Published in final edited form as:

Chem Rev. 2017 July 12; 117(13): 9163–9227. doi:10.1021/acs.chemrev.6b00661.

Transition Metal-Catalyzed C–H Bond Addition to Carbonyls, Imines, and Related Polarized π -Bonds

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Abstract

The transition metal-catalyzed addition of C–H bonds to carbonyls, imines and related polarized π -bonds has emerged as a particularly efficient and powerful approach for the construction of an incredibly diverse array of heteroatom substituted products. Readily available and stable inputs are typically employed, and reactions often proceed with very high functionality group compatibility and without the production of waste byproducts. Additionally, many transition metal-catalyzed C–H bond additions to polarized π -bonds occur within cascade reaction sequences to provide rapid access to a diverse array of different heterocyclic as well as carbocyclic products. This review highlights the diversity of transformations that have been achieved, catalysts that have been used, and types of products that have been prepared through the transition metal catalyzed addition of C–H bonds to carbonyls, imines and related polarized π -bonds.

Graphical abstract

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The authors declare no competing financial interest.

1. INTRODUCTION

The addition of nucleophiles to carbonyls, imines and related polarized π -bonds is one of the most important and extensively used approaches for the convergent synthesis of diverse products incorporating heteroatom functionality. While a variety of different classes of nucleophiles have been employed, the transition metal-catalyzed addition of C–H bonds to polarized π -bonds has recently emerged as a particularly efficient and powerful approach. Because the nucleophile is generated catalytically without the need for prefunctionalization, this approach employs readily available and stable nucleophile inputs and does not produce waste byproducts. Moreover, transition-metal catalyzed C–H bond functionalization typically requires neither strongly basic nor acidic conditions, and proceeds with very high functionality group compatibility. To date, a number of powerful catalyst systems derived from both precious metals and their earth abundant first-row congeners have been developed for C–H bond additions carbonyls, imines and related polarized π -bonds to provide convergent and atom-economical methods for the construction of an incredibly diverse array of heteroatom substituted products. In this article advances in this important area are reviewed.^{1–3}

The overriding organization of this review is based upon the polarized π -bond employed for C–H bond addition according to the following sequence: aldehydes, ketones, aldimines, carbon dioxide, isocyanates, carbon monoxide, isocyanides and nitriles. Additions to the C1 carbon sources carbon dioxide and carbon monoxide have been extensively reviewed. For this reason, leading references and only brief discussion of C–H bond additions to these C1 electrophiles are provided. Each polarized π -bond functional group section is further sub-divided according to the type of C–H bond addition as appropriate. For example, C–H bond additions to aldehydes are sub-divided by methods to overcome the reversibility of the reaction, including: direct addition to activated aldehydes, addition with in situ alcohol hydrosilylation, addition with in situ oxidation, and addition with cyclization upon the directing group. Finally, within each section reactions are organized according to the transition metal catalyst used, and the order in which transition metals are discussed is determined chronologically beginning with the seminal publication in each area. For example, in the section titled “Additions with in situ Alcohol Hydrosilylation,” Ir catalysis is presented first because Murai and coworkers published the seminal report on this approach with their very early report on Ir-catalyzed additions of imidazoles to aldehydes with alcohol hydrosilylation. All further applications of Ir catalysis to this approach are then discussed prior to moving chronologically to the next transition metal.

Sections 10 and 11 are organized differently because each involves C–H bond additions to C=C π -bonds followed by a second addition to polarized π -bonds. In Section 10 additions to C=C π -bonds followed by cyclization upon polarized π -bond directing groups are discussed. This section is further sub-divided by type of electrophilic directing group that is cyclized upon according to the sequence; imine, *N*-aryl nitron, ketone, *N*-acylamino, carboxylic acid derivative and urea directing groups. Within each directing group section further sub-division is based upon the C=C π -bond electrophile according to the sequence; alkynes, enoates and enones, allenes, dienes and allylic alcohols. Section 11 describes an emerging area wherein three-component additions are performed by C–H bond additions to

C=C π -bonds and polarized π -bonds. Finally, Section 12 contains miscellaneous transformations that both could not be assigned to other categories and also comprised only one or two reports and as such are not appropriate as isolated sections.

2. ALDEHYDES

2.1. Approaches for Overcoming Reversible Addition

Strategies for C–H bond additions to aldehydes are highly attractive due to the large number and diversity of commercially available aldehydes. However, due to the strong carbonyl π -bond, transition metal-catalyzed C–H bond addition to aldehydes is a reversible process,^{4,5} and the alcohol products are only favored for destabilized, highly electron-deficient aldehydes (Scheme 1). To enable transition metal-catalyzed C–H bond additions to aldehydes, several strategies have been developed to overcome the inherent reversibility of this transformation. In seminal reports, the reversibly formed Ir-catalyzed alcohol addition products were captured as silyl ethers,⁶ and this approach has now been extended to Mn, and Re. Trapping of alcohol addition products via irreversible in situ oxidation to the corresponding ketone has also been achieved, and significant progress has been accomplished for Pd and Rh catalysis. A different conceptual approach that enables efficient C–H bond addition to aldehydes employs a C–H functionalization directing group that serves a second role of capturing the alcohol intermediate **1** by irreversible cyclization to provide a pharmaceutically relevant heterocycle **2** (Scheme 2). Our and other laboratories have published multiple contributions to this area using different directing groups and cyclization pathways to provide a variety of different heterocycle products.

2.2. Direct Additions to Activated Aldehydes

While transition metal-catalyzed C–H bond additions to aldehydes is a reversible process, when destabilized, highly electron-deficient aldehydes are employed the alcohol products are thermodynamically more stable than the starting materials. Consequently, a trapping agent is not required to prevent reversibility and unprotected alcohol products can be directly isolated from reaction mixtures.

2.2.1. Rh Catalysis—In the seminal report on additions to activated aldehydes, Li and co-workers employed Rh(III) catalysis for direct addition of aromatic C–H bonds to destabilized, electron-deficient aldehydes to furnish unprotected alcohols **4** (Scheme 3).⁷ When ethyl glyoxylate was employed, addition products were obtained in high yield, and several nitrogen heterocycles were shown to be effective directing groups. Favorable formation of alcohol products was also achieved for aromatic aldehydes bearing electron-withdrawing functionalities. Similar to other reports of Rh(III)-catalyzed C–H functionalization,^{8–10} the reaction displays high functional group compatibility, tolerating phenols on either coupling partners without the need for protecting groups. Moreover, the reaction is not sensitive to oxygen or moisture, and similar yields were obtained for reactions conducted under air and in the presence of water.

Following this report, a similar study conducted by Shi and co-workers expanded the scope of Rh(III)-catalyzed direct C–H bond additions to aldehydes to include a broader range of

aromatic derivatives (Scheme 4).¹¹ A variety of functional groups were tolerated, with C–H addition to electron-deficient aldehydes necessary to obtain high yields. For example, C–H addition to benzaldehyde provided the corresponding benzhydrol in only 11% yield. In evaluating reaction scope, the authors noted that an *N*-containing directing group was essential for C–H functionalization, and a range of directing groups including quinoline, pyridine, pyrimidine, and pyrazole were shown to be effective.

Subsequently, the same group reported on the Rh(III)-catalyzed addition of substrates **7** with alkenyl C–H bonds to electron-deficient aromatic aldehydes (Scheme 5).¹² Notably, the conditions reported for arene C–H functionalization were found to be ineffective, however, use of the preformed catalyst [Cp*Rh(CH₃CN)₃][SbF₆]₂ in the presence of catalytic pivalic acid promoted the desired reactivity. With respect to the alkene coupling partner, the functionalization of cyclopentenyl C–H bonds showed higher efficiency than the corresponding cyclohexenyl derivative, and the former was used for the majority of substrate scope. In analogy to their earlier report on Rh(III)-catalyzed arene C–H bond additions to aldehydes,¹¹ C–H additions to electron-deficient aldehydes proceeded in moderate to good yields while additions to electron-neutral benzaldehyde proceeded in poor yield.

In 2016, Kim and co-workers reported Rh(III)-catalyzed *N*-pyrimidyl directed C–H bond addition of heterocycles **9** to ethyl glyoxylate (Scheme 6).¹³ The indole heterocycle class was the most extensively evaluated, and functionalization selectively occurred at the C2 position. A range of electron-rich and electron-poor functionality was compatible at the C3–C7 positions, and the alcohol products were obtained in high yield. In addition to indole C–H bond partners, pyrroles were also evaluated. Fused cyclic pyrroles were well tolerated, leading to the desired alcohol products in moderate to good yield. When pyrroles were substituted solely at the 3-position, over addition to the aldehyde occurred, and this double addition product was obtained with poor diastereoselectivity. A mixture of single and double addition products was also observed for the unsubstituted *N*-pyrimidyl pyrrole. Interestingly, aldehyde addition did not occur for the corresponding *N*-pyrimidyl pyrazole.

2.2.2. Ru Catalysis—In conjunction with their work on Rh(III)-catalyzed functionalization of indoles at the C2 position with ethyl glyoxylate, the Kim laboratory reported the seminal examples of Ru(II)-catalyzed C–H bond additions to ethyl glyoxylate using *N*-pyrimidyl indolines **11** to direct functionalization to the C7 position (Scheme 7).¹³ The alcohol products were obtained in good yield when electron-rich groups or halogen substituents were placed around the aromatic portion of the indoline ring. The reaction also tolerated alkyl and aryl functionality at the C2 and C3 positions. However, when a stereocenter was introduced at either of these sites, poor diastereoselectivity was observed. In place of the *N*-pyrimidyl directing group the heterocyclic *N*-pyridyl group was also efficient, although other directing groups such as *N,N*-dimethyl urea and acetamide coupled in poor yield. For *N*-methyl-*N*-2-pyrimidylaniline, which lacks the conformational constraint provided by the indoline ring, no reaction occurred.

2.3. Additions with in situ Alcohol Hydrosilylation

2.3.1. Ir Catalysis—In 2002, Murai and co-workers published the seminal report of formal transition metal-catalyzed C–H bond additions to aldehydes (Scheme 8).⁶ The authors demonstrated that $[\text{Ir}_4(\text{CO})_{12}]$ catalyzes the coupling of *N*-methylimidazole, **13**, and aldehydes in the presence of diethylmethylsilane to provide silyl protected alcohols **14**. Interestingly, dimethyl acetylenedicarboxylate (DMAD) as an additive significantly improved the reaction yield, which the authors proposed acts either as a hydrogen acceptor or a ligand. In the absence of diethylmethylsilane the reaction did not occur.

The mechanism of this reaction was proposed to proceed by addition of an Ir–SiR₃ species **15** to the aldehyde to provide intermediate **16** (Scheme 9). Subsequent insertion into the C=N π -bond of *N*-methylimidazole, **13**, provides an amidoiridium intermediate **17**, which then undergoes a β -hydride elimination to furnish the product **14** while generating an Ir–H species **18**. The regeneration of the active catalyst is then proposed to proceed via reaction of the Ir–H **18** with H–SiR₃ to give Ir–SiR₃ **15** and an equivalent of H₂. While this report showcases the first example of formal transition metal-catalyzed C–H bond additions to aldehydes, the proposed mechanism does not proceed via direct C–H activation.

Following this report, Shi and co-workers developed an unprecedented Ir-catalyzed *meta*-selective C–H functionalization of pyridine derivatives **19** (Scheme 10).¹⁴ A number of C–H functionalization catalysts were evaluated, including Mn, Re, Ru, and Rh catalysts, but only Ir catalysts were found to be effective. Reaction optimization revealed that $\text{Ir}_4(\text{CO})_{12}$ was a superior precatalyst and that the addition of phenanthroline (phen) as a ligand greatly improved reaction yield. Unsubstituted pyridine resulted in a mixture of mono- and bis-*meta* functionalized products, with the latter resulting from over addition. To address this issue, pyridines with 3-aryl, alkyl and alkoxy substituents were employed to block one *meta* site from C–H functionalization. Using this strategy single aldehyde addition products were obtained in moderate to good yields. In contrast, 2-substituted pyridines such as 2-methylpyridine and 2,6-lutidine coupled in poor yield. Fused bicyclic pyridines were also evaluated, with isoquinoline coupling in higher yield than quinoline. Finally, a range of substituted aromatic and heteroaromatic aldehydes coupled efficiently, although a linear alkyl aldehyde proceeded in low yield.

2.3.2. Mn Catalysis—In 2007, Takai and co-workers reported the first example of earth abundant Mn-catalyzed C–H bond additions to aldehydes (Scheme 11).¹⁵ While a series of metal complexes derived from Mn, Re, Ru, Rh, and Ir were explored, only $[\text{MnBr}(\text{CO})_5]$ and $[\text{Mn}_2(\text{CO})_{10}]$ were found to be active toward this transformation. Initially, the authors investigated the coupling of 1-methyl-2-phenyl-1*H*-imidazole, **21**, and benzaldehyde to provide the unprotected alcohol product in the absence of silane. When a stoichiometric amount of $[\text{MnBr}(\text{CO})_5]$ was employed the desired alcohol was obtained, presumably due to stabilization as the Mn-adduct prior to reaction work up. In contrast, only trace alcohol was obtained under catalytic conditions, likely because the alcohol product is less stable than the starting imidazole and aldehyde. The addition of triethylsilane proved critical to achieving a high yield under catalytic conditions by trapping alcohol intermediates through protection as silyl ethers **22**. The substrate scope of the transformation was demonstrated with a broad

range of aldehydes, including linear and branched alkyl, aromatic, and heteroaromatic derivatives. An asymmetric variant of the transformation was also evaluated through the use of chiral imidazoline directing groups **23**, which resulted in products **24** with moderate to high diastereomeric excess.

2.3.3. Re Catalysis—Kuninobu, Takai and co-workers also reported the first examples of alkenyl C–H bond additions to aldehydes using alkenyl imidazole **25** (Scheme 12).¹⁶ Although the [MnBr(CO)₅] catalyst employed for arene C–H functionalization was found to be catalytically active toward the transformation,¹⁵ the third-row congener [ReBr(CO)₃(thf)]₂ proved to be an optimal catalyst. Electron-rich and poor aromatic, heteroaromatic, and alkyl aldehydes all coupled efficiently. The mechanism was proposed to proceed by a Re(I)-catalyzed or Mn(I)-catalyzed C–H activation via an oxidative addition pathway to furnish cyclometallated Re(III)/Mn(III) hydrides. Subsequent 1,2-insertion into an aldehyde, followed by silyl protection of the metal-alkoxide provides the desired product with concomitant release of dihydrogen.

2.4. Additions followed by in situ Oxidation

Another effective and popular strategy for overcoming the thermodynamically disfavored formation of alcohol products is through transition metal-catalyzed oxidative C–H bond coupling with aldehydes to give ketones.¹⁷ The high functional group compatibility and selectivity of this approach nicely complements traditional electrophilic aromatic substitution reactions such as Friedel-Crafts acylation¹⁸ and direct lithiation/acylation reactions.¹⁹

2.4.1. Pd Catalysis—In 2009, Cheng and co-workers published the seminal report of transition metal-catalyzed formal oxidative coupling of C–H bonds with aldehydes to give ketones **28** (Scheme 13).²⁰ The reaction employs commercially available Pd(OAc)₂ as catalyst and uses air as a terminal oxidant. In addition to the functionalization of 2-phenylpyridines, directed oxidative C–H bond acylation of 2-phenoxy pyridines with aldehydes was also efficient. Additional nitrogen heterocycle directing groups were also found to be effective. With respect to the aldehyde substrate scope, a variety of electron-poor and neutral aromatic derivatives proved to be effective inputs, although the authors note that C–H acylations with alkyl aldehydes did not proceed under the reaction conditions. In 2010, Li and co-workers were able to expand the scope of this transformation to include Pd-catalyzed oxidative C–H acylation with alkyl aldehydes with the reaction conducted under neat conditions and employed *tert*-butyl hydroperoxide (TBHP) as oxidant.²¹

Following Cheng's initial report on oxidative *ortho* C–H bond acylation of 2-phenylpyridines and 2-phenoxy pyridines (Scheme 13), Chu, Wu, and co-workers expanded the scope of this Pd-catalyzed oxidative process for 2-phenoxy pyridines **29** (Scheme 14).²² In this report, detailed mechanistic experiments were conducted including intra- and intermolecular kinetic isotope effects, radical trapping, and controlled experiments. The authors proposed a Pd(III) or Pd(IV) π -complex as a key intermediate along the catalytic cycle and a reaction pathway that proceeds via conversion of the aldehyde to an acyl radical. Further synthetic application of the acylated products obtained from Pd catalysis was

demonstrated by the synthesis of (2-hydroxyphenyl)-(phenyl)methanones and 1-hydroxy-9H-fluoren-9-ones via removal of the pyridyl directing group and Pd-catalyzed intramolecular C–C bond coupling, respectively.

Following the seminal report of Pd-catalyzed oxidative C–H acylation by Cheng and coworkers,²⁰ the Yu laboratory developed a protocol for *O*-methyl oxime-directed Pd-catalyzed C–H bond acylation using TBHP as oxidant (Scheme 15).²³ The reaction displays good functional group compatibility and tolerates a range of aryl, heteroaryl, and alkyl aldehydes. In this report, the direct sp³ C–H bond acylation of 8-methylquinoline was also achieved, providing the corresponding ketone in 42% yield. Following this report, an analogous report on *O*-methyl oxime directed C–H acylation using Rh(III) catalysis appeared (See Section 2.4.2, Scheme 33).²⁴

In 2011, three groups independently reported the Pd-catalyzed *ortho* acylation of anilide C–H bonds using aldehydes as an acyl source.^{25–27} The first report by Li, Kwong, and co-workers employed Pd(TFA)₂ as catalyst with TBHP as terminal oxidant for the acylation of anilides **33** (Scheme 16).²⁵ A variety of functional groups were compatible with this reaction, and in analogy to earlier reports of Pd-catalyzed acylation with aldehydes, both aryl and alkyl aldehydes coupled efficiently. Moreover, amides with R² = Me, Ph, *i*-Pr, and *t*-Bu were effective directing groups. Notably, when *N*-2-pyridinyl acetamide was submitted to the reaction conditions, in situ deacetylation occurred to provide the *ortho*-amino diaryl ketone in 86% yield. Novak and coworkers have also published on Pd-catalyzed anilide C–H bond acylation with aldehydes under aqueous conditions, demonstrating an observable rate acceleration with the use of acid and the detergent sodium dodecyl sulfate (SDS).²⁸ In a subsequent paper the same group then developed a three-step one-pot procedure for the synthesis of 2-amino benzophenone derivatives via (1) protection or acylation of anilines, (2) Pd-catalyzed cross dehydrogenative coupling of aldehydes under aqueous conditions at ambient temperature, and (3) hydrolytic amide deprotection.²⁹

Another example of Pd(II)-catalyzed oxidative C–H bond acylation with aldehydes was accomplished by the Wu and co-workers using 2-arylbenzoxazoles **35** (Scheme 17).³⁰ By evaluating various ligands, the authors found that triphenylphosphine provided the highest yield. For the aromatic aldehyde coupling partner, substitution was well tolerated about every position of the aromatic ring, and C–H bond acylation with substrates bearing both electron-rich and halogen groups proceeded in moderate to good yields. For 2-arylbenzoxazoles, electron-rich and halogen substituents on the aromatic ring of the C–H bond partner were also well tolerated with placement of functionality at the *ortho*, *meta* or *para* positions. Substrates containing methyl and chloro groups on the benzoxazole ring were also shown to be effective, although the chloro functionalized benzoxazole provided only 37–55% yields of the desired products.

The synthesis of acylated azobenzenes **38** through Pd-catalyzed azo-directed C–H bond acylation with aldehydes using TBHP as oxidant was first reported by Wang and co-workers (Scheme 18).³¹ Unsubstituted azobenzene was employed for evaluating aldehyde scope, with a large variety of aromatic and aliphatic aldehydes coupling in moderate to good yield. In addition, acylation of symmetric azobenzenes bearing either electron-donating or

electron-withdrawing functionality were also demonstrated. Further synthetic application was demonstrated by the reductive cyclization of acylated azobenzenes to provide the corresponding *N*-aryl-2*H*-indazoles in high yield. Following this study, Xiao, Deng, and co-workers reported on the Pd-catalyzed oxidative direct *ortho* acylation of azobenzene and other arenes with aldehydes under aqueous conditions.³² Recently, the Pd-catalyzed *ortho* C–H acylation of an amide-substituted azobenzene **39** was also reported by Wang and coworkers (Scheme 19).³³

Kim and co-workers have also reported Pd-catalyzed acylation of *N*-benzyltriflamides **41** (Scheme 20).³⁴ While the reaction tolerated a range of functional groups, a notable limitation of the chemistry was that diacylation was observed for substrates bearing two accessible *ortho* C–H bonds. To address this issue, the majority of the substrate scope was carried out using *ortho*- or *meta*-substituted benzyltriflamides.

Following the demonstration of the Rh(III)-catalyzed synthesis of hydroxyisoindolinones (See Section 2.4.2, Scheme 31),³⁵ Huang, Zhao, and co-workers developed a related synthesis using a Pd catalyst (Scheme 21).³⁶ In contrast to an earlier report using Rh(III) catalysis where oxidative couplings to aromatic aldehydes were achieved using stoichiometric Ag₂CO₃, the Pd-catalyzed conditions allowed the authors to expand the scope of this chemistry to include C–H acylation with alkyl aldehydes using relatively inexpensive and abundant TBHP as the internal oxidant.

Employing identical coupling partners and similar catalytic conditions, the same group achieved the synthesis of imino carboxylic acids **46** via the addition of catalytic amounts of the Lewis acid BF₃(OEt)₂ to the reaction mixture (Scheme 22).³⁷ Oxidative C–H couplings with aromatic aldehydes were highly efficient, however, alkyl aldehydes were ineffective in the transformation.

In 2014, Wang, Zhang, Zhou and co-workers developed a strategy to access 1,2-benzisoxazoles **48** by a Pd-catalyzed intermolecular [4+1] annulative coupling of *N*-phenoxyacetamides **47** with aldehydes under oxidative conditions (Scheme 23).³⁸ A broad range of substituted benzaldehydes and heteroaromatic aldehydes coupled efficiently to provide the corresponding 1,2-benzisoxazoles in 47–90% yield. C–H bond acylations with heteroaromatic aldehydes were also efficient, and both linear and branched alkyl aldehydes coupled in 40–64% yield. A series of substituted *N*-phenoxyacetamides were also explored, and electron-donating and withdrawing functionalities were well tolerated at nearly all positions of the aromatic ring. For *meta*-substituted derivatives bearing methoxy, methyl, and halogen groups, single regioisomers were obtained resulting from C–H acylation and annulation exclusively at the less sterically encumbered *ortho* C–H bond. Based on density functional theory (DFT) calculations the authors propose a trifluoroacetate-assisted concerted metallation deprotonation (CMD) mechanism for C–H activation.

Patel and co-workers have exploited the higher directing ability of nitrogen relative to oxygen in regioselective Pd-catalyzed monoacylation of 3,5-diarylisoxazoles **49** with aldehydes (Scheme 24).³⁹ In this transformation it is notable that C–H bond functionalization only occurs at one out of the four possible *ortho* sites of this molecular

scaffold. Although a series of Pd(II) salts were evaluated as catalysts, Pd(OAc)₂ showed the highest activity. In addition, the use of either hydrogen peroxide (H₂O₂) or benzoyl peroxide (PhCO₂)₂ in place of TBHP failed to promote the desired reactivity. Under the optimal conditions, a range of aromatic and heteroaromatic aldehydes were well tolerated. This study also provides the first examples of catalytic *ortho* C–H functionalizations of 3,5-diarylisoindazoles **49**.

Methods for heteroaromatic C–H bond acylation have also been accomplished. Han, Pan, and co-workers reported the Pd-catalyzed pyridine directed oxidative C3 acylation of benzofurans and benzothiophenes **51** with aromatic aldehydes (Scheme 25).⁴⁰ Using Pd(OAc)₂ as catalyst and TBHP as stoichiometric oxidant, a broad range of aromatic aldehydes bearing electron-withdrawing or electron-donating functionalities coupled efficiently. Heteroaromatic aldehydes were also tolerated, providing the C3-acylated benzofurans and benzothiophenes in 86–92% yield. However, heteroaromatic C–H bond acylation with a linear aliphatic aldehyde did not proceed under the reaction conditions.

Following the demonstration of Rh(III)-catalyzed C2 acylation of indoles via oxidative C–H bond additions to aldehydes (See Section 2.4.2, Scheme 32),⁴¹ Liu and co-workers developed a related strategy using a Pd catalyst system (Scheme 26).⁴² The majority of substrate scope was carried out using the 2-pyridyl directing group, although 2-pyrimidine was also effective. Electron-withdrawing and electron-donating functionalities were well tolerated at nearly every position of the indole ring. With respect to the aldehyde coupling partner, C–H acylations with aromatic, heteroaromatic, and alkyl derivatives allowed for the introduction of a variety of functionality. In addition to the functionalization of indoles, the authors also reported the functionalization of *N*-(2-pyridyl)pyrrole; however, both of the *ortho* C–H bonds were functionalized resulting in formation of a diacylated product.

Employing a removable pyrimidine directing group, Sekar and co-workers also reported the Pd-catalyzed oxidative C–H functionalization of indoles **55** using aldehydes as the acyl source (Scheme 27).⁴³ C–H acylations were carried out for aromatic, heteroaromatic and alkyl aldehydes. By simply increasing the equivalents of aldehyde and oxidant employed in the transformation the authors established a strategy for C2/C7 diacylation of *N*-pyrimidylindole, **57**. Diacylation with two different aldehydes was also demonstrated by sequential aldehyde addition to the reaction mixture. For these examples, C2 acylation of indoles upon addition of the first aldehyde occurred prior to C7 acylation with the second aldehyde. These results established that while Pd-catalyzed C–H bond acylations is feasible for both sites, directed functionalization of indoles is more facile at C2 than at C7. Proof-of-principle for direct C7 acylation of an *N*-pyrimidylindole **59** with substitution at the C2 and C3 positions of the indole has also been recently demonstrated by Lin and Yao (Scheme 28).⁴⁴

In 2015, the Kim laboratory accomplished the Pd-catalyzed oxidative C–H acylation of indolines **61** at the C7 position (Scheme 29).⁴⁵ Functionality was tolerated at almost every position of the indoline ring, and both aryl and alkyl aldehydes were shown to couple efficiently. To demonstrate the utility of this chemistry, the *N*-pivaloyl group was removed by basic hydrolysis to provide free (NH)-indoline in good yield. Moreover, the authors also

demonstrated the oxidative dehydrogenation of a 7-acylated indoline with DDQ to provide a biologically relevant 7-acylated indole.

To date, a number of alternative strategies for Pd-catalyzed directed *ortho* C–H bond acylation have also emerged that employ reagents other than aldehydes as acyl precursors, including benzyl alcohols, benzyl amines, benzyl halides, benzyl ethers, alkylbenzenes, diketones, carboxylic acids, acyl chlorides, anhydrides, and terminal aryl alkenes and alkynes. Further examples of decarboxylative *ortho* C–H bond acylation via the use of α -keto and α -hydroxy carboxylic acids have also been reported. A review on these alternative acyl precursors has recently appeared.¹⁷

2.4.2. Rh Catalysis—Kim and co-workers were the first to employ Rh(III) catalysts for oxidative C–H bond coupling with aldehydes to give ketones. In their study, tertiary benzamides **63** were coupled with aromatic aldehydes using silver carbonate (Ag_2CO_3) as the stoichiometric oxidant (Scheme 30).⁴⁶ The influence of the amide directing group on the reaction outcome was also explored. While the *N,N*-dimethyl, *N,N*-diethyl, and pyrrolidine amides provided comparable reactivity, the sterically hindered *N,N*-dibenzyl and electron-deficient morpholine amide derivatives coupled in low yield. Furthermore, the use of a secondary benzamide proved ineffective in the transformation. Employing *N,N*-diethyl benzamide to evaluate substrate scope, oxidative C–H bond acylations were demonstrated for electron-rich and electron-deficient aryl aldehydes, as well as heteroaryl derivatives. Substitution was also tolerated at all sites around the aryl ring of the benzamide.

As an extension to this method, the Kim laboratory also demonstrated the coupling of secondary benzamides **65** with aromatic aldehydes to form hydroxyisoindolinones **66** (Scheme 31).³⁵ This transformation proceeds by Rh(III)-catalyzed oxidative C–H acylation with aldehydes followed by intramolecular attack of the benzamide nitrogen upon the ketone to furnish the cyclic product **66**. A broad range of aryl aldehydes were efficient coupling partners, and electron-rich and neutral substituents about the aryl ring of the benzamide were compatible with the transformation. An analogous method was also developed later that featured a Pd(II) catalyst system (See Section 2.4.1, Scheme 21).³⁶

Li and co-workers reported *N,N*-dimethyl-1*H*-indole-1-carboxamides **67** as the C–H functionalization substrate for Rh(III)-catalyzed aldehyde addition with in situ oxidation (Scheme 32).⁴¹ For these substrates, aldehyde addition occurred exclusively at the C2 position of the indole to provide ketones **68**. Moreover, a range of aryl aldehydes as well as linear and branched alkyl aldehydes coupled efficiently. Substitution about the indole ring with both electron-donating and electron-withdrawing groups was well tolerated. Notably, the C2 acylation of a 7-azaindole was also achieved in 45% yield. The authors also showed that under basic conditions at ambient temperature the amide directing group could be removed to provide the unprotected indole product in high yield. Two related transformations were later published by the laboratories of Liu and Sekar for Pd-catalyzed oxidative C2 acylation of pyridyl- and pyrimidylindoles, respectively (See Section 2.4.1, Scheme 26–27).^{42,43}

Following the demonstration of Pd-catalyzed oxidative coupling of aryl ketone oximes and aldehydes (See Section 2.4.1, Scheme 15),²³ Zhou, Li, and co-workers developed a related method employing a Rh(III) catalyst system (Scheme 33).²⁴ In this report, cationic Rh(III) is generated in situ using $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$, and stoichiometric Ag_2CO_3 is used as the internal oxidant to trap the initially formed alcohol addition products in the ketone oxidation state. Under these conditions, the reaction displays high functional group compatibility and tolerates both aryl and alkyl aldehydes. In contrast to previous reports of transition metal-catalyzed oxidative C–H acylations with aldehydes, when highly electron-deficient benzaldehydes were employed the authors observed the direct addition of a second equivalent of aldehyde following the initial acylation. When over addition occurred, none of the mono-acylated products were observed. Further synthetic application was demonstrated by the removal of the oxime directing group under acidic conditions to generate 1,2-diacylbenzenes.

2.4.3. Ru Catalysis—In 2015, Yi and co-workers reported that a cationic ruthenium hydride catalyst promoted oxidative coupling of phenolic C–H bonds and aldehydes to provide 2-acylphenols **73** (Scheme 34).⁴⁷ The substrate scope of this transformation was carried out using electron-rich, Friedel-Crafts type phenolic coupling partners, and a broad range of aryl and alkyl aldehydes were tolerated. In contrast to traditional Friedel-Crafts acylations, which typically provide a mixture of regioisomers, this reaction is highly regioselective for *ortho* acylated products **73**. The authors note that at least two equivalents of aldehyde are necessary, because the aldehyde coupling partner serves the auxiliary role of acting as an internal oxidant through hydrogenation to the corresponding alcohol. Thus, in the absence of an external oxidant the sacrificial second equivalent of aldehyde facilitates turnover in the catalytic cycle to provide acylated products **73**. Further synthetic application was achieved when α,β -unsaturated aldehydes were employed. For these substrates, initial *ortho* C–H acylation was followed by conjugate addition and dehydrative annulation to provide flavenes.

2.5. Additions with Cyclization upon Directing Group

The directed, metal-catalyzed C–H bond addition to aldehydes followed by cyclization between the alcohol and the directing group has proven to be a very effective strategy for the preparation of a large variety of useful heterocycles. Importantly, irreversible cyclization enables high yields of heterocyclic products to be attained even when the alcohol intermediate is thermodynamically disfavored relative to the starting C–H activation substrate and aldehyde. A number of different directing groups have been employed in this approach with the directing group serving as either an electrophile or nucleophile in the cyclization step. Our group has invested significant effort into this area, and we have coined the term “cyclative capture” to describe this cascade process.⁴⁸

2.5.1. Re Catalysis—In 2006, Kuninobu, Takai and co-workers published the first example of transition metal-catalyzed C–H bond additions to aldehydes where the metal-carbon bond derived from C–H activation directly adds to the aldehyde (Scheme 35).⁴⁹ Notably, this report also represents the first example of a cyclative capture cascade. Using a clever design strategy, a Re(I) catalyst is shown to promote ketimine directed arene C–H

bond additions to aldehydes followed by an intramolecular cyclization to access isobenzofurans **75**. The proposed mechanism of this transformation begins with the coordination of the imine nitrogen atom to the Re(I) catalyst followed by C–H bond activation. Subsequent steps include: insertion of the aldehyde into the rhenium-carbon bond of the aryl-rhenium intermediate, intramolecular nucleophilic cyclization via attack of an alkoxy-rhenium intermediate onto the electrophilic carbon of the ketimine, reductive elimination, and release of aniline to regenerate the active catalyst. The authors note that two observable side-products of the reaction included (1) the aldimine obtained upon condensation of the aldehyde with the aniline released upon cyclization, and (2) benzophenone formed upon hydrolysis of the ketimine C–H bond coupling partner. To improve the reaction yield, an extra equivalent of aldehyde was used to trap the aniline released upon cyclization and molecular sieves were added to the reaction mixture to remove water. Isobenzofurans **75** were obtained in good yields for a number of aromatic aldehydes bearing a variety of functionality, as well as for cinnamaldehyde. This chemistry was further applied to three-component couplings where in situ Diels Alder reactions of the isobenzofuran C–H functionalization products with dienophiles followed by extrusion of water provided naphthalenes in good yield. In a subsequent report the scope of this method was expanded to a broader range of both intra and intermolecular examples.⁵⁰

An interesting example reported by Kuninobu, Takai and co-workers in 2010 showcases a Re(I)-catalyzed reaction that produces a single indenone product **77** from three equivalents of an aryl aldehyde (Scheme 36).⁵¹ Here *N*-phenylacetamide is used in catalytic amounts to condense with an aldehyde to generate a more effective directing group for C–H activation. The Re(I) metalacycle generated upon C–H activation adds to a second equivalent of the aldehyde. The resulting alcohol cyclizes with release of *N*-phenylacetamide and water to give isobenzofurans **76**. At the high temperature at which the reaction is performed, the isobenzofurans **76** further condenses with a third equivalent of the aldehyde to furnish indenones **77**. This transformation was shown to proceed in high yields for electron-rich, neutral and poor aromatic aldehydes. Additionally, high regioselectivity was observed for 3-methylbenzaldehyde with the major product of the reaction resulting from functionalization of the less sterically encumbered *ortho* C–H bond.

Recently, Wang and co-workers developed the Re(I)-catalyzed synthesis of *N*-aryl-2*H*-indazoles **79** from azobenzenes **78** and aromatic aldehydes (Scheme 37),⁵² analogous to related transformations previously reported for Rh(III) and Co(III) catalysts (See Section 2.5.2, Scheme 42, and Section 2.5.3, Scheme 43).^{53,54} For the evaluation of aldehyde substrate scope, unsubstituted azobenzene was employed. While aromatic and heteroaromatic aldehydes coupled in moderate to good yields, linear and cyclic alkyl aldehydes provided the desired indazoles in poor yields. A variety of substituted, symmetrical azobenzenes were also shown to give indazoles in 18–90% yield. The authors report the first catalytic application of an isolated Re(I)-metalacycle obtained by C–H activation, and demonstrated that the complex displays similar catalytic efficiency to that achieved under their standard reaction conditions. Furthermore, acetate was shown to be essential to the reaction. Deuterium labeling experiments established that C–H bond activation is likely reversible, and kinetic isotope effect (KIE) experiments further suggested

that C–H bond activation is involved in the rate-determining step. Mechanistic experiments also suggested an irreversible aldehyde insertion pathway for Re(I), perhaps due to rapid cyclization between the alcohol and the directing group under the reaction conditions. Unlike earlier reports of Re(I)-catalyzed C–H functionalization that were proposed to proceed via oxidative C–H bond addition to provide a Re(III)–hydride,^{16,49} for indazole synthesis the reaction was proposed to proceed through a redox neutral deprotonation analogous to earlier reports for Rh(III) and Co(III) catalysis.^{53,54}

2.5.2. Rh Catalysis—The first example of a Rh(III)-catalyzed cyclative capture strategy was reported by our lab for the synthesis of phthalides **81** (Scheme 38).⁴⁸ In this work, the previously unexplored imidate directing group was employed, such that the alcohol intermediate cyclizes upon the electrophilic C=N π -bond of imidate. Hydrolytic release of methanol and the amine then provides 5-membered lactones **81**. Electron-donating substituents on the aryl ring of the imidate were well tolerated, while the electron-poor CF₃ group provided only 27% yield of the desired phthalide. A broad range of aryl aldehydes and ethyl glyoxylate coupled efficiently in the transformation. In addition, a number of linear and branched alkyl aldehydes also provided phthalides in good yield. However, for most alkyl aldehydes, the optimal R² substituent on the nitrogen of imidate was a bis-3,5-trifluoromethylphenyl group rather than the methoxy group originally used for aromatic aldehydes.

Later, Li and co-workers found that at higher temperatures, the Rh(III)-catalyzed coupling of benzoic acid derivatives **82** and electron-deficient aldehydes could also be carried out to give phthalides **83** (Scheme 39).⁵⁵ Both electron-neutral and electron-rich benzoic acid motifs were employed as coupling partners, although unsubstituted benzoic acid coupled in only 18% yield. As exemplified for heptanal, alkyl aldehydes provided the desired phthalide product in very low yield. In addition to the typical silver halide abstractor, excess Ag₂CO₃ was also required, which the authors postulate was necessary for formation of a rhodium-bound carboxylate to facilitate C–H activation.

In 2013, another example of phthalide synthesis via C–H activation was demonstrated using a dual Rh(III) and amine catalyst system (Scheme 40).⁵⁶ The in situ formation of the imine provided an effective transient directing group for this transformation, with the imine cleaved during cyclization and oxidation to form phthalides **84**. Homocoupling of aryl aldehydes with electron-donating, neutral, and withdrawing substituents all gave the desired products in good yields. Heterocoupling of aromatic aldehydes was also achieved. In most cases *meta* and *ortho* substituents were placed on one of the aromatic aldehydes to prevent C–H functionalization, thereby enabling the selective synthesis of only one of the two possible heterocoupling products. When the two aromatic aldehydes had different electronic properties, selective C–H functionalization of the more electron-rich aldehyde occurred along with selective addition to the more electrophilic, electron-deficient aldehyde. Alkyl aldehydes were also evaluated in the heterocoupling reaction, but gave low yields of phthalides.

The Rh(III)-catalyzed alkenyl C–H bond addition of unsaturated *O*-methyl oximes **85** to aldehydes followed by cyclative capture to give furans **86** was accomplished in our lab

(Scheme 41).⁵⁷ For this transformation, after cyclization of the alcohol intermediate upon the electrophilic C=N π -bond of the oxime directing group, aromatization with loss of methoxyamine occurs to give the furan **86**. Multiple different di- and tri-substituted alkenyl *O*-methyl oximes **85** provided the desired products in good to excellent yields, including for aryl, alkyl, and fused cycloalkyl derivatives. In addition, a variety of electron-poor and neutral aryl aldehydes coupled efficiently. Other aldehydes such as the highly activated ethyl glyoxylate coupled in high yield, and both branched and cyclic alkyl aldehydes provide moderate yields of the furan products. This methodology was also extended to pyrroles, another important heterocycle class that will be addressed in the imine portion of the review (See Section 4.2, Scheme 73).⁵⁷

Expanding upon our previous reports of heterocycle synthesis via Rh(III)-catalyzed C–H bond addition to aldehydes followed by cyclative capture, we next developed a convergent, single-step synthesis of *N*-aryl-2*H*-indazoles **88** (Scheme 42).⁵³ These valuable heterocycles display important pharmacological and fluorogenic properties, and are present in multiple drugs and drug candidates. While previous examples of cyclative capture relied on nucleophilic hydroxyl group attack upon an electrophilic directing group, here the directing group acts as a nucleophile to displace a hydroxyl leaving group. This report also provided the first example of Rh(III)-catalyzed C–H functionalization of azobenzenes.⁵⁸ Exploration of unsymmetrical azobenzenes provided valuable insight about the steric and electronic parameters that governed the regioselectivity of this reaction. For unsymmetrical *para*-nitro and *meta*-methoxy monosubstituted azobenzenes, selective C–H functionalization of the more electron-rich aromatic ring was observed. Sterics provided an even stronger regiochemical bias. In all cases, *meta* substitution on either aromatic ring of the azobenzene completely blocked C–H functionalization of the proximal *ortho* C–H bond. For exploring the substrate scope of this reaction, 4-hydroxyl-3,5-dimethylsubstituted azobenzenes were primarily used because this group could readily be removed from the indazoles products with cerium ammonium nitrate (CAN) to provide the corresponding 1*H*-indazoles lacking *N*-substitution. With respect to the azobenzene C–H bond partner, electron-donating and withdrawing groups were well tolerated, and diverse functionality could be placed at *ortho*, *meta*, and *para* positions of the aromatic ring. Aromatic aldehydes bearing both electron-rich and poor functionalities coupled efficiently, providing indazoles in 63–81% yield. In addition, cyclohexanecarboxaldehyde also provided the expected indazole, albeit in only 38% yield. A number of *N*-aryl-2*H*-indazoles prepared via this method were found to be fluorescent and displayed high extinction coefficients and large Stokes shifts. These fluorescent properties have encouraged the preparation and study of other *N*-aryl-2*H*-indazole derivatives and related structures.⁵⁹

Kim and co-workers reported another example of indazole synthesis via Rh(III) catalysis (Scheme 43).⁶⁰ Azobenzenes **89** were coupled with α -keto aldehydes to provide 3-acyl-(2*H*)-indazoles **90–91**. Symmetrical azobenzenes with a range of electron-donating and withdrawing substituents coupled in good yield, but predominately gave the product **91** resulting from double addition of the keto aldehyde. A variety of aryl and heteroaryl keto aldehydes coupled efficiently, including derivatives with electron-rich, neutral and poor substituents. An alkyl keto aldehyde was also evaluated, but provided the 3-acyl-(2*H*)-

indazole in poor yield. In one case, using an unsymmetrical 3,5-disubstituted azobenzene led to the indazole product as a single regioisomer, demonstrating that sterics, as previously reported for unactivated aldehyde additions (Scheme 42, and Section 2.5.3, Scheme 44), play a key role in selective azobenzene C–H functionalization. Finally, unsymmetrical *para*-substituted azobenzenes were also evaluated and provided products in high yield with regioselectivity that paralleled the steric and electronic effects previously reported for Rh(III)-catalyzed indazole synthesis with unactivated aldehydes (Scheme 42).⁵³

2.5.3. Co Catalysis—The seminal examples of earth abundant Co(III)-catalyzed C–H bond additions to aldehydes were established in our lab by the synthesis of *N*-aryl-2*H*-indazoles **93** and furans **96** (Schemes 44–47).⁵⁴ A new air-stable cationic Co(III) catalyst was developed and used for these transformations and was prepared on multigram scale without the use of any precious metals. While a variety of acetate additives were shown to be beneficial for catalysis, a sub-stoichiometric amount of acetic acid was key to achieving high yielding reactions in the absence of precious metal additives. For added convenience, both indazole and furan synthesis can be performed on the benchtop under standard reflux conditions, and on large scale. A diverse array of aryl, hetero, and alkyl aldehydes participate in this reaction, providing efficient entry into highly substituted indazole and furan heterocycles from simple inputs.

The *N*-aryl-2*H*-indazoles **93** were synthesized using a broad range of both azo and aldehyde coupling partners (Scheme 44). Monosubstituted unsymmetrical azobenzenes were employed to evaluate the influence of steric and electronic parameters on the regioselectivity of C–H bond functionalization. In both cases, the major regioisomer resulted from reaction on the more electron-rich aromatic ring. In analogy to our previous reports on Rh(III)-catalyzed C–H bond additions to polarized π -bonds (See Section 2.5.2),⁵³ *meta*-substituted arenes underwent functionalization exclusively at the less sterically hindered *ortho* C–H bond. To selectively introduce functionality into the core of the indazole scaffold, a series of 3,5-disubstituted azobenzenes were employed and in all cases indazoles were obtained as single regioisomers.

A number of experiments were conducted to provide insight into the mechanism of Co(III)-catalyzed indazole synthesis via C–H bond addition to aldehydes followed by cyclative capture (Schemes 45–46). The reversibility of cyclometallation was first demonstrated by subjecting site-specifically-deuterated azobenzenes to the reaction conditions (Scheme 45). At low conversion significant protio-deutero scrambling was observed in both recovered azobenzenes and indazole products. Furthermore, this result demonstrated that although the steric hindrance of 3,5-disubstitution completely blocks an aromatic ring from C–H functionalization, cyclometallation readily occurs at these sites.

The reversibility of Co(III)-catalyzed aldehyde insertion was also established by subsection of an independently prepared aldehyde addition product **94** to the reaction conditions in the presence of 4-methylbenzaldehyde (Scheme 46). A mixture of indazole products was obtained, providing conclusive evidence that Co(III)-catalyzed C–H bond additions to aldehydes is a reversible process.⁵

The synthesis of highly functionalized furans **96** via Co(III)-catalyzed aldehyde addition and cyclative capture was also demonstrated (Scheme 47). A range of α,β -unsaturated *O*-methyl oximes provided trisubstituted furans in good yields. A tetrasubstituted furan containing a fused bicyclic framework was also synthesized, although in lower yield. With respect to the aldehyde coupling partner, C–H bond additions to both aromatic and alkyl derivatives proceeded efficiently.

2.6. Miscellaneous Approaches to Overcome Reversible Aldehyde Addition

2.6.1. Rh Catalysis—In a very early example of C–H bond additions to aldehydes, Kakiuchi and co-workers reported the Rh(I)-catalyzed C–H bond activation of one aldehyde in *o*-phthalaldehyde, **97**, followed by intramolecular addition to a second aldehyde to provide phthalide **98** (Scheme 48).⁶¹ Much more extensive development of C–H bond activation of aldehydes followed by intramolecular addition to ketones has occurred and is discussed in detail in Section 3.3 of this review.

2.6.2. Mn Catalysis—In 2015, Wang and co-workers reported another strategy for overcoming the reversibility of C–H bond additions to aldehydes through the use of stoichiometric zinc additives (Scheme 49).⁶² They found that a full range of aldehydes from aryl and heteroaryl to linear and branched alkyl aldehydes coupled efficiently. They also found that a variety of substitution patterns about the 2-phenylpyridine motif were well tolerated and further demonstrated that a range of 2-alkenylpyridines were effective substrates. Other heterocycle directing groups were also shown to be effective. The authors proposed that the zinc reagents activate the catalyst. They also proposed that these reagents, which are used in stoichiometric quantities, result in a zinc alkoxide addition product that is subsequently protonated during reaction workup. Because C(sp²)–H bond additions to unactivated aldehydes are not thermodynamically favored (See Section 2.1), the high reaction yields for these aldehydes are achieved presumably because the addition products are trapped as the zinc alkoxide prior to aqueous workup.

3. KETONES

Similar to C–H bond additions to aldehydes, additions to ketones are also desirable due to the large number and diversity of commercially available inputs. However, ketone carbonyl π -bonds are even stronger than the corresponding aldehyde π -bonds due to enhanced resonance stabilization, and therefore, intermolecular C–H bond additions to ketones are generally thermodynamically disfavored. To achieve favorable thermodynamics that allow C–H bond ketone additions to occur, two strategies have been employed; (1) inter- or intramolecular additions to destabilized ketones such as keto esters or isatins, and (2) intramolecular additions often with aromatization of the initial addition product. Finally, additions of aldehyde C–H bonds to ketones is a sub-category that has provided an elegant approach to lactones and esters in particular in the context of asymmetric synthesis.

3.1. Intermolecular Additions of C–H Bonds to Activated Ketones

3.1.1. Pd Catalysis—In 2013, Yang and co-workers reported on the Pd-catalyzed intermolecular addition of heteroaryl C–H bonds to the highly electron-deficient and

destabilized ketone carbonyl present in isatins **101** (Scheme 50).⁶³ They found that isatins **101** bearing a range of electron-rich to poor substituents on the aromatic ring coupled to give the desired 3-substituted 3-hydroxy-2-oxindoles **103** in high yield. While *N*-methyl isatin gave the highest yield of the desired product, *N*-benzyl and *N*-H isatins also were acceptable substrates. In addition to a range of electron-rich and deficient benzoxazole coupling partners, other azole derivatives were also effective, including *N*-methylimidazole, benzimidazoles, thiazoles and benzothiazoles. The reaction of 1,3,4-oxadiazole was also examined and provided a high yield of the desired 3-hydroxy-2-oxindole product.

In the same report, Yang and co-workers found that acetonitrile also coupled through a Pd(II)-catalyzed C–H activation sequence to a variety of *N*-methyl isatins **104** displaying electron-donating and withdrawing functionalities (Scheme 51).⁶³

3.1.2. Rh Catalysis—Rh(III)-catalyzed C–H bond additions to highly electron-deficient ketones was reported by the Shi laboratory (Scheme 52).⁶⁴ After an extensive screening, only 2-methylpyridine and quinoline were identified as effective directing groups for this transformation, with the latter being optimal. The highly electron-deficient ketone, ethyl trifluoropyruvate, coupled in high yield for a variety of 2-aryl quinolones **106** displaying electron-donating, neutral, and withdrawing groups at the *para* position. Electron-donating groups were also tolerated at the *ortho* and *meta* positions. In addition, 2-thiophenylquinoline was an effective substrate. Other ketone electrophiles were also examined. Not surprisingly, methyl trifluoropyruvate was similarly effective to ethyl trifluoropyruvate, but a derivative with a longer fluorinated chain resulted in a lower yield. Additionally, ninhydrin coupled efficiently while *N*-methylisatin led to lower yield of the desired alcohol product.

The Kim laboratory has more recently shown the Rh(III)-catalyzed addition of indolines and indoles to a highly electron-deficient ketone (Scheme 53).¹³ While a majority of their study centered on C–H bond additions to aldehydes, (See Section 2.2.1, Scheme 6, and Section 2.2.2, Scheme 7) they also demonstrated that ethyl trifluoropyruvate was a competent electrophile. For *N*-pyrimidyl indoles, derivatives with halogens at the C4 and C5 positions were effective substrates, but methyl substitution at the C3 position resulted in only a moderate yield of the alcohol product. Moreover, pyrimidyl carbazole gave the alcohol in modest yield, and when pyrimidyl pyrrole was evaluated, it resulted in high yield of the over addition product. When *N*-pyrimidyl indoline was used in place of the indole, selective C–H functionalization at the C7 position occurred to provide the alcohol product in moderate yield.

Li and co-workers have published an innovative example of Rh(III)-catalyzed C–H bond additions to destabilized ketones, with their investigation of cyclopropenones **111** as electrophiles to give enones **112** by way of an addition and ring opening sequence (Scheme 54).⁶⁵ They identified that a 3:1 AgSbF₆ to Rh stoichiometry was crucial, as compared to the typical 2:1 ratio that is required for complete halide abstraction. Cyclopropenone additions using 2-arylpyridines displaying a variety of electron-neutral and poor substituents about the aryl ring furnished the desired enone products in high yield. Substitution around the pyridyl ring also gave high yields of the enone products, with electron-donating and withdrawing

groups both well tolerated. Benzoquinoline, 2-thiophenylpyridine and 2-thiophenylquinoline were also effective substrates. In addition, other directing groups such as pyrimidine, pyrazole, and *N*-methoxy oxime were all shown to be competent in the reaction. Beyond diphenylcyclopropanone, cyclopropanones bearing electron-rich aryl, heteroaryl, and alkyl groups at R² also coupled in high yield.

3.2. Intramolecular Addition of Aryl C–H Bonds to Ketones

3.2.1. Pd Catalysis—In 2006, Lu and co-workers reported a Pd-catalyzed approach to prepare benzofurans **114** from aryl boronic acids and *O*-3,5-dimethoxyphenyl cyanohydrins **113** (Scheme 55).⁶⁶ Of the solvents evaluated, nitromethane was optimal but water was also effective. Both Pd(I) and a Pd(II) catalyst were competent, although the Pd(II) catalyst system provided higher yields for most substrates. A number of aryl boronic acids were effective coupling partners, with a range of electron-rich to poor derivatives utilized to achieve the desired benzofuran products in good to high yield. Both unsubstituted (R = H) and substituted (R = Me) *O*-aryl cyanohydrins **113** were effective substrates for this transformation.

A potential mechanistic pathway was proposed by Lu (Scheme 56).⁶⁶ First the aryl boronic acid couples to the nitrile group via the Pd catalyst to create an aryl ketimine, which is hydrolyzed to the aryl ketone **115**. From this intermediate, two potential reaction pathways were proposed. In the first pathway, the Pd catalyst serves as a Lewis acid to activate the ketone as shown by intermediate **116**, leading to Friedel-Crafts cyclization to form alcohol intermediate **118**. Subsequent aromatization by loss of water provides the benzofuran product **114**. This first pathway does not involve C–H bond activation and rather constitutes a formal C–H bond addition to the ketone carbonyl. The second proposed pathway proceeds by coordination of Pd to the ketone followed by C–H activation of the aryl ring, leading to palladacycle **117**. Addition of the Pd–C bond to the ketone generates the alcohol intermediate **118**, which upon aromatization and loss of water furnishes the desired product **114**.

3.2.2. Ir Catalysis—The Shibata laboratory reported a formal Ir(I)-catalyzed intramolecular C–H bond addition to ketones **119** to generate functionalized benzofurans **120** (X = O) and indoles **120** (X = NH) (Scheme 57).⁶⁷ They found that the counter ion of the Ir(I) catalyst was crucial, with the highly non-coordinating tetrakis[3,5-bis(trifluorophenyl)]borate or BA[−]₄ anion proving to be optimal. Methyl, *tert*-butyl and phenyl ketones coupled efficiently, as did a cyclic ketone. Only electron-donating groups were shown to be tolerated on the aromatic ring of the ketone starting materials **119**. The R¹ position could be substituted with alkyl and electron-rich aromatic groups and also could be left unsubstituted. In addition to the methyl ketone directing group used for most of the examples, methyl ester and acetanilide directing group were also shown to be effective. Finally, the authors extended the reaction scope to include indole products **120**(X = NH). Shibata and coworkers subsequently published optimized reaction conditions using [Cp*IrCl₂]₂, AgSbF₆, Cu(OAc)₂ in DCE that allowed the reaction temperature to be reduced from 135 °C to ambient temperature.⁶⁸

The Shibata laboratory later applied their method to an efficient synthesis of the natural product *cis*-clavicipitic acid (Scheme 58).⁶⁹ Using an alkenyl ketone as the directing group, cyclization of **121** provided the desired indole product **122** in 79% yield, and from this key intermediate *cis*-clavicipitic acid was synthesized in only three steps.

In 2014, Yamamoto and co-workers reported an Ir(I)-catalyzed enantioselective synthesis of 3-substituted 3-hydroxy-2-oxindoles **124** (Scheme 59).⁷⁰ In their optimization experiments they identified that the BAr^F₄ counter ion was crucial and that 1,2-dimethoxyethane (DME) not only allowed for efficient reactivity but also greatly enhanced enantioselectivity relative to the other solvents investigated. Of the directing groups examined, the *N,N*-dimethyl amide directing group provided the highest yields and enantioselectivities. Substrate scope included a large variety of ketones **123** with electron-rich, neutral and poor aryl substituents at the R² position as well as alkyl groups. Substitution on the aromatic ring of the C-H bond substrate was less well studied, but an electron-poor substituent was shown to be compatible with this reaction. Yamamoto and coworkers also reported a follow-up study centered on the mechanism of this interesting reaction.⁷¹

3.3. Addition of Aldehyde C–H Bonds to Ketones

3.3.1. Rh Catalysis—In 2008, the Dong laboratory showcased an elegant approach for the catalytic asymmetric synthesis of lactones **127**, using Rh(I)-catalyzed C–H bond activation of an aldehyde followed by cyclization upon a ketone (Scheme 60).⁷² After screening various chiral phosphine ligands, they found that ligand **126** provided the highest enantioselectivity and yield. A variety of aryl ketones were effective substrates, with phenyl, naphthyl and 4-chlorophenyl ketones all providing the desired lactones in high yields and enantioselectivities. In addition, alkyl ketones were also efficient substrates, with linear, branched and benzyl ketones all furnishing the desired lactones in high yield and with exceptional enantioselectivities.

Following their seminal report on C–H activation of aldehydes via Rh(I) catalysis, Dong and coworkers thoroughly investigated the mechanistic details of their transformation (Scheme 61).⁷³ In their proposed mechanism, two molecules of the starting material **125** are bound to Rh(I) in resting state **128**. In order to undergo catalysis, one molecule of **125** dissociates to form a coordinatively unsaturated Rh(I) intermediate **129**. Computational modeling suggested that **129** then reorganizes to form square-planar complex **129'** with both carbonyl and ether coordination. Reversible C–H activation occurs to generate Rh(III) intermediate **130**, which undergoes rate-limiting insertion of the hydride to the ketone carbonyl, furnishing Rh(III) intermediate **131**. Reductive elimination then generates Rh(I) complex **132** with the product **127** still bound to the rhodium. Product release and reversible coordination of starting material **125**, restarts the catalytic cycle. A competitive side-reaction can also take place where the Rh(III)-hydride **130** undergoes decarbonylation to furnish Rh(III)-carbonyl complex **133**. Reductive elimination of the rhodium-carbonyl complex **133** generates the decarbonylated ketone byproduct **134** and the catalytically inactive Rh(I)-carbonyl complex **135**.

The Dong lab extended their aldehyde C–H activation approach to the Rh(I)-catalyzed asymmetric synthesis of phthalides **137** (Scheme 62).⁷⁴ Unlike their previous system, which incorporated an ether linkage for coordination to the Rh(I)-catalyst (Scheme 60), cyclization precursor **136** does not contain that extra coordinating group. To compensate, a coordinating counter ion was utilized to bind the rhodium. In their screen of silver counter anions, they found that nitrate had the optimal coordination strength to facilitate the desired reaction, while not being so strongly coordinating that undesired decarbonylation occurred. In their evaluation of substrate scope, they found that aromatic ketones with electron-donating and withdrawing substituents as well as alkyl ketones all cyclized to provide phthalides **137** in good yields and with high enantioselectivities. Moreover, they identified an intriguing counter anion effect. While the mesylate counter ion provided high yields for electron-rich and neutral aryl ketones, the triflate anion was most effective for electron-poor aryl ketones.

The Dong laboratory also demonstrated that they could apply their approach to the asymmetric synthesis of benzoazepinones **139** by incorporating an amine tether (Scheme 63).⁷⁵ While *N*-tosyl and *N*-mesyl tethers were not effective, the *N*-methyl tether enabled efficient cyclization presumably due to productive coordination to the Rh catalyst. A phenyl ketone as well as linear and branched alkyl ketones were effective substrates, giving the desired benzoazepinones **139** in high yield, albeit with variable levels of enantioselectivity. Interestingly, by increasing the length of the tether to form an 8-membered lactone, benzoxazecinones **141** could be obtained in high yields and enantioselectivities (Scheme 64).⁷⁵ Aryl ketones with electron-donating and halogen substituents were effective substrates as were naphthyl, methyl, and ethyl ketones.

Recently, Dong and co-workers extended their approach to the first example of enantioselective intermolecular hydroacylation with activated ketones **142** (Scheme 65).⁷⁶ After screening various phosphine ligands, they found that bisphosphine ligand **143** with bulky benzofuran groups and a ferrocene scaffold was optimal. Various *N,N*-disubstituted amides furnished the α -acyloxy amide products **144** in good yield and enantioselectivities, including amides with *N*-methyl, -phenyl, and -benzyl groups as well as a morpholine amide. Broad scope was also observed for the aromatic ring of ketoamide **142**, which upon substitution at the *ortho*, *meta*, or *para* positions, maintained good yields and selectivities. In addition, an isatin substrate provided the desired α -acyloxy amide product in moderate yield albeit with poor enantioselectivity. Upon investigating aldehyde scope, the authors established that a number of alkyl derivatives were competent C–H bond activation substrates, with linear, α - and β -branched derivatives all providing good to excellent yields and enantioselectivities. Achiral Rh(I) catalysts were later applied to the synthesis of racemic products to expand upon the types of α -ketoamides, isatins and α -branched aldehydes that could be employed.⁷⁷

3.3.2. Co Catalysis—Yoshikai and co-workers have synthesized phthalides **146** by intramolecular addition of the C–H bond of aldehydes across ketones using an in situ generated Co(I) catalyst system (Scheme 66),⁷⁸ in analogy to the Rh(I)-catalyzed transformation previously reported by Dong (see Section 3.3.1, Scheme 62). Yoshikai and co-workers found that to achieve the most efficient reaction, catalytic amounts of indium

powder was needed to reduce the Co(II)-precatalyst to the active Co(I) species. A range of electron-rich to neutral aromatic and alkyl ketones furnished the desired phthalides **146** in good to excellent yields and enantioselectivities. Electron-donating and withdrawing groups on the aryl ring of the ketone starting input were also tolerated.

4. ALDIMINES

α -Branched amines are prevalent in drugs and natural products, and therefore convergent and atom-economical methods for their synthesis are of enormous importance. Organometallic reagent addition to imines is one of the most important approaches for the convergent synthesis of α -branched amines, but this approach often suffers from the limited availability of diverse organometallic reagents and the poor functional group compatibility of many of these types of transformations. In addition, stoichiometric inorganic waste byproducts are inherently produced. Transition metal-catalyzed C–H bond additions into imines has the potential to overcome all of these limitations due to the theoretically enormous number of available C–H bond activation substrates, the high functional group compatibility of many transition metal-catalyzed processes, and the complete lack of undesired waste byproducts.

4.1. Pd Catalysis

Inspired by Pd-catalyzed reactions that proceed via the addition of enolates and enolate equivalents to imines,⁷⁹ in 2010 Huang and co-workers reported on the Pd-catalyzed addition of the acidic C(sp³)–H bond of 2-alkylazines **147** to aldimines **148** to provide α -branched amines **149** (Scheme 67).⁸⁰ They found that Pd(OAc)₂ and 1,10-phenanthroline was the most effective of the different Pd(II) catalyst and ligand combinations evaluated. C–H bond additions to a variety of aryl *N*-tosyl imines were evaluated. Imines substituted with electron-deficient groups on the aryl ring provided the branched amine products in high yield, while electron-poor substituents resulted in the addition products in a more modest yield. Moreover, the cinnamaldehyde derived *N*-tosyl imine also coupled efficiently. In addition to *N*-tosyl imines, more electrophilic *N*-nosyl imines also coupled in good yield. Beyond 2,6-lutidine, a number of nitrogen heterocycles were investigated as C–H bond coupling partners, including functionalized pyridines, quinolines, and quinoxalines.

4.2. Rh Catalysis

In 2011, the first Rh(III)-catalyzed arylation of imines via C–H bond functionalization was reported by our laboratory (Scheme 68).⁸¹ Nitrogen heterocycle directed C(sp²)–H bond additions to imines **151** showed very broad scope for both coupling partners with respect to both substitution patterns and functional group compatibility. Imines **151** with *N*-Boc, *N*-nosyl and *N*-tosyl substituents were all shown to be effective coupling partners, and given the popularity and ease of cleaving the Boc group, additions were most extensively evaluated with *N*-Boc imines. A large variety of *N*-Boc aryl imines with electron-poor to electron-rich substituents at the *ortho*, *meta*, and *para* positions provided the branched amine products in good to high yields. The transformation also showed very high functional group compatibility with halides, acidic functionality such as acetanilides, and electrophilic functionality such as aldehydes, ketones and esters, all being tolerated. Only the cyano group

resulted in a significant reduction in the reaction yield. Additions to *N*-Boc alkyl imines were problematic due to competitive imine self-condensation. However, C–H addition to *N*-tosyl pentaldimine, which incorporates the less activating tosyl *N*-substituent, proceeded in 72% yield. Electron-poor, neutral, and rich substituents on the aromatic ring of 2-arylpyridines provided the branched amine products in high yield, and when the substituent was placed on the *meta* position, high regioselectivity for C–H functionalization only at the distal *ortho*-site occurred.

Following our lab's initial investigation of imine hydroarylation via Rh(III) catalysis, a detailed mechanistic analysis was conducted and relevant catalytic intermediates were isolated and characterized by X-ray diffraction (Scheme 69).^{82,83} For detailed kinetic analysis, the isopropoxycarbonyl nitrogen substituent was employed to avoid any potential for competitive Boc deprotection under the slightly acidic reaction conditions. Importantly, Rh(III)-catalyzed 2-phenylpyridine C–H bond addition to the isopropoxycarbonyl protected aldimine used in this study provided nearly identical yield to that achieved previously with the analogous *N*-Boc aldimine. Abstraction of chloride ions on the rhodium dimer by the silver counteranion generates active cationic Rh(III) in situ. 2-Phenylpyridine C–H activation then proceeds by a redox neutral concerted metallation deprotonation pathway with a second equivalent of 2-phenylpyridine acting as base to provide the 18 valence-electron cyclometallated complex **153** containing a third equivalent of 2-phenylpyridine bound through the nitrogen.⁸⁴ Complex **153** was also prepared stoichiometrically and characterized by single crystal X-ray diffraction. Detailed kinetics experiments revealed that the reaction is first order in complex **153**. The reaction was also found to be inverse first order in 2-phenylpyridine, indicating substrate inhibition. To enter the catalytic cycle, resting state **153** must liberate the solely *N*-bound 2-phenylpyridine to generate a reactive 16 valence-electron rhodium species **155** that now contains an open coordination site for binding to the imine electrophile to form intermediate **156**. Subsequent insertion of the Rh–C bond into the imine C=N π -bond generates **157**, which was also characterized by X-ray crystallography. Another 2-phenylpyridine substrate can then bind to the open coordination site on the rhodium, leading to intermediate **158**. Presumably, the anionic amide ligand acts as the base for the next round of concerted-metallation deprotonation to regenerate the active rhodium complex **155** with simultaneous release the amine product **159**.

In the same year that our lab published on additions to imines, the Shi group also reported on Rh(III)-catalyzed additions of 2-arylpyridines **160** to *N*-sulfonyl aryl imines **161** (Scheme 70).⁸⁵ While a number of sulfonyl-protected imines coupled efficiently with 2-phenylpyridine, the tosyl protecting group was selected for its high reaction yield. An *N*-*tert*-butanesulfinyl imine was also evaluated, but was not sufficiently electrophilic for addition to occur. A variety of electron-rich to poor substituents at multiple sites about the 2-phenylpyridine were well tolerated and provided branched amines **162** in good to high yields. The one notable exception was 2-(2-methoxyphenyl)pyridine for which no imine addition was observed. Moreover, a variety of aryl *N*-tosyl imines were competent coupling partners in the transformation, with weakly donating functionalities and halogens displayed about the aryl ring. C–H bond addition to a 2-thiophenyl *N*-tosyl imine also proceeded smoothly. The Shi lab also carried out mechanistic studies for their Rh(III)-catalyzed C–H

bond addition reaction to *N*-sulfonyl aryl imines,⁸³ including the X-Ray structural characterization of analogous rhodacycle intermediates discussed previously (Scheme 69).

Our lab expanded on the scope of Rh(III)-catalyzed aromatic C(sp²)-H additions to imines with the report that amides, which are commonly found in drugs and natural products and are versatile functional group handles, could also be used as directing groups for this transformation (Scheme 71).⁸⁶ In an initial screen of silver halide abstractors, the extremely non-coordinating tetrakis(pentafluorophenyl)borate in place of the more commonly used hexafluoroantimonate counteranion led to a modest increase in yield. Of the tertiary benzamides **163** investigated, the pyrrolidine benzamide provided the highest yield, and secondary benzamides were not suitable substrates for the reaction. For this transformation, *N*-tosyl and nosyl imine substituents proved to be effective, but *N*-Boc imines coupled with very poor efficiency. A variety of *N*-tosyl aromatic imines were evaluated, and while derivatives with electron-poor substituents provided branched amine products in good yield, electron-donating substituents only resulted in moderate yield. Heteroaryl *N*-tosyl imines also coupled efficiently. In addition, substitution of the benzamide on the *meta* and *para* positions was well tolerated for both electron-rich and poor functionalities. To highlight the synthetic utility of tertiary pyrrolidine amide directing groups, representative benzamide products were efficiently converted to isoindolines and isoindolinones.

Shi and co-workers demonstrated the first Rh(III)-catalyzed alkenyl C(sp²)-H bond additions to imines (Scheme 72).¹² Here, they found that it was important to include pivalic acid as an additive and that *N*-tosyl imines coupled in higher yield than the corresponding *N*-Boc imines. A variety of cycloalkenylpyridines **166** with ring sizes ranging from cyclopentene to cycloheptene were efficient C-H bond partners, as was a cyclic alkene derivative with an oxygen incorporated into the ring system. A number of *N*-tosyl aryl imines bearing electron-poor and neutral substituents coupled with 2-cyclohexenylpyridine in moderate to good yield. An electron-rich *N*-tosyl 2-thiophenyl imine also was an effective substrate.

Another application of Rh(III)-catalyzed alkenyl C(sp²)-H bond addition to imines was developed in our lab for the cascade synthesis of *N*-tosyl pyrroles **171** (Scheme 73).⁵⁷ While α,β -unsaturated *O*-methyl oximes **169** did not couple with *N*-tosyl aryl imines, efficient reaction was observed with activated *N*-tosyl imino ester **170**. Alkenyl oximes with di- and trisubstitution, including fused cycloalkyl derivatives, provided *N*-tosyl pyrroles **171** in 62–78% yield.

The Rh(III)-catalyzed coupling of *N,N*-dimethylcarbamoyl protected indoles **172** with *N*-sulfonyl aldimines **173** was reported by Zhou, Li, and co-workers (Scheme 74).⁸⁷ The authors screened multiple indole nitrogen directing groups and found that the *N,N*-dimethylcarbamoyl group, which can be cleaved under basic conditions, provided the highest yield. A number of *N*-tosyl aryl imines coupled efficiently with a variety of electron-rich to poor substituents displayed around the aryl ring. Significantly, linear and branched alkyl imines also coupled, though in more moderate yield. Functionalized indoles were also examined with substituents having varied electronic character tolerated at the C3–C6 positions of the indole heterocycle.

The Bolm lab extended the scope of Rh(III)-catalyzed C–H bond additions to imines to access cyclic sulfamates **177** (Scheme 75).⁸⁸ A range of electron-rich and poor 2-arylpyridines were efficient coupling partners, and 2-(2-thiophenyl)pyridine and 2-(2-benzofuranyl)pyridine also coupled in good yield. *N*-Pyridyl and pyrimidyl indoles were also effective coupling partners. 2-Quinoline and benzo[*h*]quinoline were also evaluated as directing groups, but the heterocyclic products were obtained in more modest 56% and 27% yields, respectively. Aromatic substituents were placed on the cyclic imine without compromising reaction yield.

In 2014 our group reported the first examples of intermolecular asymmetric additions of non-acidic C–H bonds to imines with C–H bond additions to *N*-perfluorobutanesulfinyl aromatic aldimines **178** (Scheme 76).⁸⁹ The use of the highly activating *N*-perfluorobutanesulfinyl substituent^{90–95} proved to be essential for achieving acceptable reaction yields. The Rh(III)-catalyzed ortho C–H bond addition of benzamides to electron-deficient and neutral *N*-perfluorobutanesulfinyl aromatic aldimines provided branched amines in reasonable yields and with uniformly very high diastereoselectivity. Moreover, the *N*-perfluorobutanesulfinyl imino ester derived from ethyl glyoxylate served as a versatile substrate for the preparation of diverse *N*-sulfinyl protected arylglycine derivatives. High diastereoselectivities were observed for a range of pharmaceutically relevant directing groups, including pyrrolidine carboxamide, azo, sulfoximine, 1-pyrazole, and 1,2,3-triazole functionalities.⁹⁶ The utility of this method is enhanced by the straightforward cleavage of the perfluorobutanesulfinyl group from representative branched amine products with acid to provide the corresponding amine hydrochlorides in high yields without any loss in stereochemical purity.

Recently, Wang and co-workers developed a Rh(III)-catalyzed C–H bond addition of *N*-methoxy benzamides **181** to ketenimines **182** to provide 3-aminoisoindolin-1-ones **183** after cyclization (Scheme 77).⁹⁷ The authors found that it was important to include cesium trichloroacetate as an additive. Substitution around the benzamide ring was tolerated, with electron-rich substituents allowing for high yield and electron-poor motifs giving modest to good yields. Different aryl groups on the ketenimine nitrogen also furnished the desired 3-aminoisoindolin-1-ones in 46–89% yield. In addition, aminoisoindolinones were obtained in 37–40% yield when the aryl group on the ketenimine was substituted with either methoxy or chloro substituents at the *para* position. When *N*-methoxy-2-naphthamide was examined, regioisomers were obtained with a near 1:1 ratio.

Interestingly, switching to *N*-methoxy-1-naphthamide resulted in a different reaction pathway to give 3-(diarylmethylene)isoindolin-1-ones **186** (Scheme 78).⁹⁷ Here the amine intermediate formed from initial C–H bond addition acted as the nucleophile to cyclize upon the amide directing group. Both electron-deficient and electron-donating aryl groups on the ketenimine nitrogen resulted in high yields of 3-(diarylmethylene)isoindolin-1-ones, and electron-donating substituents on the aryl ketenimine were also tolerated. The authors found that *ortho* substituents on the aryl ring of *N*-methoxybenzamide were required for the reaction to proceed according to the pathway shown in Scheme 78. This class of products exhibited strong aggregation-induced emission (AIE) properties, with strong green-yellow

emissions in both nanoparticles and in solids. These AIE attributes could possibly be useful for optoelectronic devices or for biomedical imaging.

4.3. Co Catalysis

In 2012, Yoshikai and co-workers published the seminal report of first-row transition metal-catalyzed direct C–H bond additions to imines using low-valent cobalt catalysis (Scheme 79).^{98,99} Successful catalysis required catalytic CoBr₂ in conjunction with an NHC precursor along with the addition of stoichiometric *t*-BuCH₂MgBr. Unlike the earlier reports of redox-neutral Rh(III)-catalyzed C–H bond additions to imines, additions to Boc- and tosyl-protected imines did not occur under their low valent Co reaction conditions. Alkyl, alkoxy, dialkylamine and fluoro substituents were tolerated on the 2-arylpyridine, and additions to a series of *N*-*p*-methoxyphenyl aromatic aldimines proceeded smoothly with functionality tolerated at every position on the aromatic ring. In addition to the 2-pyridyl group, the 1-pyrazolyl directing group was also effective. An interesting reaction occurred when the *N*-*p*-methoxyphenyl aldimine was submitted to the reaction conditions without including a C–H bond functionalization substrate. Under these conditions, self-condensation of the *N*-*p*-methoxyphenyl aldimine gave an unstable isoindole intermediate, which could then be taken on to additional products.

In 2013, Kanai, Matsunaga, and co-workers disclosed the seminal report of Co(III)-catalyzed C–H functionalization via the addition of 2-phenylpyridine C–H bonds to *N*-sulfonyl protected aldimines **191** (Scheme 80).¹⁰⁰ Although several cationic Co(III) catalysts bearing different Cp-type ligands were investigated, the high-valent preformed cobalt catalyst [Cp*Co(C₆H₆)](PF₆)₂ bearing the archetypal Cp* ligand displayed the highest catalytic activity. Notably, this complex is stable to air and moisture and can be synthesized in gram quantities without the use of expensive or precious reagents from commercially available CoCl₂. The scope of Co(III)-catalyzed C–H bond additions were demonstrated for a variety of aryl and heteroaryl aldimines bearing both electron-withdrawing and electron-donating functionalities.

Following this study, the same group reported the Co(III)-catalyzed addition of 2-pyrimidylindoles **193** to *N*-sulfonyl protected imines **194** (Scheme 81).¹⁰¹ The addition of catalytic amounts of KOAc provided increased reaction yields, and a high turnover number of 1.8×10^2 was achieved using only 0.5 mol % of cationic Co(III) catalyst. In analogy to their earlier report, additions to aromatic and heteroaromatic imines proceeded smoothly providing products in 58–93% yield. Although the majority of substrate scope was demonstrated using *N*-2-thiophenylsulfonyl imines, C–H bond additions to both aryl and alkyl tosyl-protected aldimines were also shown to proceed in good yield.

5. CO₂

Carbon dioxide (CO₂) is the most earth abundant source of carbon in the atmosphere and consequently serves an inexhaustible and extremely low cost carbon resource. However, an inherent challenge for C–H functionalization of CO₂ is the thermodynamic stability of this fully oxidized C1 carbon source. To overcome this thermodynamic challenge a number of strategies have emerged for transition metal-catalyzed C–H bond additions to CO₂ to

directly access useful carboxylic acids. The general topic of CO₂ fixation, which includes C–H functionalization, has been extensively reviewed in the recent literature and therefore will not be covered here.^{102–110}

6. ISOCYANATES

Isocyanates are isoelectronic to carbon dioxide, and although not nearly as low in cost as carbon dioxide, have added value due the diversity of functionality that can be introduced via the nitrogen substituent. Catalytic C–H bond additions to isocyanates provides for a convergent and completely atom economical approach for the preparation of amides, which are the fundamental linkages in peptides and proteins and are commonly found in drugs and natural products. Moreover, amides serve as versatile precursors to many nitrogen heterocycles. It is therefore not surprising that catalytic amide synthesis by C–H bond additions to isocyanates are often coupled with in situ cyclization to give heterocyclic products. Finally, it is noteworthy that C–H bond additions to isocyanates relies on a different bond connection and inputs than much more routinely employed condensations between amines and carboxylic acid derivatives.

6.1. Rh Catalysis

In 1978, Hong, Yamazaki, Sonogashira, and Hagihara published the seminal report of transition metal-catalyzed direct C–H bond addition to isocyanates (Scheme 82).¹¹¹ In the presence of Rh₄(CO)₁₂, the direct C–H bond addition of benzene to phenyl isocyanate provided benzanilide in 41% yield. The authors report ca. 35–95 turnovers per Rh₄(CO)₁₂, noting that a series of aryl isocyanates such as *p*-tolyl, *p*-chlorophenyl, and α -naphthyl isocyanates reacted to furnish the corresponding benzamides, although additional details and yields were not provided.

In 2011, our laboratory published the seminal report of Rh(III)-catalyzed C–H bond additions to isocyanates to give amides **197** (Scheme 83).¹¹² Proof-of-principle for the insertion of C–H bonds across isocyanates to provide amides was initially established using the 2-pyridyl directing group, and additions to aromatic isocyanates were demonstrated in 72–85% yield. The practical utility this chemistry was demonstrated through the use of the *N*-acyl amino directing group to enable an efficient and atom-economic approach for the synthesis of *N*-acyl anthranilamides, which are present in drugs and clinical candidates and serve as intermediates to privileged heterocycles. A series of substituted anilides were found to be effective, and functionalization of both aryl and heteroaryl C–H bonds was also demonstrated. Furthermore, both aryl and alkyl isocyanates were efficient coupling partners, proving the corresponding *N*-acyl anthranilamides in good yield. The C–H amidation of enamides to provide enamine amides proceeded at room temperature, providing one of the first examples of Rh(III)-catalyzed alkenyl C–H functionalization. The coupling of a phenylalanine-derived isocyanate in 65% yield showcased the potential for incorporating chiral scaffolds into the amide products. In the absence of the Rh catalyst or in the presence of either Lewis acidic AgSbF₆ or Brønsted acids alone there was no reaction. This result suggests that isocyanate addition proceeds by a transition metal-catalyzed C–H functionalization. Moreover, the regioselectivity observed for aromatic C–H bond additions

to isocyanates is also consistent with a metal-catalyzed C–H activation pathway rather than an electrophilic aromatic substitution mechanism.

When alkenyl C–H amidation was performed at elevated temperatures, cascade intramolecular cyclodehydration of the initially formed enamine amides afforded pyrimidinones **199** (Scheme 84). This reaction was effectively carried out for substrates derived from both phenyl and sterically encumbered *tert*-butyl enamides in 96% and 92% yields, respectively.

In 2012, Shibata and co-workers published on additions of ferrocene C–H bonds to isocyanates via Rh(III) catalysis (Scheme 85).¹¹³ Evaluation of [Cp*IrCl₂]₂ in conjunction with AgSbF₆ halide abstractor provided no reaction, while several cationic Cp*Rh(III) catalysts showed activity with [Cp*Rh(OAc)₂(H₂O)] in the presence of HBF₄(OEt)₂ being most effective. Acidic work-up of crude reaction mixtures resulted in imine hydrolysis, providing 1,2-keto amide substituted ferrocenes **201**. C–H bond additions to both electron-rich and electron-poor aromatic isocyanates proceeded smoothly. Couplings of branched and linear isocyanates were also reported, although prolonged reaction times were required for hexyl and cyclohexyl derivatives. The construction of products displaying planar chirality was also achieved through the use of a commercially available chiral oxazolinyl ferrocene **202**. In all cases, products **203** were obtained as single diastereomers, and both aromatic and aliphatic amide moieties were effectively introduced with this chiral derivative. The authors postulated that the lower coordinating ability of the oxazolinyl directing group relative to the *N*-phenyl ketimine was responsible for decreased reactivity, and thus only moderate yields were observed for these substrates. The absolute stereochemistry was also rigorously determined to be the (*S*)-configuration by X-ray structural analysis.

In 2013, Zhou, Li, and co-workers reported the synthesis of 3-methyleneisindolin-1-ones **205** by Rh(III)-catalyzed C–H bond addition to isocyanates followed by an intramolecular cyclization/elimination cascade (Scheme 86).¹¹⁴ Several directing groups were investigated in the transformation. While weakly coordinating benzophenone gave no product, more strongly coordinating nitrogen-based directing groups were effective. Both *N*-phenyl and *N*-benzyl ketimines provided the desired 3-methyleneisindolin-1-ones in moderate yield; however, the corresponding *O*-methyl oxime was found to be optimal. Functionality about the aromatic ring was well tolerated with respect to the oxime coupling partner, and the reaction was not sensitive to sterics. α -Alkyl and aryl substituents at the R² position of acetophenone *O*-methyl oximes were competent in this cascade reaction, but the methylisindolin-1-one products were obtained with modest *E/Z* selectivities.

In 2013, the same group expanded the scope of this strategy to include Rh(III)-catalyzed alkenyl C–H bond additions to isocyanates followed by intramolecular cyclization to furnish 5-ylidenepyrrrol-2(5*H*)-ones **207** (Scheme 87).¹¹⁵ In analogy to their earlier report describing the synthesis of 3-methyleneisindolin-1-ones **205** (Scheme 86), good functional group tolerance was demonstrated. With respect to aromatic isocyanates, functionalities such as methoxy, fluoro, chloro, bromo, trifluoromethyl, and nitro groups, as well as an ethyl ester motif were introduced in 82–93% yield. Moreover, both linear and branched aliphatic isocyanates were coupled efficiently. A series of α,β -unsaturated *O*-methyl oximes **206** with

different substitution patterns, including cyclic derivatives, provided 5-ylidenepyrrol-2(5*H*)-ones **207** in good yield. Methyl substitution at the R¹ position of the *O*-methyl oxime led to a fully separable 1:3 mixture of *E/Z* isomers, and removal of functionality at R² provided a moderate 47% yield of a trisubstituted 5-ylidenepyrrol-2(5*H*)-one.

In 2014, Li and co-workers reported the Rh(III)-catalyzed aminocarbonylation of benzoic acids **208** with isocyanates followed by intramolecular cyclization to provide phthalimides **209** (Scheme 88).¹¹⁶ The reaction employs readily available inputs and proceeds with catalytic [Cp*RhCl₂]₂ and stoichiometric NaOAc in the absence of a silver halide abstracting agent. A variety of functionalized benzoic acids bearing both electron-donating and electron-withdrawing substituents were coupled efficiently, including diversifiable groups such as chloro and NHBoc. For *meta*-substituted benzoic acids, mixtures of regioisomers were obtained, although in all cases the major product of the reaction resulted from activation of the less sterically hindered *ortho* C–H bond. In general, benzoic acids bearing multiple electron-donating substituents provided higher yields than unsubstituted or monosubstituted derivatives. With respect to aromatic isocyanates, methoxy, methyl, and chloro functionalities were introduced in 72–91% yield. However, none of the desired phthalimide was obtained in the reaction of benzoic acid and 4-nitrophenyl isocyanate. Branched and linear alkyl isocyanates provided phthalimides albeit in lower 26–30% yields.

The following year, Li and co-workers reported on the synthesis of *N*-aryl benzamides **211** by the Rh(III)-catalyzed coupling of benzoic acids **210** and aromatic isocyanates followed by in situ decarboxylation (Scheme 89).¹¹⁷ Notably, this strategy demonstrates the synthetic utility of a removable carboxylic acid directing group that both initiates Rh(III)-catalyzed *ortho* C–H aminocarbonylation and subsequently undergoes decarboxylative cleavage. Out of a variety of alkali phosphonate salts that were examined, K₂HPO₄ was identified to be optimal, and in the absence of this additive none of the desired product was obtained. Moreover, the introduction of catalytic Cu₂O, which is known to promote decarboxylation reactions, improved the reaction yield. Although functionalities such as methyl, chloro, and methoxy were well tolerated at nearly all positions of the benzoic acid coupling partner, reaction of highly electron-deficient 2-nitrobenzoic acid provided none of the desired product. Among the benzoic acid derivatives that were examined, the highest yield of 81% was obtained for the decarboxylative coupling of 2,4-dimethylbenzoic acid with phenyl isocyanate. Given the superior reactivity of this substrate, the scope of the isocyanate coupling partner was then explored with 2,4-dimethylbenzoic acid, and a series of aromatic isocyanates bearing aliphatic and halogen functionalities were found to couple in 46–80% yield.

In 2015, Kim and co-workers reported the first examples of transition metal-catalyzed C–H bond additions to arylsulfonyl isocyanates to provide *N*-acylsulfonamides.¹¹⁸ Employing azobenzenes **212** as substrates for Rh(III)-catalyzed *ortho* C–H bond aminocarbonylation (Scheme 90), the reaction was shown to be applicable to a range of isocyanates including arylsulfonyl, aryl, and alkyl derivatives. A series of symmetrical azobenzenes were first evaluated for additions to arylsulfonyl isocyanates. For unsubstituted azobenzene, both *N*-tosyl and *N*-benzenesulfonyl amides were formed efficiently in 85% and 75% yields, respectively. Employing *N*-tosyl isocyanate, high functional group compatibility was

demonstrated for *para*-substituted symmetrical azobenzenes, providing the corresponding *N*-acylsulfonamides in 44–77% yield. For *meta*-substituted symmetrical azobenzenes, selective functionalization occurred at the less sterically hindered *ortho* C–H bond. While functionalities such as methoxy, methyl, and fluoro, chloro, and bromo were all tolerated, no product was observed when the azobenzene was substituted with electron-deficient acetyl group at the *meta*-position. Evaluation of unsymmetrical *para*-substituted azobenzenes revealed important information about the electronic factors that governed the regioselectivity of this reaction. For an unsymmetrical azobenzene containing an electron-donating methyl substituent, a 1:1 mixture of inseparable regioisomers was isolated in a 44% combined yield. In contrast, in the case of an unsymmetrical azobenzene bearing an electron-deficient CF₃ substituent, a 4:1 mixture of separable regioisomers was obtained in 76% overall yield, with functionalization favored on the more electron-rich aromatic ring.

Further demonstration of reaction scope was carried out with aromatic and alkyl isocyanates using a series of *meta*- and *para*-substituted azobenzenes (Scheme 90). The authors reported that while couplings to arylsulfonyl isocyanates provided exclusively the *E* isomers of the isolated products, additions to aromatic and alkyl isocyanates gave a mixture of *E/Z* isomers. Similar to other reports of Rh(III)-catalyzed C–H bond additions to isocyanates, high functional group compatibility was achieved, and products derived from aryl and alkyl isocyanates were obtained in 32–72% yield.

The same year Kim and co-workers published a related transformation describing the Rh(III)-catalyzed direct aminocarbonylation of indoles and pyrroles **214** with aryl and alkyl isocyanates (Scheme 91).¹¹⁹ Evaluation of several directing groups revealed that *N*-heterocycles were key to achieving the desired reactivity. While indoles bearing pivaloyl, benzoyl, and *N,N*-dimethylcarbamoyl directing groups failed to promote the desired C–H functionalization, both *N*-pyridyl and *N*-pyrimidyl indoles were effective coupling partners affording the corresponding aminocarbonylation products in 48% and 81% yields, respectively. Both electron-donating and electron-withdrawing functionalities were well tolerated, and substituents were effectively introduced at all positions of the indole ring. In addition to the functionalization of indoles, the Rh(III)-catalyzed C–H aminocarbonylation of a cyclohexanone-fused pyrrole proceeded in 45% yield. Pyrroles that were unsubstituted or contained only a C3 substituent coupled in high 91–94% yield; however, selective formation of the diamide occurred through over addition of the isocyanate. A variety of aromatic isocyanates were shown to couple efficiently, and with respect to alkyl isocyanates, linear and branched derivatives coupled with product yields ranging from 30 to 81%. In contrast to their report describing the functionalization of azobenzenes with arylsulfonyl isocyanates (Scheme 90),¹¹⁸ indole C–H bond addition to benzenesulfonyl isocyanate did not proceed under their reported conditions. The authors also demonstrated that the pyrimidyl directing group can be removed upon treatment with strong base at 100 °C. To explain the low conversion obtained for certain substrates, the authors conducted experiments to evaluate the reversibility of Rh(III)-catalyzed C–H aminocarbonylation with isocyanates. For example, the C2 amide **216** obtained by coupling indole with *p*-tolylisocyanate was re-subjected to the standard reaction conditions, and provided unsubstituted *N*-pyrimidylindole, **217**, with a C–H bond at C2 in 50% yield (Scheme 92).

In a concurrent report, Eycken and co-workers demonstrated a similar strategy for the C2 functionalization of indoles via Rh(III)-catalyzed C–H bond additions to isocyanates (Scheme 93).¹²⁰ In addition to the combination of [Cp*RhCl₂]₂/AgSbF₆ to provide a cationic Cp*Rh(III) catalyst in situ, NaOAc was found to be beneficial as an additive. A survey of several directing groups established that only the *N*-pyridyl and *N*-pyrimidyl directing groups promoted the desired indole C–H functionalization, with the latter providing a higher yield. Substrate scope was evaluated using a variety of substituted indoles and isocyanates. Functionalization about the indole ring was well tolerated, although a sterically hindered C3 methyl substituent resulted in only 35% yield. Pyrrole C–H bond addition to phenyl isocyanate was also evaluated and provided the desired amide in 71% yield. With respect to the isocyanate coupling partner, a series of aromatic derivatives bearing bistrifluoromethyl, methoxy, methyl, fluoro, acetyl, and chloro substituents provided the corresponding amides in 42–80% yield. Alkyl isocyanates were also well tolerated, and to highlight the ability to introduce chiral functionalities into products, isocyanates derived from L-phenylalanine and L-valine were coupled in 93% and 51% yields, respectively.

Recently, Yao, Lin, and co-workers reported the C7 functionalization of indole **218** using Rh(III) catalysis (Scheme 94).⁴⁴ The authors demonstrated that by installing a blocking group at the C2 position of an *N*-pyrimidyl indole, Rh(III)-catalyzed C–H bond addition to benzyl isocyanate is directed to the C7 position.

6.2. Ir Catalysis

In 2002, Murai and co-workers reported an Ir-catalyzed C–H bond addition to an isocyanate (Scheme 95).⁶ The reaction was an extension of their strategy for Ir-catalyzed coupling of *N*-methylimidazole and aldehydes in the presence of silane to provide silyl protected ethers (See section 2.3.1, Scheme 8). The conditions developed for aldehydes were directly applied to the coupling of *N*-methylimidazole and propyl isocyanate to provide the corresponding amide **220** in 55% yield. The authors proposed that the reaction may proceed via a silylated intermediate, although the isolated addition products **220** no longer incorporated the silyl moiety.

6.3. Re Catalysis

In 2006, Kuninobu, Takai, and co-workers reported the first example of Re-catalyzed addition of aromatic C–H bonds to isocyanates (Scheme 96).¹²¹ In addition to acting as a directing group for initial *ortho* C–H bond additions to isocyanates, the aldimine moiety served the auxiliary role of promoting intramolecular cyclization to furnish phthalimidines **222**. Although several Re and Mn complexes were evaluated as catalysts for this reaction, only ReBr(CO)₅ and [ReBr(CO)₃(thf)]₂ provided the desired reactivity. The latter was selected for substrate scope because it displayed higher catalytic activity under the reaction conditions. Aldimines containing electron-donating and electron-withdrawing functionalities at the *para*-position were well tolerated providing phthalimidines in 80–92% yield. On the other hand, aldimines substituted at the *ortho*-position furnished phthalimidines in lower 32–51% yield. While C–H additions to aromatic isocyanates were highly efficient, no reaction was observed for allyl or phenyl isothiocyanate. Both *N*-*tert*-hexyl and *N*-benzyl aldimines were effective directing groups, while *N*-phenyl and *N*-methoxy aldimines did not react.

In subsequent reports, Kuninobu and Takai expanded the scope of aldimine-directed Re-catalyzed C–H bond additions to isocyanates to include the functionalization of heteroaromatic C–H bonds (Scheme 97).^{122,123} In contrast to the functionalization of aromatic aldimines reported previously (Scheme 96), the vast majority of heteroaromatic aldimine C–H bond additions to isocyanates resulted in aminocarbonylation products **224** that did not undergo intramolecular cyclization in situ. While high yields of aminocarbonylated products with the *N*-*tert*-butyl aldimine intact could be observed by ¹H NMR, to facilitate isolation, an acidic work up to hydrolyze the imine was performed to obtain the corresponding aldehyde products **224**. Additions to both aryl and alkyl isocyanates proceeded smoothly, and selective C–H functionalization was achieved for a variety of heterocyclic aldimines, including for thiophene, furan, pyrrole, and indole derivatives.

Kuninobu and co-workers employed imidate directing groups for the synthesis of 3-imino-1-isoindolinones **226** via Re-catalyzed C–H aminocarbonylation with isocyanates followed by intramolecular cyclization (Scheme 98).¹²⁴ The substrate scope of this transformation was carried out with a series of functionalized imidates **225** and isocyanates. Aromatic isocyanates with electron-donating and electron-withdrawing substituents and alkyl isocyanates underwent the C–H addition/annulation cascade in high yields. A broad range of functionality was tolerated at the *para*-position of the aromatic imidates including: methoxy, bromo, trifluoromethyl, and cyano groups, in addition to a methyl ester group. In the case of a *meta*-methyl substituted aromatic imidate, a 63:37 regioisomeric mixture was obtained in 81% yield, with the major product arising from functionalization of the more sterically accessible C–H bond. An *ortho*-methyl substituted aromatic imidate was also evaluated, but provided the cascade product in a lower 36% yield. An *N*-butyl imidate coupled in good yield as did the functionalization of an alkenyl C–H bond to furnish the desired cyclized product in 72% yield. Further synthetic application of this Re-catalyzed C–H aminocarbonylation and cyclization cascade was demonstrated through the synthesis of polyimides, which display high utility in the fields of aerospace engineering and electronic materials. Proof-of-principle was initially carried out through dimerization reactions with diimides and diisocyanates. This protocol was then applied toward the first synthesis of polyimide derivatives bearing imino groups. Following the introduction of alkyl substituents on the *N*-aryl imidate, an alternating co-polymerization was achieved to provide a polyimide derivative in 53% yield that displayed high solubility in several common organic solvents.

In 2015, Wang and co-workers reported the Re-catalyzed C–H aminocarbonylation of azobenzenes **227** with isocyanates (Scheme 99).³³ Although carbonyl complexes of Re, Mn, and Ru catalysts previously employed for other C–H functionalization reactions displayed low reactivity, [Re₂(CO)₁₀] was highly effective. Furthermore, addition of catalytic NaOAc as additive provided a dramatic rate enhancement, furnishing *ortho*-azobenzamides **228** in good yields. Unsubstituted azobenzene was employed in the evaluation of substrate scope for the isocyanate coupling partner, and a variety of functionalized aryl and alkyl derivatives were introduced in 42–86% yields. Of the four potential C–H activation sites about unsubstituted azobenzene only monosubstituted amide products were obtained. The majority of the azobenzene substrate scope was evaluated with symmetric derivatives to avoid the

potential formation of regioisomeric mixtures. For *para*-substituted symmetrical azobenzenes a notable electronic effect on the reaction yield was observed such that electron-donating groups provided higher yields than electron-deficient functionalities. Sterically encumbered *ortho*-substituted symmetrical azobenzenes also reacted efficiently, and in the case of a *meta*-methyl substituted derivative, C–H aminocarbonylation of the less sterically hindered *ortho* C–H bond occurred in high regioselectivity. Unsymmetrical azobenzenes bearing 3,5-dimethylphenyl and 2,4,6-trimethylphenyl blocking groups were also employed to access the corresponding *ortho*-azobenzamides in 70% and 84% yields, respectively.

6.4. Ru Catalysis

In 2012, Cheng and co-workers demonstrated the first examples of Ru(II)-catalyzed C–H bond additions to isocyanates (Scheme 100).¹²⁵ With non-cationic [RuCl₂(*p*-cymene)]₂ in conjunction with catalytic NaOAc the direct *ortho* aminocarbonylation products **230** from 2-arylpyridines were obtained in 61–90% yield. For the isocyanate coupling partner, aromatic derivatives bearing a range of functionalities including methoxy, methyl, chloro, and bromo substituents were tolerated. Moreover, coupling of cyclohexyl isocyanate proceeded smoothly to furnish the corresponding amide in 72% yield. 2-Arylpyridines with both electron-donating and electron-withdrawing groups coupled in good yields. The 1-pyrazolyl directing group was also examined and provided the aminocarbonylation product in 79% yield.

Ackermann and co-workers reported the synthesis of cyclic imides **232** via Ru(II)-catalyzed C–H bond additions to isocyanates followed by intramolecular cyclization (Scheme 101).¹²⁶ Cationic Ru(II) was generated in situ from [RuCl₂(*p*-cymene)]₂/AgSbF₆ and pyrrolidine amide was employed as the directing group for this reaction. Pyrrolidine benzamides with halides and donating groups at the *para*-position provided phthalimides in 44–82% yield. In the case of *meta*-methyl substituted pyrrolidine benzamide, selective functionalization occurred at the less sterically hindered *ortho* C–H bond. Interestingly, introduction of fluorine at the *meta*-position of the aromatic ring resulted in C–H functionalization primarily at the more sterically hindered *ortho* C–H bond. Furthermore, a variety of aryl and alkyl isocyanates also coupled efficiently. To showcase the potential of this strategy to access biologically relevant phthalimides, a COX-2 enzyme inhibitor was directly accessed from the Ru(II) C–H bond addition/cyclization cascade. The scope of this transformation was extended to include the functionalization of an alkenyl C–H bond to provide a maleimide in 52% yield.

Notably, the functionalization of heteroaromatic thiophene and indole C–H bonds proceeded in the absence of intramolecular cyclization and furnished only the direct addition products **234** (Scheme 102).¹²⁶ This is analogous to the reactivity observed earlier for Re(I) catalysis, where the laboratory of Kuninobu and Takai demonstrated that arene C–H bond partners cyclized to provide phthalimidines **222**, while additions of heteroaromatic C–H bonds to isocyanates provided amides **224** without cyclization (See Section 6.3, Schemes 96–97).^{121–123} The authors also carried out selective reduction of either the secondary or tertiary amides present in the 1,2-diamide product obtained from this Ru(II) catalyzed reaction.

In 2015, Shi, Wei, and co-workers reported on the synthesis of phthalimides **236** via the Ru(II)-catalyzed addition of benzoic acid C–H bonds to isocyanates followed by intramolecular cyclization (Scheme 103).¹²⁷ The reaction was catalyzed by a cationic Ru catalyst prepared in situ from [RuCl₂(*p*-cymene)]₂ and AgOTf, and did not proceed without stoichiometric NaOAc. Moreover, the introduction of catalytic CuI greatly improved the reaction yield. Evaluation of substituted benzoic acids **235** revealed a strong electronic effect. While electron-donating functionalities were well tolerated, upon introduction of the electron-deficient NO₂ substituent, none of the desired phthalimide was obtained. *Meta*-toluic acid provided a single regioisomer with the reaction occurring exclusively at the less sterically hindered *ortho* C–H bond. In contrast, *meta*-alkoxy and *meta*-*N*-Boc-amino substituted benzoic acids provided a mixture of regioisomers resulting from reaction at both sites *ortho* to the carboxylic acid directing group. For the evaluation of isocyanate substrate scope, 3,4,5-trimethoxybenzoic acid was employed as the C–H bond partner for addition to a variety of aryl and alkyl isocyanates. For aromatic isocyanates, both electron-donating and electron-withdrawing substituents were well tolerated. Coupling of the alkyl isocyanates with *N*-butyl and *N*-2-chloroethyl substituents also occurred, albeit in lower yields.

6.5. Co Catalysis

In 2015, our laboratory published the first examples of Co(III)-catalyzed C–H bond additions to isocyanates (Scheme 104).¹²⁸ Using an air and moisture stable catalyst, this transformation could be performed on the benchtop and does not require the use of any precious metal additives either in the C–H functionalization reaction or in catalyst preparation.¹⁰⁰ Given that methods for C–H bond additions to isocyanates had previously been reported for several precious metal-based catalysts, inductively coupled plasma mass spectrometry (ICP-MS) analysis of the [Cp*Co(C₆H₆)](PF₆)₂ catalyst was performed to rigorously establish that less than one part per million of Re, Ru, Rh, Ir, and Pt and only one part per million of Pd were present. In addition to the Co(III) catalyst, KOAc as an additive greatly improved the reaction yield. The substrate scope was first evaluated with a series of isocyanates, and for aromatic derivatives, electron-rich, electron-neutral, and electron-deficient functionalities were all well tolerated. Linear and branched alkyl isocyanates also coupled efficiently, providing the corresponding amides in moderate to good yields. Substituents on the aromatic ring of 1-arylpyrazoles were next evaluated with methoxy, methyl, bromo, and acetyl substituted derivatives each providing the amide products in good yields. Several directing groups were also investigated in the transformation, and in addition to 1-pyrazolyl directing group, other *N*-heterocyclic directing groups including 2-pyridyl and 2-pyrimidyl functionalities effectively directed Co(III)-catalyzed C–H bond additions to isocyanates. Moreover, the 2-pyrimidyl group was successfully applied to heteroaromatic indole functionalization. Although our group had previously shown that acetanilides were effective substrates for Rh(III)-catalyzed aminocarbonylation with isocyanates (See Section 6.1, Scheme 83),¹¹² this substrate proved ineffective for Co(III)-catalyzed C–H aminocarbonylation due to the basic KOAc additive that resulted in competitive *N*-aminocarbonylation rather than the desired C–H functionalization pathway.

In a concurrent report, Ackermann and co-workers described a similar strategy for Co(III)-catalyzed C–H aminocarbonylation with isocyanates (Scheme 105).¹²⁹ To generate cationic

Cp*Co(III) in situ the authors employed a [Cp*Co(CO)I₂]/AgSbF₆ catalyst combination, and the reaction did not proceed in the absence of catalytic AgOPiv as an additive. Substrate scope was first evaluated with a series of functionalized pyrazoles, demonstrating that the reaction was tolerant of diverse functionality such as chloro, bromo, ester and ketone substituents. High regioselectivity was observed for a *meta*-methyl substituted 1-arylpyrazole, which exclusively underwent functionalization at the less sterically hindered *ortho* C–H bond. For the isocyanate coupling partner, a series of aromatic derivatives were employed to access an array of functionalized amides **240** containing both electron-donating and electron-withdrawing groups. Reaction of 1-alkenylpyrazoles **241** was also shown to provide the thermodynamically less stable (*Z*)-olefins **242** in 53–63% yield (Scheme 106). In analogy to an earlier report of C–H aminocarbonylation with acyl azides employing a Rh(III) catalyst system,¹³⁰ the use of acyl azides to generate isocyanates in situ through a Curtius rearrangement was also demonstrated.

6.6. Mn Catalysis

In 2015, Ackermann and co-workers reported the first examples of earth abundant Mn-catalyzed aminocarbonylation by C–H bond additions to isocyanates (Scheme 107).¹³¹ Both [Mn₂(CO)₁₀] and [MnBr(CO)₅] were effective catalysts, although the latter displayed slightly higher reactivity and was selected for the evaluation of substrate scope. C–H bond additions to functionalized aromatic and aliphatic isocyanates provided amidated indoles in 60–99% yield. Several indoles substituted with electronic-donating and deficient groups were also shown to couple in good yield. Moreover, pyrroles were also shown to be competent coupling partners.

7. CO

Transition metal-catalyzed carbonylation using carbon monoxide (CO) as a simple carbon (C1) feedstock is a powerful and versatile process with important synthetic utility. The activation of CO has significant industrial applications, many of which rely on the steam and heat driven conversion of coal or natural gas (CH₄) into synthesis gas, a mixture of CO/H₂, which can then be taken on to higher carbon fuels and commodity chemicals.¹³² Among the most notable of these processes includes: (1) the Fischer-Tropsch reaction that converts a mixture of hydrogen and carbon monoxide (syngas) into longer chain hydrocarbons, (2) the Monsanto and Cativa processes that produce acetic acid via the carbonylation of methanol using Rh- and Ir-based catalyst systems, respectively, and (3) the water-gas shift reaction that drives the conversion of CO and H₂O into useful H₂ with CO₂ as a byproduct. In recent years, a number of strategies for transition metal-catalyzed C–H bond carbonylation have emerged that allow for the synthesis of a broad variety of synthetically useful carbonyl derivatives including acids, esters, amides, and heterocycles. The vast majority of these transformations employ Pd catalysts, although a number of other metals such as Ru, Rh, and Co have been shown to catalyze C–H carbonylation reactions. In addition, a range of diverse directing groups have been employed, including nitrogen heterocycles, amides, carboxylic acids, amines, and hydroxyl groups. The topic of C–H carbonylation reactions has been reported extensively in recent reviews and therefore will not be covered here.^{133–142}

8. ISOCYANIDES

Isocyanides are isoelectronic with carbon monoxide and enable the introduction of diverse functionality via the nitrogen substituent. Catalytic C–H bond additions to isocyanides are analogous to additions to isocyanates in that they have typically been employed for the preparation of amides, often with in situ cyclization to nitrogen heterocycles. However, for C–H bond additions to isocyanides to provide products in the desired amide oxidation state, a stoichiometric terminal oxidant such as oxygen, Cu(OAc)₂, or TBHP must be added.

8.1. Ru Catalysis

Jones and co-workers published one of the first reports of C–H bond additions to isocyanides in 1986 (Scheme 108).^{143,144} They found that stoichiometric reaction of a Ru(II)-complex with isocyanide **245** resulted in the formation of indole **246** in near quantitative yield. The authors proposed that the reaction proceeds through C(sp³)–H activation of one of the methyl groups on isocyanide **245** followed by intramolecular addition of the Ru–C bond to the isocyanide.

8.2. Pd Catalysis

In 2011, Zhu and co-workers published the Pd-catalyzed amidine-directed C–H bond addition of **247** to isocyanides to give 4-amino-2-substituted quinazolines **248** (Scheme 109).¹⁴⁵ Upon screening different bases and oxidants, they found that stoichiometric amounts of Cs₂CO₃ as base and O₂ as oxidant gave the highest yields. Electron-donating groups, as well as fluoro and chloro groups, were well tolerated at the *ortho*, *meta*, and *para* positions of the aromatic ring of amidine coupling partners to provide 4-amino-2-substituted quinazolines in good to excellent yields. Electron-rich and neutral aryl functionality at the R² position of amidines also provided the desired products in good yield. Alkyl R² substituents were examined, with a *tert*-butyl group leading to a high yield and the cyclohexyl group resulting in a more moderate yield of the quinazoline products. The scope of the isocyanide component was also investigated. Alkyl isocyanides such as *tert*-butyl, isopropyl, and cyclohexyl isocyanide produced the desired 4-amino-2-substituted quinazolines in good to high yield. A number of aryl isocyanides were effective inputs, including quite sterically hindered derivatives such as 2,6-dimethylphenyl and 2-*tert*-butylphenyl isocyanides.

The following year, Zhu and co-workers extended their isocyanide methodology to include the Pd(II)-catalyzed C–H bond additions of indoles **249** to isocyanides (Scheme 110).¹⁴⁶ Indole-3-carboxamides **250** could be obtained in good yields by using Cu(OAc)₂ as an oxidant in conjunction with TFA and water as additives, which were crucial for preventing the formation of undesired side products. Functionalized indoles with electron-withdrawing or donating groups placed about the aromatic ring were effective coupling partners. Methyl and phenyl groups at the C2 position of the indole also provided the desired products in good yields. While free N–H indoles were primarily used in this methodology, *N*-substituted indoles bearing *N*-benzyl, -ethyl, or -allyl substituents were also effective substrates. In addition, different types of isocyanides were evaluated. While *tert*-butyl isocyanide was utilized for most of the coupling reactions, other alkyl isocyanides such as isopropyl,

cyclohexyl, and 1-adamantyl isocyanides were all successful coupling partners. A sterically hindered aromatic isocyanide, 2,6-dimethylphenyl isocyanide, also gave the desired product in 58% yield.

8.3. Rh Catalysis

The first Rh(III)-catalyzed C–H bond addition to isocyanides was reported by Falck and coworkers.¹⁴⁷ Here they found that reaction of *N*-tosyl benzamides **251** with isocyanides in the presence of a Rh(III) catalyst and a Cu(II)-oxidant generated 3-(imino)isoindolinones **252** (Scheme 111). Both electron-donating and withdrawing groups at the *para* position of the aryl ring of the *N*-tosyl benzamide were examined, with donating groups providing higher yields of 3-(imino)isoindolinone products than withdrawing substituents. In all cases, the product was obtained with moderate selectivity for the *E* imine isomer. Introduction of a fluoro group at the *ortho* position of the *N*-tosyl benzamides provided the product in moderate yield and with slight *Z* selectivity. While 2,6-dimethylphenyl isocyanide was used in a majority of the reported reactions, other isocyanates also served as effective inputs. When benzyl, pentyl, or cyclohexyl isocyanides were used, only moderate yields of products were obtained, but with complete *Z* selectivity. Modest *Z* selectivity was also observed for 2-Cl-6-MeC₆H₃-isocyanide.

8.4. Cu Catalysis

The Miura laboratory reported the Cu-catalyzed synthesis of 3-(imino)isoindolinones **254** from *N*-benzoyl 8-aminoquinolines **253** and isocyanides (Scheme 112).¹⁴⁸ Use of *N*-benzoyl 8-aminoquinolines **253** was necessary because it allowed for bidentate coordination to the Cu catalyst. Although only sterically hindered isocyanides such as *tert*-butyl, 1-adamantyl and 2,6-dimethylphenyl isocyanides were effective coupling partners, a variety of *N*-benzoyl 8-aminoquinolines **253** proved to be suitable substrates. Electron-rich to poor substituents were tolerated at the *para* position of the *N*-benzoyl 8-aminoquinoline coupling partner. An *ortho*-methyl derivative also coupled to give the desired product in 52% yield. A number different groups were evaluated at the *meta* position leading to good yields of the desired products, albeit often with low to moderate regioselectivity. Other types of C–H bond partners were also tested. Heterocyclic scaffolds for the aminoquinoline amide substrates gave variable yields with *N*-methyl pyrrole, pyridine and benzo thiophene derivatives coupling in modest yields and an *N*-methyl indole derivative coupling in 60% yield.

8.5. Ni Catalysis

Directly analogous to Miura's Cu-catalyzed approach (see section 8.4), Lei and co-workers reported a Ni(II) catalyst system for the preparation of 3-(imino)isoindolinones **254** from *N*-benzoyl 8-aminoquinolines **253** (Scheme 113).¹⁴⁹ Di-*tert*-butyl peroxide in trifluoromethylbenzene was identified as an optimal oxidant/solvent combination. A variety of *N*-benzoyl 8-aminoquinolines **253** were effective substrates. While *tert*-butyl isocyanide was used for the majority of the reactions, sterically hindered 2,6-dimethylphenyl isocyanide was also an effective coupling partner.

9. NITRILES

Nitriles are very stable and a large variety of different derivatives are commercially available. These compounds therefore represent useful starting materials for direct C–H bond addition reactions, and as described in the following sections, formal C–H bond additions to nitriles have provided efficient access to diverse ketone products.

9.1. Pd Catalysis

The first transition metal-catalyzed examples of formal C–H bond additions to nitriles was reported by the Larock laboratory in 2004 (Scheme 114).¹⁵⁰ They found that DMSO was an essential additive, which they presumed played a role by coordinating to Pd(II) and/or facilitating oxidation of any undesired Pd(0) that might have formed during the reaction. In their investigation of arene scope, they found that toluene and methoxybenzene coupled efficiently, with subsequent hydrolysis of the ketimine products furnishing the desired ketones in good yield but as a mixture of regioisomers due to the lack of electronic or steric bias of these monosubstituted arenes. Consistent with Friedel-Crafts type reactions, more highly substituted arenes with appropriately placed methyl, *tert*-butyl, methoxy, or hydroxyl groups led to single regioisomers in good to high yields. Interestingly, the mesityl arene exclusively furnished the ketimine product presumably due to the severe steric hindrance about the imine, which prevented hydrolysis. When looking at the nitrile scope, they found that unsubstituted, *para*-methoxy and *para*-bromo benzonitriles as well as acetonitrile all coupled efficiently. In addition, arenes tethered to nitrile groups that had either alkyl or ether linkages underwent intramolecular coupling to give cyclic ketone products in good yield.

Shortly after Larock's initial report, his laboratory published a follow-up study (Scheme 115).¹⁵¹ Benzene and a number of different multisubstituted arenes were coupled with benzonitriles to produce ketones in moderate to high yield with substitution patterns and scope that parallel Friedel-Crafts type reactivity. While, *para*-substituted phenol derivatives coupled in more modest yield, high regioselectivity was observed. Multi-substituted arenes coupled with unsubstituted or halogenated benzonitriles to generate the corresponding ketimines in high yield. When the ketimines produced were 2,6-disubstituted on one of the aromatic rings, imine hydrolysis was not observed presumably due to steric hindrance. Additional arene tethered nitriles were also evaluated, and lead to cyclic ketones albeit in relatively low yields.

In 2013, two labs independently published on the Pd(II)-catalyzed acylation of indoles via formal C–H bond additions with nitriles.^{152,153} The Wang laboratory investigated the addition of free N–H indoles **257** with aryl and alkyl nitriles through the use of Pd(OAc)₂ (Scheme 116).¹⁵² They found that use of stoichiometric D-(+)-camphorsulfonic acid (D-CSA) and water in conjunction with *N*-methylacetamide as solvent gave the C3-acylated indole products **258** in the highest yields. A number of aryl nitriles bearing electron-donating or electron-withdrawing groups were effective substrates. Substituents were well tolerated at the *meta* and *para* positions, but when placed at the *ortho* position, the desired product was not obtained. Alkyl nitriles such as acetonitrile or 4-phenylbutanenitrile were also effective substrates. Substitution on the indole coupling partner was also evaluated, with methyl, methoxy and fluoro groups well tolerated at the C4 through the C7 positions.

Methyl and phenyl substitution on the C2 position was also tolerated and furnished the desired acylated indoles in high yield.

Song and co-workers concurrently developed a Pd(II)-catalyzed method for producing acylated indoles **260** using both substituted and free N–H indoles (Scheme 117).¹⁵³ They found that use of acetic acid and water as additives with 1,4-dioxane as solvent gave the best yields of acylated indoles **260**. Evaluating the indole substrate scope, they found that electron-donating groups and halogen functionalities were well tolerated at the C4–C7 positions of the indole ring. Moreover, a good yield of the ketone product was obtained when nitrogen was substituted in place of carbon at the C7 position. The reaction also proceeded in high yield when a methyl group was placed at the C2 position. Indoles substituted on the nitrogen atom with methyl, phenyl, *p*-ClC₆H₄, and *p*-Me₂NC₆H₄ groups were effective substrates in addition to free (N–H) indoles. A variety of different nitriles were shown to be efficient coupling partners. Aryl nitriles ranging from electron-rich to poor character provided ketones in good yields, and functionalities were well tolerated at the *ortho*, *meta*, and *para* positions. In addition, heteroaryl nitriles such as pyridyl, furanyl, thiophenyl, pyrrole, and *N*-Me indole derivatives all coupled to give the desired products in good yield. Alkyl nitriles such as acetonitrile, propionitrile, and benzyl cyanide also were efficient coupling partners.

Using similar conditions to those developed for the functionalization of indoles (Scheme 117), Wang and co-workers also reported on the C2-site selective coupling of thiophenes **261** with nitriles (Scheme 118).^{154,152} A variety of C2-substituted thiophenes **261** coupled in good yields and with complete regioselectivity, including derivatives with methyl, phenyl and 2-thiophenyl groups. However, 2-methoxythiophene and 2-iodothiophene provided the ketone products in only modest yield. The thiophene with C3 methyl substitution led to a 4:1 regioisomer ratio, with C2 functionalization favored over the C5 position due to sterics. An array of aryl nitriles were effective coupling partners, with both electron-donating and withdrawing substituents well tolerated at the *meta* and *para* positions. 2-Thiophenyl and benzyl nitrile as well as acetonitrile were also efficient coupling partners.

9.2. Mn Catalysis

At the same time that Wang and co-workers published on Mn(I)-catalyzed additions to aldehydes using stoichiometric zinc additives (See Section 2.6.2, Scheme 49), they also demonstrated that their method could be applied to additions to nitriles (Scheme 119).⁶² A number of different nitriles were coupled with 2-phenylpyridine to give ketones **264** after aqueous acidic workup. Both electron-rich and electron-poor aryl nitriles were effective coupling partners. Moreover, different heteroaryl and alkyl nitriles coupled in good yields. A variety of substituents on 2-phenylpyridine were tolerated. In addition, 2-pyridyl substituted thiophenes, naphthalene, and cyclopentene provided the desired ketones in moderate to good yield. Other heterocycle directing groups were also shown to be effective, namely quinoline, pyrimidine and pyrazole.

10. ADDITIONS TO C=C π -BONDS FOLLOWED BY CYCLIZATION UPON POLARIZED π -BOND DIRECTING GROUP

Directing groups for transition metal-catalyzed C–H functionalization inherently interact with the catalyst via heteroatom coordination, and it is therefore not surprising that a variety of different types of polarized π -bonds serve as effective directing groups. Polarized π -bond directed C–H bond activation followed by C=C π -bond insertion typically results in a seven-membered metalacycle **265** that can then collapse by addition of the carbon metal bond to the polarized π -bond directing group to give a five-membered ring product **266** (Scheme 120). Although less common, the structure/connectivity of some polarized π -bond directing groups results in an eight-membered metalacycle upon C=C π -bond insertion. Subsequent addition of the carbon metal bond to the polarized π -bond directing group then gives a six-membered ring product.

A large variety of the different polarized π -bond directing groups have been employed in this type of reaction sequence, including imines, *N*-aryl nitrones, ketones, *N*-acyl amino groups, carboxylic acid derivatives and ureas. Moreover this reaction sequence has been implemented with many different types of C=C π -bonds, including alkynes, enones and enoates, allenes, dienes, and allylic alcohols. As noted in the following sections, after the initial reaction sequence, additional transformation to give more stable products often occur in situ such as tautomerizations, elimination reactions and cyclizations. Finally, a number of the reviewed transformations result in the generation of new stereocenters often with high diastereoselectivity and in some cases with the use of chiral catalysts very high enantioselectivity.

10.1 Imine Directing Group

10.1.1. Alkynes

10.1.1.1. Re Catalysis: The first example of an intramolecular addition to a polarized π -bond directing group via an alkenyl metal-intermediate was reported by Takai, Kuninobu, and co-workers (Scheme 121).^{121,155} Re(I)-catalyzed imine-directed C–H bond addition to an alkyne was followed by insertion into the imine. Double-bond isomerization of the initially formed Re-bound cyclic allylic amine then provided indene **268**. A variety of electron-rich *para*-substituted aryl imines were effective coupling partners, with an electron-poor trifluoromethyl substituent leading to a low yield of the indene product. *Ortho*-substitution was not well tolerated, with the methyl substituent resulting in a moderate yield of product. In addition, the aryl imine substituted with the *ortho*-methoxy group did not provide any product. Both symmetrical and unsymmetrical internal alkynes were evaluated, with sterics playing a key role in determining regioselectivity. Interestingly, *N*-*tert*-butyl imine and *N*-phenyl imine, gave opposite regioselectivities when coupled with 1-phenylpropyne.

Very recently Wang and co-workers expanded this reaction to include free N–H ketimines **269** (Scheme 122).¹⁵⁶ A variety of substituted aryl ketimines were effective substrates, and while the majority of examples employed symmetrical diaryl internal alkynes, some

examples of unsymmetrical internal alkynes with aryl and alkyl substituents were shown to couple with high regioselectivity.

10.1.1.2. Ru Catalysis: The Li laboratory reported that Ru(II)-catalysis could be applied to the synthesis of amine-functionalized indenenes **272** from *N*-sulfonyl aromatic aldimines **271** (Scheme 123).¹⁵⁷ A variety of aryl imines were utilized as C–H bond substrates, with substitutions tolerated at the *ortho*, *meta*, and *para* positions of the aryl ring. Symmetrical diaryl and dialkyl internal alkynes were effective substrates. Unsymmetrical internal alkynes coupled efficiently, but in general gave low to moderate regioselectivity. The terminal alkyne phenylacetylene also coupled in 70% yield to give a single regioisomer.

In a study conducted by Zhao and co-workers, amino indenenes **275** were prepared from free N–H aryl ketimines **273** using a Ru-catalyst along with NHC ligand **274** (Scheme 124).¹⁵⁸ High yields of the indene products were obtained when the aryl rings of the ketimine were substituted, including with halogens or the electron-withdrawing CF₃ group. Notably, when substituents were placed on only one aryl ring low regioselectivity was observed. A ketimine bearing an aryl and a butyl group also coupled in high yield. A number of symmetrical internal alkynes were effective substrates, and a range of unsymmetrical internal alkynes were shown to couple efficiently and with high regioselectivity.

The Cheng laboratory investigated the synthesis of amino indenenes **277** using *N*-sulfonyl aldimine starting materials **276** and found that a copper additive was crucial for their transformation (Scheme 125).¹⁵⁹ A variety of aryl aldimines were shown to be effective coupling partners, primarily with symmetrical diaryl internal alkynes. Unsymmetrical internal alkynes were also evaluated and were shown to couple with moderate to high regioselectivity.

10.1.1.3. Rh Catalysis: Zhao and co-workers reported the Rh(I)-catalyzed coupling of free N–H aryl ketimines **278** with alkynes to generate amino indene products **279** (Scheme 126).¹⁶⁰ Symmetrical internal alkynes were predominantly explored and furnished indenenes in high yields. A couple of unsymmetrical internal alkynes were also shown to undergo the transformation in high yield and regioselectivity. Substituents on the aryl rings of the ketimine were well tolerated, and resulted in good to high yields of the desired products. However, in most cases low regioselectivity was observed. An aryl butyl ketimine also coupled in high yield.

In 2011, the Cramer laboratory designed the first catalytic enantioselective addition of free N–H ketimines to alkynes to generate chiral amino indene products **282** (Scheme 127).¹⁶¹ In their evaluation of chiral phosphine ligands, they found that ligand **281** not only allowed for efficient coupling, but also provided the desired amino indene with high enantioselectivity. Diaryl ketimines were most extensively used, though an alkyl-aryl ketimine was also shown to be an effective coupling partner in the transformation. Electron-neutral and electron-poor aryl ketimines furnished the desired indenenes in good yield and high enantioselectivity. Investigation of the alkyne substrate scope showed that internal alkynes with specific heteroatom substitution patterns were necessary for the transformation to proceed in good yield. Symmetrical internal alkynes were highly efficient substrates and furnished the

desired products in 62–90% yield and with high enantioselectivity. Unsymmetrical internal alkynes were well tolerated in the reaction and provided good yields and enantioselectivities for the desired products, albeit with low regioselectivity for many of the substrates.

Li and co-workers found that Rh(III) catalysis could be used to carry out cascade alkyne addition/cyclization reactions using starting material **283** with an azomethine ylide as the directing group (Scheme 128).¹⁶² A range of electron-donating and electron-withdrawing moieties on the aryl azomethine ylides were well tolerated in the reaction, generating the desired indene products **284** in good to high yield. A range of symmetric and unsymmetrical internal alkynes were evaluated and gave the desired products in good yield and with high regioselectivity.

Li and co-workers also used another imine surrogate, an aryl nitron, to generate indenone products **286** (Scheme 129).¹⁶³ Here the hydroxyl amine intermediate obtained upon cyclization loses water to generate an imino indene that upon hydrolysis furnishes indenone **286**. A wealth of electron-rich and electron-poor aryl nitrones were effective substrates in the transformation. Symmetrical diaryl or diheteroaryl alkynes were efficient coupling partners, with a couple of unsymmetrical internal alkynes also showing good reactivity to provide single regioisomers.

The Li laboratory published another variant of this Rh(III)-catalyzed annulation reaction for the conversion of *O*-methyl oximes **287** to amino indenones **288** (Scheme 130).¹⁶⁴ Here the use of electron-deficient alkynes was crucial for achieving good yields, and reactions proceeded with high regioselectivity to give the regioisomer shown. A variety of substituents were also tolerated on the aryl ring of the *O*-methoxy oxime.

Deng and co-workers reported that cyclic ketimines **289** undergo Rh(III)-catalyzed C–H annulation with alkynes to give spirocyclic benzosultams **290** (Scheme 131).¹⁶⁵ An array of electron-rich to electron-poor substituents were tolerated on the aryl ring that undergoes C–H activation, generating the desired sultam products **290** in high yield. The aryl ring embedded within the cyclic ketimine also tolerated alkyl and halogen functionality, and a cyclic imine lacking the aryl ring also provided the spirocyclic product in moderate yield. A range of symmetrical diaryl and dialkyl internal alkynes were found to couple effectively in the transformation. A couple of unsymmetrical internal alkynes were also evaluated, and gave the desired sultams in high yield but with low regioselectivity.

Following this report, Dong and co-workers employed similar conditions except that an aldehyde and Boc-anhydride electrophile were added (Scheme 132).¹⁶⁶ Under these conditions, the initial spirocyclic intermediate presumably underwent Rh(III)-catalyzed sulfonamide-directed addition to the aldehyde electrophile followed by cyclization to give **292**. The use of Boc-anhydride was found to be crucial, which the authors presume helps generate a more efficient leaving group from the alcohol intermediate obtained upon aldehyde addition. A range of aryl aldehydes coupled in high yield and diastereoselectivity. Heteroaryl and alkyl aldehydes as well as glyoxalate esters provided the expected products but in a more modest yield. Different substituted ketimines also coupled with good to high

yields. Mainly symmetrical aryl alkynes were investigated, with unsymmetrical alkynes showing either low regioselectivity or modest product yields.

10.1.1.4. Co Catalysis: Another study on the use of cyclic ketimine C–H bond partners was later performed by Wang and co-workers using Co(III) catalysis (Scheme 133).¹⁶⁷ A range of electron-rich to electron-poor substituents were tolerated on both aryl rings of cyclic ketimine **293**. Symmetrical diaryl internal alkynes were primarily employed with one example of an unsymmetrical internal alkyne, phenylpropyne, giving the benzosultam product **294** in high yield but with 3:1 regioselectivity. The terminal alkyne TMS-acetylene was also evaluated but gave the product in poor yield.

10.1.2. Enoates and Enones

10.1.2.1. Re Catalysis: In 2006, Kuninobu and Takai reported that enoate instead of alkyne electrophiles could be employed in these cascade reactions (Scheme 134).¹⁶⁸ An imine generated in situ from ketone **295** and *p*-anisidine directs Re(I)-catalyzed conjugate addition to the enoate. Cyclization of the resulting enolate upon the imine directing group is followed by elimination of *p*-anisidine to provide indene **296**. Ethyl and methyl enoates were shown to be effective electrophiles, while the corresponding phenyl enoate provided only a modest yield. Aryl ketones bearing methyl, pentyl, and phenyl groups were efficient coupling partners, giving the desired indenenes in high yield. *Para*-substitution with electron-donating and electron-withdrawing groups on the aryl ring of the ketone was well tolerated. However, *ortho*-substitution resulted in low yields of the indene products. *Meta*-substituted as well as disubstituted and naphthyl ketones all performed well in the transformation, but coupled with only moderate regiocontrol.

Takai and Kuninobu later found that preformed imines **297** were also effective for the preparation of indenenes **298** (Scheme 135).¹⁶⁹ Both enoate and enone coupling partners provided the indene products **298** in good yield. Interestingly, while *N*-phenyl imines coupled efficiently to give the desired indene products, *N*-benzyl imines gave high yields of the aminoindane intermediates instead of the expected indenenes, highlighting that benzylamine eliminates more slowly than aniline under the reaction conditions.

10.1.2.2. Mn Catalysis: Ackermann and co-workers later reported the Mn-catalyzed synthesis of aminoindanes **300** from *N*-aryl ketimines **299** and enoate coupling partners (Scheme 136).¹⁷⁰ High *cis*-diastereoselectivity was observed with respect to the amine and ester substituents on the indane products **300**.

Although acrylates were primarily explored, a crotonate was also evaluated and coupled efficiently to give the desired indane product in good yield and with high diastereoselectivity. Indane products were also obtained in good to excellent yields for imines **299** incorporating a variety of R¹ substituents and both aryl and alkyl R² substituents.

10.1.3. Allenes

10.1.3.1. Rh Catalysis: In 2010, the Cramer laboratory demonstrated that allene electrophiles **302** could also be used in cascade addition/cyclization reactions with imine

directing groups (Scheme 137).¹⁷¹ Aminoindanes **304** were obtained from free N–H aryl ketimines **301** in good yields and with high diastereoselectivity using a Rh(I) catalyst and phosphine ligand **303**. Both diaryl and aryl alkyl ketimines were effective substrates as were both electron-rich and electron-poor derivatives. A range of alkyl and electron-deficient allenes were effective coupling partners, furnishing the desired products in good to high yields. Allenes tethered to ester functionality featured additional reactivity. Upon formation of the aminoindane, the newly formed amine cyclized upon the ester to form five- and six-membered lactams in good to high yield. Unsymmetrical diaryl ketimines typically provided the aminoindane products with low to moderate regioselectivity.

10.1.3.2. Re Catalysis: In the same year, Takai and Kuninobu published on the Re-catalyzed addition of ketimines **305** to allenes **306** to generate aminoindanes **307** (Scheme 138).¹⁷² A variety of substituted aryl ketimines coupled to give aminoindanes in good yield and diastereoselectivity as did *N*-phenyl and *N*-benzyl ketimines. Both phenyl and alkyl allenes were effective substrates, and a disubstituted allene also provided the aminoindane product in good yield albeit with low *E/Z* selectivity.

10.1.4. Dienes by Ir Catalysis—The Nishimura laboratory reported that dienes **309** can also be used as electrophiles to obtain aminoindanes **310** in highly diastereoselective fashion (Scheme 139).¹⁷³ An Ir(I)-catalyst along with catalytic amounts of DABCO was found to be most effective for this transformation. The ketimine C–H bond partner accommodated both electron-donating and electron-withdrawing groups at the *para*-R¹ position. *Meta*-substituents were also well tolerated with the desired products obtained in high yields and with good regioselectivity. The ring bearing the imine was found to be an effective directing group with or without a fused aryl ring. A range of dienes bearing alkyl, alkenyl or aryl substituents coupled in high yield and with high regio- and diastereoselectivity. Dienes bearing electron-withdrawing groups such as esters, amides and sulfones were also shown to be effective substrates in the transformation.

The Nishimura laboratory subsequently published expanded scope both for the C–H bond coupling partner **311** and the diene electrophile **312** (Scheme 140).¹⁷⁴ Instead of using solely cyclic ketimines, they found that an array of *N*-sulfonyl ketimines provided the desired aminoindane products **313** in good yield and with high diastereoselectivity. In addition to alkyl substituted and electron-deficient dienes, cyclohexenyl dienes were also employed and gave good yields of the aminoindane products.

10.2. *N*-Aryl Nitron Directing Group

10.2.1. Alkynes by Rh Catalysis—*N*-arylnitrones also direct C–H bond addition to a π -bond followed by cyclization upon the directing group.¹⁷⁵ In 2015, Cheng and co-workers reported that a Rh(III)-catalyst with pivalic acid as an additive provides indolines **315** from *N*-arylnitrones **314** and alkyne coupling partners (Scheme 141). The authors note that the Rh(III)-catalyst not only facilitates addition to the alkyne and cyclization upon the C=N π -bond, it also catalyzes O-atom transfer to generate the indoline products **315** with a ketone carbonyl appended to the five-membered ring. In their exploration of scope, the aryl ring distal to the nitrogen on the *N*-arylnitron was first evaluated. A wealth of electron-rich aryl

systems in addition to a few electron-neutral and electron-poor systems furnished the desired indolines **315** in good to high yields and modest to high diastereoselectivities. On the *N*-aryl ring, in addition to phenyl, naphthyl and *para*-chlorophenyl were also evaluated and coupled in good to high yield, but in low to modest dr. Symmetrical diaryl alkynes were effective coupling partners, in particular those bearing halogens and weakly electron-donating groups. In contrast, 1,2-di(thiophen-2-yl)ethyne coupled in only moderate yield and with poor dr. A couple of unsymmetrical internal alkynes coupled with high regioselectivity but in only moderate yield.

10.3. Ketone Directing Group

10.3.1. Alkynes

10.3.1.1. Rh Catalysis: In 2011, the Glorius laboratory reported the Rh(III)-catalyzed cascade alkyne addition/cyclization reaction using ketones as directing groups to give two types of products, indenols **317** (Scheme 142) or indenenes **319** (Scheme 143) and **321** (Scheme 144) depending on starting ketone structure and reaction conditions.¹⁷⁶ Aryl ketones **316** bearing sterically bulky alkyl or aryl R² substituents generated indenols **317** in good to high yield (Scheme 142). As might be expected, low regioselectivity was observed for 4-bromobenzophenone where the two aryl rings have similar electronic and steric properties. In contrast, for unsymmetrical alkyl phenyl internal alkynes high regioselectivity was observed.

Indenenes **319** preferentially formed over indenols for ketones **318** (R² = H or Me) due to the relative ease of dehydration after cyclization (Scheme 143). To effect the dehydration a higher reaction temperature of 140°C was also employed. When ethyl phenyl ketone is used, indene was formed in good yield, but with low *E/Z* selectivity. Benzophenones **320** could also be used to generate indene products **321**, but only when certain alkynes bearing an abstractable proton were used (Scheme 144). While the desired products were isolated in good to high yield, the *E/Z* selectivity was low for alkynes bearing an ethyl group.

Following the publication by Glorius, Cheng and co-workers reported on an expanded scope for the formation of indenols **323** from ketones **322** and alkyne coupling partners (Scheme 145).¹⁷⁷ Substituted acetophenones were predominantly used, and both symmetrical and unsymmetrical internal alkynes provided the desired indenol products in good to excellent yields. Other ketone examples such as benzophenone, ethyl phenyl ketone, and isopropyl phenyl ketone also coupled effectively to give the desired indenols. When using unsymmetrical alkynes, the addition was found to be governed by sterics and proceeded in good yields and with high regioselectivity. In this study, where a protic rather than an aprotic reaction solvent was employed, dehydration did not compete as often as occurred in the related study carried out by Glorius (Schemes 142 to 144).

10.3.1.2. Ru Catalysis: In addition to Rh(III), the Jeganmohan laboratory also demonstrated that Ru(II) catalysis can also be applied to the synthesis of indenols **325** from ketones **324** and alkynes (Scheme 146).¹⁷⁸ Though diphenyl acetylene was the most commonly used alkyne, unsymmetrical internal alkynes bearing alkyl, silyl, and 1-cyclohexenyl substituents also provided indenols in good yields and with high regioselectivity. A number of

acetophenone derivatives and the related 3-acetylidole were effective coupling partners in the transformation. Other ketones such as benzophenone and isopropyl phenyl ketone also coupled in high yield. The authors also noted that by increasing the amount of AgSbF₆ used in the reaction, dehydration to indene products occurred.

10.3.2. Enones by Rh Catalysis—In 2013, Li and co-workers reported the Rh(III)-catalyzed coupling of ketones **326** with enones to form indenenes **327** (Scheme 147).¹⁷⁹ Ketone directed concerted-metallation-deprotonation followed by addition to the enone presumably generates a Rh(III)-enolate, which then cyclizes upon the ketone carbonyl. Subsequent dehydration of the resulting alcohol then gives indene **327**. Of the various additives screened, the authors identified that AgOAc was the most effective. A variety of electron-rich acetophenone derivatives provided the desired indene products in good to high yields. However, many *meta*-substituted derivatives provided mixtures of regioisomeric products. Aryl ethyl ketones and 1-tetralone were also competent ketone inputs. Although ethyl vinyl ketone was the predominant enone coupling partner used in this study, in a single example, methyl vinyl ketone was also shown to be effective.

10.3.3. Allylic Alcohols by Rh Catalysis—Analogous to Li's work on the synthesis of indenenes **327** from enones (Section 10.3.2, Scheme 147), Glorius and co-workers showed that allylic alcohols could also be used with an in situ oxidant to generate indene products **329** (Scheme 148).¹⁸⁰ A diverse array of acetophenone derivatives **328** were shown to couple effectively with allylic alcohols to form the desired indenenes **329**. Additionally, a number of diaryl and aryl alkyl ketones were competent inputs. Both 2-propenol and 3-buten-2-ol were effective in the coupling reaction, though 2-propenol was used for the majority of the indene products that were generated.

10.4. *N*-Acylamino Directing Group

10.4.1. Alkynes by Co Catalysis—While ketone and imine directing groups have been the most extensively studied for C–H bond additions and cyclizations upon the directing group, methods have also recently been developed that rely on cyclization upon the amide directing group present in anilides.^{181,182} Li published the first method in this area with the Co(III)-catalyzed synthesis of quinolines **331** from anilides **330** and alkyne coupling partners (Scheme 149).¹⁸¹ Here the Co(III)-intermediate formed upon addition of the alkyne presumably cyclizes upon the amide carbonyl to generate a hemiaminal intermediate, which then undergoes aromatization with loss of water to generate quinoline **331**. While catalytic amounts of the silver additive were found to facilitate the reaction, stoichiometric quantities provided the highest yields. A number of electron-donating and withdrawing substituents were well tolerated on the aryl ring of the acetanilide, leading to the desired quinolines **331** in good to high yield. Notably, *meta*-fluoro substitution resulted in a high yield but with low regioselectivity. In addition to acetanilide, *N*-propanoyl, *N*-butanoyl, *N*-isobutyryl and *N*-benzoyl anilides were all competent substrates. However, *N*-trifluoroacetyl and *N*-pivaloyl anilides were not effective substrates. While diphenyl acetylene was used to prepare a majority of the quinoline products, other symmetrical diaryl and heteroaryl internal alkynes were also shown to furnish quinolines in high yields. Unsymmetrical internal alkynes were

also efficient coupling partners and provided quinolines with moderate to good levels of regiocontrol.

Shortly after, Glorius and co-workers also reported on the Co(III)-catalyzed synthesis of quinolines **331** from anilides **330** and alkyne coupling partners (Scheme 150).¹⁸² A range of *para*-functionalized acetanilides were shown to be effective substrates, while a *meta*-fluoro substituent provided only modest regioselectivity. Anilides with *N*-propanoyl and *N*-formyl groups were also reported to give the desired products in good yield. A range of diaryl alkynes were shown to be effective coupling partners, and 1-phenylpropyne and 1-phenylbutyne furnished the desired quinolines in good yields and with high regioselectivities.

Zhang and co-workers also reported the synthesis of quinolines **331** from anilides **330** and alkynes (Scheme 151).¹⁸³ In their study, addition of catalytic amounts of zinc triflate and lithium carbonate were found to be beneficial for obtaining quinolines **331** in good yield. A variety of acetanilides were effective coupling partners. In addition, ethyl and phenyl substitution at the R² position were tolerated. While symmetrical aryl alkynes were primarily employed, unsymmetrical aryl alkyl alkynes also coupled efficiently and with good regioselectivity. In addition, the symmetrical dialkyl alkyne, 4-octyne, provided the quinoline product in 43% yield.

10.5. Carboxylic Acid Derivatives as Directing Groups

10.5.1. Alkynes

10.5.1.1. Rh Catalysis: Several carboxylic acid derivatives have been reported as effective directing groups for C–H bond addition/cyclization reactions, with the first example provided by Shi and co-workers in 2012 (Scheme 152).¹⁸⁴ After an extensive screen of different amides, the activated *N*-acyl oxazolidinone was found to be the most effective for directing Rh(III)-catalyzed concerted-metallation-deprotonation and addition to an alkyne while simultaneously providing the acidic oxazolidinone leaving group upon cyclization. A number of substituted *N*-benzoyl oxazolidinones **332** were investigated. A range of electron-donating and electron-withdrawing substituents were well tolerated at the *para*-position. While *meta*-, *ortho*-, and di-substitution were also tolerated, a low yield was observed for the *N*-benzoyl oxazolidinone with an *ortho*-methyl substituent. A variety of symmetrical diaryl internal alkynes also provided the desired indenones in high yield, with the exception of 1,2-di-*o*-tolylethyne which coupled in <10% yield. A number of unsymmetrical alkyl phenyl internal alkynes were also tested, and provided the desired products in good yield but generally with moderate regioselectivity. Interestingly, the dialkyl internal alkyne 4-octyne was a very poor coupling partner and provided the desired indenone in <10% yield.

10.5.1.2. Co Catalysis: In addition to imides, esters have also recently emerged as useful directing groups for addition/cyclization reactions.^{185,186} In early 2016, Zhang and co-workers reported the Co(III)-catalyzed coupling of methyl benzoates **334** with alkynes to form indenones **335** (Scheme 153).¹⁸⁵ For this transformation, catalytic amounts of potassium acetate were found to provide indenones **335** in highest yields. Methyl, ethyl and isopropyl benzoate all were converted to the indenone product, but the methyl ester provided

the highest yield. An array of benzoates with electron-rich to electron-poor *para*-substituents gave variable yields of indenone products **335**. While *meta*- and *ortho*-substituents were generally tolerated, dimethyl *o*-phthalate coupled in only 22% yield. A variety of symmetrical diaryl alkynes provided indenones in good to high yield, and 1-phenylpropyne coupled in a more modest 44% yield and with low 2:1 regioselectivity.

Very shortly after Zhang's study, Li and Yu published a similar approach to the formation of indenones **335** via a Co(III)-catalyzed addition of benzoate esters **334** and alkynes (Scheme 154).¹⁸⁶ After screening a range of different benzoate esters, the ethyl ester was determined to provide the highest yield under their reaction conditions, which included an excess of Zn(OAc)₂ as an additive. A variety of substituted ethyl benzoates were explored, with electron-donating and halogen motifs well tolerated at the *ortho*, *meta* and *para* positions. Symmetrical internal alkynes were exclusively studied and in general provided the desired indenones in good yields.

10.6. Urea Directing Group

10.6.1. Alkynes

10.6.1.1. Co Catalysis: Ureas also can serve as directing groups for concerted-metallation-deprotonation and alkyne addition, which followed by cyclization upon the carbonyl can extrude an amine leaving group. Kanai and Matsunaga first reported on the Co(III)-catalyzed synthesis of pyrroloindolones **337** from *N*-carbamoyl indoles **336** and alkynes (Scheme 155).¹⁸⁷ A variety of substituents, including electron-donating and electron-withdrawing groups were tolerated on the aryl ring of the indole. Symmetrical diaryl and unsymmetrical aryl alkyl alkynes coupled in high yield, and for the unsymmetrical derivatives, the reactions proceeded with high regioselectivity. However, for dialkyl and terminal alkynes the desired pyrroloindolone products were not detected.

10.6.1.2. Rh Catalysis: Loh and co-workers subsequently reported on this strategy employing a morpholine urea directing group for the related Rh(III)-catalyzed synthesis of pyrroloquinolinones **339** from *N*-carbamoyl indolines **338** (Scheme 156).¹⁸⁸ Substitution was tolerated on both the five- and six-membered rings of the indoline. In addition, a number of symmetrical internal alkynes were highly efficient coupling partners, with both diaryl and dialkyl systems furnishing the desired pyrroloquinolinones in good to high yields. A variety of unsymmetrical alkynes bearing alkyl and/or aryl systems generated the desired products in only moderate to good yield, but with high regioselectivity.

11. THREE-COMPONENT ADDITIONS TO C=C π -BONDS AND POLARIZED π -BONDS

As reviewed above in Section 10, a number of studies have been published on C–H bond additions to C=C π -bonds followed by cyclization upon the polarized π -bond directing group to create two C–C bonds within a newly formed ring. In contrast, very few examples have been reported for C–H additions to C=C π -bonds followed by sequential addition to a polarized π -bond that is not a directing group. This approach provides an exciting opportunity for accessing complex structures from simple precursors particularly when one

considers the number and diversity of possible permutations for combining C=C π -bond inputs such as alkenes, alkynes, dienes and allenes with polarized π -bond electrophiles such as carbonyls, imines, isocyanates, isocyanides and nitriles.^{189,190} The initial reports reviewed here provide key proof-of-principle examples, which demonstrated that this approach can be achieved with high levels of regiocontrol, and when stereocenters are introduced, also diastereocontrol.

11.1. Rh Catalysis

The authors of this review first reported this approach for the Rh(III)-catalyzed C–H bond addition to enone tethered aldehydes **341** to give diastereomerically pure cyclic β -hydroxy ketones **342** (Scheme 157).¹⁸⁹ Here, the C–H bond partner first undergoes conjugate addition to the enone, presumably generating a Rh(III)-enolate. Intramolecular addition of the Rh(III)-enolate intermediate upon the aldehyde generates the cyclic β -hydroxy ketone **342**. The desired products formed in good yield in a number of solvents, but acetic acid was found to give the highest yield for the most starting inputs. Aldehydes tethered to aromatic ketones with electron-rich and electron-poor character afforded the desired cyclic β -hydroxy ketones in high yield. An aldehyde tethered methyl ketone also led to the desired product in 61% yield. Moreover, incorporating *N*-tosyl and ether linkages resulted in pharmaceutically relevant pyran and piperidine heterocycles in moderate and high yields respectively. An aromatic tether also provided the corresponding cyclic β -hydroxy ketone in good yield. For the C–H bond coupling partner, electron-donating and withdrawing substituents on the aryl ring of 2-phenylpyridine gave the desired products in high yield, and an alkenyl variant was also effective providing the corresponding product in 82% yield. In addition to the pyridyl directing group, pyrazole and pyrimidine heterocycles were also effective, and pyrimidine was shown to facilitate C–H functionalization of both phenyl and indole C–H bonds. The more synthetically versatile *N*-methoxy benzamide and *O*-methyl oxime directing groups also provided the desired cyclic β -hydroxy ketones in good to modest yield.

To characterize the Rh(III)-enolate that was postulated to serve as an intermediate in this transformation, model enone substrate **343** was treated with 2-phenylpyridine and stoichiometric cationic Cp*Rh(III) to provide a near quantitative yield of the Rh(III)-enolate **344** after only 30 min at ambient temperature (Scheme 158). The X-ray structure showed a clear η^3 -bound enolate and thus a coordinatively saturated Rh(III) complex.

This C–H bond enone addition/aldehyde cyclization cascade reaction was then extended a three-component reaction with separate enone and aldehyde components (Scheme 159). Using phenyl vinyl ketone **343** as the enone coupling partner and ethyl glyoxylate as an activated aldehyde partner, the three-component products **346** were obtained in moderate to good yields albeit with low diastereoselectivity for 2-pyridyl, 1-pyrazole and secondary and tertiary amide directing groups. The *N*-tosyl imine derived from ethyl glyoxylate was also an effective coupling partner, generating the desired β -amino ketone in high yield, but again with only modest diastereoselectivity. Due to the poor stability of this *N*-tosyl imino ester in acetic acid, 1,2-dichloroethane (DCE) was instead used as solvent.

11.2. Co Catalysis

We found that Co(III)-catalyzed three component additions of C–H bond substrates, enones, and aldehydes proceeded with much broader enone and aldehyde scope than was achieved with Rh(III)-catalysis (Scheme 160).¹⁹⁰ Moreover, the reactions proceeded with high diastereoselectivity. Air-stable $[\text{Cp}^*\text{Co}(\text{C}_6\text{H}_6)][\text{B}(\text{C}_6\text{F}_5)_4]_2$ ⁵⁴ in combination with lithium acetate provided the highest yield and diastereoselectivity. A variety of enones **348** were effective coupling partners, including phenyl vinyl ketone, ethyl vinyl ketone and methyl vinyl ketone. A very broad range of aldehydes provided the desired products with good yields and high diastereoselectivity, including a variety of aryl aldehydes bearing electron-donating to electron-withdrawing groups, heteroaryl aldehydes, linear and α - and β -branched alkyl aldehydes, and an alkenyl aldehyde. Alkenyl C–H bonds were also found to be effective in the transformation, leading to the desired β -hydroxy ketone in high yield and good diastereoselectivity. Additionally, *N*-pyridylisoquinolinone was also an effective C–H bond coupling partner.

Mechanistic experiments defined key features of the reaction (Scheme 161). When simple conjugate addition product **350** was submitted to the reaction conditions in the presence of benzaldehyde, near-quantitative recovery of **350** was observed with no formation of the three-component product **352** (Scheme 161a). Moreover, pyrazole **353** was reacted with enone **343** and benzaldehyde in the presence of conjugate addition product **350** (Scheme 161b). The only three-component product formed was product **354** from pyrazole **353**, which was observed along with recovered conjugate addition product **350**, both in high yields. The results of these two experiments clearly illustrates that aldehyde addition solely proceeds via attack from a nucleophilic Co(III)-enolate that is generated in situ from C–H activation and enone addition. When the three-component product **352** was subjected to the reaction conditions complete recovery of the three-component addition product **352** was observed without any degradation of the diastereomeric purity indicating that a retro-aldol type pathway does not occur (Scheme 161c).

In the proposed mechanism, formation of cobaltacycle **355** is followed by conjugate addition to the enone coupling partner **348** to provide the racemic (*E*)-Co(III)-enolate **356** (Scheme 162). The cobalt enolate **356** then undergoes diastereoselective addition to the aldehyde to generate cobalt alkoxide **357**. Proto-demetalation of cobalt alkoxide **357** yields the desired alcohol **349** and regenerates the cationic Co(III)-catalyst.

The three-component coupling of *N*-*tert*-butanesulfinyl imines **358** bearing electron-withdrawing CF_3 or CO_2Et groups was also demonstrated (Scheme 163). The β -amino ester products **359** were obtained in good yield and with high diastereoselectivity, showcasing both the first asymmetric $\text{Cp}^*\text{Co(III)}$ transformation and the first additions to *N*-*tert*-butanesulfinyl imines via transition metal-catalyzed C–H functionalization.

12. MISCELLANEOUS

12.1. Additions using DMF as Carbon Source

12.1.1. Ni Catalysis—In 2015, Ge and co-workers reported on chelation-assisted oxidative C(sp²)-H bond carbonylation of amides **360** using *N,N*-dimethylformamide (DMF) as the carbonyl source to prepare phthalimides **361** (Scheme 164).¹⁹¹ This reaction employs bimetallic Ni/Cu synergistic catalysis with atmospheric O₂ as the terminal oxidant. The Ni catalyst is responsible for C-H activation while the Cu catalyst promotes in situ generation of an iminium ion derived from DMF. The reaction tolerated a variety of functional groups including methoxy, methyl, halogen, trifluoromethyl, nitro, and cyano groups. For *meta*-substituted amides high regioselectivity for the functionalization of the less sterically encumbered *ortho* C-H bond was observed. The authors also demonstrated that treatment of an imide product with ammonia in methanol at room temperature resulted in ammonia displacement of the amino quinoline directing group to provide an N-H phthalimide in good yield.

With slight modification of reaction conditions, the Ni/Cu synergistic catalyst system was also applicable to the functionalization of C(sp³)-H bonds (Scheme 165).¹⁹¹ High selectivity toward the functionalization of β -methyl C-H bonds over γ - and δ -methyl bonds was observed, suggesting that a five-membered metalacycle is favored over six- and seven-membered congeners. Furthermore, the reaction was highly selective for methyl C(sp³)-H functionalization over benzyl C(sp³)-H or phenyl C(sp²)-H bonds. The authors note that both a quaternary α -carbon and a β -methyl group are required for this reaction.

12.1.2. Pd Catalysis—Following this report, Das and co-workers published a similar strategy for the synthesis of pyrido-fused quinazolinone **365** and phenanthridinone **367** products using DMF as the carbon source for C(sp²)-H carbonylation using a Pd/Ag synergistic catalyst system and with atmospheric O₂ as the terminal oxidant (Scheme 166).¹⁹² In analogy to the work of Ge and coworkers (See Section 12.1.1, Schemes 164–165), control experiments demonstrated that the carbon of the carbonyl group was derived from DMF.¹⁹¹ Notably, the Ni/Cu catalyst system developed by Ge and co-workers also promoted the desired reactivity, but a lower yield was obtained.

12.2. Additions to Carbodiimides by Re Catalysis

In 2016, Kuninobu and co-workers published the seminal examples of transition metal-catalyzed C-H bond additions to carbodiimides (Scheme 167).¹⁹³ Using a Re₂(CO)₁₀ catalyst, imidate directed C-H bond addition to carbodiimides **369** followed by intramolecular cyclization provided a novel strategy for the synthesis of 1,3-diiminoisoindolines **370**. When an aromatic imidate with a phenyl substituent on the directing group nitrogen was employed for C-H bond addition to *N,N'*-diisopropylcarbodiimide, the desired 1,3-diiminoisoindoline was obtained in 85% yield. Further improvement in reaction yield was achieved through the use of an *N*-octyl aromatic imidate, which provided near quantitative yield under identical conditions. A broad range of aromatic and heteroaromatic imidates were tolerated, and for *para*-substituted derivatives both electron-donating and electron-withdrawing substituents were introduced in 96–99%

yield. When a *meta*-substituted aromatic imide was employed, a mixture of regioisomers was obtained, with the major product derived from C–H functionalization of the more sterically accessible *ortho* C–H bond. C–H bond additions to a range of carbodiimide coupling partners, was reported and both branched and linear alkyl and aromatic derivatives provided the desired products in high yield. Notably, for an unsymmetrical carbodiimide, cyclization selectively occurred at the least sterically encumbered site to furnish a single product in 49% yield.

13. CONCLUSION

As presented in this review, the transition metal-catalyzed addition of C–H bonds to carbonyls, imines and related polarized π -bonds has emerged as a particularly efficient and powerful approach for the construction of an incredibly diverse array of heteroatom substituted products. Readily available and stable inputs are typically employed, and reactions generally proceed without the production of waste byproducts. Moreover, transition metal catalyzed C–H bond additions to polarized π -bonds typically occur without of the need for either strong acid or base additives and therefore often proceed with very high functionality group compatibility. As additionally presented in this review, many of these C–H bond addition reactions occur within cascade reaction sequences to provide rapid access to a diverse array of different heterocyclic as well as carbocyclic products. Finally, a large variety of different transition metal catalysts and ancillary ligands have been applied to these transformations. In future work, improvements in catalyst efficiency and selectivity as well as access to an increasing breadth of heteroatom substituted products can be anticipated.

Acknowledgments

The authors gratefully acknowledge funding from the National Institutes of Health (GM069559).

ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
Ad	adamantyl
AIE	aggregation-induced emission
Ar	aryl
BAr^F₄	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bpy	2,2'-bipyridine

Bu	butyl
CAN	cerium ammonium nitrate
Cbz	carboxybenzyl
CMD	concerted metallation deprotonation
cod	1,5-cyclooctadiene
coe	cyclooctene
COX	cyclooxygenase
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
Cyp	cyclopentyl
<i>c</i>-Pr	cyclopropyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	dichloroethane
DFT	density functional theory
DG	directing group
DMAD	dimethyl acetylenedicarboxylate
DME	dimethoxyethane
DMF	dimethylformamide
DMPE	1,2-bis(dimethylphosphino)ethane
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
DTBM-SEGPPOS	5,5'-bis[di(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
Duanphos	2,2'-di- <i>tert</i> -butyl-2,3,2',3'-tetrahydro-1 <i>H</i> ,1' <i>H</i> -(1,1')biisophosphindolyl
Et	ethyl
EWG	electron withdrawing group
Het	heteroaryl

<i>i</i>-Bu	isobutyl
<i>i</i>-Pr	isopropyl
ICP-MS	inductively coupled plasma mass spectrometry
IPr•HCl	1,3-bis(2,6-diisopropylphenyl)imidazolium chloride
KIE	kinetic isotope effect
Me	methyl
Me-BIPAM	2,2'-(oxybis(methylene))bis(<i>N,N</i> -dimethyldinaphtho[2,1- <i>d</i> :1',2'- <i>f</i>][1,3,2]dioxaphosphepin-4-amine)
min	minutes
MOM	methoxymethylene
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
Naph	naphthyl
NHC	<i>N</i> -heterocyclic carbene
NMA	<i>N</i> -methylacetamide
Ns	nosyl (4-nitrobenzenesulfonyl)
PG	protecting group
Ph	phenyl
Ph-BPE	1,2-bis((2 <i>S</i> ,5 <i>S</i>)-2,5-diphenylphospholano)ethane
phen	1,10-phenanthroline
Piv	pivaloyl
PMP	<i>p</i> -methoxyphenyl
Pr	propyl
Py	pyridyl
Q	8-quinoline
rt	room temperature
SDS	sodium dodecyl sulfate
<i>t</i>-Am	<i>tert</i> -amyl
<i>t</i>-Bu	<i>tert</i> -butyl

TBAPF₆	tetrabutylammonium hexafluorophosphate
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
THAB	tetraheptylammonium bromide
Tf	triflyl (trifluoromethylsulfonyl)
TFA	trifluoroacetate or trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol	toluene
Ts	tosyl (<i>p</i> -toluenesulfonyl)
Xyl	<i>o</i> -xylene

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Biographies

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Jeffrey A. Boerth was born and raised in Somerset, MA, and began his undergraduate studies in 2009 at the University of Massachusetts Amherst. There, he received an honors B.S. in chemistry in 2013 and conducted research under the supervision of Vincent M. Rotello. His work in the lab was focused on the development of nanoparticle-stabilized capsules for the treatment of bacterial biofilms. He then began his graduate career in 2013 at Yale University under the supervision of Jonathan A. Ellman. Currently, he is engaged in new methodology pertaining to Rh(III)- and Co(III)-catalyzed multi-component C–H bond additions to polarized π -bonds.

Jonathan A. Ellman is the Eugene Higgins Professor of Chemistry and Professor of Pharmacology at Yale University. He received his B.S. degree from MIT and his Ph.D. degree from Harvard University under the direction of David Evans. He carried out postdoctoral research with Peter Schultz at the University of California at Berkeley. His laboratory is focused on the development of new synthetic methods and their application to drug and natural product synthesis, particularly in the areas of C–H bond functionalization and asymmetric amine synthesis. His lab is also engaged in the development of chemical tools to study enzymes with an emphasis on proteases, phosphatases and protein arginine deiminases.

Scheme 1.
Reversibility of C–H Bond Additions to Aldehydes

Scheme 2.

Capture of Reversibly Formed Alcohols via Reaction with the Directing Group for C-H Functionalization

Scheme 3.
Rh(III)-Catalyzed Arene C–H Bond Addition to Electron-Deficient Aldehydes

Scheme 4.

Rh(III)-Catalyzed Arene C–H Bond Addition to Activated Aromatic Aldehydes

Scheme 5.

Rh(III)-Catalyzed Alkenyl C–H Addition to Activated Aromatic Aldehydes

Scheme 6.

Rh(III)-Catalyzed C2 Functionalization of Indoles with Ethyl Glyoxylate

Scheme 7.

Ru(II)-Catalyzed C7 Functionalization of Indolines with Ethyl Glyoxylate

Scheme 8.

Ir-Catalyzed Coupling Reaction of *N*-Methylimidazole and Aldehydes in the Presence of Hydrosilane

Scheme 9.

Proposed Reaction Mechanism for Ir-Catalyzed Coupling Reaction

Scheme 10. Ir-Catalyzed *Meta* C–H Functionalization of Pyridines with Aldehydes and Triethylsilane

R = 4-OMeC₆H₄, 87%
 R = 4-CF₃C₆H₄, 87%
 R = 2-MeC₆H₄, 59%
 R = octyl, 75%
 R = Cy, 56%
 R = 2-furan, 66%
 R = 2-thiophene, 48%

R¹ = Ph, R² = Ph, 60% (60% de)
 R¹ = Bn, R² = Ph, 72% (30% de)
 R¹ = *i*-Pr, R² = Ph, 80% (95% de)
 R¹ = *i*-Pr, R² = octyl, 68% (38% de)

Scheme 11.

Mn-Catalyzed Arene C–H Addition to Aldehydes followed by Silylation

Scheme 13.

Pd-Catalyzed Oxidative C–H Acylation with Aryl Aldehydes

Scheme 14.

Pd-Catalyzed Oxidative C–H Acylation of 2-Phenoxy pyridines with Aldehydes

Scheme 15. Pd-Catalyzed Oxidative C–H Acylation using an *O*-Methyl Oxime Directing Group

Scheme 16. Pd-Catalyzed *Ortho* C–H Acylation of Anilides with Aldehydes

Scheme 17.
Pd-Catalyzed *Ortho* C–H Acylation of 2-Arylbenzoxazoles

Scheme 18.

Pd-Catalyzed Oxidative C–H Acylation of Azobenzenes with Aldehydes

Scheme 19. Pd-Catalyzed *Ortho* C–H Acylation of an Aminocarbonylated Azobenzene

Scheme 20. Pd-Catalyzed Oxidative C–H Acylation of *N*-Benzyltriflamides with Aldehydes

Scheme 21.

Pd-Catalyzed Synthesis of Hydroxyisoindolinones via an Oxidative C–H Acylation/
Annulation Cascade

Scheme 22.

Synthesis of Imino Carboxylic Acids using Pd/Lewis Acid Cooperative Catalysis

Scheme 23.

Pd-Catalyzed 1,2-Benzisoxazole Synthesis by C–H Activation/[4+1] Annulation

Scheme 24. Pd-Catalyzed Nitrogen Directed *Ortho* C–H Acylation of 3,5-Diarylisoxazoles

Scheme 25.

Pd-Catalyzed Pyridine-Directed C3 Acylation of Benzofurans and Benzothiophenes with Aryl Aldehydes

Scheme 26.

Pd-Catalyzed C2 Acylation of Indoles with Aryl and Alkyl Aldehydes

Scheme 27.
Pd-Catalyzed C2 Acylation and C2/C7 Diacylation of Indoles

Scheme 28.

Pd-Catalyzed C7 Acylation of a C2/C3 Disubstituted Indole

Scheme 29.

Pd-Catalyzed C7 Acylation of Indolines with Aldehydes

Scheme 30.

Rh(III)-Catalyzed Oxidative C–H Acylation of Benzamides with Aryl Aldehydes

Scheme 31.

Rh(III)-Catalyzed Synthesis of Hydroxyisoindolinones

Scheme 32.

Rh(III)-Catalyzed Oxidative C2 Acylation of Indoles with Aryl and Alkyl Aldehydes

Scheme 33.

Rh(III)-Catalyzed Oxidative *Ortho* Acylation of Aryl Ketone *O*-Methyl Oximes with Aryl and Alkyl Aldehydes

Scheme 34.

Ru-Catalyzed Oxidative C–H Acylation of Phenols with Aldehydes

Scheme 35.
Re-Catalyzed Synthesis of Isobenzofurans

Scheme 36.

Re-Catalyzed Synthesis of Indenones via Dehydrative Trimerization of Aryl Aldehydes

Scheme 37.
Re(I)-Catalyzed Synthesis of *N*-Aryl-2*H*-Indazoles

Scheme 38.

Rh(III)-Catalyzed Synthesis of Phthalides by Cascade Addition and Cyclization of Benzimidates with Aldehydes

Scheme 39.

Rh(III)-Catalyzed Synthesis of Phthalides from Aromatic Acids and Aldehydes

Scheme 40.

Phthalide Synthesis using Dual Rh(III) and Amine Catalysis for Oxidative Aldehyde Coupling by Directed C–H Functionalization

Scheme 41.

Rh(III)-Catalyzed Synthesis of Furans by an Alkene C–H Bond Addition/Cyclization Cascade

Scheme 42.

Rh(III)-Catalyzed Indazole Synthesis by C–H Bond Functionalization and Cyclative Capture

Scheme 43.

Rh(III)-Catalyzed 3-Aryl-(2*H*)-Indazole Synthesis from Azobenzenes and α - Keto Aldehydes

Scheme 44.
Co(III)-Catalyzed Synthesis of *N*-Aryl-2*H*-Indazoles

Scheme 45.
Reversibility of Co(III)-Catalyzed C–H Functionalization Using Deuterated Azobenzenes

Scheme 46.
Reversibility of Co(III)-Catalyzed Aldehyde Insertion Using a Synthetic Intermediate

Scheme 47.
Co(III)-Catalyzed Synthesis of Furans

Scheme 48.
Rh(I)-Catalyzed Intramolecular Aldehyde Coupling

Scheme 49.

Mn-Catalyzed C–H Bond Addition to Unactivated Aldehydes to Access Alcohols

Scheme 50.
Pd-Catalyzed Nucleophilic Additions of Heteroarenes to Isatins

Scheme 51.
Pd-Catalyzed Addition of Acetonitrile to Isatins

Scheme 52.

Rh(III)-Catalyzed Additions of Aryl C–H Bonds to Activated Ketones

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Scheme 54.

Rh(III)-Catalyzed Additions of Aryl C–H Bonds to Cyclopropanones

Scheme 55.

Synthesis of Benzofurans via a Cationic Palladium Complex

Scheme 56.
Possible Pathways for Benzofuran Formation

Scheme 57.

Ir(I)-Catalyzed Synthesis of Benzofurans and Indoles

Scheme 58. Ir-Catalyzed Ketone Addition a Key Step in *cis*-Clavicipitic Acid Synthesis

Scheme 59. Ir(I)-Catalyzed Asymmetric Hydroarylation of α -Ketoamides

Scheme 60.

Asymmetric Intramolecular Hydroacylation of Ketones via Rh(I) Catalysis

Scheme 61.

Proposed Mechanism of Rh(I)-Catalyzed Aldehyde C–H Bond Addition to Ketones

Scheme 62.

Synthesis of Phthalides via Rh(I)-Catalyzed C–H Activation of Aldehydes

Scheme 63.

Rh(I)-Catalyzed Synthesis of Chiral Benzoxazepinones

Scheme 64.

Rh(I)-Catalyzed Synthesis of Chiral Benzoxazecinones

Scheme 65. Intermolecular Coupling of Aldehydes and α -ketoamides via Rh(I) Catalysis

Scheme 66.

Co-Catalyzed Enantioselective Intramolecular Hydroacylation of Ketones

Scheme 67. Pd-Catalyzed Benzylic C–H Bond Addition of 2-Methyl Azaarenes to *N*-Sulfonyl Aldimines

Scheme 68.

Rh(III)-Catalyzed Arene C–H Bond Additions to Boc and Sulfonyl Imines

Scheme 69.

Mechanism of Rh(III)-Catalyzed Arylation of Imines via C-H Functionalization

Scheme 70. Rh(III)-Catalyzed C–H Bond Additions to *N*-Sulfonyl Imines

Scheme 71.

Rh(III)-Catalyzed Synthesis of Branched Amines by Amide Directed C–H Bond Additions to Imines

Scheme 72.

Rh(III)-Catalyzed Alkene C–H Bond Additions to Aryl Aldimines

Scheme 73.
Rh(III)-Catalyzed Pyrrole Synthesis

Scheme 74. Rh(III)-Catalyzed Indole C–H Bond Addition to *N*-Sulfonylaldimines

Scheme 75.

Rh(III)-Catalyzed (Hetero)Arene C–H Bond Additions to Cyclic Imines

Scheme 76. Rh(III)-Catalyzed Asymmetric C–H Bond Additions to *N*-Perfluorobutanesulfinyl Imines

Scheme 77.

Rh(III)-Catalyzed Synthesis of 3-Aminoisoindolin-1-ones

Scheme 78.
Rh(III)-Catalyzed Synthesis of 3-(Diarylmethylene)isoindolin-1-ones

Scheme 79. Co-Catalyzed C–H Bond Additions to *N*-Aromatic Aldimines

Scheme 80. Co(III)-Catalyzed Directed C–H Bond Additions to *N*-Sulfonyl Imines

Scheme 81. Co(III)-Catalyzed Indole C–H Bond Additions to *N*-Sulfonyl Imines

Scheme 82.

Seminal Report of Rh-Catalyzed Direct C–H Bond Addition to Isocyanates

Scheme 83.

Rh(III)-Catalyzed Aryl and Alkenyl C–H Bond Additions to Isocyanates

Scheme 84.

Rh(III)-Catalyzed Synthesis of Pyrimidinones via Isocyanate Addition

Scheme 85.

C–H Functionalization of Ferrocenes with Isocyanates

Scheme 86. Rh(III)-Catalyzed C–H Bond Additions of *O*-Methoxy Oximes with Isocyanates

Scheme 87. Alkenyl C–H Bond Additions of *O*-Methoxy Oximes with Isocyanates

Scheme 88.
Rh(III)-Catalyzed Synthesis of Phthalimides

Scheme 89.

Rh(III)-Catalyzed C–H Functionalization/Decarboxylation of Benzoic Acids

Scheme 90.

Rh(III)-Catalyzed C–H Bond Additions of Azobenzenes to Isocyanates

Scheme 91.

Rh(III)-Catalyzed C–H Bond Additions of Indoles and Pyrroles to Isocyanates

Scheme 92.

Reversibility of Pyrimidine Directed Indole C–H Bond Addition to Isocyanates

Scheme 93.**Rh(III)-Catalyzed Aminocarbonylation of Indoles and Pyrroles**

Scheme 94.
Aminocarbonylation at the C7 Position of an Indole

Scheme 95.
Ir-Catalyzed Amidation of *N*-methylimidazole

Scheme 96.

Re-Catalyzed Synthesis of Phthalimidines via C–H Bond Activation

Scheme 97.

Re-Catalyzed Amidation of Heteroaromatic Aldimines

Scheme 98.

Re-Catalyzed C–H Bond Additions of Imidates with Isocyanates

Scheme 99.
Re-Catalyzed C–H Aminocarbonylation of Azobenzenes

Scheme 100.

Ru(II)-Catalyzed Aryl C–H Bond Additions to Isocyanates

Scheme 101.

Ru(II)-Catalyzed Phthalimide Synthesis via C–H Activation

Scheme 102.

Ru(II)-Catalyzed Amidation of Heteroaromatic Amides

Scheme 103.

Ru(II)-Catalyzed Synthesis of Phthalimides from Benzoic Acids and Isocyanates

Scheme 104.

Co(III)-Catalyzed C–H Bond Additions to Isocyanates

Scheme 105.

Co(III)-Catalyzed Additions of Arene C–H Bonds to Isocyanates

Scheme 106.

Co(III)-Catalyzed Additions of Alkene C-H Bonds to Isocyanates

Scheme 107.

Mn-Catalyzed C–H Aminocarbonylation with Isocyanates

Scheme 108.

An Early Example of a Metal-Catalyzed C–H Bond Addition to an Isocyanide

Scheme 109.

Pd-Catalyzed Quinazoline Synthesis via C–H Bond Additions to Isocyanides

Scheme 110.

Pd(II)-Catalyzed C3 Amidation of Indoles via C–H Activation

Scheme 111.

Rh(III)-Catalyzed Annulation of N-Tosylbenzamide with Isocyanide

Scheme 112.
Cu-Catalyzed Additions of *N*-benzoyl 8-Aminoquinolines to Isocyanides

Scheme 113. Ni-Catalyzed Additions of *N*-benzoyl 8-Aminoquinolines to Isocyanides

Scheme 114.
Pd-Catalyzed Coupling of Arenes and Nitriles

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Scheme 116.

Pd-Catalyzed Acylation of Free N–H Indoles with Nitriles

Scheme 117.

Pd-Catalyzed Acylation of Substituted and Free N-H Indoles with Nitriles

Scheme 118.

Pd-Catalyzed Addition of Thiophenes to Nitriles

Scheme 119.

Mn(I)-Catalyzed C–H Bond Additions to Nitriles

Scheme 120.

General Scheme for Additions to $C=C$ π -Bonds followed by Cyclization upon Polarized π -Bond Directing Group

Scheme 121.

Re(I)-Catalyzed Alkyne Addition/Cyclization Cascade with Aldimines

Scheme 122.

Re(I)-Catalyzed Alkyne Addition/Cyclization Cascade with Free N–H Ketimines

Scheme 123. Ru(II)-Catalyzed Alkyne Addition/Cyclization with *N*-Sulfonyl Imines

Scheme 124.

Ru-Catalyzed Alkyne Addition/Cyclization with Free N–H Ketimines

Scheme 125. Ru(II)-Catalyzed Synthesis of Amino Indenes from *N*-Sulfonyl Imines and Alkynes

Scheme 126.

Rh(I)-Catalyzed Alkyne Addition/Cyclization with Free N–H Ketimines

Scheme 127.

Asymmetric Rh(I)-Catalyzed Alkyne Addition/Cyclization with Free N–H Ketimines

Scheme 128.

Rh(III)-Catalyzed Alkyne Addition/Cyclization with Azomethine Ylides

Scheme 129.

Rh(III)-Catalyzed Synthesis of Indenones from Aryl Nitrones and Alkynes

Scheme 130. Rh(III)-Catalyzed Annulation of *O*-Methyl Oximes and Alkynes

Scheme 131.

Rh(III)-Catalyzed Annulation of Cyclic Ketimines and Alkynes

Scheme 132.

Rh(III)-Catalyzed Three-Component Coupling of Alkynes and Aldehydes

Scheme 133.

Co(III)-Catalyzed Annulation of Cyclic Ketimines and Alkynes

Scheme 134.

Re(I)-Catalyzed Annulation of Aryl Ketones and Enoates

Scheme 135.

Re(I)-Catalyzed Annulation of Aryl Ketimines and Enones/Enoates

Scheme 136. Mn-Catalyzed Annulation of *N*-Aryl Ketimines and Enoates

Scheme 137.

Rh(I)-Catalyzed Allene Addition/Cyclization with Free N–H Ketimines

Scheme 138.

Re-Catalyzed Allene Addition/Cyclization with Aryl Ketimines

Scheme 139.

Ir(I)-Catalyzed Annulation of Cyclic Ketimines and Dienes

Scheme 140. Ir(I)-Catalyzed Annulation of *N*-Sulfonyl Ketimines and Dienes

Scheme 141. Rh(III)-Catalyzed Synthesis of Indolines from *N*-Aryl Nitrones and Alkynes

Scheme 142.
Rh(III)-Catalyzed Synthesis of Indenols

Scheme 143. Rh(III)-Catalyzed Synthesis of Indenes Using Ketones with α -Hydrogens

Scheme 144.
Rh(III)-Catalyzed Synthesis of Indenes Using Alkynes with Propargylic Hydrogens

Scheme 145.

Rh(III)-Catalyzed Annulation of Aryl Ketones and Alkynes

Scheme 146.

Ru(II)-Catalyzed Annulation of Aryl Ketones and Alkynes

Scheme 147.

Rh(III)-Catalyzed Enone Addition/Cyclization with Aryl Ketones

Scheme 148.

Rh(III)-Catalyzed Allylic Alcohol Addition/Cyclization with Aryl Ketones

Scheme 149.

Co(III)-Catalyzed Annulation of Anilides and Alkynes

Scheme 150.
Co(III)-Catalyzed Synthesis of Quinolines

Scheme 151.
Co(III)-Catalyzed Synthesis of Quinolines

Scheme 152.

Rh(III)-Catalyzed Annulation of Imides and Alkynes

Scheme 153.

Co(III)-Catalyzed Annulation of Aryl Esters and Alkynes

Scheme 154.

Co(III)-Catalyzed Synthesis of Indenones from Aryl Esters and Alkynes

Scheme 155.
Co(III)-Catalyzed Synthesis of Pyrroloindolones

Scheme 156.
Rh(III)-Catalyzed Synthesis of Pyrroloquinolinones

Scheme 157.

Rh(III)-Catalyzed Cascade Addition of Enone Tethered Aldehydes

Scheme 158.
Synthesis of a Cationic Rh(III)-Enolate

Scheme 159.

Rh(III)-Catalyzed Three-Component Addition of Enones and Aldehydes

Scheme 160.

Co(III)-Catalyzed Diastereoselective Three-Component Coupling

Scheme 161.

Mechanistic Experiments for Co(III)-Catalyzed Three-Component Coupling

Scheme 162.

Proposed Mechanism for the Co(III)-Catalyzed Three-Component Coupling

Scheme 163. Asymmetric Co(III)-Catalyzed Three-Component Additions to *N*-*tert*-Butanesulfinyl Imines

Scheme 164. Ni/Cu-Catalyzed Aerobic C(sp²)-H Carbonylation using DMF as Carbonyl Source

Scheme 165. Ni/Cu-Catalyzed Aerobic C(sp³)-H Carbonylation using DMF as Carbonyl Source

Scheme 166. Pd/Ag-Catalyzed Aerobic C(sp²)-H Carbonylation using DMF as Carbon Source

Scheme 167.

Re-Catalyzed Synthesis of 1,3-Diiminoisoindolines by C(sp²)-H Bond Insertion into Carbodiimides