

# Recent catalytic approaches to chemical synthesis from carbon feedstocks\*

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*Abstract:* Traditional organic synthesis is driven by the need for functional molecules. The development of green chemical methods, however, is an increasingly important challenge in the context of global sustainability. To this end, the direct use of abundant carbon feedstocks in synthesis (such as CO, CO<sub>2</sub>, methanol, arenes, alkanes,  $\alpha$ -olefins, and biological raw materials) aims to minimize waste production and increase efficiency.

*Keywords:* C–H bond functionalization; carbon dioxide; carbon feedstocks; catalysis; fine chemicals; transition metals.

## INTRODUCTION

Transition-metal catalysis is a powerful tool for organic synthesis and provides a platform to develop chemical methods that are increasingly environmentally benign [1]. While traditional synthesis has been guided by the logic and intrinsic reactivity of functional groups [2], modern approaches have focused on enabling chemical transformations of otherwise unactivated building blocks and bonds (e.g., CO<sub>2</sub>, C–H bonds). By designing new catalysts and reagents capable of using feedstocks directly, we eliminate unnecessary functional group manipulations and shorten synthetic sequences, resulting in enhanced step, redox, and atom economy [3]. This critical review aims to highlight selected recent advances in the use of carbon feedstocks in fine chemical production with an emphasis on understanding catalytic mechanisms and a focus in asymmetric processes.

## C1 SYNTHONS

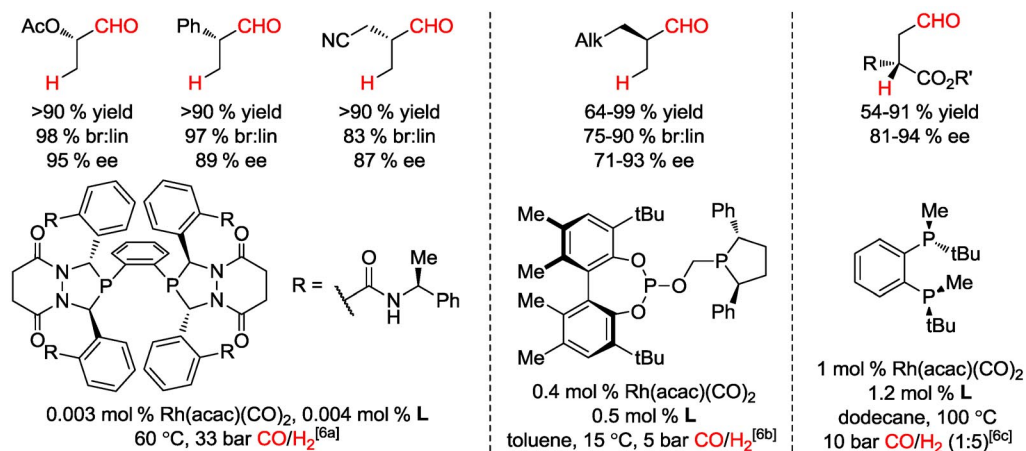
The industrial use of raw materials containing a single carbon atom largely revolves around CO. CO<sub>2</sub> and methanol are also important C1 synthons and are related to CO by the water–gas shift reaction and reduction, respectively.

### Carbon monoxide

CO is widely used in the chemical industry and currently finds use in olefin hydroformylation (the oxo process), Fischer–Tropsch synthesis, and the Monsanto acetic acid process [4]. For the purposes of this review, we will only highlight stereoselective carbonylations [5]. Enantioselective reactions involving CO incorporation are particularly suited to transition-metal catalysis. Asymmetric hydroformylation, in particular, is a longstanding goal in fine chemical synthesis due to the importance of chiral aldehydes. Chiral phosphine-bound rhodium catalysts are the most prevalent, such as in the hydroformylation of

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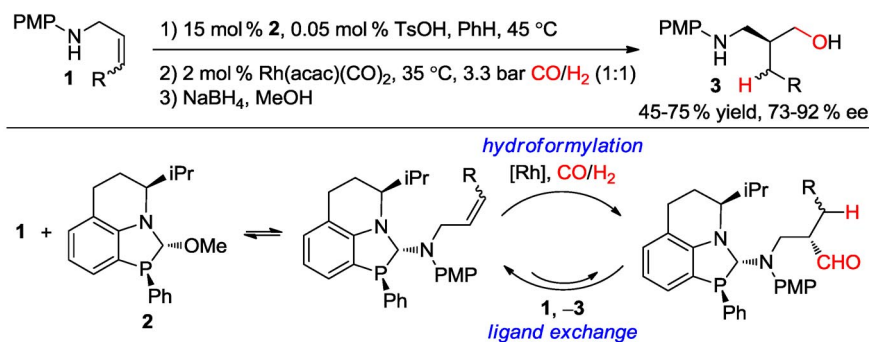
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**Fig. 1** Recent examples of asymmetric hydroformylation [6].

vinyl acetate, styrene,  $\alpha$ -olefins, and acrylates (Fig. 1) [6]. The ability to control stereo- and regioselectivity while maintaining high efficiencies, however, is often highly empirical and depends significantly on the electronic bias of the alkene of interest.

Recently, the concept of using reversible covalent linkages between catalyst and substrate to both enhance rates and promote selective reactions has emerged [7]. Terms such as “scaffolding catalysis” and “catalytic catalyst directing group” have been coined to describe this phenomenon. In hydroformylation, designer alkoxybenzoazaphosphole and phosphinite ligands have been successfully applied to (homo)allylic alcohols and amines [8]. Notably, the Tan group has demonstrated that enantioselective hydroformylation of allylic amines is viable using chiral alkoxybenzoazaphosphole **2** under mild conditions (Fig. 2) [9]. “Scaffolding catalysis” and “induced molecularity” have additionally been demonstrated in organocatalysis [7f–h] and will be an important consideration in future catalyst design.



**Fig. 2** Tan’s Rh-catalyzed regio- and enantioselective hydroformylation of allylic amines [9].

Asymmetric carbonylation has also found limited application in ester and lactone synthesis, but simultaneously achieving high efficiencies and stereoselectivity has been difficult [5,10]. One particularly important reaction is the oxycarbonylation of vinylarenes for the preparation of nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen (not shown) [11].

## Carbon dioxide

CO<sub>2</sub>, the primary form of carbon in the Earth's atmosphere and a renewable resource, is an ideal source of C1 from an environmental standpoint. Unlike CO, however, industrial uses of CO<sub>2</sub> have remained limited largely due to its relative inertness [12]. The activation of CO<sub>2</sub> with transition metals is a promising approach to promoting carboxylations [13].

The coordination chemistry of CO<sub>2</sub> was first investigated by Aresta in 1975 [14]. The so-called Aresta complex, Ni(η<sup>2</sup>-CO<sub>2</sub>)(PCy<sub>3</sub>)<sub>2</sub> (**4**), has undoubtedly been a source of inspiration for the development of many catalytic carboxylation methods. Work from the Dong group has confirmed that an η<sup>2</sup>-bound molecule of CO<sub>2</sub> can be intercepted by a weak carbon nucleophile, hence achieving a mild and functional group tolerant carboxylation (Fig. 3) [15]. It is reasonable to assume that the Aresta complex is a catalytically active species in many related Ni- and Pd-catalyzed carboxylic acid syntheses, although mechanisms including direct insertion into Ni–C (or Pd–C) bonds and radical intermediates have also been proposed (Fig. 4) [16]. Current state-of-the-art in C–C bond-forming carboxylations include reductive coupling of C=C double bonds and C–X bonds with CO<sub>2</sub>. Of note, Mori's cyclization remains one of the best examples of a synthetic method for asymmetric CO<sub>2</sub> incorporation [16e]. Yet, enantioselective methods for CO<sub>2</sub> incorporation remain scarce in the literature.

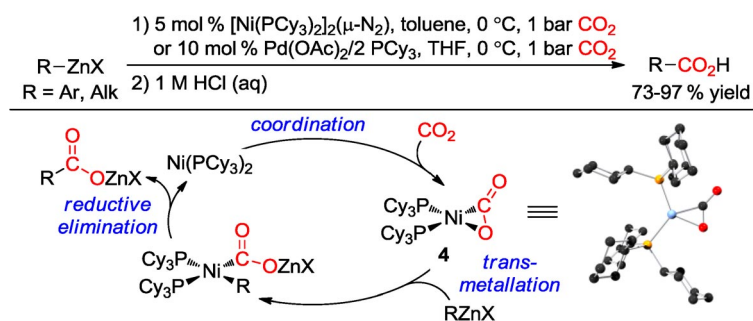


Fig. 3 Dong's Ni- and Pd-catalyzed carboxylation of organozinc reagents [15].

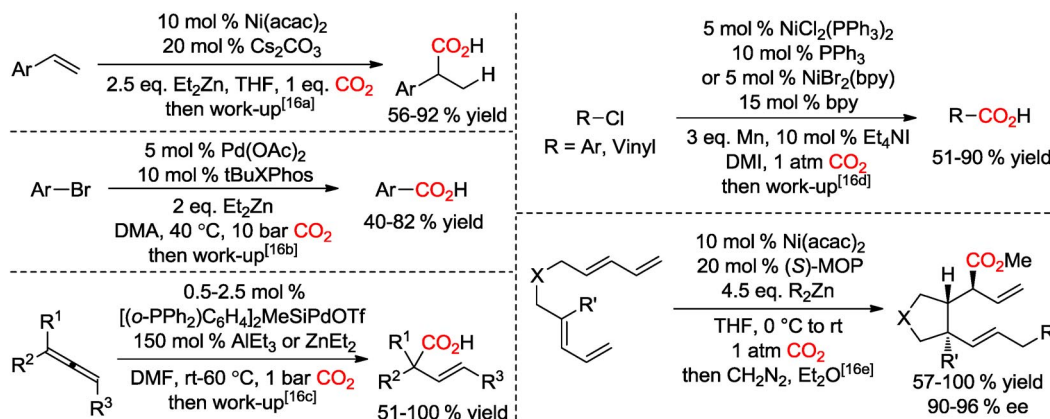


Fig. 4 Recent examples of Ni- and Pd-catalyzed carboxylations [16].

In contrast to Ni- and Pd-catalyzed carboxylations, reactions of CO<sub>2</sub> involving Rh, Cu, or Au salts are believed to occur through the direct insertion of CO<sub>2</sub> into M–C bonds (Fig. 5) [17]. This claim is substantiated by the fact that isolated arylcopper [17b] and arylgold complexes [17c] undergo car-

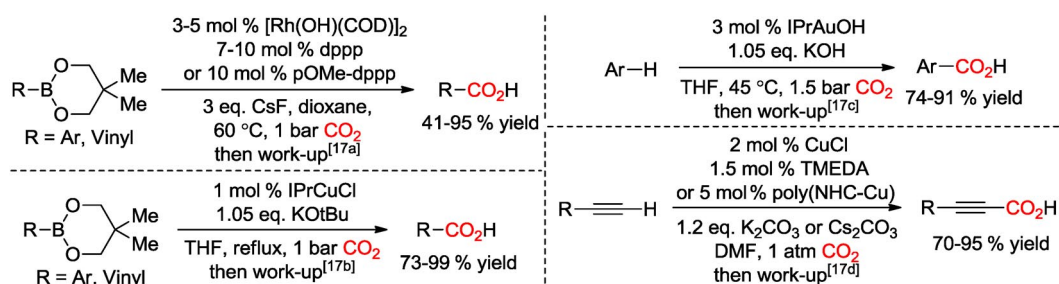


Fig. 5 Recent examples of Rh-, Cu-, and Au-catalyzed carboxylations [17].

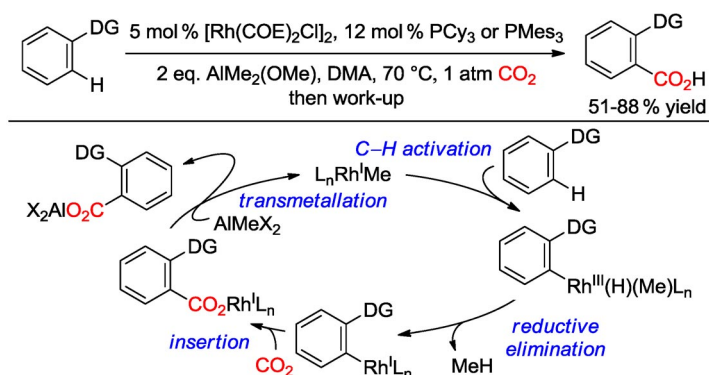


Fig. 6 Iwasawa's Rh-catalyzed carboxylation of C-H bonds [18].

boxylations in the presence of  $\text{CO}_2$ . Reagents including boronic esters, alkynes, unactivated electron-deficient arenes, and heteroarenes can readily undergo carboxylation. The combination of  $\text{CO}_2$  activation and other green processes such as C-H activation, exemplified by Iwasawa's work (Fig. 6) [18], will dominate future research in this field in attempts to simulate Nature's masterful carboxylations (e.g., photosynthesis, polyketide synthesis).

### Methanol as a C1 source

Although methanol is most commonly employed as an organic solvent, its relevance as a clean fuel has been suggested to have important economic implications in the years to come [19]. The current primary use of methanol as a C1 source is in acetic acid production. Methods for applying methanol as a formaldehyde equivalent, however, remain underdeveloped. Based on work in homogeneous transfer hydrogenation, the Krische group achieved a C-C coupling reaction between alkenes and methanol in the presence of an iridium catalyst (Fig. 7) [20]. By using a redox active metal such as iridium, formal  $\alpha$ -C-H functionalization occurs under mild conditions. This account is an important practical advance given the attractiveness of methanol as a chemical reagent. Research in transition-metal-catalyzed C-H activation may provide a general method for functionalizing the  $\alpha$  position of alcohols and ultimately impact the synthesis of complex molecules by providing alternative bond disconnections.

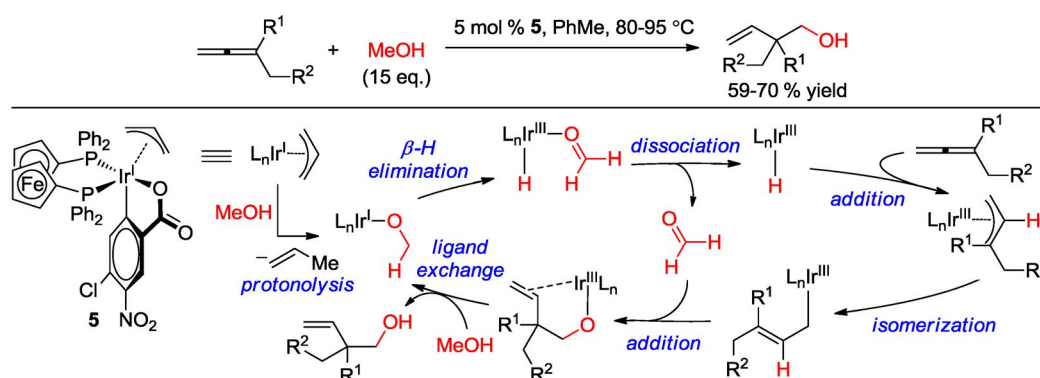


Fig. 7 Kricheldorf's Ir-catalyzed C-C coupling of allenes with methanol [20].

## PETROCHEMICALS

Petrochemicals are the current foundation of the chemical industry and global economy. While petrochemicals do not represent a renewable resource, alternatives such as coal and natural gas are rapidly emerging. The importance of olefins and aromatics to chemical synthesis and polymer production both today and in the future, however, is undeniable. Enabling new catalytic transformations of hydrocarbon feedstocks directly will continue to have implications to carbon management and is tied closely to CO<sub>2</sub> emission [21]. In light of the developing energy crisis, it is critical therefore to develop new catalysts to improve the utilization of hydrocarbons.

## Aromatic hydrocarbons

Arenes are widely used as solvents and as building blocks for synthesis. The functionalization of aromatic compounds traditionally requires strong acids and highly reactive reagents. Inspired by the need for green and sustainable methods, there is an interest in achieving C-C, C-O, and C-N bond formation by directly functionalizing C-H bonds, eliminating the need for halogen-containing intermediates [22]. The use of aromatic hydrocarbons in C-C coupling is particularly significant due to the prevalence of biaryl compounds in agrochemicals and pharmaceuticals.

The challenges in arene C-H functionalization are twofold: (i) overcoming low inherent reactivity, and (ii) achieving site-selectivity. The most common approaches to arylation take advantage of electronic biases of the starting materials or require the installation of a Lewis basic functionality to direct C-H activation (e.g., see Fig. 6). Transition-metal-catalyzed and metal-free direct arylation have been reviewed, and only selected examples will be described [23].

The Fagnou group reported an early example of using benzene as a coupling partner to replace more functionalized reagents such as boronic acids (Fig. 8) [24]. In this Suzuki-type cross-coupling,

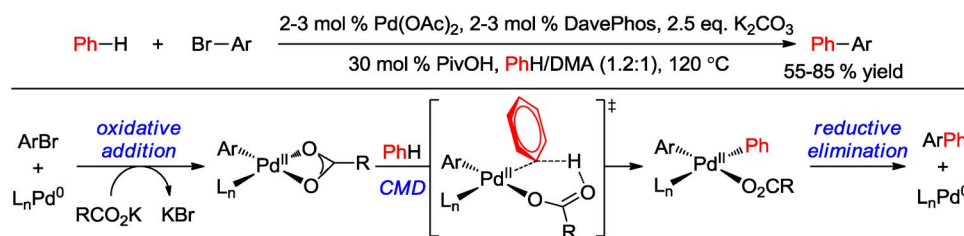
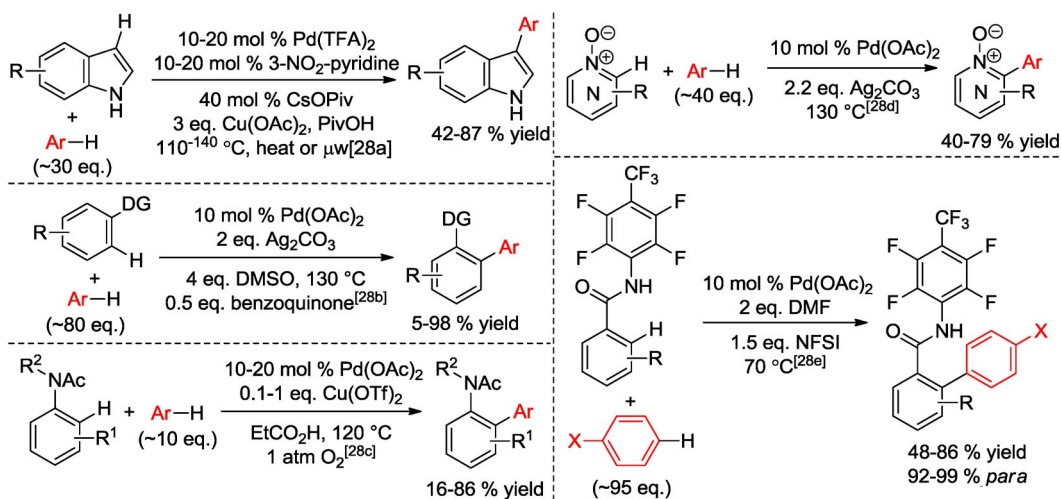


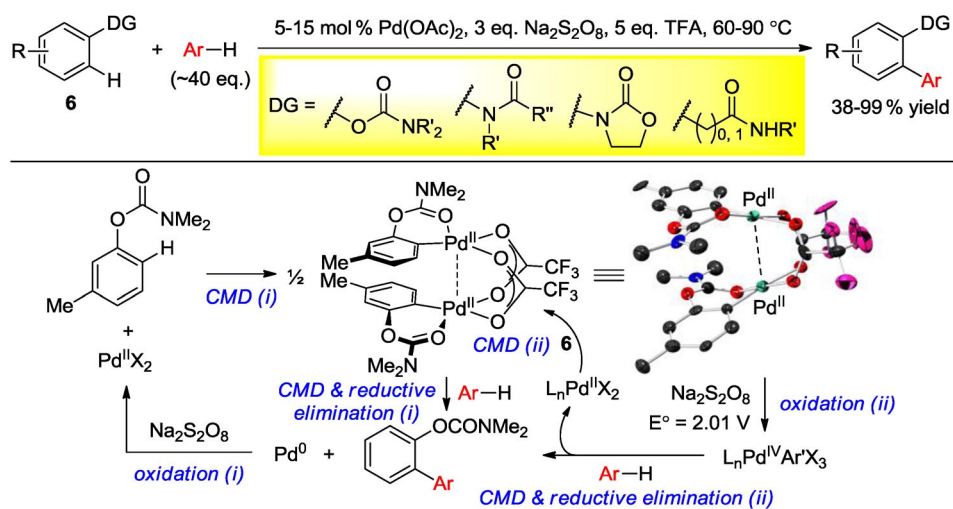
Fig. 8 Fagnou's Pd-catalyzed phenylation of aryl bromides [24,25].

pivalic acid exchanges with halide anion on the Pd catalyst and acts as a proton shuttle in a concerted metalation deprotonation (CMD) mechanism [25]. The six-membered transition state invoked for benzene palladation is likely active in many Pd-catalyzed C–H activations. Recent work has suggested alternative mechanisms as well [25e–i].

Coupling two C–H bonds for C–C bond formation is considered by many to be an ideal approach to synthesis [26]. Often used in large excess, unactivated arenes find widespread use in these oxidative cross-couplings [27]. Pd catalysts are typically used under basic conditions (Fig. 9) [28,29]. The Dong group disclosed the development of a complementary strategy using acidic sodium persulfate, an environmentally benign oxidant, and suggests the possibility of high valent Pd intermediates (Fig. 10) [30].



**Fig. 9** Recent examples of Pd-catalyzed oxidative cross-coupling [28].



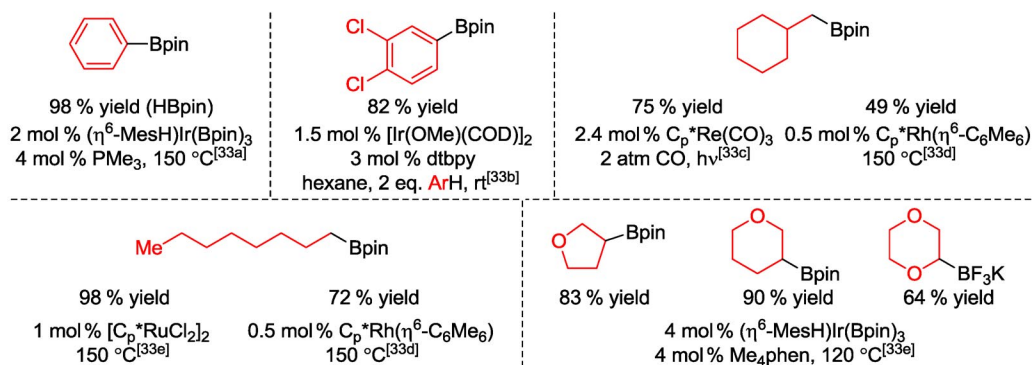
**Fig. 10** Dong's Pd-catalyzed oxidative cross-coupling [30]. Two mechanistic cycles are envisioned. In (i), turnover occurs between Pd(II) and Pd(0) oxidation states, where  $\text{Na}_2\text{S}_2\text{O}_8$  transforms Pd(0) into catalytically active Pd(II) salts. In (ii), turnover occurs between Pd(II) and Pd(IV), where  $\text{Na}_2\text{S}_2\text{O}_8$  transforms Pd(II) complexes into a Pd(IV) salt. Alternately, a dimeric bimetallic Pd(III) complex may also be an important intermediate.

Isolated bimetallic Pd(II) complexes have been shown to be active catalytically and may be a catalyst resting state. A rare example of a broadly applicable C–H functionalization was thus achieved. The Yu group described a closely related highly *para*-selective coupling using *N*-fluorobenzenesulfonimide (NFSI) as a bystander oxidant [28e]. While promising, the search for catalytic systems with high efficiencies and that can operate without large excesses of arene remains a significant challenge. Traditional cross-coupling (e.g., Suzuki, Negishi, Heck) will remain the standard for biaryl C–C bond formation until better alternatives are discovered.

### Aliphatic hydrocarbons

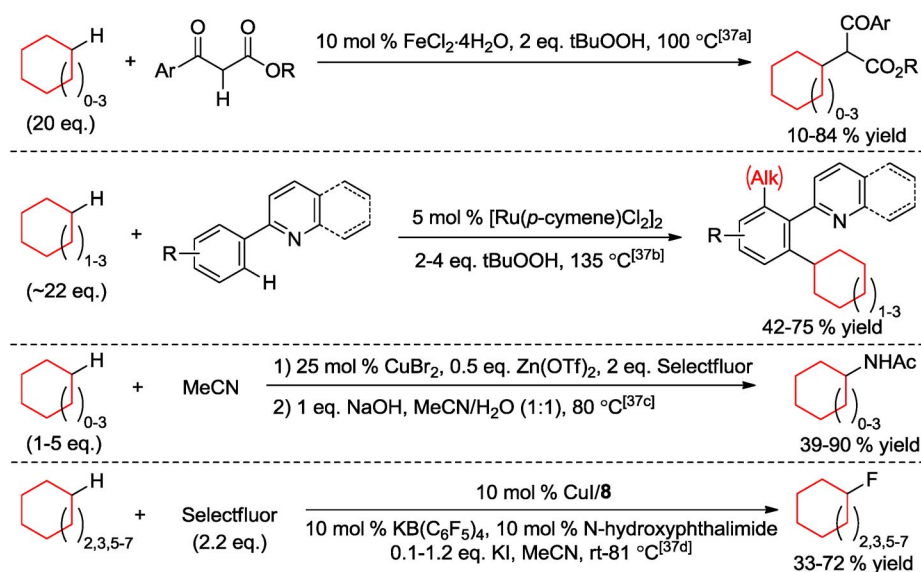
Alkanes, unlike arenes, are significantly less reactive to transition metals. Mechanisms such as CMD are not generally relevant to  $sp^3$  C–H bond functionalization. Instead, using alkanes as feedstocks typically requires highly reactive intermediates and catalysts. The direct conversion of methane to methanol is a fundamental problem and will not be covered in this review [31].

Direct borylation of C–H bonds is a well-studied process that applies to both aromatic and aliphatic hydrocarbons [32]. With Rh, Ir, Ru, and Re catalysts under thermal or photochemical conditions, borylation of primary and aromatic C–H bonds is facile, and recent developments suggest that ligand control can enable secondary C–H bond borylation (Fig. 11) [33]. Depending on the nature of the starting material, large excesses may not be required. Application to more complex scaffolds, particularly directed towards total synthesis, remains an area of active research.



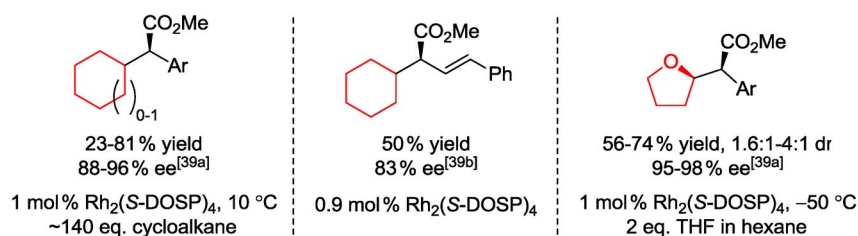
**Fig. 11** Hartwig's catalytic C–H bond borylation [33]. Excess arene or alkane is used with limiting  $B_2pin_2$  unless otherwise indicated. Other seminal accounts from Smith III, Miyaura, and Ishiyama were critical to advances in this field (not shown).

Alkyl radical formation is an alternative approach to direct  $sp^3$  C–H bond activation with a transition metal. Enzymatic methods mediated by high valent iron [34] and copper [35]-oxo complexes are ideal for C–H bond hydroxylation, but practical synthetic variants are rare [36]. In the context of oxidative C–C and C–N bond formation, reactive oxidants are commonly employed, such as in Li's couplings, Baran's Ritter-type amination, and Lectka's fluorination (Fig. 12) [37]. Controlling regio- and chemoselectivity can be particularly difficult when branched alkanes are used as substrates given the numerous C–H bonds available for functionalization. This is the result of the highly active radical intermediates formed in the presence of strong oxidants.

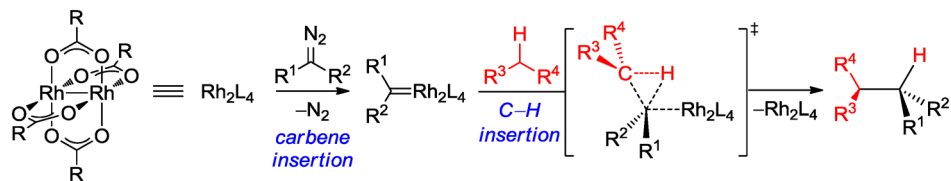


**Fig. 12** Recent examples of alkane C–H bond alkylation, arylation, amination, and fluorination [37].  
**8:**  $\text{PhCH=NCH}_2\text{CH}_2\text{N=CHPh}$ .

Metal carbenoids generated from diazoacetates are known to insert selectively into aliphatic C–H bonds [38]. In particular, the  $\text{Rh}_2(\text{S-DOSP})_4$  catalyst is able to promote intermolecular couplings with alkane solvents with high efficiencies and stereoselectivities (Fig. 13) [39]. Recent mechanistic investigations suggest that C–H insertion occurs in a concerted three-centered transition state with a preference for secondary C–H bonds (Fig. 14). The observed selectivity is complementary to that of other transition-metal-catalyzed methods, such as the aforementioned C–H borylation, which favors primary C–H bonds (Fig. 11), and enzymatic transformations, which typically occur at tertiary C–H bonds. The ability to perform selective C–H activation at low catalyst loadings with high levels of regio- and enantiocontrol is an important advance in this field both practically and fundamentally. Identifying



**Fig. 13** Davies' Rh-catalyzed carbenoid C–H insertion [39].



**Fig. 14** Proposed mechanism for Rh-catalyzed carbenoid C–H insertion [39].



alternative catalytic systems to replace precious transition metals with more inexpensive and abundant ones (e.g., Cu) is desirable.

### $\alpha$ -Olefins

Ethylene is the simplest olefin and is the starting material for the industrial production of acetaldehyde via the Wacker process [40]. Additionally, the oligomerization of ethylene is a major route to linear  $\alpha$ -olefins (e.g., Shell higher olefin process) [41]. This simple C2 building block, however, has not been widely used in synthesis until recently within the context of Heck couplings, hydrovinylation, and difunctionalization (Fig. 15) [42].

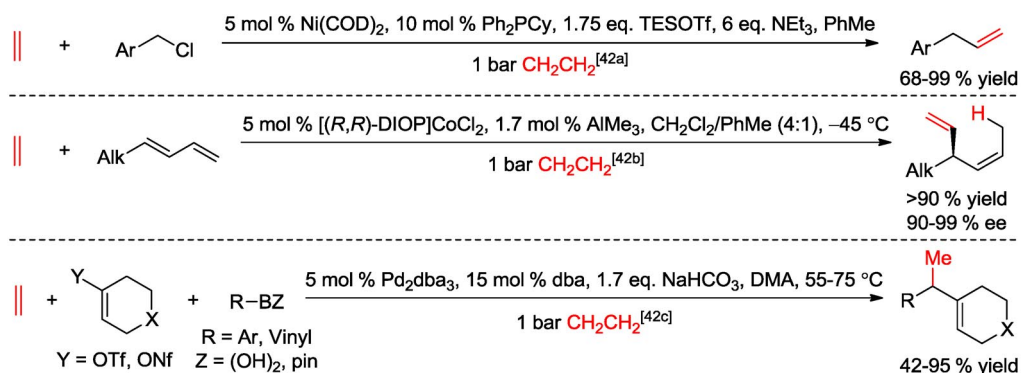
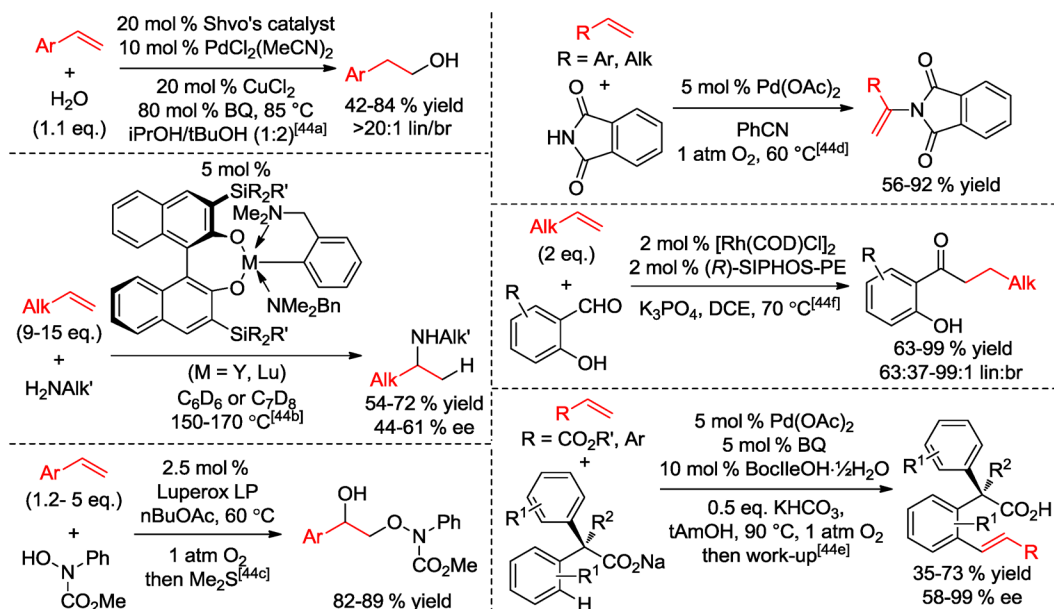


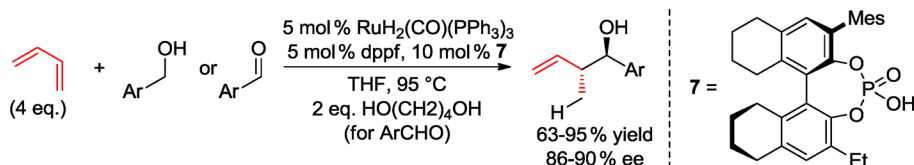
Fig. 15 Recent examples of catalytic reactions of ethylene [42].

$\alpha$ -Olefins, such as styrenes and acrylates, are typical substrates in many reactions, including Mizoroki–Heck cross-couplings, Fujiwara–Moritani oxidative Heck couplings, hydroarylations, and Stetter reactions [43]. The invention of new methods for the use of  $\alpha$ -olefins in synthesis could thus have important practical implications. To this end, research groups have achieved alkene anti-Markovnikov hydration, hydroamination, radical dioxygenation, oxidative amination, hydroacylation, and oxidative couplings, particularly including success in establishing enantioselective variants (Fig. 16) [44]. In a related report, Krische disclosed the use of 1,3-butadiene as a surrogate of traditional crotylmetal reagents by a transfer hydrogenation mechanism using a chiral Ru catalyst (Fig. 17) [45]. Typically, catalytic reactions that have been developed for simple  $\alpha$ -olefins are also applicable to more complex architectures both in inter- and intramolecular settings.

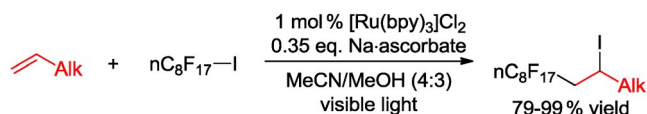
Recently, transition metals have been shown to act as initiators for single electron transfers, such as in atom transfer radical additions by photoredox catalysis (Fig. 18) [46]. In these transformations, the Ru catalyst harnesses the power of light, resulting in the production of alkyl radicals capable of addition to  $\text{C}=\text{C}$  double bonds. In particular, this method provides direct access to highly fluorinated products with high efficiencies and selectivities in a modern version of fluorinous tagging [47].



**Fig. 16** Recent examples of catalytic reactions of  $\alpha$ -olefins [44]. (*R*)-SIPHOS-PE = *N*-di[(*R*)-1-phenylethyl]-[(*R*)-1,1'-spirobiindane-7,7'-diyl]-phosphoramidite.



**Fig. 17** Krische's Ru-catalyzed enantioselective crotylation with 1,3-butadiene [45].



**Fig. 18** Stephenson's Ru-catalyzed atom transfer radical addition of perfluoroalkyl iodides [46].

In addition to reactions at C=C double bonds as functional groups themselves, their presence in a molecule imparts additional reactivity at the allylic positions. This enhanced ability to cleave  $sp^3$  C–H bonds has been applied to oxidative C–N [44d], C–C, and C–O bond formations primarily employing Pd salts as catalysts (Fig. 19) [48]. C–F bond formation has also recently been demonstrated (Fig. 20) [37d]. Depending on the nucleophile used to intercept the putative  $\pi$ -allyl Pd complex, linear and branched products can be obtained. In C–H bond acetoxylation, linear products predominate in the presence of dimethyl sulfoxide (DMSO) [48a], while the addition of bissulfoxide PhS(O)CH<sub>2</sub>CH<sub>2</sub>(O)SPh (**9**) can render the process branched selective [48c]. The development of analogous reactions using alternative transition metals or that are metal-free has been met with reasonable success. Methods for controlling enantioselectivity on prochiral substrates will also be critical to future applications. White has demonstrated that allylic C–H functionalization is useful within the context of a new macro-lactonization strategy toward the synthesis of 6-deoxyerythronolide [49].

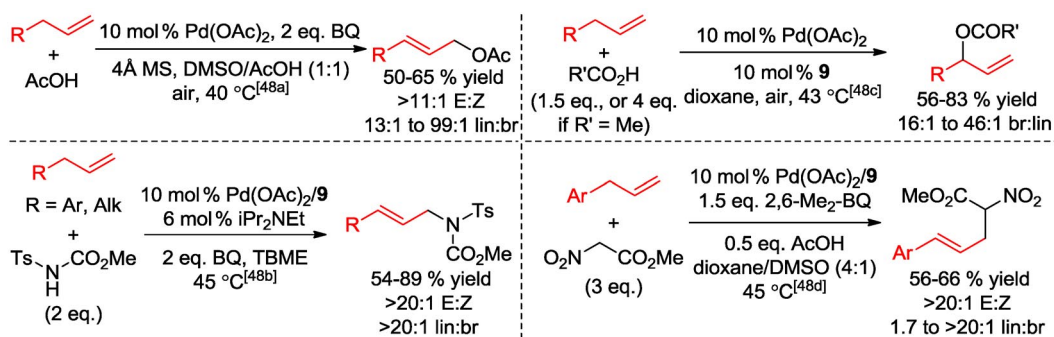


Fig. 19 White's Pd-catalyzed allylic C–H bond functionalization [48].

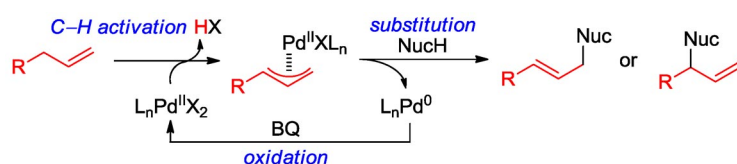


Fig. 20 Mechanism of Pd-catalyzed allylic C–H bond functionalization.

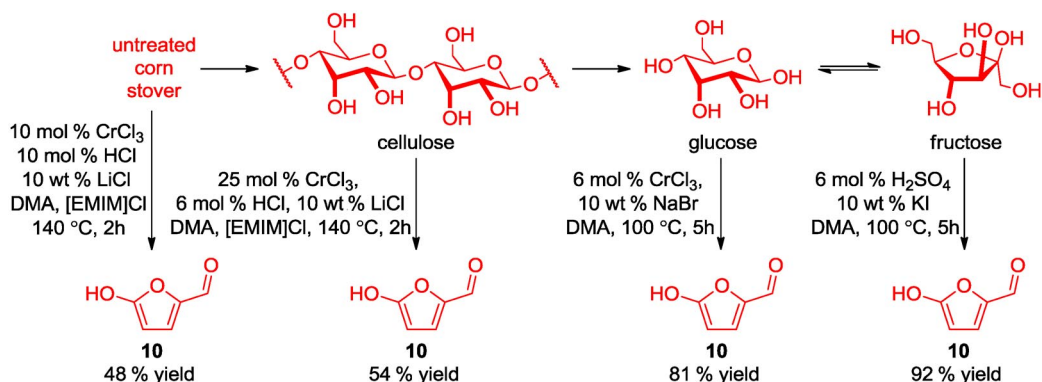
## BIOLOGICAL FEEDSTOCKS

Biomass is a renewable and potentially ideal carbon feedstock for synthesis because it harnesses the power of sunlight and converts  $\text{CO}_2$  and water into carbohydrates. Hence, there is an increasing interest in the scientific community to use vegetable biomass as a feedstock [50]. While biologically derived ethanol is a potential alternative for conventional fuels, fine chemical synthesis from biomass remains challenging. Ironically, the use of natural products as starting materials for total synthesis is a well-established and classical approach to architecturally complex natural products, taking advantage of Nature's chiral pool [51].

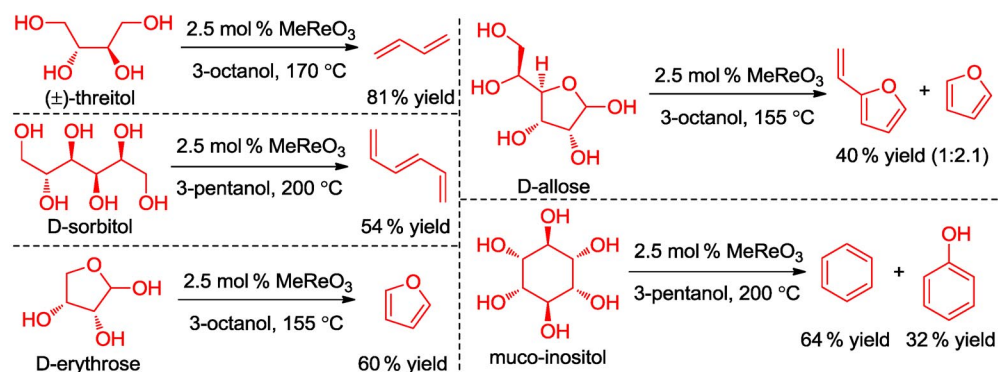
### Polyols

To address the issue of global sustainability and dependence on petroleum products, it is imperative that alternative sources of carbon (i.e., fuel) be discovered. It is widely believed that lignocellulosic biomass will be the foundation of our future economy. In principle, biomass-derived platform chemicals will support current petroleum technologies. 5-Hydroxymethylfurfural (5-HMF, **10**) is a particular target of interest given its rich chemical functionality yet accessibility from biological sources [53]. 5-HMF has been considered “a key substance between carbohydrate chemistry and mineral-oil-based industrial organic chemistry” [54]. Recent efforts have revealed that while fructose and sucrose are suitable starting materials [53,54], the direct use of cellulose is also possible in the presence of [EMIM]Cl, an ionic liquid (Fig. 21) [52].

Controlled deoxygenation can also afford alternative added-value products such as 1,3-butadiene, benzene, and furan (Fig. 22) [56]. In a recent account, Toste demonstrated that Re catalysts are broadly applicable catalysts for double deoxygenation aimed toward olefin synthesis.



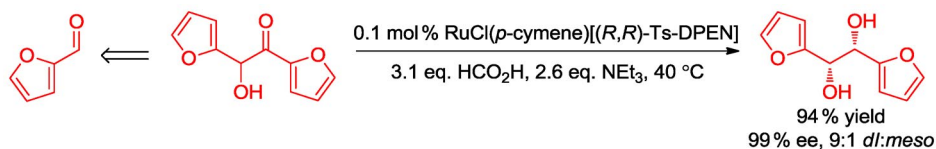
**Fig. 21** Catalytic 5-HMF formation from biomass [52]. [EMIM]Cl = 1-ethyl-3-methylimidazolium chloride.



**Fig. 22** Toste's Re-catalyzed deoxygenation of polyols [56].

## Furfural

Having its biosynthetic origin in polysaccharides, furfural (**11**) is generated by thermal dehydration of pentoses. This aldehyde can be readily transformed into 2-methyltetrahydrofuran and tetrahydrofuran, both important organic solvents; 2-methylfuran and furan are also isolable intermediates. Grushin and van Leeuwen recently devised an approach to a chiral vicinal diol using furfural by a homobenzoïn condensation and dynamic kinetic asymmetric hydrogenation, transforming this commodity chemical into a valuable enantioenriched product with potential use as a ligand for a transition metal or as (a precursor to) an organocatalyst (Fig. 23) [57].



**Fig. 23** Grushin and van Leeuwen's Ru-catalyzed synthesis of chiral hydrofuroin [57].

## CONCLUSION

The development of catalysts that enable reactions of simple building blocks is an important step in achieving sustainable organic synthesis. As carbon feedstocks shift its dependence away from petroleum sources, the identification of new routes for bulk and fine chemical production will be at the forefront of chemistry and chemical engineering. Innovations in catalyst and ligand design will require in-depth investigations into the molecular processes relevant to bond construction and control of selectivity. This will remain a central focus of future research.

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