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C–H nitrogenation and oxygenation by ruthenium catalysis

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Remarkable recent progress has been accomplished in direct C–H functionalizations for the formation of C–N and C–O bonds through the use of readily accessible ruthenium catalysts. Particularly, ruthenium(II) complexes allowed for challenging direct C(sp^2)–H hydroxylation of arenes. These catalysts set the stage for step-economical C–H functionalization with electron-rich as well as electron-deficient (hetero)arenes and, therefore, provided versatile access to diversely decorated phenols. While a number of synthetically useful protocols for ruthenium-catalyzed C(sp^3)–H bond nitrogenation have been elaborated, the analogous transformations of more stable C(sp^2)–H bonds were very recently achieved.

1. Introduction

Oxygenated and nitrogenated aromatic molecules are key intermediates in organic synthesis and constitute important structural motifs of useful pharmaceuticals, agrochemicals, polymers, and biologically active compounds (Scheme 1).[1] The practical importance of substituted anilines and phenols in these applied areas has resulted in a continued strong demand for versatile methods for their preparation. The direct catalytic transformation of otherwise unreactive C(sp^2)–H or C(sp^3)–H bonds[2] into C–N or C–O bonds[3] represents an environmentally benign as well as economically attractive strategy (Scheme 2). This approach compares favorably to classical protocols with respect to the overall minimization of by-product formation (atom-economy), and the optimization of the required reaction steps (step-economy).[4] For instance, the direct C–H amination represents an appealing alternative to the useful palladium- or copper-catalyzed amination of organic electrophiles[5] or to other indirect methods.[6]

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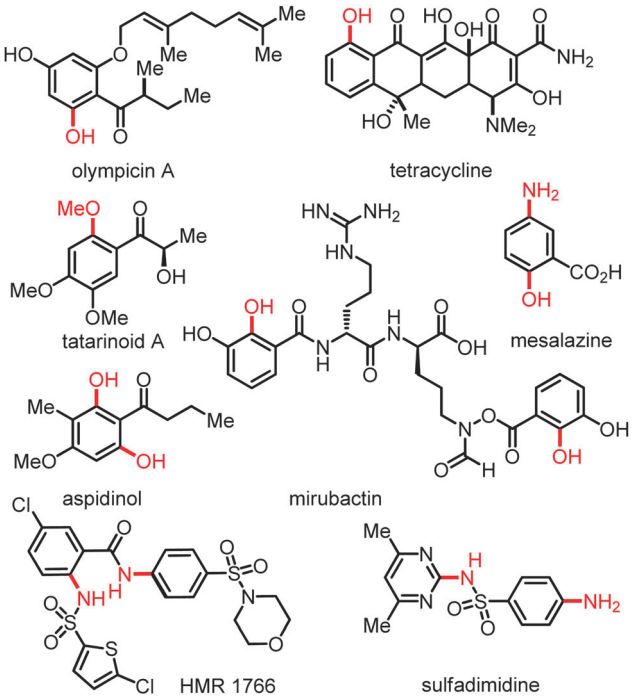
Sergei I. Kozhushkov was born in 1956 in Kharkov, USSR. He studied chemistry at Lomonosov Moscow State University, where he obtained his doctoral degree in 1983 under the supervision of Professor N. S. Zefirov and performed his "Habilitation" in 1998. From 1983 to 1991, he worked at Moscow State University and then at Zelinsky Institute of Organic Chemistry. In 1991, he joined the research group of Professor A. de Meijere (Georg-August-Universität Göttingen, Germany) as an Alexander von Humboldt Research Fellow. Since 2001 he has held a permanent position as a Senior Scientist at the Georg-August-University of Göttingen. Since 2007, he has been working in the research group of Professor L. Ackermann (Georg-August-Universität Göttingen, Germany).

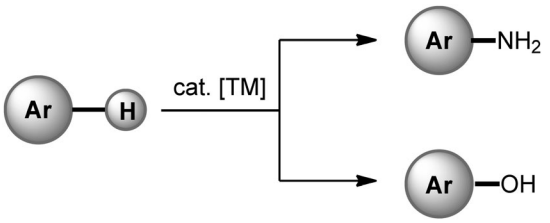


Scheme 1 Selected bioactive compounds based on phenols or anilines.

Since the early discoveries reported by Breslow and Gellman[7a,b] as well as Fujiwara,[7c] a plethora of synthetically useful protocols for catalyzed direct nitrogenation and oxygenation[8] of alkanes and arenes has been devised, mostly using palladium,[9,10] rhodium,[11] copper[12] or iron[13] catalysts. In stark contrast, readily available ruthenium complexes[14] have until recently been underdeveloped as catalysts for C–H bond nitrogenation and oxygenation. This feature article summarizes the recent rapid development of ruthenium-catalyzed chelation-assisted direct C(sp^3)–H and C(sp^2)–H bond nitrogenation and oxygenation up to autumn 2013, with a particular focus on the recent progress.

Lutz Ackermann

Lutz Ackermann (1972) studied Chemistry at the Christian-Albrechts-University Kiel, Germany, and received his PhD from the University of Dortmund in 2001 for research under the supervision of Alois Fürstner at the Max-Plank-Institut für Kohlenforschung in Mülheim/Ruhr. He was a postdoctoral coworker in the laboratories of Robert G. Bergman at the University of California at Berkeley before initiating his independent career in 2003 at the Ludwig-Maximilians-University München supported by the Emmy Noether-programme of the DFG. In 2007, he was appointed as Full Professor at the Georg-August-University Göttingen. His recent awards and distinctions include a JSPS visiting professor fellowship (2009), an AstraZeneca Excellence in Chemistry Award (2011) and an ERC Grant (2012) as well as visiting professorships at the Universita degli Studi di Milano, Italy (2007), and the University of Wisconsin at Madison (2008). The development of novel concepts for sustainable catalysis, with a particular focus on C–H functionalizations, and their applications to organic synthesis constitute his major current research interests.



Scheme 2 C–H activation-based direct aniline and phenol syntheses.

2. Direct C–H nitrogenation

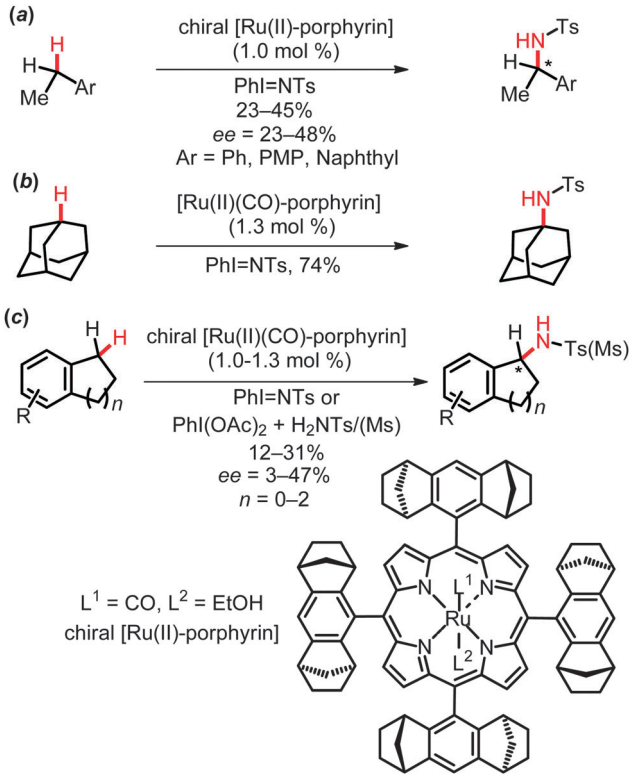
Significant advances in the development of ruthenium-catalyzed C–H bond nitrogenation were achieved over the past two decades by Che, Du Bois and Blakey as well as Cenini, Gallo and Ragaini among others.[15–18] Amidation of C(sp^3)–H bonds with ruthenium catalysts has been studied extensively and developed to a level of efficiency that proved suitable for its application to complex molecule syntheses. In contrast, only a few selected reports on ruthenium-catalyzed amination and amidation of more stable C(sp^2)–H bonds are available as of yet.

2.1 Amidation of C(sp^3)–H bonds

Several elegant protocols for the ruthenium-catalyzed intermolecular amidation of C(sp^3)–H bonds have been established by Che and co-workers.[15] Thus, amidation of aliphatic, benzylic and allylic C–H bonds proved to be viable with iminoiodinane $RSO_2N{=}IPh$ as the nitrene source, which could be conveniently generated *in situ* from RSO_2NH_2 and (diacetoxyiodo)benzene, $PhI(OAc)_2$. These reactions were conducted with both achiral and chiral ruthenium porphyrin complexes (Scheme 3). In the latter cases, only moderate to low yields and enantioselectivities were obtained.

The entropically favored intramolecular amidation of C(sp^3)–H bonds is characterized by improved efficacies, as well as excellent diastereo- and remarkable enantioselectivities. Several efficient protocols were elaborated for the catalytic amidation of benzylic and allylic C–H bonds in substrates **1** to form five- and six-membered heterocycles **2**. Indeed, the rational design of different types of complexes highlighted different ruthenium catalysts to be suitable in the presence of weak bases or molecular sieves, such as ruthenium porphyrins,[16] cationic ruthenium(II)-pybox catalysts, as for instance complex **3**,[17] or the mixed-valent paddlewheel ruthenium complexes tetrakis(2-oxypyridinato)diruthenium(II,III) chloride, $[Ru_2(hp)_4Cl]$[18] (Scheme 4).

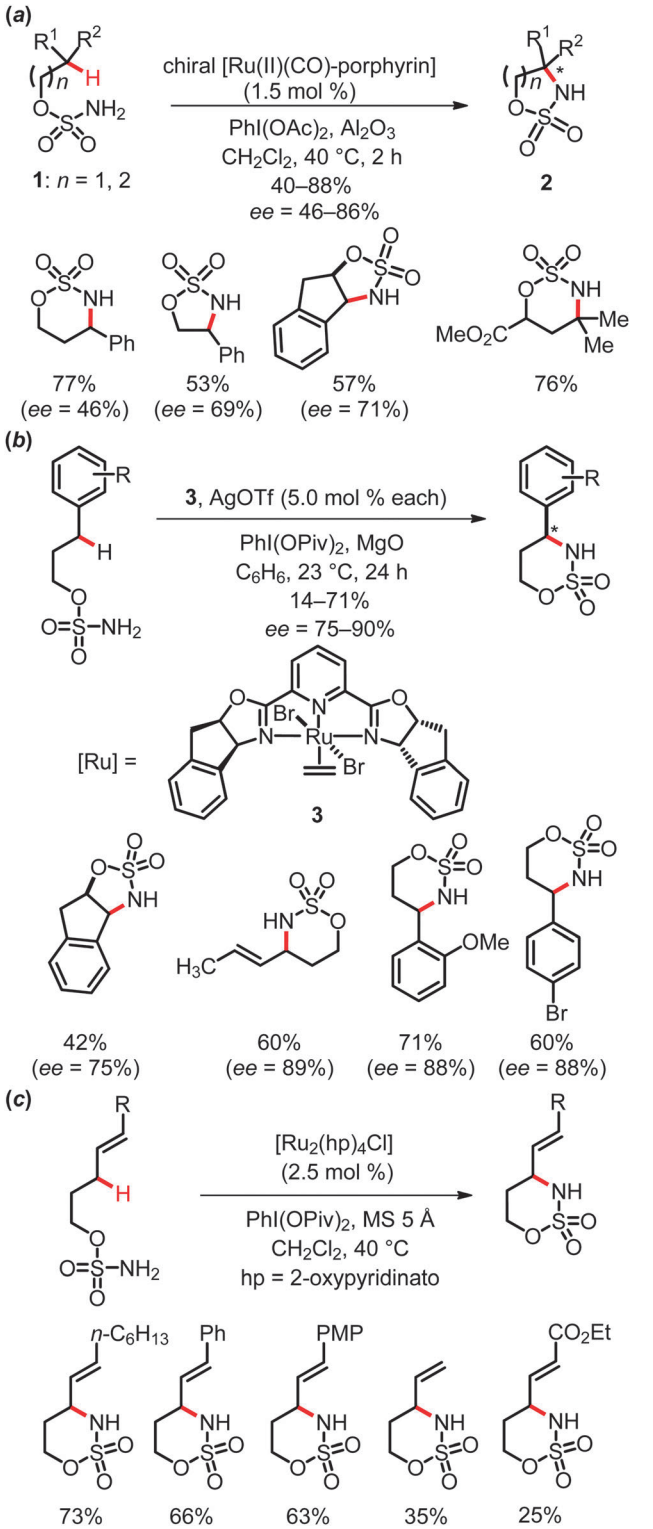
Notably, ruthenium catalysts allowed for intramolecular amidation of allylic C–H bonds, while related rhodium complexes



Scheme 3 Intermolecular amidation of aliphatic and benzylic C(sp^3)–H bonds; conditions: cat. [Ru], CH_2Cl_2, 40 °C, 2 h.

led to a different chemoselectivity, namely aziridination of the double bond.[11a,18] Mechanistically, the key step of the ruthenium-catalyzed direct amidation was found to be the insertion of ruthenium nitrenoids into C(sp^3)–H bonds, which therefore renders potential transformations of more stable C(sp^2)–H bonds significantly more challenging. Most probably, the amidation reaction initiates from iminoiodinane **4** *via* treatment of substrate **1** with (diacetoxyiodo)benzene $PhI(OAc)_2$.[10a] Coordination of compound **4** to the ruthenium complex gives rise to intermediate **A** and subsequently generates the active ruthenium nitrenoid intermediate **B**. Finally, the outer-sphere C–H bond functionalization step furnishes amide **C**, which thereafter affords the heterocyclic product **2**, regenerating the active catalyst (Scheme 5).

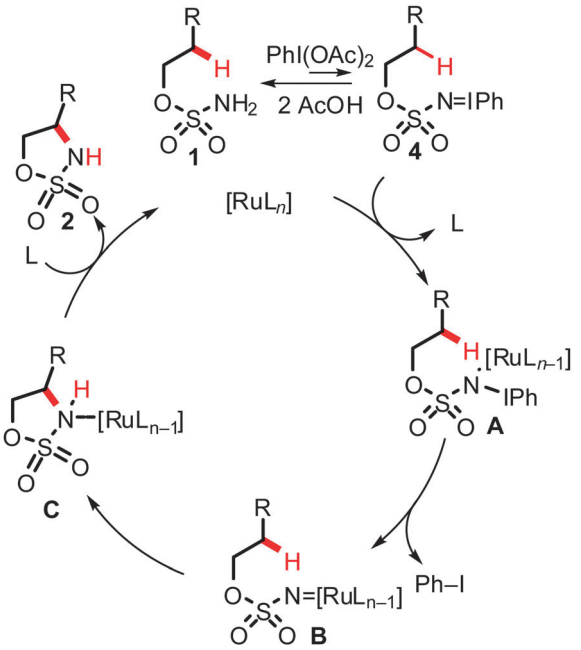
The exact working mode of the elementary transformation **B** → **C** does not only depend on the nature of the transition metal, but also on the specific coordination chemistry of the ruthenium complex. Both computational and experimental studies on $[Ru_2(hp)_4Cl]$-promoted amidation [kinetic isotope effect (KIE) $k_H/k_D \approx 4.9$][18] disclosed a stepwise C–H insertion with the formation of a short-lived diradical species, which is in contrast to the concerted insertion process postulated for rhodium catalysis (KIE ≈ 2.6). However, the two pathways of C–H bond insertion and hydrogen atom transfer were both proposed on the basis of computational studies (DFT) of reactions catalyzed by cationic ruthenium(II)-pybox complexes.[17b] These studies demonstrated the importance of ligand acceleration and substrate structure in these amidations.



Scheme 4 Intramolecular amidation of C(sp^3)–H bonds.

2.2 Amination and amidation of C(sp^2)–H bonds

Given the outer-sphere reaction mode of the above mentioned C–H bond nitrogenations, only relatively few examples of related C(sp^2)–H bond aminations and amidations are available. Yet, the versatility and mechanistic diversity of these C–N bond forming

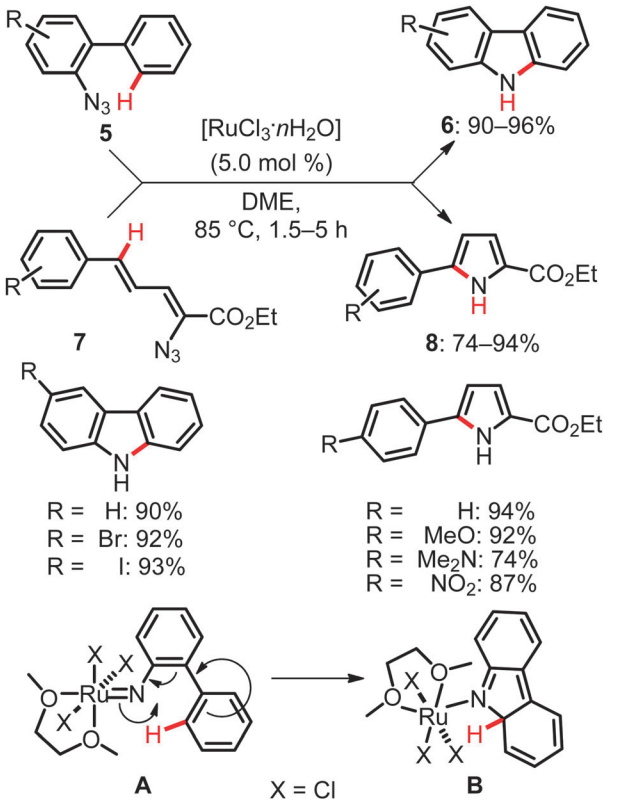


Scheme 5 Mechanistic rationalization of ruthenium-catalyzed intramolecular amidation of C(sp^3)–H bonds.

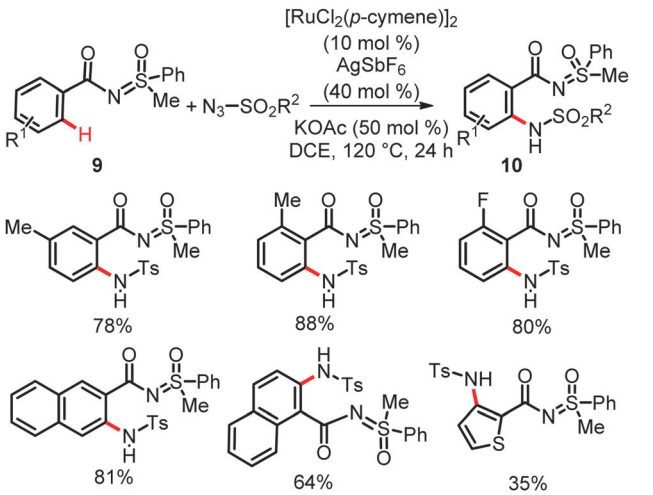
processes render them especially attractive for theoreticians and synthetically oriented chemists. These transformations can be categorized into two distinct modes of action. First, direct functionalizations were viable by the insertion of ruthenium nitrenoids into unactivated C–H bonds. Second, approaches exploiting dehydrogenative[19] aminations by C–H/N–H bond activation were realized. As an example of the former transformations, the intramolecular amination reactions of *ortho*-aryl phenylazides **5** and 1-azido-1,3-butadienes **7** furnished carbazoles **6** and pyrroles **8**, respectively. In this transformation the active catalyst was generated from the user-friendly, inexpensive [$RuCl_3 \cdot nH_2O$], which effectively facilitated the C–H bond aminations (Scheme 6).[20]

Computational studies on these aminations[20,21] indicated that (i) the ruthenium species exhibited a higher activity than typical iridium or rhodium complexes, (ii) these catalytic reactions formally invoked a Ru(III)/Ru(V) catalytic cycle and (iii) a two-step process including formal electrocyclization **A** → **B** (Scheme 6) was involved in the catalytic amination. The latter hypothesis was further experimentally supported.[20]

In contrast to these intramolecular reactions, cationic ruthenium(II) complexes derived from [$RuCl_2$(*p*-cymene)]$_2$ proved to be most effective for intermolecular nitrogenation of C(sp^2)–H bonds with an excellent site- and chemo-selectivity, along with a remarkably broad substrate scope. Thus, the catalytic system consisting of [$RuCl_2$(*p*-cymene)]$_2$, $AgSbF_6$ and KOAc appeared to be appropriate for intermolecular *ortho*-amidations through direct C(sp^2)–H bond nitrogenation on *N*-benzoylated sulfoximines **9** with sulfonyl azides (Scheme 7).[22] These transformations displayed an excellent tolerance of various functional groups and provided an expedient approach to anthranilic acid derivatives through simple base-mediated



Scheme 6 Intramolecular ruthenium-catalyzed amination of C(sp^3)–H bonds.

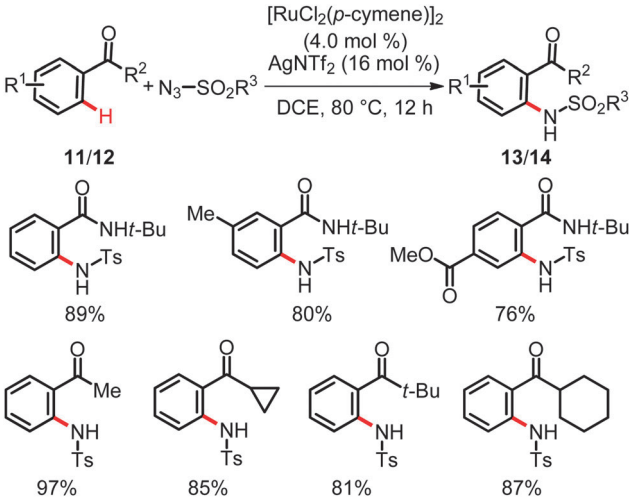


Scheme 7 Ruthenium-catalyzed amidation of *N*-benzoylated sulfoximines **9**.

hydrolysis of thus obtained amidation products **10**. Likely, KOAc facilitated the formation of a cationic ruthenium(II) carboxylate catalyst.

The power of this strategy was elegantly highlighted by the synthesis of HMR 1766 (Scheme 1), which targets deficient NO signaling in hypertension, peripheral, and coronary artery disease as well as heart failure.

Comparable catalytic conditions were utilized by Chang and co-workers in independent studies on ruthenium-catalyzed

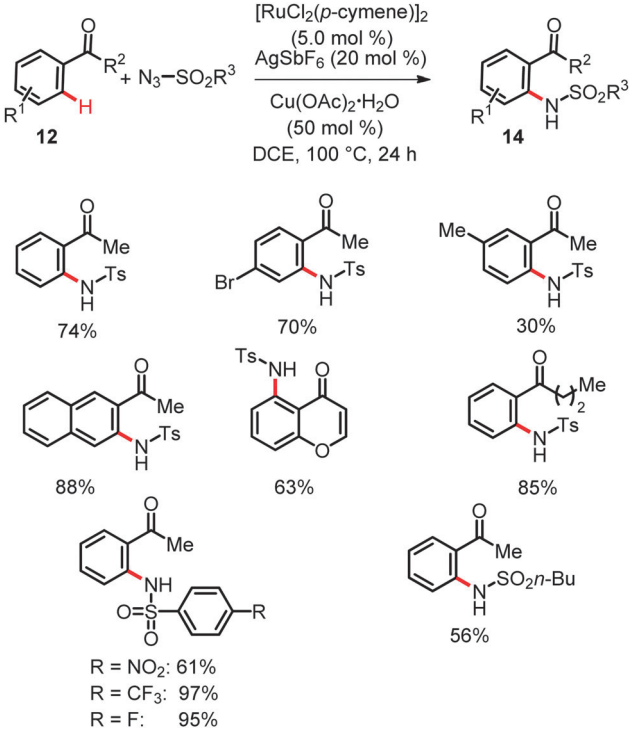


Scheme 8 Intermolecular C–H amidation of benzamides **11** and ketones **12**.

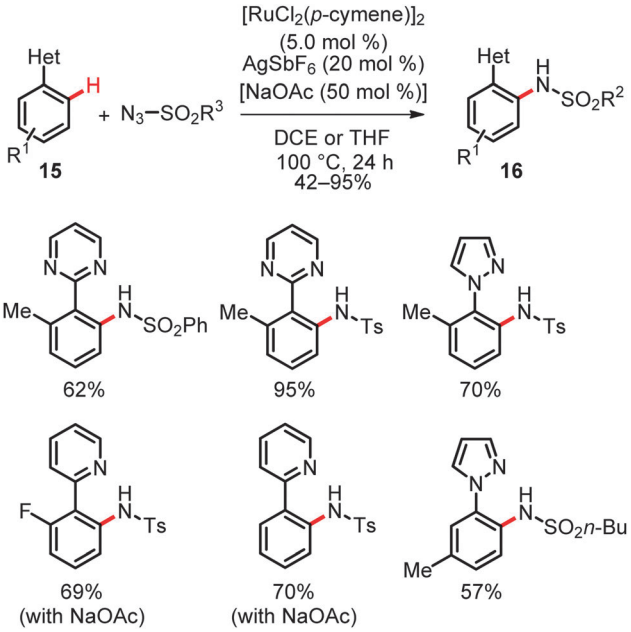
C–H bond amidations on arenes bearing synthetically useful directing groups,[23] such as amides (**11**) or ketones (**12**) (Scheme 8).[24]

A wide range of benzamides **11** and aryl ketone **12** was readily amidated at the *ortho*-position by using sulfonyl azides with excellent catalytic efficacy and selectivity. It is particularly noteworthy that such a facile nitrogenation has not been reported for rhodium or palladium catalysis. The practical importance of the thus obtained products **13** and **14** was showcased by the preparation of a wide range of heterocycles with potential biological activities.

As to the catalysts working mode, detailed mechanistic studies revealed KIE for these amidations of $k_H/k_D \approx 5.9$ for the amides **11** and $k_H/k_D \approx 2.7$ for the phenones **12**.[24] These findings



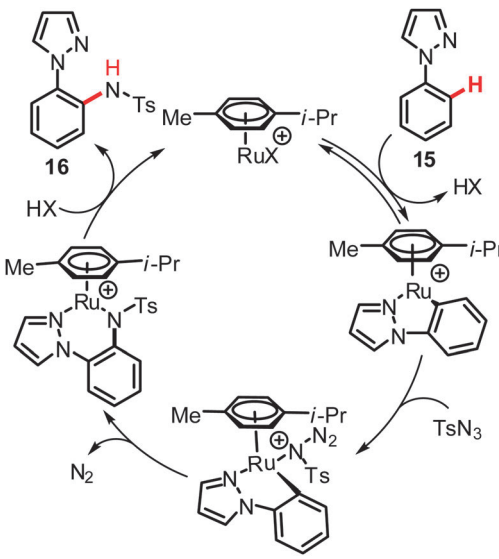
Scheme 9 Ruthenium-catalyzed C–H amidation of aromatic ketones **12**.



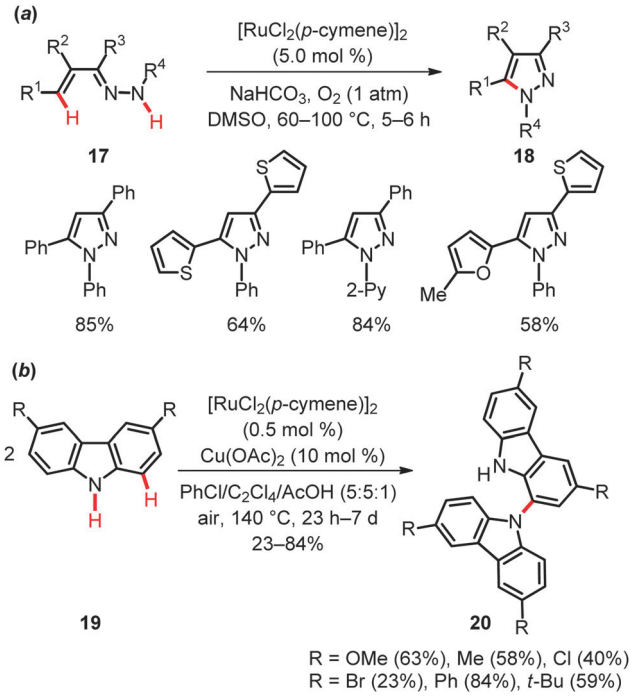
Scheme 10 C–H amidation of substrates **15**.

indicated the initial C–H bond activation to occur *via* an electrophilic-type metalation in an irreversible fashion and, thus, to be kinetically relevant. In contrast, in the related ruthenium(II)-catalyzed intermolecular *ortho*-C–H amidation of phenones **12** in the presence of substoichiometric quantities of $Cu(OAc)_2 \cdot H_2O$ (Scheme 9)[25] the C–H bond metalation was suggested to be reversible in nature. This observation can, for example, be rationalized in terms of heterobimetallic cooperative[26] catalysis being of importance in the latter case.[25a]

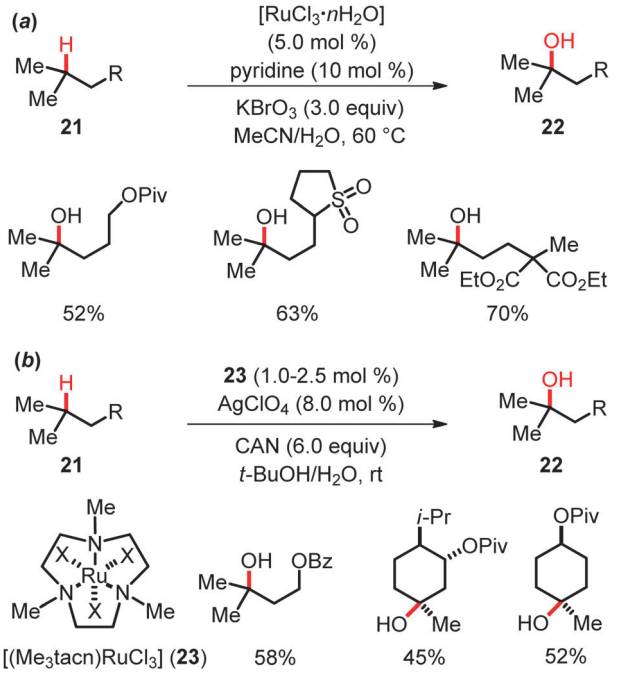
Moreover, valuable heteroaromatic groups allowed for chelation-assisted amidation of arenes with various alkyl and aryl sulfonyl azides, thereby setting the stage for C–N bond



Scheme 11 Proposed mechanism of the intermolecular C(sp^2)–H amidations (X = Cl or OAc).



Scheme 12 Ruthenium-catalyzed dehydrogenative amination.



Scheme 13 Ruthenium-catalyzed hydroxylation of C(sp^3)–H bonds.

formations on pyrazolyl-, pyrimidyl- or pyridyl-substituted arenes and heteroarenes **15** in good to excellent yields (Scheme 10).[27] Intermolecular competition experiments with isotopically labeled starting materials were indicative of a reversible ruthenation event with a KIE of $k_H/k_D \approx 1.3$. Hence, the C–H bond activation likely occurred here by a reversible electrophilic-type metalation and is not involved in the rate limiting step. The proposed working mode postulated for this catalytic system is depicted in Scheme 11.[27a]

The second approach, namely ruthenium-catalyzed dehydrogenative amination by C–H/N–H bond functionalization, was accomplished with unsaturated hydrazones **17** to furnish tri- and tetrasubstituted pyrazoles **18**[28] (Scheme 12a) and for the dehydrogenative homo-coupling of carbazoles **19** (Scheme 12b).[29] These oxidative couplings proved viable with oxygen or air, respectively, as the sacrificial oxidants. This strategy was found to be generally useful and demonstrated a broad substrate scope and a considerable tolerance of important functional groups.

The KIE value of $k_H/k_D \approx 2.4$ obtained for the pyrazole formation suggested the C–H metalation in substrate **17** to be kinetically relevant.[28] In contrast, preliminary mechanistic investigations on the oxidative carbazole homo-coupling by Patureau illustrated the initial C–H activation in carbazole **19** not to be rate limiting (*cf.* Schemes 8–11). Notably, both ruthenium and copper complexes were found to be mandatory for the C–H bond activation step.[29]

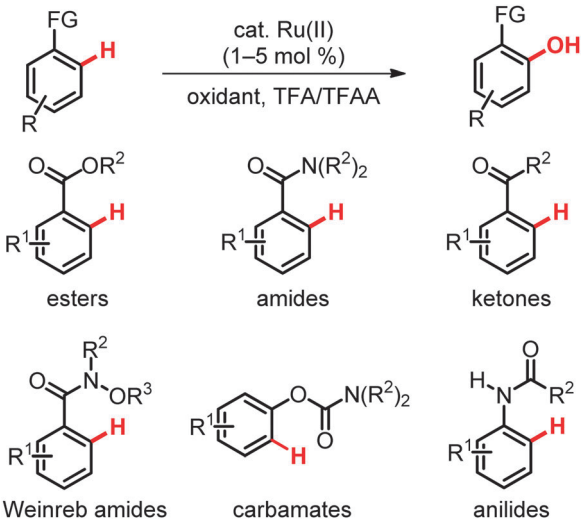
3. Direct C–H oxygenation

During the past few years, several ruthenium-catalyzed hydroxylations of C–H bonds were reported by *inter alia* Rao, Du Bois and our research group. Contrary to the corresponding nitrogenations, solely tertiary C(sp^3)–H bonds and C(sp^2)–H bonds in (hetero)arenes were thus far hydroxylated. The limitation to tertiary C(sp^3)–H bonds is likely due to the inherently high catalytic activity of ruthenium complexes as to undesired over-oxidation to the corresponding carbonyl compounds.[30,31]

3.1 Hydroxylation of C(sp^3)–H bonds

Early RuO_4-mediated hydroxylation of unactivated tertiary C(sp^3)–H bonds in hydrocarbons as well as mechanistic aspects of these oxygenations were studied in great detail by Bakke and coworkers among others.[31] Yet, novel ruthenium catalysts recently disclosed by Du Bois and coworkers[32a] allowed them to significantly improve the substrate scope of the hydroxylation. Indeed, the use of catalytic quantities of [$RuCl_3 \cdot nH_2O$], along with pyridine as the additive and $KBrO_3$ as the stoichiometric oxidant, resulted in the development of a practical, user-friendly protocol that proved applicable to variously substituted substrates **21** (Scheme 13). This reaction not only afforded hydroxylated esters, epoxides, sulfones, oxazolidinones, carbamates and sulfamates **22** in yields generally exceeding 50%, but also constituted a highly convenient method for ^{18}O-label incorporation.

However, the coordination of $RuCl_3$ by trimethyltriazacyclononane, as found in [$(Me_3tacn)RuCl_3$] (**23**), in combination with $AgClO_4$ as the additive and CAN as the oxidant, improved the yield and allowed for a reduction of the catalyst loading as well as of the reaction temperature (Scheme 13).[32b] Interestingly, the KIE value of $k_H/k_D \approx 6.7$ obtained in experiments with isotopically labeled starting materials **21** led the authors to propose a two-step mechanism, involving hydrogen atom abstraction followed by a fast, solvent-caged radical rebound. This mechanistic rationale is related to the mode of action in ruthenium-catalyzed intramolecular amidations (*cf.* Scheme 5),

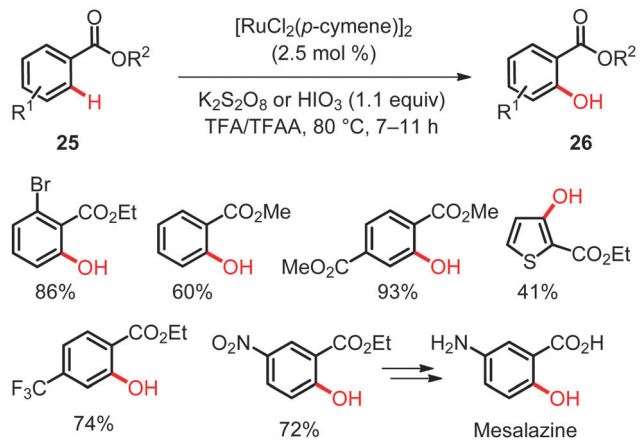


Scheme 14 Overview of ruthenium-catalyzed direct hydroxylation of C(sp^2)–H bonds.

but differs from the generally accepted concerted asynchronous (3+2) pathway previously postulated for C–H hydroxylations catalyzed with RuO_4 (KIE ≈ 5–7).[31]

3.2 Hydroxylation of C(sp^2)–H bonds

The past two years have witnessed a tremendous development in the direct hydroxylation of C(sp^2)–H bonds in arenes and heteroarenes with readily accessible ruthenium catalysts (Scheme 14).[33–42] While Rao and coworkers used the complex $[RuCl_2(p\text{-cymene})]_2$ as the precatalyst and $K_2S_2O_8$ or HIO_3 as the oxidant,[34] our group employed $[RuCl_2(p\text{-cymene})]_2$, as well as the well-defined ruthenium(II) biscarboxylate complex $[Ru(O_2CMes)_2(p\text{-cymene})]$ (**24**),[33] or inexpensive $[RuCl_3{\cdot}nH_2O]$ and (diacetoxyiodo)benzene $[PhI(OAc)_2]$ as the oxidant. For chelation-assisted C–O bond formation on arenes the solvent mixture comprising of TFA and TFAA turned out to be critical, which enabled successful hydroxylation of electron-deficient and electron-rich arenes as well as heteroarenes[33–42] with weakly coordinating directing groups,[23] such as esters or ketones.[33–42] Thus, the ruthenium-catalyzed



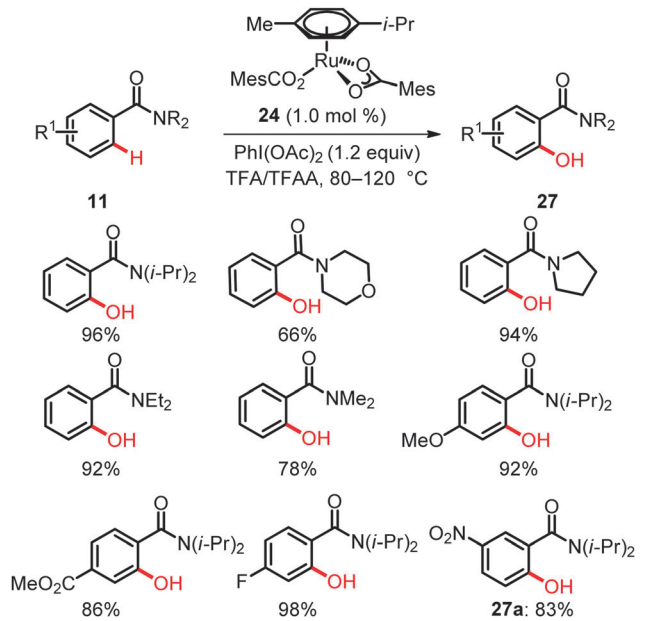
Scheme 15 *ortho*-Hydroxylation of benzoates **25**.

ortho-hydroxylation of benzoates **25** was found to be generally useful for the preparation of highly functionalized arenes, some of which are difficult to access *via* conventional approaches (Scheme 15).[34]

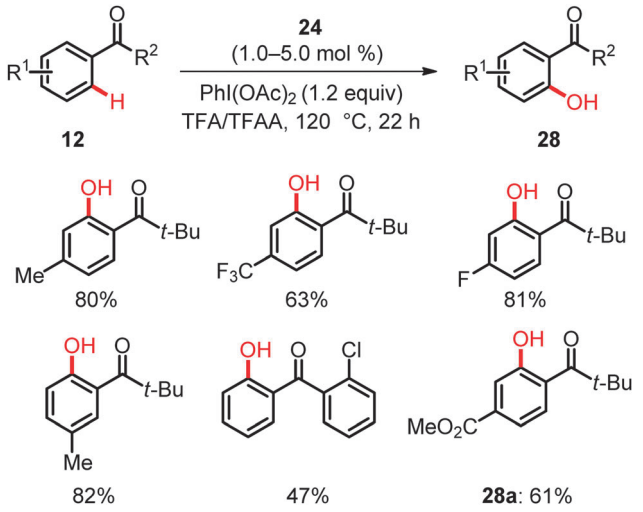
The catalytic system exhibited a good functional group tolerance and delivered the products **26** in high yields. Notably, useful heteroarenes were also compatible with these catalytic reaction conditions. The KIE value of $k_H/k_D \approx 1.8$ was suggestive of a kinetically relevant C–H metalation. These hydroxylations set the stage for a step-economical approach towards the synthesis of biologically important compounds, such as Mesalazine, an anti-inflammatory drug used for the treatment of inflammatory bowel disease. Indeed, ethyl 2-hydroxy-5-nitrobenzoate could be easily converted to Mesalazine by sequential hydrolysis and reduction.[35]

Studies on ruthenium-catalyzed C(sp^2)–H bond oxygenation of arenes **11** bearing amide directing groups identified the user-friendly, inexpensive $[RuCl_3{\cdot}nH_2O]$ as a viable catalyst. $PhI(OAc)_2$ proved to be an efficient oxidant, while O_2, $Cu(OAc)_2{\cdot}H_2O$, *t*-BuOOH, oxone, $K_2S_2O_8$ or $PhI(TFA)_2$ were found to be inferior. Interestingly, the most satisfactory results were obtained with a well-defined ruthenium(II) biscarboxylate complex $[Ru(O_2CMes)_2(p\text{-cymene})]$ (**24**) at a remarkably low catalyst loading of only 1.0 mol% (Scheme 16).[36]

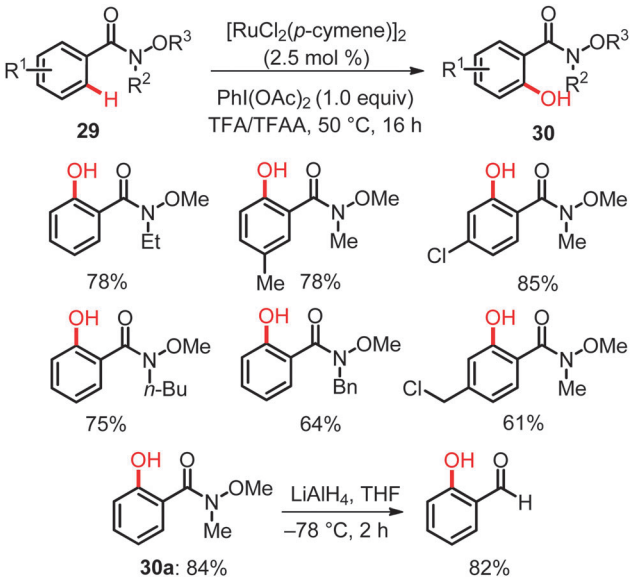
Variously decorated *N,N*-disubstituted benzamides **11** bearing dimethylamino, diethylamino, diisopropylamino, pyrrolidinyl or morpholinyl moieties afforded the corresponding amidophenols **27** in good to excellent yields with the catalytic system. In contrast to palladium-catalyzed oxidative *ortho*-hydroxylation of benzamides with a rather limited substrate scope,[9a,b] the ruthenium-catalyzed reactions were compatible with methoxy, ester, nitro and fluoro substituents on the arenes. Thus, the reaction of 4-methoxy, 4-methoxycarbonyl and 4-fluorosubstituted benzamides **11** furnished the *ortho*-hydroxylated products **27** in high yields of



Scheme 16 Oxidative hydroxylation of benzamides **11**.



Scheme 17 *ortho*-Hydroxylation of aromatic ketones **12**.



Scheme 18 C–H hydroxylation of Weinreb amides **29**.

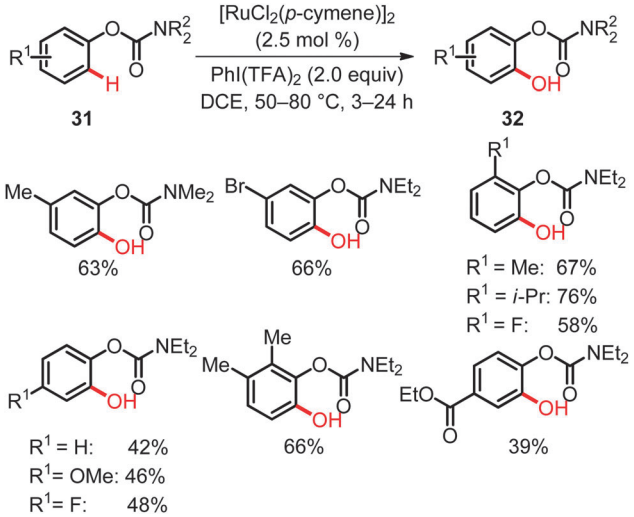
up to 98%. The optimized catalyst displayed an excellent site-selectivity, as illustrated by the exclusive formation of 2-hydroxy-*N*,*N*-diisopropyl-5-nitrobenzamide (**27a**) as the sole product (Scheme 16). Mechanistic studies provided strong support for a reversible C–H bond metalation step.[36]

The ruthenium-catalyzed hydroxylation was not limited to relatively strongly coordinating directing groups. Indeed, weakly coordinating ketones in phenones **12** proved to be applicable exploiting the ruthenium complex **24** (Scheme 17).[37] This unprecedented functionalization occurred with an excellent functional group tolerance and a broad substrate scope as well as high chemo- and site-selectivities.

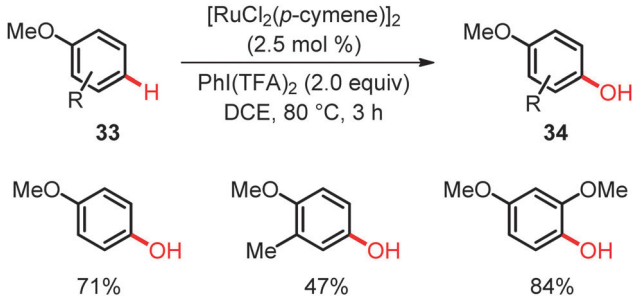
While acetophenone afforded a mixture of C(sp^2)–H- and C(sp^3)–H-functionalized products, benzophenone furnished mono- and dihydroxylated compounds in 85% yield. Variously substituted aromatic ketones **12** chemoselectively gave the corresponding phenol derivatives **28**, while hydroxylation of electron-deficient substrates was less efficient. Similar *ortho*-hydroxylations could be performed with the inexpensive [$RuCl_3 \cdot nH_2O$] precatalyst and oxone or $K_2S_2O_8$ as the terminal oxidant, albeit with a somewhat lower catalytic efficacy. The selective formation of methyl 3-hydroxy-4-pivaloylbenzoate (**28a**) in an intermolecular competition was of particular interest, since it revealed the relative directing group abilities.

Weinreb amides **29** constitute important structural motifs in a number of natural products and bioactive compounds and represent functional groups of key importance in synthetic organic chemistry. Thus, these functional groups are easily installed and can be chemoselectively transformed into the corresponding ketones and aldehydes.[38] Unfortunately, amides **29** had been underutilized in ruthenium-catalyzed C–H bond functionalizations,[14] and direct hydroxylations of aryl Weinreb amides had proven elusive until very recently. Yet, the ruthenium complex [$RuCl_2$(*p*-cymene)]$_2$, along with PhI(OAc)$_2$ (1.0 equiv.) as the oxidant in TFA/TFAA, was found to enable unprecedented C–H bond oxygenations of aryl Weinreb amides **29** to give the desired products **30** with ample scope under exceedingly mild reaction conditions (Scheme 18).[39] Mechanistic studies disclosed an irreversible, thus kinetically relevant C–H bond activation with a KIE of $k_H/k_D \approx 3.0$. The step- and atom-economical syntheses of *ortho*-hydroxylated Weinreb amides **30** also provided access to valuable *ortho*-hydroxylated aldehydes. For example, *o*-hydroxy-*N*-methoxy-*N*-methylamide (**30a**) obtained *via* the ruthenium-catalyzed C–H bond oxygenation underwent a facile reduction to afford the corresponding *ortho*-hydroxyaldehyde (Scheme 18).[39]

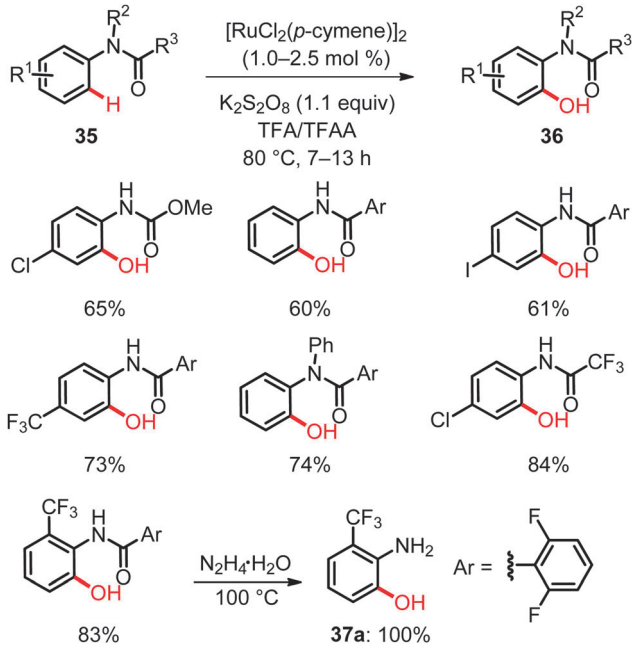
Whilst the previous studies had focused on the use of arenes bearing electron-withdrawing directing groups, we reported recently the first ruthenium-catalyzed C(sp^2)–H bond oxygenation of phenol derivatives **31** applying [$RuCl_2$(*p*-cymene)]$_2$ as the catalyst and PhI(TFA)$_2$ as the oxidant.[40] Thus, direct hydroxylation of easily removable aryl carbamates **31** proceeded under mild reaction conditions with high catalytic efficacy and excellent chemoselectivity



Scheme 19 Direct *ortho*-hydroxylation of carbamates **31**.



Scheme 20 *para*-Hydroxylation of anisoles **33**.



Scheme 21 *ortho*-Hydroxylation of anilides **35**.

(Scheme 19).[40,41] Studies with isotopically labeled substrates **31** disclosed a KIE of $k_H/k_D \approx 2.2$, which is in accordance with a kinetically relevant C–H bond metalation step.[40]

It is noteworthy that the ruthenium(II) catalyst also allowed for the direct C–H bond functionalization of anisole derivatives **33** being devoid of Lewis-basic directing groups, occurring with a remarkable *para*-selectivity (Scheme 20).[40]

Ruthenium catalysis was not restricted to direct hydroxylation of aryl carbamates as electron-rich substrates. Hence, anilide-directed oxidative C–O bond formations were very recently reported by Rao employing $K_2S_2O_8$ as the oxidant.[41] In this transformation an efficient synthesis of mono- and dihydroxylated anilides **36** by C(sp^2)–H bond oxygenation was accomplished (Scheme 21).[42] The reaction featured excellent site-selectivities and a good functional group tolerance. As found for the aryl carbamates **31**,[40] the acylated amino moiety in product **36** constituted a removable directing group.[43] Indeed, the 2-aminophenol **37a** was obtained by simple hydrazinolysis (Scheme 21).[42]

4. Conclusions

Recent years have witnessed tremendous progress in metal-catalyzed C–H bond functionalizations. Despite these advances, relatively inexpensive[44] ruthenium complexes were until very recently not fully recognized as catalysts for direct amidations and hydroxylations through challenging functionalization of otherwise unreactive C(sp^3)–H and C(sp^2)–H bonds. These difficult oxidative C–H bond nitrogenations and oxygenations have proven to be widely applicable using versatile ruthenium complexes, with considerable progress being accomplished in the last two years. Notable features of the most user-friendly ruthenium catalysts include the remarkably broad substrate scope and the extraordinarily high chemo- and site-selectivity. The outstanding selectivity was among others reflected by the high functional group tolerance and catalytic activity, which compared, for example, favorably with rhodium catalysis in *ortho*-hydroxylation of arenes.[41] Importantly, ruthenium-catalyzed nitrogenations and oxygenations enabled the challenging direct functionalization of unactivated C(sp^3)–H bonds and were accomplished with substrates displaying only weakly coordinating directing groups, such as esters and ketones. Considering the practical importance of atom- and step-economical C–H bond amidations, aminations and hydroxylations for organic synthesis, material sciences or medicinal chemistry, significant further progress is expected in this rapidly evolving research area.

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