ACCOUNTS
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Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations

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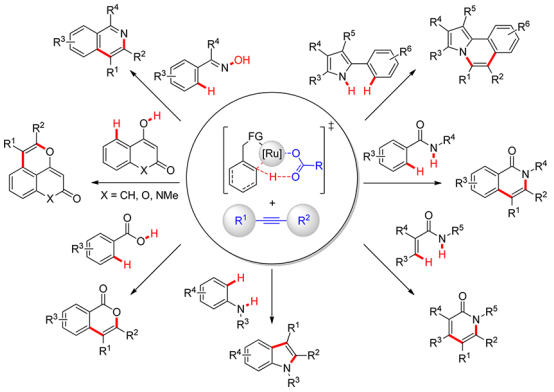
CONSPECTUS

To improve the atom- and step-economy of organic syntheses, researchers would like to capitalize upon the chemistry of otherwise inert carbon–hydrogen (C–H) bonds. During the past decade, remarkable progress in organometallic chemistry has set the stage for the development of increasingly viable metal catalysts for C–H bond activation reactions. Among these methods, oxidative C–H bond functionalizations are particularly attractive because they avoid the use of prefunctionalized starting materials. For example, oxidative annulations that involve sequential C–H and heteroatom–H bond cleavages allow for the modular assembly of regioselectively decorated heterocycles. These structures serve as key scaffolds for natural products, functional materials, crop protecting agents, and drugs. While other researchers have devised rhodium or palladium complexes for oxidative alkyne annulations, my laboratory has focused on the application of significantly less expensive, yet highly selective ruthenium complexes.



This Account summarizes the evolution of versatile ruthenium(II) complexes for annulations of alkynes via C–H/N–H, C–H/O–H, or C–H/N–O bond cleavages. To achieve selective C–H bond functionalizations, we needed to understand the detailed mechanism of the crucial C–H bond metalation with ruthenium(II) complexes and particularly the importance of carboxylate assistance in this process. As a consequence, our recent efforts have resulted in widely applicable methods for the versatile preparation of differently decorated arenes and heteroarenes, providing access to among others isoquinolones, 2-pyridones, isoquinolines, indoles, pyrroles, or α-pyrones. Most of these reactions used $Cu(OAc)_2 \cdot H_2O$, which not only acted as the oxidant but also served as the essential source of acetate for the carboxylate-assisted ruthenation manifold. Notably, the ruthenium(II)-catalyzed oxidative annulations also occurred under an ambient atmosphere of air with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$. Moreover, substrates displaying N–O bonds served as "internal oxidants" for the syntheses of isoquinolones and isoquinolines. Detailed experimental mechanistic studies have provided strong support for a catalytic cycle that relies on initial carboxylate-assisted C–H bond ruthenation, followed by coordinative insertion of the alkyne, reductive elimination, and reoxidation of the thus formed ruthenium(0) complex.

Introduction

The modular assembly of regioselectively decorated heterocycles continues to be of central importance because of their prevalence in natural products, functional materials, crop protecting agents, or drugs.[1] The transition-metal-catalyzed formation of carbon–carbon bonds via the activation of otherwise unreactive carbon–hydrogen bonds represents one of the most powerful tools for a streamlining of heterocycle synthesis, since these methods avoid the preparation and use of prefunctionalized starting materials.[2,3] Early pioneering studies were largely directed toward the challenging C–H bond activation of methane[4–6] ($D_{C(sp^3)-H} = 439$ kJ mol^{-1}).[5b] During the past decade, the organic chemistry community has, however, become increasingly aware of the unique potential offered by catalyzed C–H bond functionalization as means to improve the atom economy[7] and more importantly the step-economy of organic syntheses. The objective of implementing C–H bond activation within

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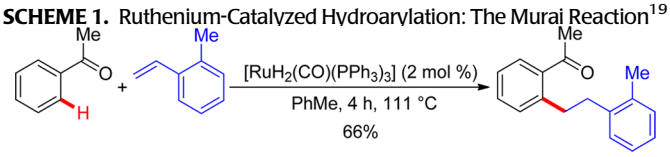
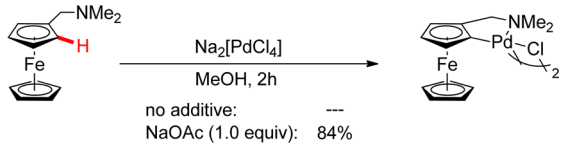
the direct functionalization of structurally complex organic molecules, as found for instance in medicinal chemistry or naturally occurring products,[8,9] represents a considerable different challenge with respect to the activation of simple hydrocarbons. First, the required catalytic systems need to display an improved chemoselectivity in that reactive electrophilic functional groups, such as ester, amide, hydroxyl, nitro, or aldehyde substituents, need to be fully tolerated. Unfortunately, the harsh reaction conditions usually employed for the activation of methane preclude broader applications of these methods to the synthesis of highly functionalized organic compounds. Second, in contrast to methane, organic molecules of interest bear numerous different C−H bonds with comparable dissociation energies. Hence, achieving site-selective,[10−12] and in certain cases even diastereo-[13] or enantioselective,[14] transformations constitutes a challenge of equal importance. In recent years, significant progress was accomplished in the area of streamlining organic synthesis through catalyzed C−H bond functionalizations,[2,3] which addressed aspects of the aforementioned key obstacles. In this context, my group became inspired in 2003 by the potential of using ubiquitous C−H bonds as latent functional groups as an environmentally benign alternative to organometallic reagents in traditional palladium-catalyzed cross-coupling reactions.[15] Hence, we started a research program initially focusing on direct arylations of otherwise inert C(sp^2)−H bonds ($D_{C(sp^2)-H}$ = 472 kJ mol^{-1})[5b] for the step-economical preparation of (hetero)biaryls. Given the plethora of data that was gathered during the past 40 years on palladium-catalyzed arylation reactions,[2] we felt particularly intrigued by the previously underexplored use of rather inexpensive ruthenium complexes (prices of rhodium, iridium, palladium, and ruthenium = $1100, $1050, $669, and $110 US per troy ounce, respectively)[16] for catalyzed biaryl[17] syntheses. Notably, pioneering studies in the area of chelation-assisted ruthenium-catalyzed C−H bond functionalizations by Lewis,[18] as well as Murai et al.[19] highlighted the potential of efficient ruthenium-catalyzed C−H bond activation with the development of effective catalysts for site-selective addition reactions of C−H bonds onto C−C multiple bonds (Scheme 1).[20,21] Yet, studies in our laboratories have in recent years unraveled the importance of carboxylate assistance for ruthenium-catalyzed C−H bond functionalization, which are surveyed in this Account with a particular focus on the scope and mechanism of oxidative alkyne annulations by C−H/Het−H bond functionalization, while previous review articles summarized direct arylations[11a] and carboxylate-assisted C−H bond activation.[22]

SCHEME 1. Ruthenium-Catalyzed Hydroarylation: The Murai Reaction[19]



SCHEME 2. Stoichiometric Acetate-Mediated Cyclometalation[23]



Evolution of Carboxylate-Assisted Ruthenium-Catalyzed C−H Bond Functionalizations

The key elementary metalation step of C−H bond activation reactions was previously proposed to predominantly proceed by oxidative addition, homolytic bond cleavage, σ-bond metathesis, or electrophilic substitution. However, sporadic early reports indicated a tantalizing alternative reaction manifold, namely, base-assisted metalation reactions.[22] Thus, the research groups of Shaw[23] and Davies[24] observed the beneficial effect exerted by NaOAc for stoichiometric cyclometalation reactions (Scheme 2).

Subsequently, the relevance of carboxylate assistance was recognized for palladium-catalyzed C−H bond functionalizations, with early DFT calculations by Sakaki on the Fujiwara−Moritani reaction.[25] Important mechanistic findings on carboxylate-assisted palladium-catalyzed C−H bond activation by Davies and MacGregor,[26] Echavarren and Maseras,[27] and Fagnou and Gorelsky,[28,29] among others, led thereafter to practically useful advances in palladium-catalyzed direct arylations.[22,28]

Until 2008, carboxylates had not been employed as cocatalytic additives in ruthenium-catalyzed C−H bond functionalizations. However, studies in our laboratories highlighted a significant rate acceleration of bifunctional secondary phosphine oxides (SPO)[30,31] in challenging[32] ruthenium-catalyzed direct arylations with organic electrophiles,[33−35] which were previously conducted by Oi, Inoue, and co-workers solely in NMP as the solvent with the tertiary phosphine PPh_3.[17] As to the working mode of our SPO-based ruthenium(II) catalyst,[33−35] we proposed base assistance to be the decisive feature via transition state **1** (Figure 1). In analogy, we embarked on exploration of other bifunctional ligands, such as carboxylates, for direct arylations that were expected to give rise to transition state **2**.

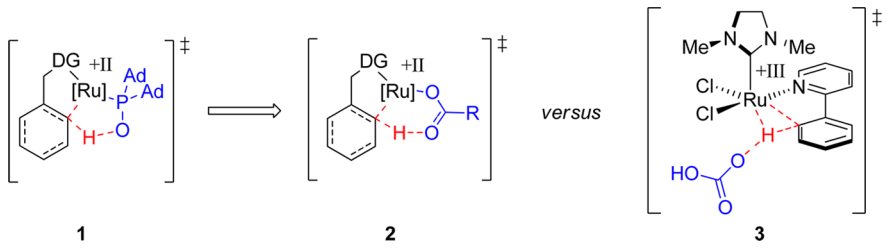
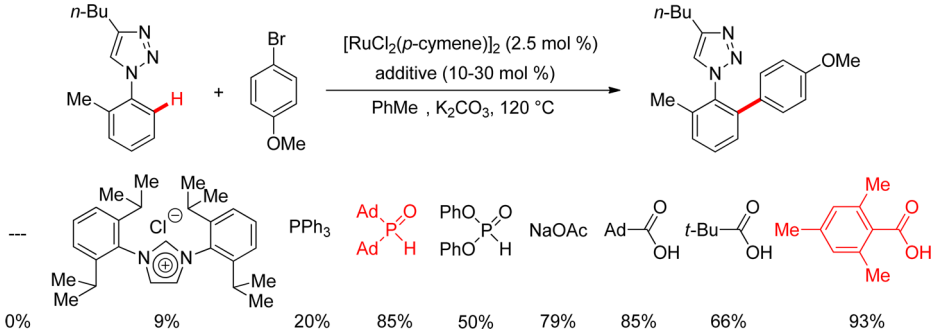


FIGURE 1. Proposed transition states for base-assisted ruthenations.

SCHEME 3. Cocatalytic Additives in the Ruthenium-Catalyzed Direct Arylation[36]



Interestingly, among more than 30 cocatalytic additives, ruthenium(II) complexes generated from sterically hindered carboxylates emerged as the most effective catalysts (Scheme 3) and exerted an optimal rate acceleration in direct C–H bond arylations.[36,37] It is noteworthy that these findings rendered an independently proposed carbonate-assisted formation of cyclometalated ruthenium(III)–NHC complexes (**3**)[38] unlikely to be operative.

On the basis of detailed mechanistic studies,[36,37] we thus suggested that ruthenium(II)-catalyzed direct arylations involve initial reversible C–H bond activations via carboxylate-assisted and thus deprotonative ruthenations (Scheme 4).

Notably, carboxylate assistance led to the most broadly applicable and most robust ruthenium(II) catalysts for direct arylations with various organic electrophiles, including aryl bromides, chlorides, and tosylates, as well as phenols.[37,39,40] In addition, C–H bond arylations proved viable in a variety of solvents[41] or on preparative scale[42] and allowed us to overcome major limitations of ruthenium(II) catalysis, such as direct arylations of heteroarenes[43] or substrates displaying removable directing groups.[44,45] Likewise, carboxylate assistance set the stage for widely applicable C–H bond benzylations[46] and for challenging direct alkylations[47,48] with unactivated, β-hydrogen-containing alkyl halides under basic reaction conditions. Remarkably, we again observed a considerable rate acceleration through carboxylate assistance (Scheme 5).

Intermolecular competition experiments revealed electron-deficient arenes to be preferentially functionalized (Scheme 6), thereby rendering a simple electrophilic aromatic substitution-type manifold unlikely to be of relevance.[47–49]

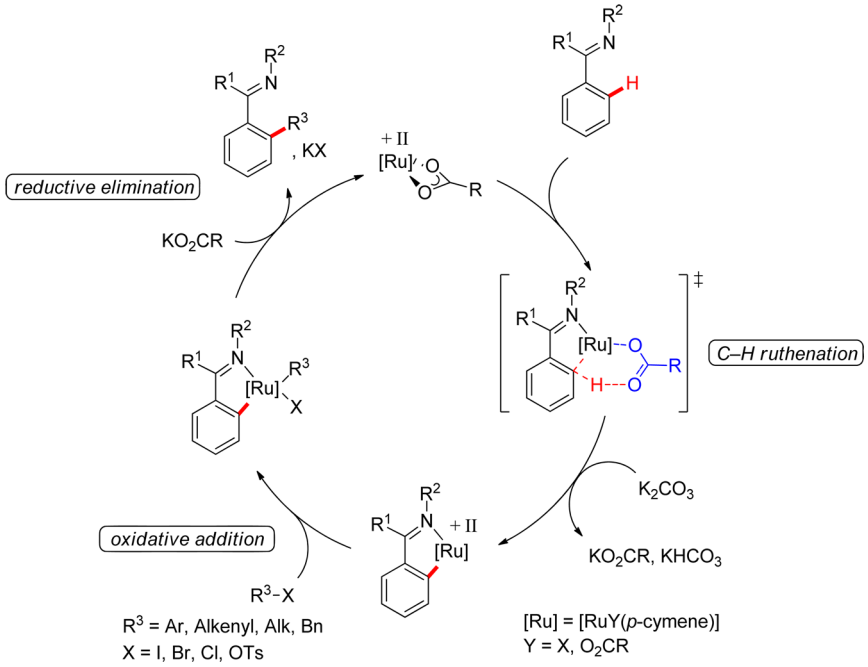
Carboxylate-Assisted Oxidative C–H Bond Functionalization

Initial Observations. During our studies on carboxylate assistance for ruthenium-catalyzed direct arylations, we observed a significantly altered chemoselectivity, specifically when employing electron-deficient *ortho*-halo benzotrifluorides and 2-alkyl heteroarylarenes as the substrates.[50] Indeed, an intermolecular dehydrogenative arylation occurred chemoselectively through twofold C–H bond cleavages, with the aryl chloride serving as the sacrificial oxidant (Scheme 7).

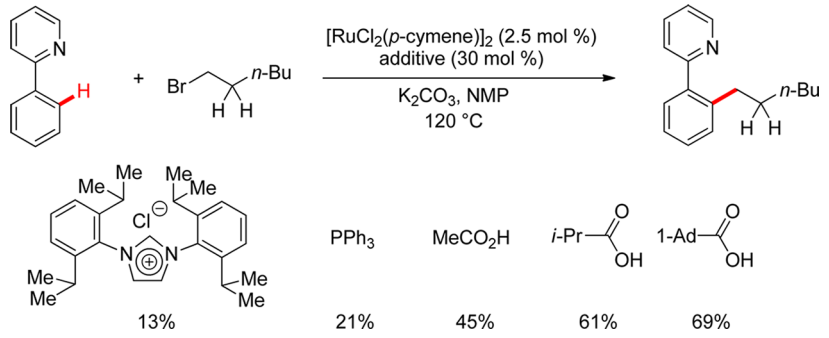
Oxidative Alkyne Annulations through C–H/N–H Bond Cleavages

On the basis of these experimental findings, we tested carboxylates as cocatalytic additives for ruthenium-catalyzed oxidative[51,52] C–H bond functionalizations, a research area that had thus far largely been dominated by the use of more expensive palladium or rhodium complexes,[53,54] with pioneering reports by Fujiwara and Moritani.[55–57] In contrast, less expensive[16] ruthenium complexes had previously been underutilized for oxidative

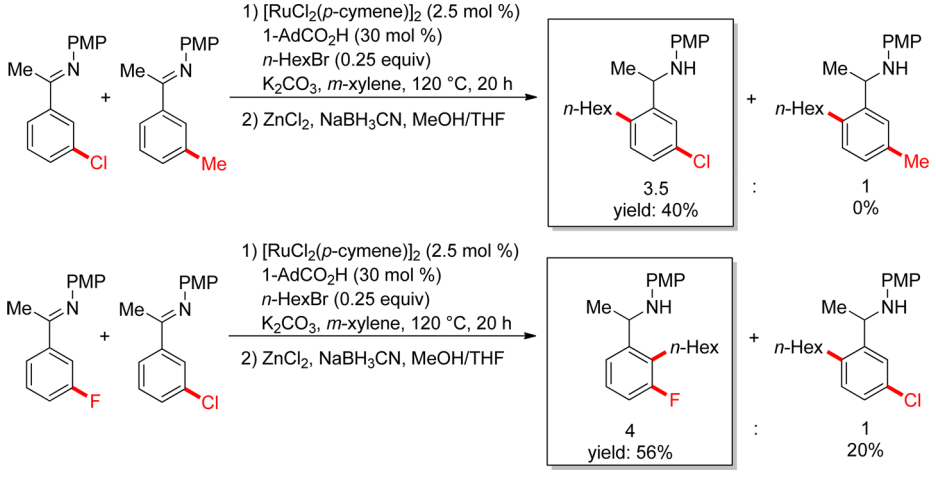
SCHEME 4. Proposed Mechanism for Direct Arylations and Alkylations by Carboxylate Assistance[37]



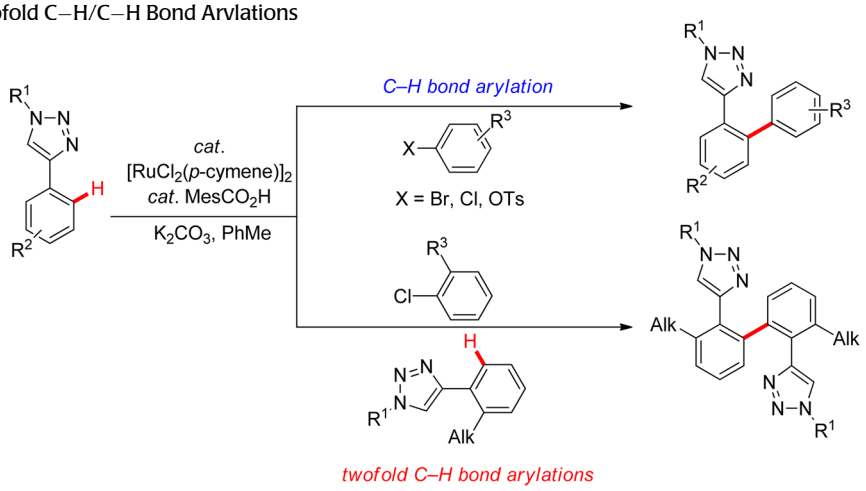
SCHEME 5. Additives in Ruthenium-Catalyzed Direct Alkylation[47]



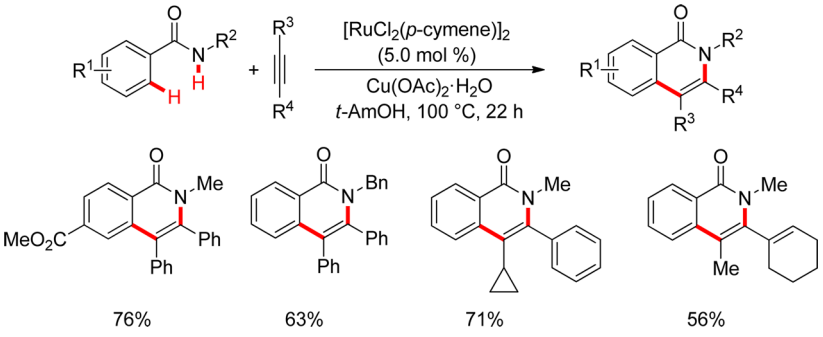
SCHEME 6. Competition Experiments[49]



SCHEME 7. Oxidative Twofold C–H/C–H Bond Arylations



SCHEME 8. Ruthenium-Catalyzed Oxidative Annulation via C–H/N–H Bond Cleavages[58]



C(sp^2)–H bond functionalizations with a notable early example by Milstein, but under rather harsh reaction conditions (6.1 atm CO and 2.0 atm O_2).[51] Considering their importance for step-economical syntheses of bioactive heterocycles,[3] we particularly became attracted by oxidative annulations through C–H/Het–H bond cleavages.

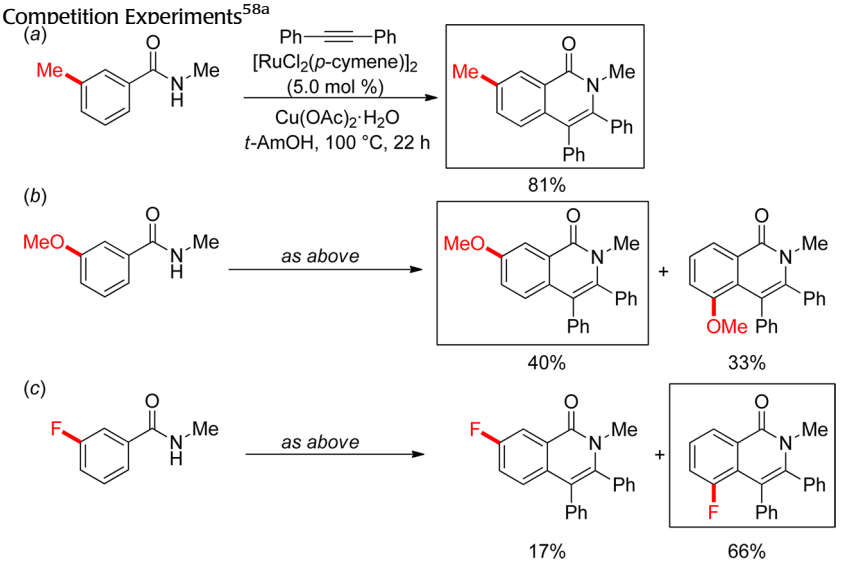
As a proof of concept, we hence set out to devise ruthenium-catalyzed oxidative annulations of alkynes through C–H and N–H bond cleavages for the synthesis of bioactive isoquinolones (Scheme 8).[58] Notably, optimization studies revealed $[RuCl_2(p\text{-cymene})]_2$ to be optimal among a variety of ruthenium complexes, while $Cu(OAc)_2 \cdot H_2O$ was found to be the terminal oxidant of choice.[58a] The annulation reaction occurred efficiently in polar protic solvent *t*-AmOH, whereas the corresponding hydroarylation product was also formed in apolar solvents. The optimized ruthenium(II) catalyst proved tolerant of valuable electrophilic functional groups, and was found to be applicable to benzamides with different N-substituents. Fortunately, the annulation process proceeded with excellent regioselectivity when using unsymmetrical aryl/alkyl or alkenyl/alkyl alkynes.

As to the C–H/N–H bond functionalization mechanism, intramolecular competition experiments with *meta*-methyl arenes were largely controlled by steric interactions (Scheme 9a).[58a] Contrarily, the use of substrates displaying electronegative heteroatoms in the *meta*-position afforded significant amounts of products through functionalizations at the sterically more congested C–H bonds (Scheme 9b,c). These observations were rationalized with the kinetic C–H bond acidity[59] governing the site selectivity of the overall annulation process within a carboxylate-assisted[22] ruthenation manifold.[58a]

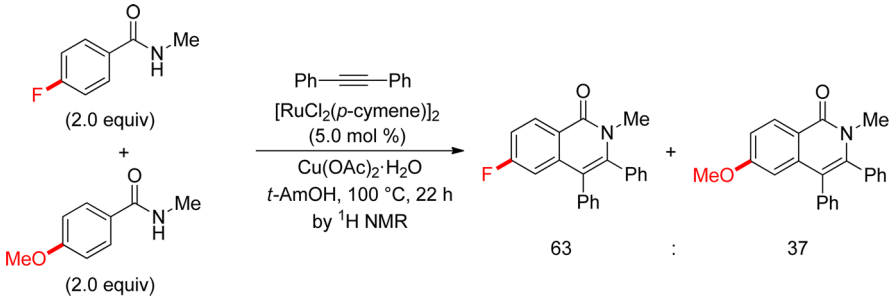
Further, intermolecular competition experiments highlighted electron-deficient benzamides to be functionalized preferentially, thus suggesting that an electrophilic C–H bond activation is less likely to be operative (Scheme 10).[58a]

Catalytic reactions with isotopically labeled starting materials provided strong support for a kinetically relevant (KIE, $k_H/k_D \approx 2.6$) C–H bond activation. Accordingly, we proposed the ruthenium(II)-catalyzed oxidative annulation to proceed by an initial carboruthenation via acetate-assisted C–H bond cleavage, followed by migratory insertion,

SCHEME 9. Intramolecular Competition Experiments[58a]



SCHEME 10. Intermolecular Competition Experiment[58a]



C–N bond-forming reductive elimination, and final reoxidation of the ruthenium(0) intermediate (Scheme 11).[58a] It is noteworthy that additional support for our proposed mechanism was very recently provided through the independent synthesis and isolation of key intermediates.[60,61]

Intriguingly, acrylamides also turned out to be competent substrates through alkenylic C–H bond activation with the ruthenium(II) catalyst. Interestingly, $Cu(OAc)_2 \cdot H_2O$ as the oxidant led to the most efficient catalysis, again being indicative of acetate assistance.[62] The ruthenium(II) catalyst gave access to 2-pyridones with ample scope, employing both electron-rich and electron-deficient acrylamides (Scheme 12). In contrast to a recently reported rhodium catalyst,[63] our ruthenium-based method allowed for the use of dialkyl alkynes as well.[62]

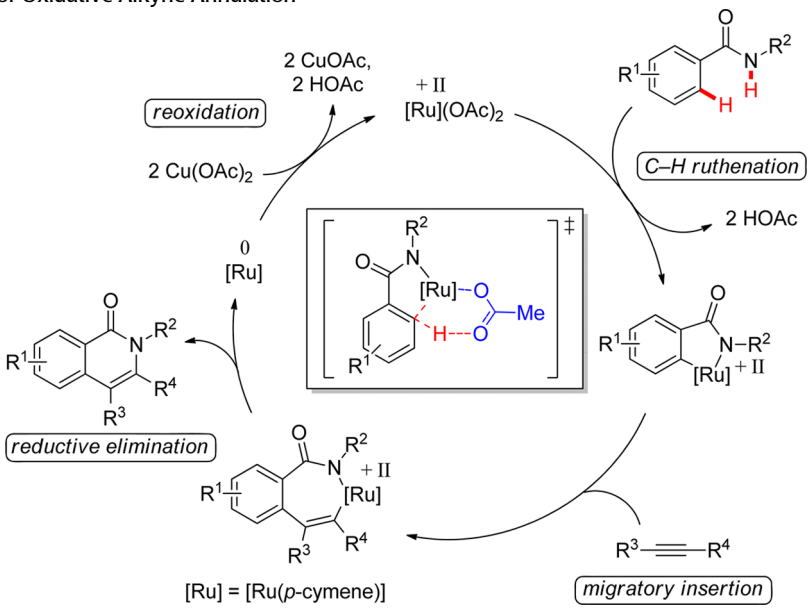
Our C–H/N–H bond functionalization strategy was not restricted to arenes bearing electron-withdrawing directing groups. Indeed, cationic ruthenium(II) complexes facilitated oxidative C–H bond functionalizations with electron-rich anilines through acetate assistance (Scheme 13).[64] A notable feature of our protocol was represented by the use of substrates bearing easily removable directing groups. The C–H/N–H bond cleavages occurred most efficiently in water[65] as a green reaction medium and provided general access to valuable bioactive indole derivatives.[64]

As to the reaction mechanism, we observed a H/D exchange when employing D_2O as the solvent, indicating an initial reversible cyclometalation by the cationic ruthenium(II) complex. Thereby, six-membered ruthenacycle **4** was formed as a key intermediate, which was proposed to undergo migratory insertion with the alkyne (Scheme 14). Finally, reductive elimination delivered the desired indole, and reoxidation of the ruthenium(0) complex regenerated the catalytically active species.[64]

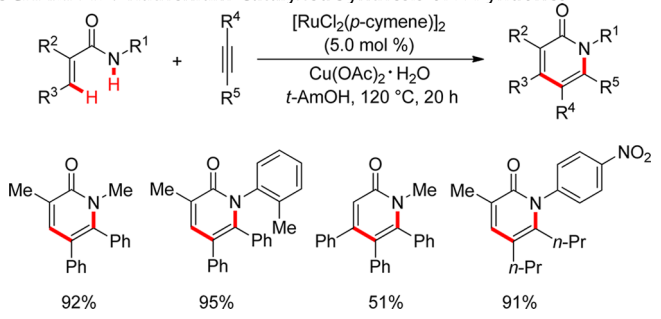
Aerobic Oxidative Alkyne Annulations

Ruthenium(II)-catalyzed oxidative annulations were also realized in an aerobic fashion with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$ under an atmosphere of ambient air.[66]

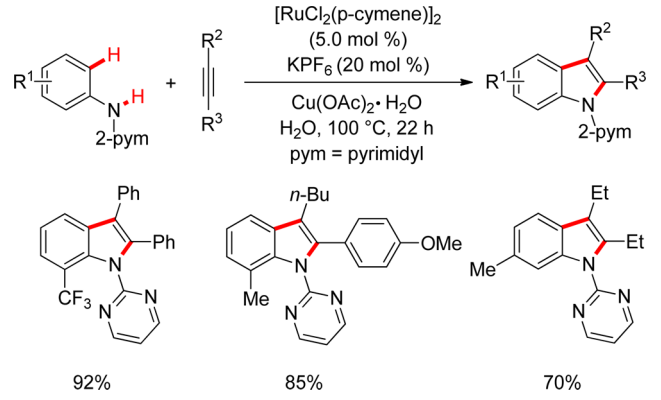
SCHEME 11. Catalytic Cycle for Oxidative Alkyne Annulation[58a]



SCHEME 12. Ruthenium-Catalyzed Synthesis of 2-Pyridones[62]

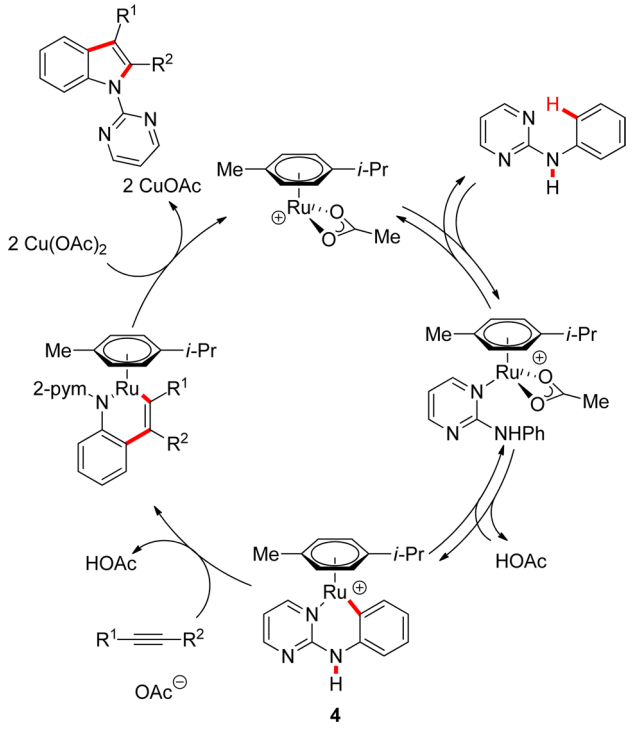


SCHEME 13. Oxidative Annulation with Electron-Rich Anilines Bearing a Removable Directing Group[64]



Pleasingly, the C–H/N–H bond functionalization occurred with unparalleled selectivities and ample scope to deliver indole and pyrrole derivatives. While reactions with $CuBr_2$ as the co-oxidant did not furnish the desired products,

SCHEME 14. Proposed Catalytic Cycle for Annulations with Anilines[64]



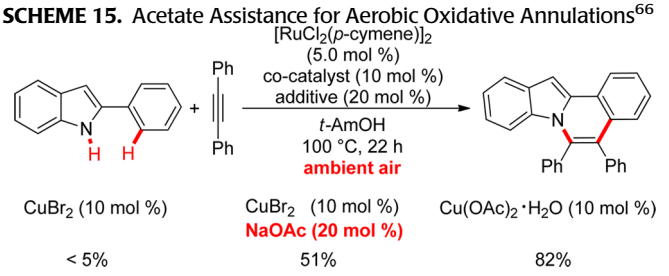
cocatalytic amounts of metal acetates restored the catalytic efficacy (Scheme 15), thus providing strong evidence for carboxylate-assisted aerobic oxidations.

The remarkably broad scope of our catalytic system was exploited for oxidative annulations with 2-arylpyrroles to deliver pyrrolo[2,1-*a*]isoquinolines, structural analogs of bioactive marine alkaloids (Scheme 16). The highly selective

conversion of *n*-alkyl alkynes constituted a strong testament to the unique features of chemoselective ruthenium catalysts.

Detailed experimental mechanistic studies[66] were suggestive of a deprotonative metalation through acetate assistance as the key C−H bond activation (Scheme 17).

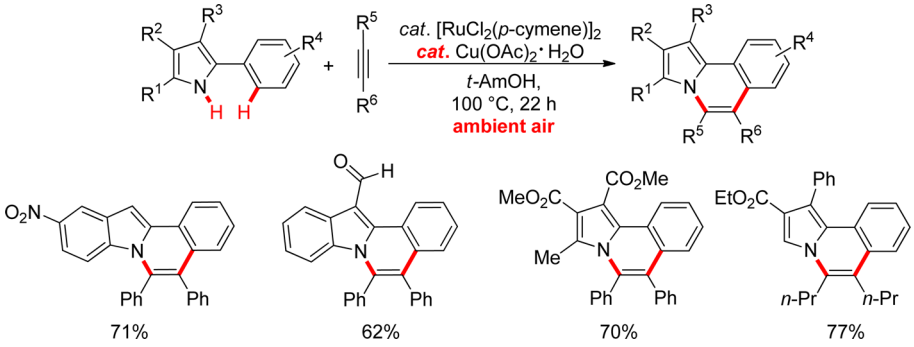
SCHEME 15. Acetate Assistance for Aerobic Oxidative Annulations[66]



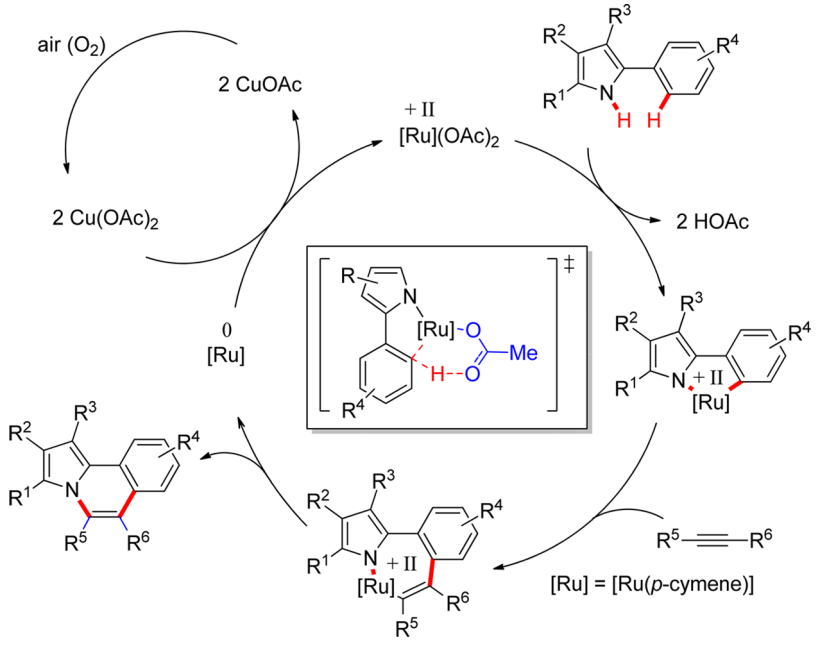
Oxidative Alkene Annulations through C−H/O−H Bond Cleavages

The considerable rate acceleration exerted by carboxylates not only was observed in ruthenium(II)-catalyzed alkyne annulations by C−H/N−H bond functionalizations but also provided efficient means for oxidative annulations via C−O bond-forming reductive eliminations.[52,67] Thus, heteroaromatic[52] and aromatic acids[67,68] were successfully utilized as weakly coordinating directing groups for mechanistically related cross-dehydrogenative[69] C−H bond alkenylations.[67] Notably, transformations of benzoic acids took place most efficiently with environmentally benign water as reaction medium.[67] Thereby, a highly chemoselective ruthenium(II) catalyst set the stage for a versatile phthalide synthesis through a reaction sequence consisting of

SCHEME 16. Ruthenium-Catalyzed Aerobic Oxidative Annulation.[66]



SCHEME 17. Proposed Catalytic Cycle for Aerobic Oxidative Alkyne Annulations[66]

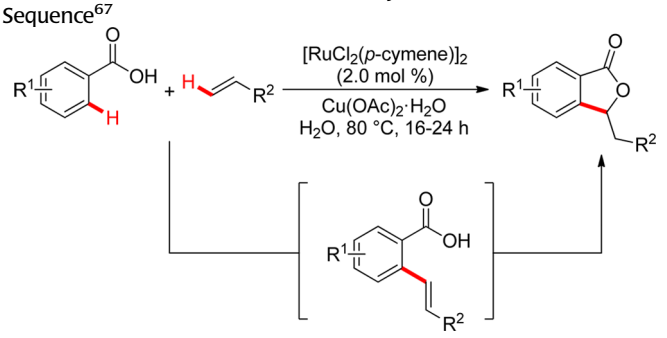


cross-dehydrogenative alkenylation and intramolecular oxa-Michael[70] reaction (Scheme 18).[67]

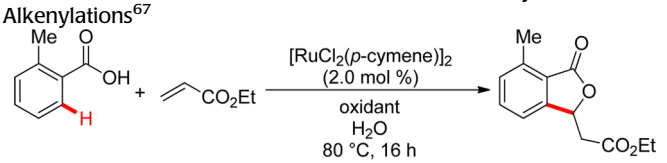
Again, we observed metal acetates to be mandatory for efficient C−H bond functionalizations (Scheme 19), thereby illustrating the power of carboxylate assistance within ruthenium(II)-catalyzed C−H/O−H bond functionalizations.

Experimental mechanistic studies were suggestive of a kinetically relevant ($k_H/k_D \approx 3.6$) C−H bond ruthenation, along with a migratory insertion of the alkene, β-hydride elimination, and reoxidation of a ruthenium(0) intermediate (Scheme 20).

SCHEME 18. Oxidative C−H Bond Alkenylation/Oxa-Michael Reaction Sequence[67]



SCHEME 19. Acetate Assistance for Ruthenium-Catalyzed Oxidative Alkenylations[67]

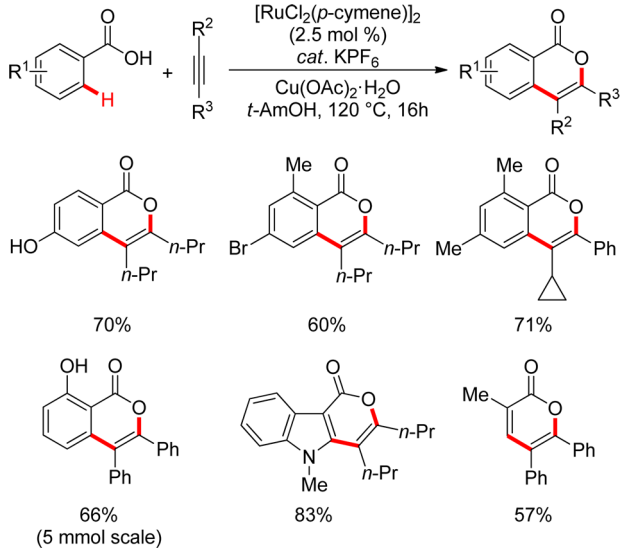


$CuBr_2$	$CuBr_2$/NaOAc	$Cu(OAc)_2 \cdot H_2O$
---	86%	95%

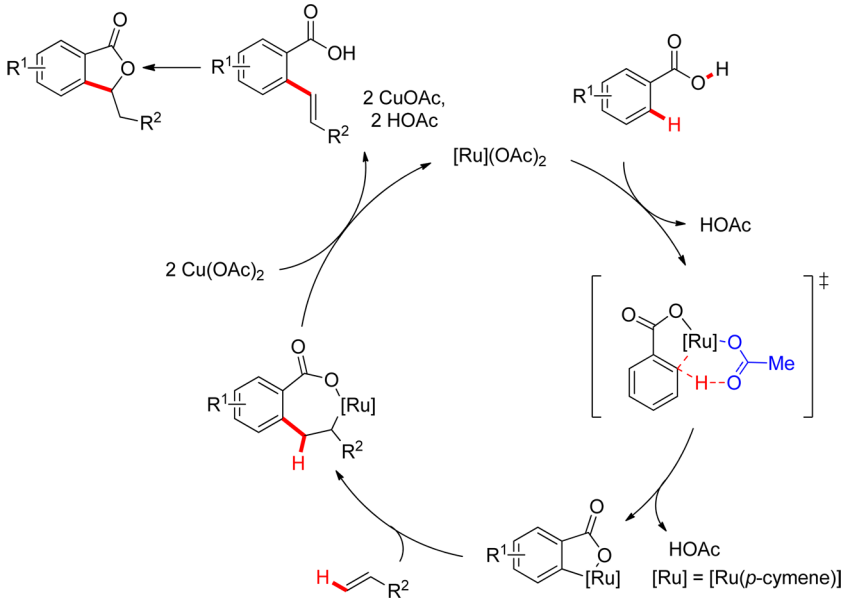
Oxidative Alkyne Annulations through C−H/O−H Bond Cleavages

Oxidative annulations of alkynes through C−H/O−H bond cleavages were recently achieved with robust ruthenium(II) complexes (Scheme 21).[71,72] Hence, a cationic ruthenium(II) catalyst derived from KPF_6 was employed for an expedient synthesis of isocoumarins through oxidative annulations of

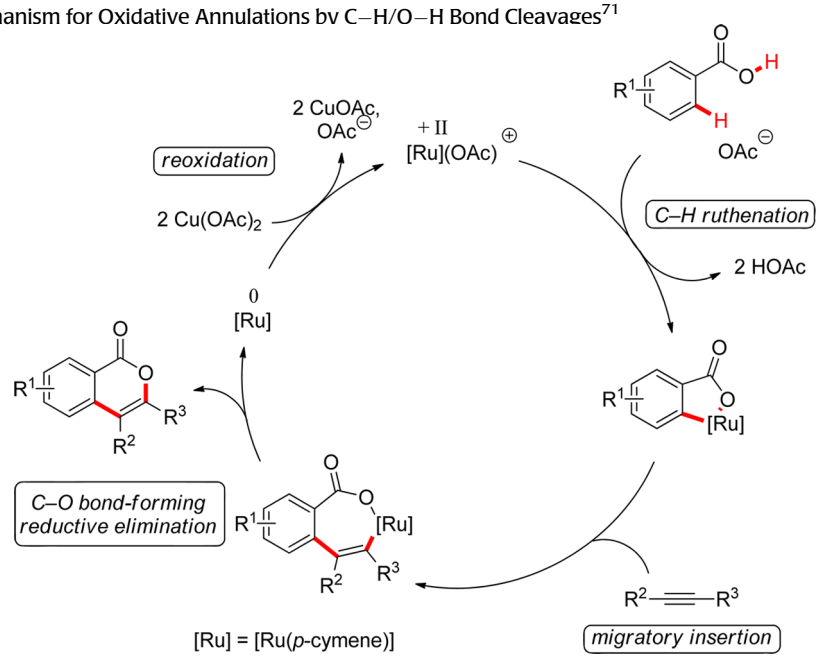
SCHEME 21. Synthesis of Isocoumarins and α-Pyrones[58b,71]



SCHEME 20. Proposed Catalytic Cycle for Oxidative Phthalide Synthesis[67]



SCHEME 22. Proposed Mechanism for Oxidative Annulations by C−H/O−H Bond Cleavages[71]



alkynes by aromatic and heteroaromatic acids and allowed for the synthesis of α-pyrones as well.[58b,71]

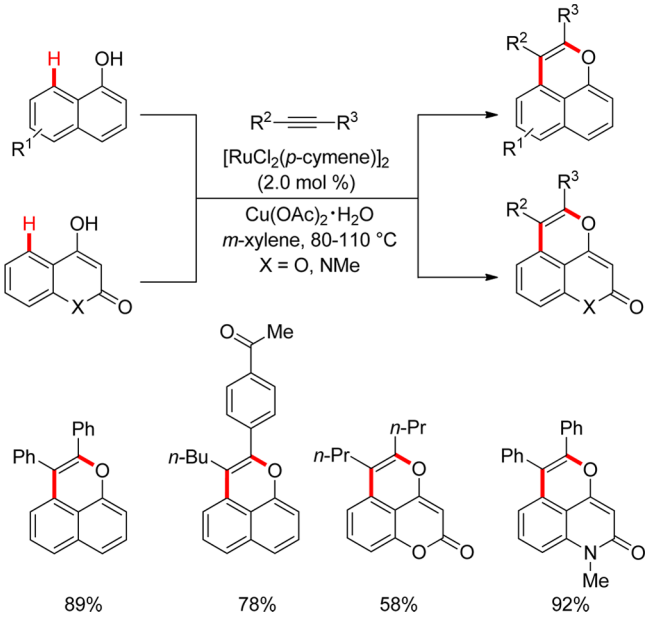
Detailed optimization studies revealed acetates to be crucial additives and provided support for a kinetically relevant C−H/O−H bond ruthenation (Scheme 22).[71]

Moreover, acetate assistance was found to be key to success for ruthenium(II)-catalyzed oxidative alkyne annulations with hydroxyl groups as versatile Lewis basic directing groups.[73] Thereby, naphthols were site-selectively functionalized, both with stoichiometric amounts of external oxidants and with $Cu(OAc)_2 \cdot H_2O$ as the cocatalyst, in an aerobic manner. Further, hydroxyl-assisted C−H bond functionalizations provided step-economical access to diversely decorated fluorescent coumarins and quinolin-2-ones (Scheme 23). As was observed with anilines derivatives (*vide supra*), mechanistic studies with electron-rich naphthols revealed a reversible H/D exchange reaction.

Carboxylate-Assisted C(sp^2)−H Bond Oxidation: C−O Bond Formation

The C−H/O−H bond functionalizations occurred via cascade reactions involving difficult C−O bond-forming reductive eliminations (Scheme 22).[71,73] During studies on the working mode of our catalytic systems, we found that a rather simple change of the terminal oxidant resulted in a considerably altered chemoselectivity, in that an intermolecular C(sp^2)−H hydroxylation proved viable.[74] Interestingly, oxidative C−O bond formations occurred most efficiently with ruthenium(II)

SCHEME 23. Hydroxyl-Directed Alkyne Annulation[73]

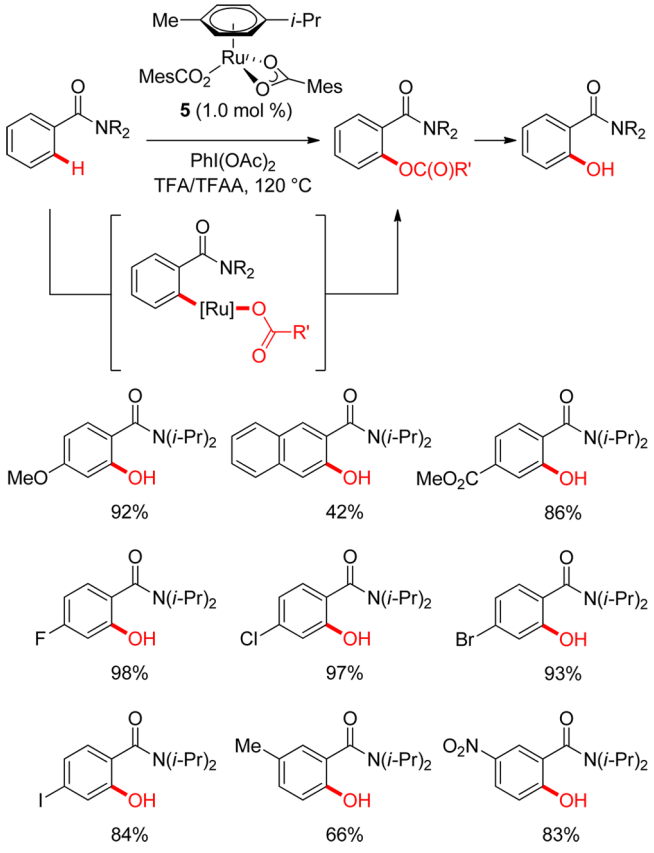


biscarboxylate complex [$Ru(O_2CMes)_2$(*p*-cymene)] (**5**) (Scheme 24),[75] illustrating the power of carboxylate assistance beyond C−C bond-forming processes.[74]

Oxidative Annulations through C−H/N−O Bond Cleavages

The ruthenium(II)-catalyzed annulations via C−H/N−H or C−H/O−H bond cleavages relied on the use of an external oxidant in stoichiometric or cocatalytic amounts (*vide supra*).

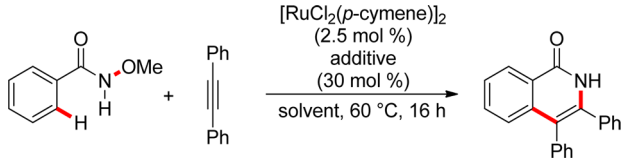
SCHEME 24. Oxidative C(sp^2)–O Bond Formation[74]



Thus, $Cu(OAc)_2 \cdot H_2O$ proved to be essential for these transformations, since it not only acted as the (co)oxidant but also served as the source of acetate for the carboxylate-assisted C–H bond activation step. Conversely, an alternative strategy was viable through the use of substrates bearing N–O bonds as "internal"[76] oxidants. Thus, *N*-methoxybenzamides, oxidized and hence prefunctionalized derivatives of benzamides, were utilized for highly selective syntheses of isoquinolones in the absence of an external oxidant under notably mild reaction conditions.[77] Remarkably, cocatalytic amounts of metal carboxylates were found to be indispensable for achieving efficient C–H bond functionalizations. The high catalytic efficacy of catalysts generated from carboxylates clearly illustrated carboxylate-assisted C–H bond functionalizations, with optimal results being accomplished with KO_2CMes as the cocatalyst and H_2O as the reaction medium (Table 1).[77] Notably, an alternative protocol by Li and Wang employed NaOAc as the additive in MeOH as the solvent,[78] which was also rationalized in terms of acetate-assisted C–H bond ruthenation.

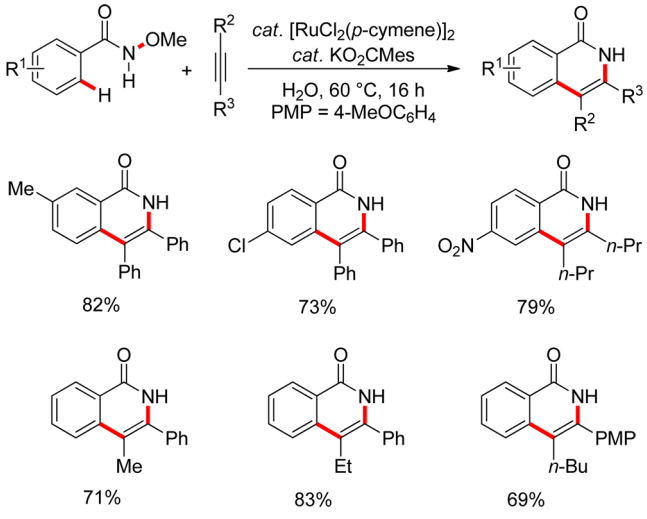
The catalytic system comprising $[RuCl_2(p\text{-cymene})]_2$ and KO_2CMes proved widely applicable and allowed for the conversion of functionalized *N*-methoxybenzamides as well as aryl and alkyl alkynes (Scheme 25).[77]

TABLE 1. Carboxylate Assistance for C–H/N–O Bond Functionalizations[77]

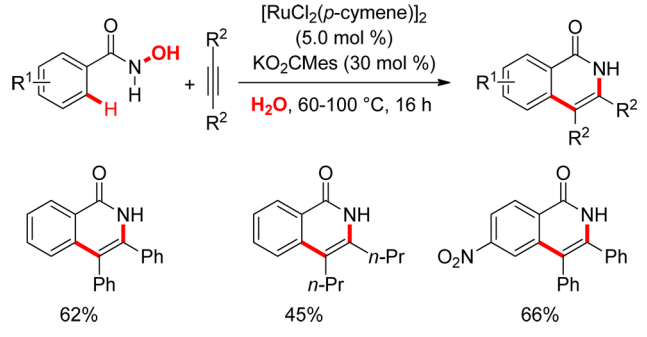


entry	additive	solvent	yield (%)
1		H_2O	17
2	KPF_6	H_2O	25
3	KOAc	H_2O	11
4	NaOAc	H_2O	17
5	KOPiv	H_2O	58
6	**KO_2CMes**	**H_2O**	**81**
7	KO_2CMes	*t*-AmOH	19
8	KO_2CMes	MeOH	65
9	KO_2CMes	DMF	3
10	**KO_2CMes (10 mol %)**	**H_2O**	**76**

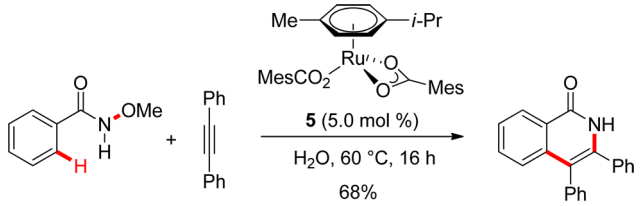
SCHEME 25. Synthesis of Isoquinolones by C–H/N–O Bond Cleavages[77]



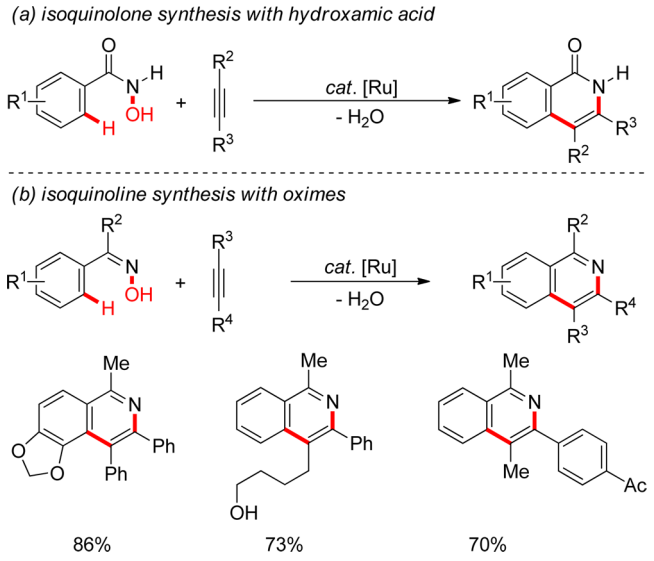
SCHEME 26. Dehydrative Isoquinolone Synthesis with Free Hydroxamic Acids[77]



SCHEME 27. Well-Defined Complex **5** as the Catalyst[77]



SCHEME 28. Dehydrative Alkyne Annulations: Syntheses of Isoquinolones and Isoquinolines[80]



The remarkably high chemoselectivity of the ruthenium(II) catalyst also set the stage for the direct use of free hydroxamic acids for annulations of alkynes (Scheme 26).[77] It is interesting to note that this dehydrative transformation occurred in high yields with H_2O as the reaction medium.

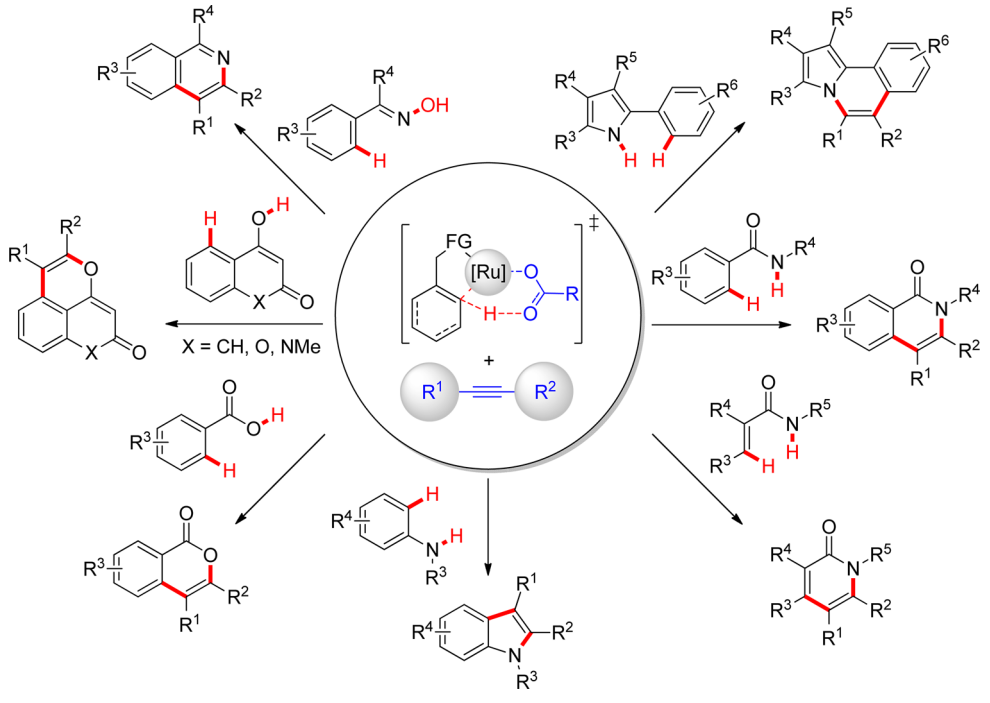
Moreover, the well-defined ruthenium(II) carboxylate complex **5** displayed a catalytic efficacy comparable to the one observed when using the *in situ* generated system (Scheme 27).[77]

The C–H/N–O bond functionalization strategy proved applicable beyond the synthesis of isoquinolones (Scheme 28a). In analogy, this approach very recently set the stage for an extension to the synthesis of isoquinolines[79] (Scheme 28b).[80,81] Thus, ketoximes[82] in lieu of *N*-methoxybenzamides were selectively converted, with base assistance proving to be essential for the dehydrative alkyne annulation to occur in an efficient manner.[80]

Conclusions

Recent years have witnessed significant progress in metal-catalyzed C–H bond functionalizations. For instance, mechanistic insight into base assistance for C–H bond metalations with ruthenium(II) complexes resulted in generally applicable, robust catalysts for direct C–H bond arylations and alkylations of (hetero)arenes. Additionally, carboxylate assistance proved to be instrumental for the

SCHEME 29. Overview of Alkyne Annulations by C–H/Het–H Bond Functionalizations



development of oxidative C−H bond transformations proceeding through C−H/C−H or C−H/Het−H bond cleavages. Hence, C−H/N−H bond functionalizations were exploited for various oxidative alkyne annulations, leading among others to valuable isoquinolones, pyridones, pyrroles, or indoles in a step-economical fashion (Scheme 29). Moreover, analogous reactions via C−H/O−H bond cleavages provided versatile access to phthalides, isocoumarines, or fluorescent pyrans. With respect to sustainable and green chemistry, it is noteworthy that the ruthenium-catalyzed oxidative annulations proved viable in an aerobic fashion with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$ under an atmosphere of ambient air. An additional valuable asset of these methods was represented by the outstanding chemoselectivity of the ruthenium(II) catalysts, which was *inter alia* reflected by an excellent functional group tolerance as well as highly efficient catalysis in water as sustainable reaction medium. As to the catalysts' mode of action, detailed mechanistic studies provided strong support for an initial carboxylate-assisted formation of ruthena(II)cycles. While this elementary step was found to be kinetically relevant for arenes bearing electron-withdrawing directing groups, more electron-rich aniline and phenol derivatives led to a reversible C−H bond ruthenation. The catalytic cycles are completed by migratory insertion, along with reductive elimination and reoxidation of the thus formed ruthenium(0) intermediate. The oxidation to regenerate the catalytically active ruthenium(II) complex was mostly accomplished with $Cu(OAc)_2 \cdot H_2O$, which served as the essential source of acetate anions as well. Annulations of alkynes were however also achieved in the absence of an external oxidant with prefunctionalized substrates displaying reactive N−O bonds, provided that metal carboxylates were added in catalytic amounts. Overall, carboxylate assistance has thus significantly expanded the scope of ruthenium-catalyzed C−H bond functionalizations beyond the limits of the conventional electrophilic activation manifold. Compared with rhodium or palladium catalysis, beneficial features of our ruthenium(II) catalysts are not limited to the significantly reduced costs, but also include their robustness and improved selectivities.[62,63,66] Considering the sustainable nature of direct C−H bond functionalizations, along with increasingly viable intra- and intermolecular C−O and C−N bond-forming reductive eliminations, further exciting developments are expected in this rapidly evolving research area.

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Lutz Ackermann studied chemistry at the Christian-Albrechts-University Kiel, and obtained his Ph.D. in 2001 under the supervision of Alois Fürstner at the Max-Plank-Institut für Kohlenforschung in Mülheim/Ruhr. He was a postdoctoral fellow with Robert G. Bergman (University of California at Berkeley) before initiating his independent research in 2003 at the Ludwig-Maximilians-University München supported within the Emmy Noether-program (DFG). In 2007, he became full professor at the Georg-August-University Göttingen, where, since 2011, he serves as the dean of the faculty of chemistry. The development of novel concepts for homogeneous catalysis and their applications to sustainable organic synthesis are among his main current research interests.

FOOTNOTES

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The author declares no competing financial interest.

REFERENCES

1 *Modern Heterocyclic Chemistry*; Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011.

2 Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, Germany, 2009.

3 Selected reviews on C−H bond functionalizations for the synthesis of heterocycles: (a) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. Heterocycle Formation via Palladium-Catalyzed C−H Functionalization. *Synthesis* **2012**, *44*, 1778–1791. (b) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215–1292. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation. *Chem. Rev.* **2010**, *110*, 624–655. (d) Thansandote, P.; Lautens, M. Construction of Nitrogen-Containing Heterocycles by C−H Bond Functionalization. *Chem.—Eur. J.* **2009**, *15*, 5874–5883 and references cited therein.

4 Hashiguchi, B. G.; Bischof, S. M.; Konnick, M. M.; Periana, R. A. Designing Catalysts for Functionalization of Unactivated C−H Bonds Based on the CH Activation Reaction. *Acc. Chem. Res.* **2012**, *45*, 885–898.

5 (a) Schwarz, H. Chemistry with Methane: Concepts Rather than Recipes. *Angew. Chem., Int. Ed.* **2011**, *50*, 10096–10115. (b) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36*, 255–263.

6 Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. Selective Intermolecular Carbon−Hydrogen Bond Activation by Synthetic Metal Complexes in Homogeneous Solution. *Acc. Chem. Res.* **1995**, *28*, 154–162.

7 Trost, B. M. On Inventing Reactions for Atom Economy. *Acc. Chem. Res.* **2002**, *35*, 695–705.

8 Chen, D. Y.-K.; Youn, S. W. C−H Activation: A Complementary Tool in the Total Synthesis of Complex Natural Products. *Chem.—Eur. J.* **2012**, *18*, 9452–9474.

9 McMurray, L.; O'Hara, F.; Gaunt, M. J. Recent Developments in Natural Product Synthesis Using Metal-Catalysed C−H Bond Functionalisation. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898.

10 Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Rhodium Catalyzed Chelation-Assisted C−H Bond Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 814–825.

11 (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. Transition-Metal-Catalyzed Direct Arylation of (Hetero)Arenes by C−H Bond Cleavage. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (b) Ackermann, L.; Potukuchi, H. K. Regioselective Syntheses of Fully-Substituted 1,2,3-Triazoles: The CuAAC/C−H Bond Functionalization Nexus. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513.

12 Satoh, T.; Miura, M. Catalytic Arylation and Vinylation Reactions Directed by Anionic Oxygen Functions via Cleavage of C−H and C−C Bonds. *Top. Organomet. Chem.* **2007**, *24*, 61–84.

13 Herrmann, P.; Bach, T. Diastereotopos-Differentiating C−H Activation Reactions at Methylene Groups. *Chem. Soc. Rev.* **2011**, *40*, 2022–2038.

14 Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition Metal-Catalyzed C−H Activation Reactions: Diastereoselectivity and Enantioselectivity. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272.

15 Ackermann, L. Catalytic Arylations with Challenging Substrates: From Air-Stable HASPO Preligands to Indole Syntheses and C−H Bond Functionalizations. *Synlett* **2007**, 507–526.

16 September 2012, http://www.platinumgroupmetals.org/: Prices of gold, platinum, rhodium, iridium, palladium and ruthenium: $1730, $1600, $1100, $1050, $669, and $110 US per troy ounce, respectively.

17 Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. Ruthenium Complex-Catalyzed Direct Ortho-Arylation and Alkenylation of 2-Arylpyridines with Organic Halides. *Org. Lett.* **2001**, *3*, 2579–2581.

18 Lewis, L. N.; Smith, J. F. Catalytic Carbon−Carbon Bond Formation via ortho-Metalated Complexes. *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735.

19 Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Efficient Catalytic Addition of Aromatic Carbon−Hydrogen Bonds to Olefins. *Nature* **1993**, *366*, 529–531.

20 Kakiuchi, F.; Chatani, N. Catalytic Methods for C−H Bond Functionalization: Application in Organic Synthesis. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101.

21 (a) Kakiuchi, F.; Kochi, T. Transition-Metal-Catalyzed Carbon-Carbon Bond Formation via Carbon−Hydrogen Bond Cleavage. *Synthesis* **2008**, 3013–3039. (b) An early study on amides as directing groups in palladium catalysis: Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahderon Lett* **2000**, *41*, 2655–2658.

22 Ackermann, L. Carboxylate-Assisted Transition Metal-Catalyzed C−H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315–1345.

23 Gaunt, J. C.; Shaw, B. L. Transition Metal−Carbon Bonds: XL. Palladium(II) Complexes of [(Dimethylamino)methyl]-Ferrocene. *J. Organomet. Chem.* **1975**, *102*, 511–516.

24 Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. Room-Temperature Cyclometallation of Amines, Imines and Oxazolines with $[MCl_2Cp^*]_2$ (M = Rh, Ir) and $[RuCl_2(p\text{-cymene})]_2$. *Dalton Trans.* **2003**, 4132–4138.

25 Biswas, B.; Sugimoto, M.; Sakaki, S. C−H Bond Activation of Benzene and Methane by $M(\eta^2\text{-}O_2CH)_2$ (M = Pd or Pt). A Theoretical Study. *Organometallics* **2000**, *19*, 3895–3908.

26 Boutadla, Y.; Davies, D. L.; MacGregor, S. A.; Poblador-Bahamonde, A. I. Mechanisms of C−H Bond Activation: Rich Synergy between Computation and Experiment. *Dalton Trans.* **2009**, 5820–5831.

27 Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. Proton Abstraction Mechanism for the Palladium-Catalyzed Intramolecular Arylation. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.

28 Lapointe, D.; Fagnou, K. Overview of the Mechanistic Work on the Concerted Metallation−Deprotonation Pathway. *Chem. Lett.* **2010**, *39*, 1118–1126.

29 Gorelsky, S. I.; Lapointe, D.; Fagnou, K. Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation Across a Broad Range of Aromatic Substrates. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

30 Ackermann, L. Air-Stable Bifunctional HASPO Preligands for Metal-Catalyzed Cross-Couplings and Direct C−H Bond Arylations. *Isr. J. Chem.* **2010**, *50*, 652–663.

31 Ackermann, L. Air- and Moisture-Stable Secondary Phosphine Oxides as Preligands in Catalysis. *Synthesis* **2006**, 1557–1571.

32 For direct arylations with inexpensive $[RuCl_3(H_2O)_n]$: (a) Ackermann, L.; Althammer, A.; Born, R. $[RuCl_3(H_2O)_n]$-Catalyzed Direct Arylations with Bromides as Electrophiles. *Synlett* **2007**, 2833–2836. (b) Ackermann, L.; Althammer, A.; Born, R. $[RuCl_3(H_2O)_n]$-catalyzed Direct Arylations. *Tetrahedron* **2008**, *64*, 6115–6124.

33 Ackermann, L. Phosphine Oxides as Preligands in Ruthenium-Catalyzed Arylations via C−H Bond Functionalization Using Aryl Chlorides. *Org. Lett.* **2005**, *7*, 3123–3125.

34 Ackermann, L.; Althammer, A.; Born, R. Catalytic Arylation Reactions by C−H Bond Activation with Aryl Tosylates. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622.

35 Ackermann, L.; Born, R.; Alvarez Bercedo, P. Ruthenium(IV) Alkylidenes as Precatalysts for Direct Arylations of Alkenes with Aryl Chlorides and an Application to Sequential Catalysis. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364–6367.

36 Ackermann, L.; Vicente, R.; Althammer, A. Assisted Ruthenium-Catalyzed C−H Bond Activation: Carboxylic Acids as Cocatalysts for Generally Applicable Direct Arylations in Apolar Solvents. *Org. Lett.* **2008**, *10*, 2299–2302.

37 Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. Mechanistic Insight into Direct Arylations with Ruthenium(II) Carboxylate Catalysts. *Org. Lett.* **2010**, *12*, 5032–5035.

38 Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. Direct Arylation of Arene C−H Bonds by Cooperative Action of NHCarbene−Ruthenium(II) Catalyst and Carbonate via Proton Abstraction Mechanism. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157.

39 Ackermann, L.; Mulzer, M. Dehydrative Direct Arylations of Arenes with Phenols via Ruthenium-Catalyzed C−H and C−OH Bond Functionalizations. *Org. Lett.* **2008**, *10*, 5043–5036.

40 Ackermann, L.; Pospech, J.; Potukuchi, H. K. Well-Defined Ruthenium(II) Carboxylate as Catalyst for Direct C−H/C−O Bond Arylations with Phenols in Water. *Org. Lett.* **2012**, *14*, 2146–2149.

41 (a) Ackermann, L.; Vicente, R. Catalytic Direct Arylations in Polyethylene Glycol (PEG): Recyclable Palladium(0) Catalyst for C−H Bond Cleavages in the Presence of Air. *Org. Lett.* **2009**, *11*, 4922–4925. (b) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. C−H Bond Functionalization in Water Catalyzed by Carboxylato Ruthenium(II) Systems. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629–6632.

42 Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J.-F.; O'Shea, P. D.; Davies, I. W. Preparative Scale Synthesis of the Biaryl Core of Anacetrapib via a Ruthenium-Catalyzed Direct Arylation Reaction: Unexpected Effect of Solvent Impurity on the Arylation Reaction. *J. Org. Chem.* **2011**, *76*, 1436–1439.

43 Ackermann, L.; Lygin, A. V. Ruthenium-Catalyzed Direct C−H Bond Arylations of Heteroarenes. *Org. Lett.* **2011**, *13*, 3332–3335.

44 Ackermann, L.; Diers, E.; Manvar, A. Ruthenium-Catalyzed C−H Bond Arylations of Arenes Bearing Removable Directing Groups via Six-Membered Ruthenacycles. *Org. Lett.* **2012**, *14*, 1154–1157.

45 Dastbaravardeh, N.; Schnürch, M.; Mihovilovic, M. D. Ruthenium(II)-Catalyzed sp^3 C−H Bond Arylation of Benzylic Amines Using Aryl Halides. *Org. Lett.* **2012**, *14*, 3792–3795.

46 Ackermann, L.; Novák, P. Regioselective Ruthenium-Catalyzed Direct Benzylations of Arenes through C−H Bond Cleavages. *Org. Lett.* **2009**, *11*, 4966–4969.

47 Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. Ruthenium-Catalyzed Regioselective Direct Alkylation of Arenes with Unactivated Alkyl Halides through C−H Bond Cleavage. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048.

48 Ackermann, L. Metal-Catalyzed Direct Alkylations of (Hetero)Arenes via C−H Bond Cleavages with Unactivated Alkyl Halides. *Chem. Commun.* **2010**, *46*, 4866–4877.

49 Ackermann, L.; Hofmann, N.; Vicente, R. Carboxylate-Assisted Ruthenium-Catalyzed Direct Alkylations of Ketimines. *Org. Lett.* **2011**, *13*, 1875–1877.

50 Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. Ruthenium-Catalyzed C−H Bond Functionalizations of 1,2,3-Triazol-4-yl-Substituted Arenes: Dehydrogenative Couplings versus Direct Arylations. *Synthesis* **2010**, 2245–2253.

51 Weissman, H.; Song, X.; Milstein, D. Ru-Catalyzed Oxidative Coupling of Arenes with Olefins Using O_2. *J. Am. Chem. Soc.* **2001**, *123*, 337–338.

52 Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. Ruthenium-Catalyzed Oxidative Vinylation of Heteroarene Carboxylic Acids with Alkenes via Regioselective C−H Bond Cleavage. *Org. Lett.* **2011**, *13*, 706–708.

53 Song, G.; Wang, F.; Li, X. C−C, C−O and C−N Bond Formation via Rhodium(III)-Catalyzed Oxidative C−H Activation. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678.

54 Zhu, C.; Wang, R.; Falck, J. R. Amide-Directed Tandem C−C/C−N Bond Formation through C−H Activation. *Chem.—Asian J.* **2012**, *7*, 1502–1514.

55 An early example: (a) Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. Aromatic Substitution of Olefins. VI. Arylation of Olefins with Palladium(II) Acetate. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169. An early report on rhodium-catalyzed oxidative alkenylations: (b) Hong, P.; Yamazaki, H. Reactions of Ethylene and Benzenes Catalyzed by Rhodium Carbonyls under Carbon Monoxide. The Formation of Styrenes and 3-Pentanone. *Chem. Lett.* **1979**, 1335–1336.

56 For recent progress with rhodium catalysts, see: Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem.—Eur. J.* **2010**, *16*, 11212–11222.

57 (a) Recent advances with palladium catalysts: Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C−H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788–802. (b) A notable nickel-catalyzed example: Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. Nickel-Catalyzed Chelation-Assisted Transformations Involving ortho C−H Bond Activation: Regioselective Oxidative Cycloaddition of Aromatic Amides to Alkynes. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955.

58 (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. Ruthenium-Catalyzed Oxidative Annulation via C−H/N−H Bond Cleavages. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382. (b) Deponti, M.; Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. Ruthenium-Catalyzed C−H/O−H and C−H/N−H Bond Functionalizations: Oxidative Annulations of Cyclopropyl-Substituted Alkynes. *Org. Biomol. Chem.* **2013**, *11*, 142–148.

59 Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. What are the pK_a Values of C−H Bonds in Aromatic Heterocyclic Compounds in DMSO? *Tetrahedron* **2007**, *63*, 1568–1576.

60 Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. Ruthenium-Catalyzed Oxidative Coupling/Cyclization of Isoquinolones with Alkynes through C−H/N−H Activation: Mechanism Study and Synthesis of Dibenzo[a,g]quinolizin-8-one Derivatives. *Chem.—Eur. J.* **2012**, *18*, 12873–12879.

61 Li, B.; Roisnel, T.; Darcel, C.; Dixneuf, P. H. Cyclometallation of Arylimines and Nitrogen-Containing Heterocycles via Room-Temperature C−H Bond Activation with Arene Ruthenium(II) Acetate Complexes. *Dalton Trans.* **2012**, *41*, 10934–10937.

62 Ackermann, L.; Lygin, A. V.; Hofmann, N. Ruthenium-Catalyzed Oxidative Synthesis of 2-Pyridones through C−H/N−H Bond Functionalizations. *Org. Lett.* **2011**, *13*, 3278–3281.

63 Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. Synthesis of 2-Pyridones and Iminoesters via Rh(III)-Catalyzed Oxidative Coupling between Acrylamides and Alkynes. *Org. Lett.* **2010**, *12*, 5462–5465.

64 (a) Ackermann, L.; Lygin, A. V. Cationic Ruthenium(II) Catalysts for Oxidative C−H/N−H Bond Functionalizations of Anilines with Removable Directing Group: Synthesis of Indoles in Water. *Org. Lett.* **2012**, *14*, 764–767. (b) See also: Wang, L.; Ackermann, L. Versatile Pyrrole Synthesis through Ruthenium(II)-Catalyzed Alkene C−H Bond Functionalization on Enamines. *Org. Lett.* **2013**, *15*, 176–179.

65 Butler, R. N.; Coyne, A. G. Water: Nature's Reaction Enforcer—Comparative Effects for Organic Synthesis "In-Water" and "On-Water". *Chem. Rev.* **2010**, *110*, 6302–6337.

66 Ackermann, L.; Wang, L.; Lygin, A. V. Ruthenium-Catalyzed Aerobic Oxidative Coupling of Alkynes with 2-Aryl-Substituted Pyrroles. *Chem. Sci.* **2012**, *3*, 177–180.

67 Ackermann, L.; Pospech, J. Ruthenium-Catalyzed Oxidative C−H Bond Alkenylations in Water: Expedient Synthesis of Annulated Lactones. *Org. Lett.* **2011**, *13*, 4153–4155.

68 A review: Satoh, T.; Miura, M. Transition-Metal-Catalyzed Regioselective Arylation and Vinylation of Carboxylic Acids. *Synthesis* **2010**, 3395–3409.

69 (a) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, DOI: 10.1039/C2SC21524A. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C−H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879–5918. A recent example from our laboratories: (c) Graczyk, K.; Ma, W.; Ackermann, L. Oxidative Alkenylation of Aromatic Esters by Ruthenium-Catalyzed Twofold C−H Bond Cleavages. *Org. Lett.* **2012**, *14*, 4110–4113.

70 Related ruthenium(II)-catalyzed alkenylations by aza-Michael addition: Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. Ruthenium-Catalyzed Oxidative C−H Alkenylations of Anilides and Benzamides in Water. *Org. Lett.* **2012**, *14*, 728–731.

71 Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. Versatile Synthesis of Isocoumarins and α-Pyrones by Ruthenium-Catalyzed Oxidative C−H/O−H Bond Cleavages. *Org. Lett.* **2012**, *14*, 930–933.

72 Chinnagolla, R. K.; Jeganmohan, M. Regioselective Synthesis of Isocoumarins by Ruthenium-Catalyzed Aerobic Oxidative Cyclization of Aromatic Acids with Alkynes. *Chem. Commun.* **2012**, *48*, 2030–2032.

73 Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. Hydroxyl-Directed Ruthenium-Catalyzed C−H Bond Functionalization: Versatile Access to Fluorescent Pyrans. *Org. Lett.* **2012**, *14*, 3416–3419.

74 Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. Ruthenium-Catalyzed Oxidative $C(sp^2)$−H Bond Hydroxylation: Site-Selective C−O Bond Formation on Benzamides. *Org. Lett.* **2012**, *14*, 4210–4213.

75 For independent hydroxylations of benzoic esters largely with Selectfluor or $K_2S_2O_8$ as the oxidant, see: Yang, Y.; Lin, Y.; Rao, Y. Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with Ester as an Effective Directing Group. *Org. Lett.* **2012**, *14*, 2874–2877.

76 Patureau, F. W.; Glorius, F. Oxidizing Directing Groups Enable Efficient and Innovative C−H Activation Reactions. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977–1979.

77 Ackermann, L.; Fenner, S. Ruthenium-Catalyzed C−H/N−O Bond Functionalization: Green Isoquinolone Syntheses in Water. *Org. Lett.* **2011**, *13*, 6548–6551.

78 Li, B.; Feng, H.; Xu, S.; Wang, B. Ruthenium-Catalyzed Isoquinolone Synthesis through C−H Activation Using an Oxidizing Directing Group. *Chem.—Eur. J.* **2011**, *17*, 12573–12577.

79 See also: Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. Ru(II)-Catalyzed C−H Bond Activation for the Synthesis of Substituted Isoquinolinium Salts from Benzaldehydes, Amines, and Alkynes. *Org. Lett.* **2012**, *14*, 3478–3481.

80 Kornhaaß, C.; Li, J.; Ackermann, L. Cationic Ruthenium Catalysts for Alkyne Annulations with Oximes by C−H/N−O Functionalizations. *J. Org. Chem.* **2012**, *77*, 9190–9198.

81 Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. Ruthenium-Catalyzed Highly Regioselective Cyclization of Ketoximes with Alkynes by C−H Bond Activation: A Practical Route to Synthesize Substituted Isoquinolines. *Org. Lett.* **2012**, *14*, 3032–3035.

82 Reaction sequences comprising ortho-selective hydroarylation and subsequent nucleophilic attack on aromatic ketones: Chinnagolla, R. K.; Jeganmohan, M. Ruthenium-Catalyzed Regioselective Cyclization of Aromatic Ketones with Alkynes: An Efficient Route to Indenols and Benzofulvenes. *Eur. J. Org. Chem.* **2012**, 417–423.