^2)$ - or $C(sp^3)$ -H bond functionalization assisted by removable directing groups. *Angew. Chem. Int. Ed.* 58, 8304–8329 (2019).
24. Jun C-H & Lee H Catalytic carbon-carbon bond activation of unstrained ketone by soluble transition-metal complex. *J. Am. Chem. Soc.* 121, 880–881 (1999). (Demonstrates the first use of temporary DGs in activation of unstrained C–C bonds.)
25. Willis MC Transition metal catalyzed alkene and alkyne hydroacylation. *Chem. Rev.* 110, 725–748 (2010). [PubMed: 19873977]
26. Suggs JW Activation of aldehyde carbon-hydrogen bonds to oxidative addition via formation of 3-methyl-2-aminopyridyl aldimines and related compounds: rhodium based catalytic hydroacylation. *J. Am. Chem. Soc.* 101, 489 (1979).
27. Jun C-H, Lee D-Y, Lee H & Hong J-B A highly active catalyst system for intermolecular hydroacylation. *Angew. Chem. Int. Ed.* 39, 3070–3072 (2000).
28. Ahn J-A et al. Solvent-free chelation-assisted catalytic C–C bond cleavage of unstrained ketone by rhodium(I) complexes under microwave irradiation. *Adv. Synth. Catal.* 348, 55–58 (2006).

29. Jun C-H, Lee D-Y, Kim Y-H & Lee H Catalytic carbon–carbon bond activation of sec-alcohols by a rhodium(I) complex. *Organometallics* 20, 2928–2931 (2001).
30. Wang D & Astruc D The golden age of transfer hydrogenation. *Chem. Rev.* 115, 6621–6686 (2015). [PubMed: 26061159]
31. Jun C-H, Chung K-Y & Hong J-B C–H and C–C bond activation of primary amines through dehydrogenation and transimination. *Org. Lett.* 3, 785–787 (2001). [PubMed: 11259062]
32. Murakami M, Amii H & Ito Y Selective activation of carbon–carbon bonds next to a carbonyl group. *Nature* 370, 540–541 (1994).
33. Xia Y, Lu G, Liu P & Dong G Catalytic activation of carbon–carbon bonds in cyclopentanones. *Nature* 539, 546–550 (2016). [PubMed: 27806379] (Demonstrates the first use of temporary DGs in activation of C–C bonds in cyclopentanones and cyclohexanones.)
34. Chavan SP & Khatod HS Enantioselective synthesis of the essential oil and pheromonal component ar-himachalene by a chiral pool and chirality induction approach. *Tetrahedron: Asymmetry* 23, 1410–1415 (2012).
35. Davies HML & Walji AM Direct synthesis of (+)-erogorgiaene through a kinetic enantiodifferentiating step. *Angew. Chem. Int. Ed.* 44, 1733–1735 (2005).
36. Elford TG, Nave S, Sonawane RP & Aggarwal VK Total synthesis of (+)-erogorgiaene using lithiationborylation methodology, and stereoselective synthesis of each of its diastereoisomers. *J. Am. Chem. Soc.* 133, 16798–16801 (2011). [PubMed: 21936552]
37. Mukherjee P & Sarkar TK Heteroatom-directed Wacker oxidations. A protection-free synthesis of (–)-heliophenanthrone. *Org. Biomol. Chem.* 10, 3060–3065 (2012). [PubMed: 22398562]
38. Hayashi T & Yamasaki K Rhodium-catalyzed asymmetric 1,4-addition and its related asymmetric reactions. *Chem. Rev.* 103, 2829–2844 (2003). [PubMed: 12914482]
39. Hou S-H, Prichina AY, Zhang M & Dong G Asymmetric total syntheses of di- and sesqui-terpenoids via catalytic C–C activation of cyclopentanones. *Angew. Chem. Int. Ed.* 59, 7848–7856 (2020).
40. Ochi S, Xia Y & Dong G Asymmetric synthesis of 1-tetralones bearing a remote quaternary stereocenter through Rh-catalyzed C–C activation of cyclopentanones. *Bull. Chem. Soc. Jpn.* doi:10.1246/bcsj.20200147.
41. Xia Y, Wang J & Dong G Distal-bond-selective C–C activation of ring-fused cyclopentanones: an efficient access to spiroindanones. *Angew. Chem. Int. Ed.* 56, 2376–2380 (2017).
42. In Metal-Catalyzed Cross-Coupling Reactions and More. (Eds. de Meijere A, Bräse S & Oestreich M) (Wiley-VCH, Weinheim, 2014).
43. Matsuda T, Makino M & Murakami M Rhodium-catalyzed addition/ring-opening reaction of arylboronic acids with cyclobutanones. *Org. Lett.* 6, 1257–1259 (2004). [PubMed: 15070311]
44. Wang J et al. Direct Exchange of a ketone methyl or aryl group to another aryl group through C–C bond activation assisted by rhodium chelation. *Angew. Chem. Int. Ed.* 51, 12334–12338 (2012).
45. Dennis JM, Compagner CT, Dorn SK & Johnson JB Rhodium-catalyzed interconversion of quinolinyl ketones with boronic acids via C–C bond activation. *Org. Lett.* 18, 3334–3337 (2016). [PubMed: 27367643]
46. Xia Y, Wang J & Dong G Suzuki–Miyaura coupling of simple ketones via activation of unstrained carbon–carbon bonds. *J. Am. Chem. Soc.* 140, 5347–5351 (2018). [PubMed: 29652498] (Demonstrates that aryl–carbonyl bonds in aromatic ketones can be activated via the temporary DG strategy.)
47. Bergin E Cross-coupling ketones. *Nat. Catal.* 1, 309 (2018).
48. Just-Baringo X & Larrosa I Ketone C–C bond activation meets the Suzuki–Miyaura cross-coupling. *Chem* 4, 1203–1204 (2018).
49. Perez-Rodriguez M et al. C–C reductive elimination in palladium complexes, and the role of coupling additives. A DFT study supported by experiment. *J. Am. Chem. Soc.* 131, 3650–3657 (2009). [PubMed: 19231862]
50. Kakiuchi F, Kan S, Igi K, Chatani N & Murai S A ruthenium-catalyzed reaction of aromatic ketones with arylboronates: a new method for the arylation of aromatic compounds via C–H bond cleavage. *J. Am. Chem. Soc.* 125, 1698–1699 (2003). [PubMed: 12580585]

51. Dreis AM & Douglas CJ Catalytic carbon–carbon σ bond activation: an intramolecular carboacylation reaction with acylquinolines. *J. Am. Chem. Soc.* 131, 412–413 (2009). [PubMed: 19105696]
52. Wentzel MT, Reddy VJ, Hyster TK & Douglas CJ Chemoselectivity in catalytic C–C and C–H bond activation: controlling intermolecular carboacylation and hydroarylation of alkenes. *Angew. Chem. Int. Ed.* 48, 6121–6123 (2009).
53. Rong Z-Q, Lim HN & Dong G Intramolecular acetyl transfer to olefins via catalytic C–C bond activation of unstrained ketones. *Angew. Chem. Int. Ed.* 57, 475–479 (2018).
54. Xia Y, Ochi S & Dong G Two-carbon ring expansion of 1-indanones via insertion of ethylene into carbon–carbon bonds. *J. Am. Chem. Soc.* 141, 13038–13042 (2019). [PubMed: 31389237]
55. Boussard M-F et al. Preparation and pharmacological profile of 2-trifluoromethyl-benzo(8,9)-1,3-diaza-spiro(4,6)-undeca-2,8-diene and its enantiomers as new anti-obesity agents. *Arzneim.-Forsch./Drug Res.* 50, 1084–1092 (2000). [PubMed: 11190773]
56. Gingrich DE et al. Discovery of an orally efficacious inhibitor of anaplastic lymphoma kinase. *J. Med. Chem.* 55, 4580–4593 (2012). [PubMed: 22564207]
57. Gawaskar S et al. Design, synthesis, pharmacological evaluation and docking studies of glun2b-selective nmda receptor antagonists with a benzo[7]annulen-7-amine scaffold. *ChemMedChem* 12, 1212–1222 (2017). [PubMed: 28749574]
58. Jun C-H, Lee H & Lim S-G The C–C bond activation and skeletal rearrangement of cycloalkanone imine by Rh(I) catalysts. *J. Am. Chem. Soc.* 123, 751–752 (2001). [PubMed: 11456596]
59. Jun C-H, Lee H, Park J-B & Lee D-Y Catalytic activation of C–H and C–C bonds of allylamines via olefin isomerization by transition metal complexes. *Org. Lett.* 1, 2161–2164 (1999).
60. Lee D-Y, Kim I-J & Jun C-H Synthesis of cycloalkanones from dienes and allylamines through C–H and C–C bond activation catalyzed by a rhodium(I) complex. *Angew. Chem. Int. Ed.* 41, 3011–3033 (2002).
61. Lewis LN Reexamination of the deuteration of phenol catalyzed by an orthometalated ruthenium complex. *Inorg. Chem.* 24, 4433–4435 (1985). (This is a seminal work on phenol ortho-C–H activation using a temporary DG.)
62. Lewis LN & Smith JF Catalytic carbon-carbon bond formation via ortho-metalated complexes. *J. Am. Chem. Soc.* 108, 2728–2735 (1986).
63. Bedford RB, Coles SJ, Hursthouse MB & Limmert ME The catalytic intermolecular orthoarylation of phenols. *Angew. Chem. Int. Ed.* 42, 112–114 (2003).
64. Gozin M, Weisman A, Ben-David Y & Milstein D Activation of a carbon–carbon bond in solution by transition-metal insertion. *Nature* 364, 699–701 (1993). (Demonstrates the first activation of non-polar unstrained C–C bonds with homogeneous catalysis.)
65. Zhu J, Wang J & Dong G Catalytic activation of unstrained C(aryl)–C(aryl) bonds in 2,2'-biphenols. *Nat. Chem.* 11, 45–51 (2019). [PubMed: 30397321]
66. Ruhland K, Obenhuber A & Hoffmann SD Cleavage of unstrained C(sp²)–C(sp²) single bonds with Ni0 complexes using chelating assistance. *Organometallics* 27, 3482–3495 (2008).
67. Obenhuber A & Ruhland K Activation of an unstrained C(sp²)–C(sp²) single bond using chelate-bisphosphinite rhodium(I) complexes. *Organometallics* 30, 4039–4051 (2011).
68. Grein F Twist angles and rotational energy barriers of biphenyl and substituted biphenyls. *J. Phys. Chem. A* 106, 3823–3827 (2002).
69. Zhu J, Chen P. h., Lu G, Liu P & Dong G Ruthenium-catalyzed reductive cleavage of unstrained aryl–aryl bonds: reaction development and mechanistic study. *J. Am. Chem. Soc.* 141, 18630–18640 (2019). [PubMed: 31674779]
70. Li H et al. Pyridinyl directed alkenylation with olefins via Rh(III)-catalyzed C–C bond cleavage of secondary arylmethanols. *J. Am. Chem. Soc.* 133, 15244–15247 (2011). [PubMed: 21875139]
71. Lei Z-Q et al. Extrusion of CO from aryl ketones: Rhodium(I)-catalyzed C–C bond cleavage directed by a pyridine group. *Angew. Chem. Int. Ed.* 51, 2690–2694 (2012).
72. Chen K et al. Reductive cleavage of the Csp²–Csp³ bond of secondary benzyl alcohols: rhodium catalysis directed by N-containing groups. *Angew. Chem. Int. Ed.* 51, 9851–9855 (2012).

73. Lei Z-Q et al. Group exchange between ketones and carboxylic acids through directing group assisted Rh-catalyzed reorganization of carbon skeletons. *J. Am. Chem. Soc.* 137, 5012–5020 (2015). [PubMed: 25843169]
74. Ozkal E, Cacherat B & Morandi B Cobalt(III)-catalyzed functionalization of unstrained carbon–carbon bonds through β -carbon cleavage of alcohols. *ACS Catal.* 5, 6458–6462 (2015).
75. Dermenci A, Coe JW & Dong G Direct activation of relatively unstrained carbon–carbon bonds in homogeneous systems. *Org. Chem. Front.* 1, 567–581 (2014). [PubMed: 30221007]
76. Morioka T, Nishizawa A, Furukawa T, Tobisu M & Chatani N Nickel-mediated decarbonylation of simple unstrained ketones through the cleavage of carbon–carbon bonds. *J. Am. Chem. Soc.* 139, 1416–1419 (2017). [PubMed: 28099004]
77. Zhao T-T, Xu W-H, Zheng Z-J, Xu P-F & Wei H Directed decarbonylation of unstrained aryl ketones via nickel-catalyzed C–C bond cleavage. *J. Am. Chem. Soc.* 140, 586–589 (2018). [PubMed: 29303264]
78. Ackermann L & Lygin AV Ruthenium-catalyzed direct C–H bond arylations of heteroarenes. *Org. Lett.* 13, 3332–3335 (2011). [PubMed: 21644545]
79. Jiang C, Zheng Z-J, Yu T-Y & Wei H Suzuki–Miyaura coupling of unstrained ketones via chelation-assisted C–C bond cleavage. *Org. Biomol. Chem.* 16, 7174–7177 (2018). [PubMed: 30246854]
80. Jiang C et al. Rhodium-catalyzed Hiyama coupling reaction of unstrained ketones via C–C bond cleavage. *Asian J. Org. Chem.* 8, 1358–1362 (2019).
81. Zhong J et al. Rhodium-catalyzed pyridine N-oxide assisted Suzuki–Miyaura coupling reaction via C(O)–C bond activation. *Org. Lett.* 21, 9790–9794 (2019). [PubMed: 31769295]
82. Long Y et al. Rhodium-catalyzed transarylation of benzamides: C–C bond vs C–N bond activation. *ACS Catal.* 10, 3398–3403 (2020).
83. Li G, Ji C-L, Hong X & Szostak M Highly chemoselective, transition-metal-free transamidation of unactivated amides and direct amidation of alkyl esters by N–C/O–C cleavage. *J. Am. Chem. Soc.* 141, 11161–11172 (2019). [PubMed: 31203613]
84. Onodera S, Ishikawa S, Kochi T & Kakiuchi F Direct alkenylation of allylbenzenes via chelation-assisted C–C bond cleavage. *J. Am. Chem. Soc.* 140, 9788–9792 (2018). [PubMed: 29787254] (Demonstrates that unstrained, nonpolar C–C bonds can be activated via β -carbon elimination via a removable DG.)
85. Onodera S, Togashi R, Ishikawa S, Kochi T & Kakiuchi F Catalytic, directed C–C bond functionalization of styrenes. *J. Am. Chem. Soc.* 142, 7345–7349 (2020). [PubMed: 32249570]
86. Wang H, Choi I, Rogge T, Kaplaneris N & Ackermann L Versatile and robust C–C activation by chelation-assisted manganese catalysis. *Nat. Catal.* 1, 993–1001 (2018).
87. King RB & Efraty A Pentamethylcyclopentadienyl derivatives of transition metals. II. Synthesis of pentamethylcyclopentadienyl metal carbonyls from 5-acetyl-1,2,3,4,5-pentamethylcyclopentadiene. *J. Am. Chem. Soc.* 94, 3773–3779 (1972).
88. Crabtree RH, Dion RP, Gibboni DJ, Mcgrath DV & Holt EM Carbon–carbon bond cleavage in hydrocarbons by iridium complexes. *J. Am. Chem. Soc.* 108, 7222–7227 (1986).
89. Halcrow MA, Urbanos F & Chaudret B Aromatization of the B-ring of 5,7-dienyl steroids by the electrophilic ruthenium fragment “[Cp*Ru]+”. *Organometallics* 12, 955–957 (1993).
90. Youn SW, Kim BS & Jagdale AR Pd-catalyzed sequential C–C bond formation and cleavage: evidence for an unexpected generation of arylpalladium(II) species. *J. Am. Chem. Soc.* 134, 11308–11311 (2012). [PubMed: 22721172]
91. Smits G, Audic B, Wodrich MD, Corminboeuf C & Cramer N A β -Carbon elimination strategy for convenient in situ access to cyclopentadienyl metal complexes. *Chem. Sci.* 8, 7174–7179 (2017). [PubMed: 29081949]
92. Xu Y et al. Deacylative transformations of ketones via aromatization-promoted C–C bond activation. *Nature* 567, 373–378 (2019). [PubMed: 30758326] (Demonstrates that aromatization can be used as a driving force to achieve catalytic activation of C–C bonds in diverse unstrained ketones.)
93. Padwa A & Pearson WH (eds.) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products* (John Wiley & Sons, 2003).

94. Tian M, Shi X, Zhang X & Fan X Synthesis of 4-acylpyrazoles from saturated ketones and hydrazones featured with multiple C(sp³)-H bond functionalization and C-C bond cleavage and reorganization. *J. Org. Chem.* 82, 7363–7372 (2017). [PubMed: 28640624]
95. Candeias NR, Paterna R & Gois PMP Homologation reaction of ketones with diazo compounds. *Chem. Rev.* 116, 2937–2981 (2016). [PubMed: 26854865]
96. Karrouchi K et al. Synthesis and pharmacological activities of pyrazole derivatives: A review. *Molecules* 23, 134 (2018).
97. Pérez-Gómez M et al. Tandem remote Csp³-H activation/Csp³-Csp³ cleavage in unstrained aliphatic chains assisted by palladium(II). *Organometallics* 38, 973–980 (2019).
98. Xia Y, Qiu D & Wang J Transition-metal-catalyzed cross-couplings through carbene migratory insertion. *Chem. Rev.* 117, 13810–13889 (2017). [PubMed: 29091413]
99. Tran VT, Gurak JA Jr., Yang KS & Engle KM Activation of diverse carbon-heteroatom and carbon-carbon bonds via palladium(II)-catalysed β -X elimination. *Nat. Chem.* 10, 1126–1133 (2018). [PubMed: 30127512]

Figure 1 |. General strategies in C–C bond activation.

A | C–C bond activation in ring-strained systems. Three- and four-membered ring systems are well-developed substrates in this context, and the bond cleavage is driven by relief of ring strain. **B** | C–C bond activation assisted by permanent DGs. A DG can not only dictate which C–C bond to be activated, but also lower the activation energy by forming a relatively stable metallocycle. **C** | Unstrained C–C bond activation enabled by temporary or removable DGs. The substrate scope of the C–C bond activation can be significantly broadened to a variety of simple unstrained or less strained molecules. DG, directing group; FG, functional group; X, a linkage used for DG installation.

Figure 2 | Alkyl exchange via activation of unstrained C–C bonds and subsequent olefin extrusion/reinsertion.

A | Alkyl exchange in ketones. **B** | Alkyl exchange in *sec*-alcohols. **C** | Alkyl exchange in primary amines.

Figure 3 | Merging intramolecular C–H bond activation with unstrained C–C bond activation.
A | Proximal C–C bond activation in cyclopentanones. **B** | Applications in formal total syntheses. **C** | Applications in collective syntheses of terpenes. **D** | Distal C–C bond activation in cyclopentanones. The definition of distal or proximal refers to the distance of the C–C bond to the aryl moiety. **E** | C–C bond activation in cyclohexanones. IMes, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; Ts, *p*-toluenesulfonyl; IPr, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; er, enantiomeric ratio; LLS, longest linear sequence.

Figure 4 |. Merging cross-coupling reactions with C–C bond activation.

A | Reaction scope and limitations. **B |** Proposed reaction pathway. ^{Me}IMes, 1,3-bis(2,4,6-trimethylphenyl)imidazol-4,5-dimethyl-2-ylidene; Ts, *p*-toluenesulfonyl; EWG, electron-withdrawing group; EDG, electron-donating group; *p*-tol, *p*-tolyl.

Figure 5 | "Cut-and-sew" reactions via activation of unstrained C–C bonds.

A | Intramolecular "cut-and-sew" reactions in the biaryl system. **B** | Intermolecular "cut-and-sew" reactions between 1-indanones with ethylene. **C** | Application in the simplified syntheses of bioactive molecules. IMes, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; Ts, *p*-toluenesulfonyl; psi, pound per square inch; ALK, anaplastic lymphoma kinase; NMDA, *N*-methyl-D-aspartate.

A Ring-opening and skeletal rearrangement reactions of cycloketimines **B Reaction of allylamines with olefins via sequential C-H and C-C bond activation** **C Reaction of allylamines with dienes via sequential C-H and C-C bond activation** **Figure 6 | Unstrained C–C bond activation enabled by 2-amino-picoline.**

A | Ring-opening and skeletal rearrangement reactions of cycloketimines. **B** | Reaction of allylamines with olefins via sequential C–H and C–C bond activation. **C** | Reaction of allylamines with dienes via sequential C–H and C–C bond activation. coe, cis-cyclooctene; Cy, cyclohexyl.

A General reaction profiles **B Mechanistic consideration** **Figure 7 | C(aryl)–C(aryl) bond activation using phosphinites as removable DGs.**

A | General reaction profiles. **Aa** | Gram-scale reaction. **Ab** | One-pot reaction that directly converted 2,2'-biphenol to the corresponding monomer. **Ac** | The *i*-Pr₂PCl reagent used for installing the phosphinite DG can be recycled simply by treatment with dry HCl. **B** | Mechanistic consideration. The aryl–aryl bond is cleaved by a rhodium(I)–hydride species. psi, pounds per square inch.

Figure 8 | Activation of unstrained C–C bonds enabled by removable heterocycle DGs.

A | Decarbonylation of unstrained diaryl ketones. **B** | Cross-coupling reactions of unstrained ketones with aryl boronates. **C** | Alkenylation of allylbenzenes via C(aryl)–C(allyl) bond activation. **D** | Manganese-catalyzed C(aryl)–C(alkyl) bond activation in alcohols. cod, 1,5-cyclooctadiene; IMes, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; BPin, pinacol boronate; Cp*, pentamethylcyclopentadienyl; acac, acetylacetonate; *p*-anisyl, *p*-methoxyphenyl; LiHMDS, lithium bis(trimethylsilyl)amide; TMS, trimethylsilyl; TMP, 2,2,6,6-tetramethylpiperidiny1.

A Deacetylation of methyl ketones **B** Formal '1,2-oxo-migration' **C** Homologation of methyl ketones **D** Pyrazole synthesis and DG removal

Figure 9 | Deacetylation of unstrained ketones via aromatization-promoted C–C bond activation.

A | Deacetylation of methyl ketones. **B** | Formal “1,2-oxo-migration”. **C** | Homologation of methyl ketones. **D** | Pyrazole synthesis and DG removal. Ts, *p*-toluenesulfonyl; BARf, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; MS, molecular sieves; *p*-anisyl, *p*-methoxyphenyl.

Figure 10 |.
Palladium-mediated activation of unstrained C(alkyl)-C(alkyl) bonds.