CHEMICAL REVIEWS

REVIEW

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Carboxylate-Assisted Transition-Metal-Catalyzed C−H Bond Functionalizations: Mechanism and Scope

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1. INTRODUCTION

The site-selective formation of carbon−carbon bonds through direct functionalizations of otherwise unreactive carbon−hydrogen bonds constitutes an economically attractive strategy for an overall streamlining of sustainable syntheses.[1−3] In recent decades, intensive research efforts have led to the development of various reaction conditions for challenging C−H bond functionalizations,[4−6] among which transition-metal-catalyzed transformations arguably constitute thus far the most valuable tool.[3] For instance, the use of inter alia palladium,[7,8] ruthenium,[9] rhodium,[10] copper,[11] or iron[12,13] complexes set the stage for chemo-, site-,[14] diastereo-,[15,16] and/or enantioselective[17] C−H bond functionalizations. Key to success was generally a detailed mechanistic understanding of the elementary C−H bond metalation step, which depending on the nature of the metal fragment can proceed via several distinct reaction pathways. Traditionally, three different modes of action were primarily considered for C−H bond metalations, namely, (i) oxidative addition with electron-rich late transition metals, (ii) σ-bond metathesis with early transition metals, and (iii) electrophilic activation with electron-deficient late transition metals (Scheme 1).[18−20] However, more recent mechanistic studies indicated the existence of a continuum of electrophilic, ambiphilic, and nucleophilic interactions.[21] Within this continuum, detailed experimental and computational analysis provided strong evidence for novel C−H bond metalation mechanisms relying on the assistance of a bifunctional ligand bearing an additional Lewis-basic heteroatom, such as that found in (heteroatom-substituted) secondary phosphine oxides[22−27] or most prominently carboxylates (Scheme 1, iv).

This novel insight into the nature of stoichiometric metalations has served as stimulus for the development of novel transformations based on cocatalytic amounts of carboxylates, which significantly broadened the scope of C−H bond functionalizations in recent years, with most remarkable progress being made in palladium- or ruthenium-catalyzed direct arylations and direct alkylations. These carboxylate-assisted C−H bond transformations were mostly proposed to proceed via a mechanism in which metalation takes place via a concerted base-assisted deprotonation. To mechanistically differentiate these intramolecular metalations new acronyms have recently been introduced into the literature, such as CMD (concerted metalation−deprotonation),[28] IES (internal electrophilic substitution),[29] or AMLA (ambiphilic metal ligand activation),[18,30] which describe related mechanisms and will be used below where appropriate. This review summarizes the development and scope of carboxylates as cocatalysts in transition-metal-catalyzed C−H functionalizations until autumn 2010. Moreover, experimental and computational studies on stoichiometric metalation reactions being of relevance to the mechanism of these catalytic processes are discussed as well. Mechanistically related C−H bond cleavage reactions with ruthenium or iridium complexes bearing monodentate ligands are, however, only covered with respect to their working mode, and transformations with stoichiometric amounts of simple acetate bases are solely included when their mechanism was suggested to proceed by acetate-assisted metalation.

2. STOICHIOMETRIC C−H BOND METALATION

2.1. Intermolecular Metalation

In 1980, Roberts and co-workers performed detailed kinetic studies on the mercuration of arenes by $Hg(O_2CCF_3)_2$.[31] Among others, large primary kinetic isotope effects (KIE) of $k_H/k_D \approx 6$ disclosed in 1967 by Kresge and Brennan already indicated the proton transfer to be rate determining.[32] While

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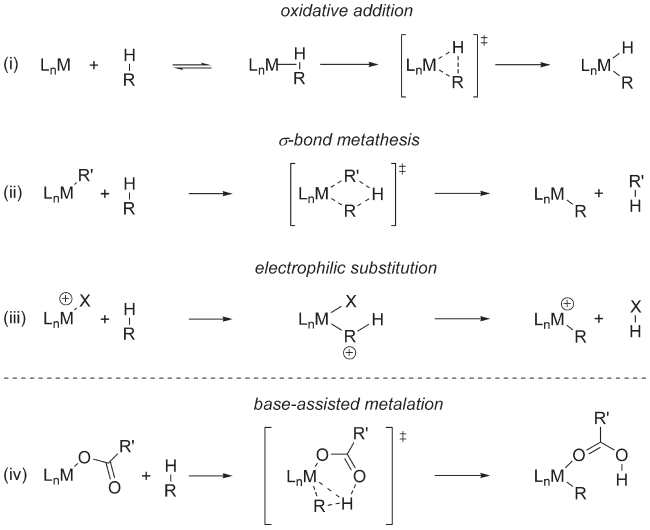
Scheme 1. Different Mechanisms for C−H Bond Metalation



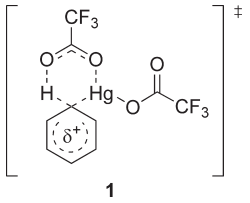
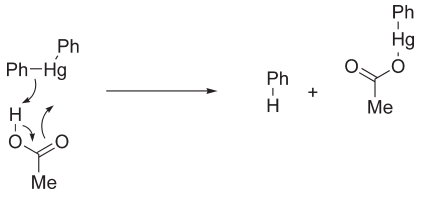
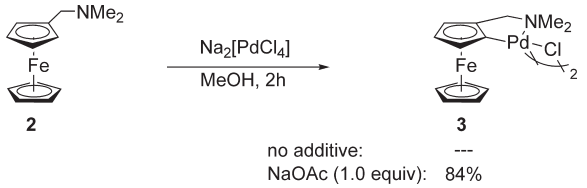


Figure 1. Transition state **1** for base-assisted mercuration.

Scheme 2. Acetolysis of Diphenylmercury(II)



Scheme 3. Effect of NaOAc on the Cyclopalladation of Amine 2 Disclosed by Shaw (1972−1975)



previous mechanistic proposals had favored a S_EAr-type manifold with discrete σ-complexes,[33,34] Roberts and co-workers rationalized their observations with transition state **1** featuring a synchronous bond fission and bond formation as illustrated in Figure 1; a S_EAr-type mechanism could not completely be ruled out.[31]

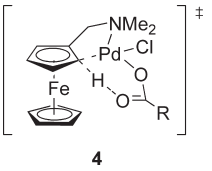


Figure 2. Transition state **4** of a carboxylate-assisted cyclopalladation as proposed by Sokolov and Reutov (1979).

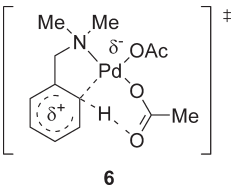


Figure 3. Proposed transition state **6** for *ortho*-palladation of DMBA-H (**5**).

Notably, this mode of action resembled the previously proposed mechanism for the reverse reaction, that is, the protodemercuration of diphenylmercury, for which Winstein and Traylor had put forward a concerted S_Ei-type mechanism in 1955 (Scheme 2).[35]

A related beneficial effect of stoichiometric amounts of pivalic acid in a gold-mediated C−H bond activation of electron-deficient arenes was disclosed by Larrosa and co-workers in 2010.[36] While detailed mechanistic data are thus far not at hand, the reaction displayed a large KIE of $k_H/k_D = 5$ and was hence proposed to occur via a base-assisted concerted deprotonation.

2.2. Stoichiometric Cyclometalations

Stoichiometric cyclometalation reactions[37−39] of arenes bearing Lewis-basic directing groups were realized with complexes of various transition metals as early as the early 1960s.[3,37−48] With respect to base-assisted metalations, Shaw and co-workers made a pioneering discovery in the early 1970s by observing that additive NaOAc accelerates cyclometalation reactions with iridium,[49] platinum,[50] or palladium complexes.[51] For example, the cylometalation of *N*,*N*-dimethylaminomethylferrocene (**2**) was found to occur efficiently in the presence of stoichiometric amounts of this base to yield dimeric product **3** (Scheme 3), whereas the corresponding adduct $[PdCl_2(\mathbf{2})_2]$ was exclusively formed in the absence of NaOAc.[51a]

On the basis of Shaw's findings, Sokolov, Troitskaya, and Reutov described in 1979 that salts of optically active amino acids promote the palladation of amine **2** to give optically active products with moderate enantiomeric excess.[52] Importantly, it was proposed that the key C−H bond metalation occurred via a carboxylate-assisted intramolecular deprotonation in a concerted fashion, as was illustrated by transition-state structure **4** (Figure 2).[52]

Subsequently, Ryabov and co-workers probed the mechanism of *ortho*-palladation reactions with *N*,*N*-dimethylbenzylamines (DMBA-H, **5**) as substrate, employing, for instance, detailed kinetic studies.[53,54] Thereby, it was shown that the C−H bond metalation in $CHCl_3$ as the solvent is rate limiting and electrophilic in nature; the slope of the corresponding Hammett plot for

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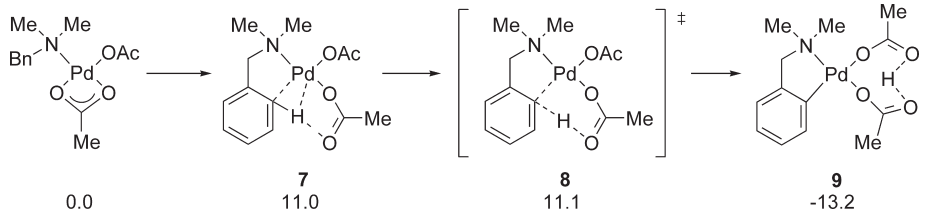
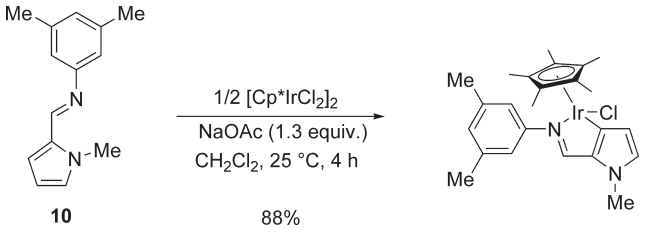
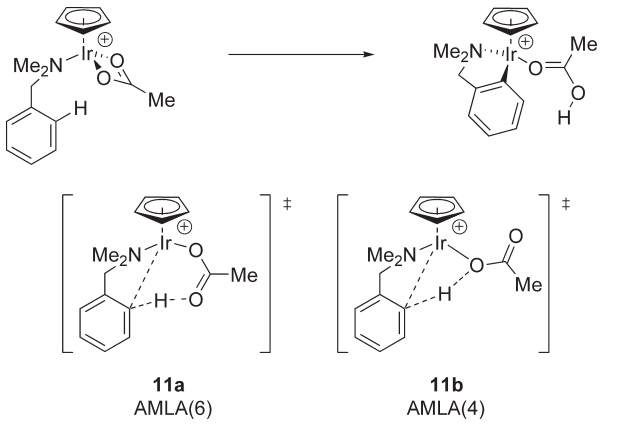
Scheme 4. Computed Reaction Profile of *ortho*-Palladation with DMBA-H (5) (values in kcal/mol)



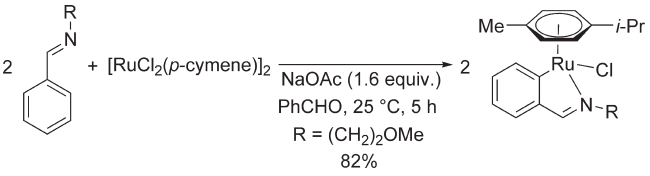
Scheme 5. Stoichiometric Cyclometalation of Pyrrole 10 in the Presence of NaOAc



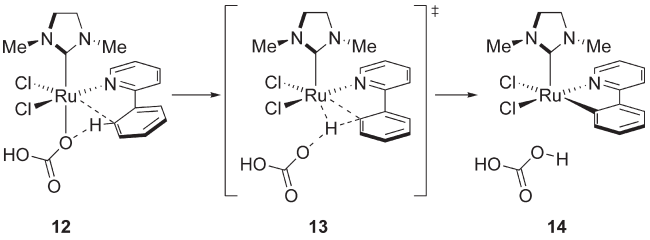
Scheme 6. Computed Transition States of Acetate-Assisted Cyclometalation with DMBA-H



Scheme 7. Cycloruthenation in the Presence of NaOAc



Scheme 8. Calculated Mechanism for a Cycloruthenation



differently substituted substrates was −1.6. A KIE of $k_H/k_D = 2.2$ was determined for DMBA-H (**5**). Interestingly, an activation entropy of around −250 J K^{-1} mol^{-1} was observed when using substrate **5**, thereby pointing toward a highly ordered transition-state structure. As a consequence, the authors proposed a mechanistic model in which the deprotonation occurred through assistance of a coordinated acetate (Figure 3).[37,53,55] On the basis of crystallographic data on related palladium precursors,[56] Ryabov and co-workers also considered the possibility of agostic interactions.

The first computational studies on the cyclometalation of DMBA-H (**5**) by $Pd(OAc)_2$ were performed by Davies, Macgregor, and Donald (Scheme 4).[57] Thus, density functional theory (DFT) calculations suggested this reaction to proceed by an initial agostic C−H bond interaction in complex **7**, rather than a Wheland intermediate. This agostic interaction enhances the acidity of the *ortho*-proton,[58] which enables a subsequent facile intramolecular deprotonation by the coordinated acetate.[57] This ambiphilic metal ligand activation through six-membered transition state **8** (AMLA(6)) hence allows for an almost barrierless proton transfer, thereby delivering cyclometalated complex **9**.

Cyclometalation reactions with iridium, rhodium, and ruthenium precursors in the presence of stoichiometric amounts of NaOAc were performed by Davies and co-workers,[59−61] resembling earlier reports by Shaw and co-workers.[49−51] With DMBA-H (**5**), alkyl and aryl imines, or an oxazoline as substrates stoichiometric cyclometalations occurred with $[Cp^*IrCl_2]_2$ at exceedingly mild reaction conditions. Similarly, an acetate-promoted cyclometalation of *N*-methylated pyrrole imine **10** proceeded readily at ambient reaction temperature (Scheme 5).[62]

The mechanism of these transformations was explored through computational studies by Davies, Macgregor, and co-workers, which provided strong evidence for AMLA(6) transition state **11a**, while the corresponding four-membered AMLA(4) transition state **11b** turned out to be less favorable (Scheme 6).[18,63,64] Contrary to the analogous cyclopalladation reactions, an intermediate agostic complex was at this point not observed on the calculated reaction path.

More recently, additional experimental and computational studies revealed the cyclometalation to be a two-step process involving initial slow $\kappa^2-\kappa^1$-displacement of the acetate ligand, along with a facile subsequent base-assisted intramolecular deprotonation.[30,65] Importantly, relative reactivities of iridium complexes generated in situ from sodium triflate, sodium bicarbonate, and various sodium carboxylates showed that C−H bond activation is not rate limiting in these stoichiometric cyclometalations. On the contrary, the added base plays a dual

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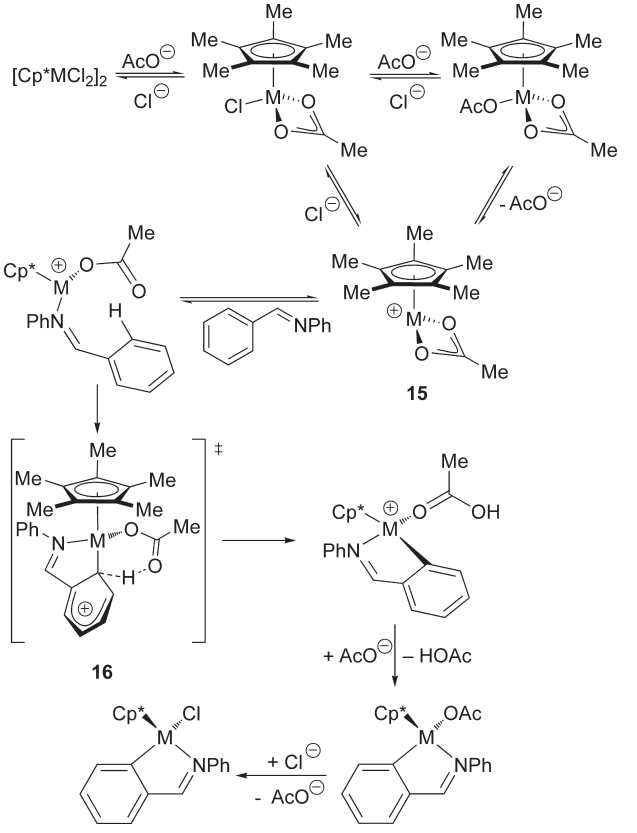
role, thus accelerating the slow dimer opening and acting as an intramolecular base in a fast C−H bond metalation.

Cocatalytic amounts of NaOAc not only affected facile C−H bond metalations with palladium, platinum or iridium complexes but proved highly valuable for the synthesis of rhoda- and ruthenacycles under mild reaction conditions as well.[59,66] While both aryl- and alkyl-substituted imines reacted readily with $[Cp^*RhCl_2]_2$, solely *N*-alkyl-substituted imines provided the desired ruthenacycles with $[RuCl_2(p\text{-cymene})]_2$ at ambient reaction temperature (Scheme 7).[59]

The mechanism of the cycloruthenation was probed by Maseras, Dixneuf, and co-workers through DFT calculations within the context of catalytic C−H bond functionalizations.[67] Specifically, two distinct reaction manifolds were considered for cyclometalations of 2-phenylpyridine by a ruthenium complex derived from a N-heterocyclic carbene (NHC)[68−71] with bicarbonate as the base.[67] An oxidative addition of the C−H bond of phenylpyridine was shown to yield an unfavorable ruthenium(IV) hydride complex with a relative energy of 28.3 kcal mol^{-1}. On the contrary, a proton abstraction mechanism was calculated to be more facile (Scheme 8). Here, coordination of bicarbonate was calculated to yield structure **12**. Complex **12** evolved to formal ruthenium(III) complex **14** through transition state **13** within a cyclometalation that was determined to be exothermic by 13.9 kcal mol^{-1}. An additional notable feature of this mechanistic proposal is represented by an outer-sphere deprotonation through three-membered transition state **13**, which interestingly is in contrast to proposals for cycloiridations and -palladations. Moreover, the formed cyclometalated species was calculated to be formally a ruthenium(III) complex (**14**), while experimentally ruthenium(II) species were usually isolated as catalytically competent complexes (vide infra).[72]

While Davies and co-workers found that efficient cyclometalations of aldimines with $[Cp^*RhCl_2]_2$ proceeded in the presence of NaOAc under mild reaction conditions,[59] Jones and co-workers performed more recently detailed mechanistic studies on the formation of irida- and rhodacycles derived from electron-rich and electron-poor imines, which indicated $[Cp^*M(OAc)]^+$ (M = Rh, Ir) **15** to be the key intermediates for acetate-assisted electrophilic activations via transition state **16** (Scheme 9).[73]

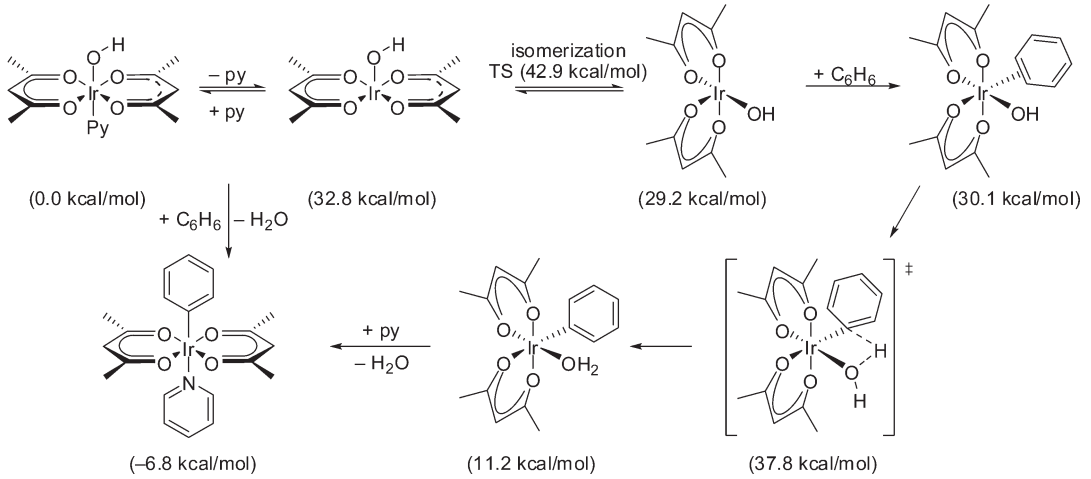
Scheme 9. Proposed Mechanism for Acetate-Assisted Cyclometalation (M = Rh, Ir)



2.3. Related Assisted Metalations with Monodentate Bases

Independent studies by Periana, Goddard, and co-workers as well as Gunnoe and co-workers provided evidence for concerted C−H bond metalation mechanisms being of relevance to the working mode of carboxylate-assisted processes. Thus, it was experimentally observed that anionic monodentate ligands would enable efficient iridiations or ruthenations, respectively; these observations were also implemented in the development

Scheme 10. Proposed Mode of Action for C−H Bond Metalation with an Iridium(III)−Hydroxide Complex



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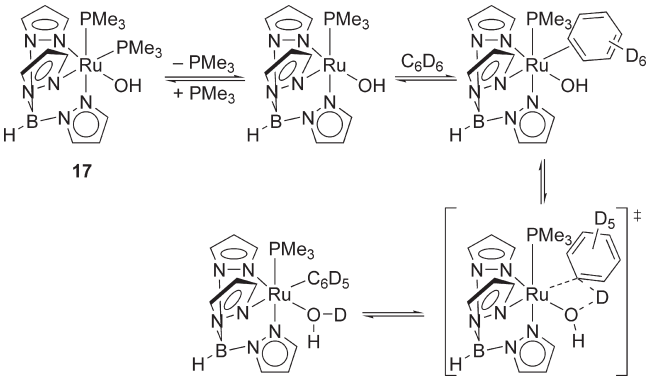
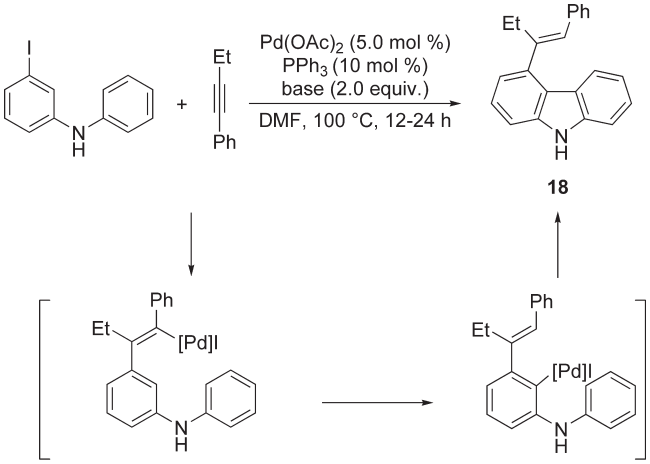
Scheme 11. Proposed Mechanism for Deuterium−Hydrogen Exchange with $TpRu(PMe_3)_2(OH)$ (17)



Scheme 12. Effect of Bases on Palladium-Catalyzed Sequential Direct Arylation



base	yield
NEt_3	0%
Na_2CO_3	0%
NaOAc	trace
CsOPiv	60%

of catalytic processes.[74] Specifically, Periana, Goddard, and co-workers reported detailed experimental and computational studies on stoichiometric and catalytic C−H bond activations with an air-, protic- and thermally-stable iridium−hydroxide complex.[75,76] The intermolecular metalation of benzene was shown to occur by assistance of the hydroxo ligand (Scheme 10), and potential alternative mechanisms, such as an oxidative addition or oxidative hydrogen migration, were all determined to be higher in energy.[75,77,78] Subsequent studies revealed that the key C−H bond metalation does not resemble a traditional σ-bond metathesis but that it is best described as an internal electrophilic substitution (IES).[29] Thus, within a continuum of electrophilic, ambiphilic, and nucleophilic interactions,[21] these transformations were calculated to be ambiphilic in nature.[29] It is noteworthy that the overall 1,2-addition of C−H bonds across a metal−heteroatom bond is related to well-established C−H bond activations of hydrocarbons by early transition-metal imido species.[79−82]

In independent studies, Gunnoe and co-workers observed hydrogen−deuterium exchange reactions on arenes with ruthenium complexes of the general structure $TpRu(PMe_3)_2(X)$ (Tp = hydridotris(pyrazolyl)borate).[74,83−86] Notably, complexes $TpRu(PMe_3)_2(OH)$ (**17**) and $TpRu(PMe_3)_2(NHPh)$ facilitated hydrogen/deuterium exchange between deteurated arenes and the nondative ligand X. The mechanism of this transformation was shown to involve initial ligand dissociation and ruthenium(II)-mediated activation of an aromatic C−D bond, as illustrated in Scheme 11.[87]

3. CATALYTIC C−H BOND FUNCTIONALIZATIONS

3.1. Key Observations with Stoichiometric Amounts of Carboxylates

3.1.1. Aryl Halides as Arylating Reagents. Larock and co-workers observed that the nature of stoichiometrically used carboxylate bases exerted a pronounced effect on palladium-catalyzed C−H bond functionalizations.[88−91] Hence, the elegant synthesis of carbazole **18** through "palladium migration"[92] proceeded efficiently only when using CsOPiv as the base (Scheme 12).[91a]

With respect to carboxylate-assisted palladium-catalyzed C−H bond functionalizations, direct arylations of imidazolinones with aryl iodides as arylating reagents and stoichiometric amounts of NaOAc as the base are noteworthy.[93] Mechanistic studies, such as the use of isotopically labeled starting materials, were suggestive of an acetate-assisted C−H bond metalation manifold, which was taken advantage of en route to marine alkaloid dibromophakellstatin.[93] Moreover, early studies on Mizoroki−Heck-terminated Catellani[94−101] reaction sequences clearly showed that the use of KOAc, in combination with K_2CO_3, was beneficial for palladium-catalyzed alkylations.[102−104]

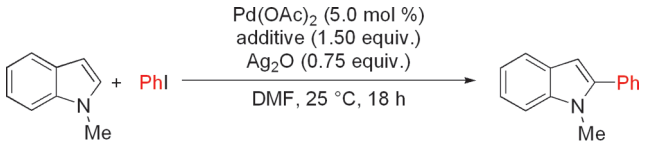
Indoles are among the most abundant heteroarenes in biologically active compounds and natural products.[24,105,106] As a consequence, significant research effort has been directed toward the development of efficient and site-selective direct C−H bond functionalizations of these ubiquitous electron-rich heteroarenes.[107,108] Site-selective direct C−2 arylations of indoles were achieved under remarkably mild reaction conditions, with aryl iodides as arylating reagents and Ag_2O as the base.[109] Here, a pronounced effect of stoichiometrically added carboxylic acids was observed, with *o*-nitrobenzoic acid (**19**) providing optimal results for reactions at ambient temperature (Scheme 13).[109−111]

The beneficial effect of stoichiometric carboxylate bases was not restricted to palladium-catalyzed transformations. Indeed, Sames and co-workers observed that particularly cesium carboxylates enabled efficient, rhodium-catalyzed[10,112] direct C-2 arylations of free (NH) pyrroles and indoles.[113] Interestingly, CsOPiv clearly stood out as the base of choice in this site-selective transformation (Scheme 14), and carbonates or phosphates of alkali metals turned out to be ineffective.[113] Detailed mechanistic studies revealed rhodium(III) pivalate **20** to be the resting state in the catalytic cycle. While further experimental studies on the nature of the C−H bond metalation are not at hand, the authors proposed that the pivalate ligand assists the C−H bond dissociation as an internal base,[113] as was recently illustrated by Beck and Gaunt with transition state **21**.[8]

3.1.2. Dehydrogenative Arylations. The palladium-catalyzed direct oxidative coupling of arenes with alkenes,

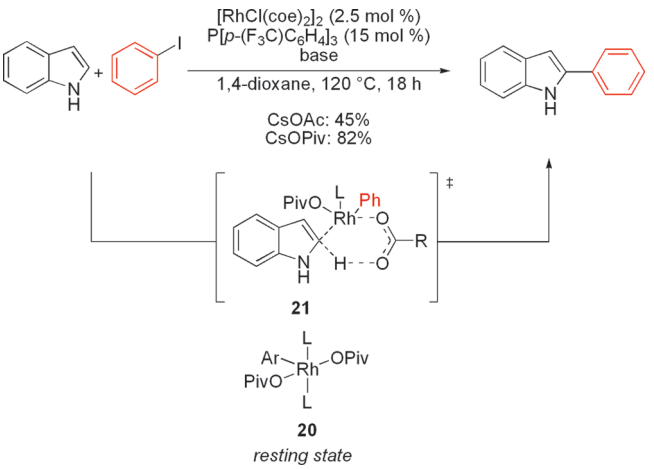
the Fujiwara−Moritani reaction, represents an early example of efficient catalytic C−H bond functionalizations, which is frequently conducted in carboxylic acids as (co)solvent.[114−120]

Scheme 13. Site-Selective Palladium-Catalyzed Direct Arylation

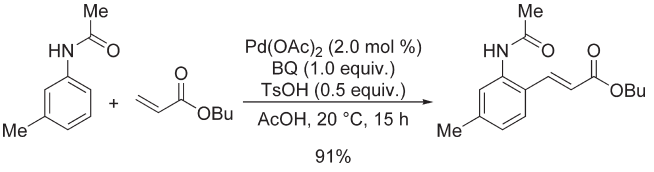


additive	conversion (GC)
---	12%
CH_3CO_2H	49%
o-$MeOC_6H_4CO_2H$	13%
p-$O_2NC_6H_4CO_2H$	81%
o-$O_2NC_6H_4CO_2H$ (**19**)	>99%

Scheme 14. CsOPiv as the Base in Rhodium-Catalyzed Direct Arylations



Scheme 15. Palladium-Catalyzed Fujiwara−Moritani Reaction at Ambient Temperature



During the last decades, this process has matured to being a highly useful tool for diastereoselective syntheses of substituted alkenes,[121] which is, for example, reflected by efficient oxidative arylations at ambient reaction temperature (Scheme 15).[122,123]

In 2000, the mechanism of the key C−H bond metalation step of this palladium-catalyzed direct arene functionalization was probed through DFT calculations by Sakaki and co-workers.[124] Previously, experimental studies provided evidence for the electrophilic character of $Pd(OAc)_2$ in reactions of simple arenes, and a KIE of k_H/k_D = 4.5−5.1 was observed for these palladation reactions.[125] Sakaki and co-workers found computationally that the C−H bond activation of benzene is significantly more facile with $Pd(\kappa^2\text{-}O_2CH)_2$ as compared to $Pd(PH_3)_2$.[124] Thus, the reaction with the former species was shown to be exothermic (ΔE = −16.5 kcal mol^{-1}), whereas the metalation with the palladium(0) complex was calculated to be endothermic. The palladation with $Pd(\kappa^2\text{-}O_2CH)_2$ was determined to occur through κ^1,π-complex (R = Ph) **22** as intermediate, which gives rise to six-membered transition state **23** (Scheme 16). The exothermic nature of this process was attributed to formation of the strong O−H bond through assistance of the coordinated formate ligand.

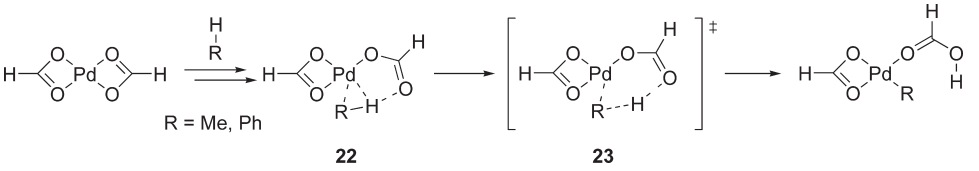
Very recently, CsOAc has been employed as cocatalytic additive in a rhodium(III)-catalyzed isoquinolone synthesis through annulation[126] of benzhydroxamic acids with alkynes, but detailed mechanistic understanding as to the role of the additive is unfortunately as of yet not available.[127,128]

3.2. Catalytic Amounts of Carboxylates

3.2.1. Palladium. *3.2.1.1. Carbonate-Assisted C−H Bond Functionalizations.* Transition-metal-catalyzed direct arylations with aryl (pseudo)halides are economically attractive alternatives to conventional cross-coupling reactions with prefunctionalized organometallic or main-group element arylating reagents.[129−131] Contrary to oxidative direct arylations,[132−135] these overall redox-neutral (isohypsic) processes do not require stoichiometric metal salts as terminal oxidant and can ensure regioselectivity through the use of easily accessible yet ecologically benign halides as leaving groups (Scheme 17).[129]

The first palladium-catalyzed direct arylations of (hetero)arenes were reported as early as 1982 by the research groups of Tajima[136] and Ames,[137−139] which proved to be generally applicable to aryl iodides or bromides as coupling partners.[129] Significant progress has been made in the following decades, which led to different mechanisms being proposed for the key C−H bond metalation, with electrophilic substitutions and oxidative additions traditionally being favored. However, more recent mechanistic findings indicated base-assisted metalations to be of relevance in an increasing number of transformations. Thus, during studies on palladium-catalyzed intramolecular direct arylations,[140−145] Fagnou and co-workers observed that the selectivity in intramolecular competition experiments depended

Scheme 16. Calculated Intermolecular Palladation within the Fujiwara−Moritani Reaction



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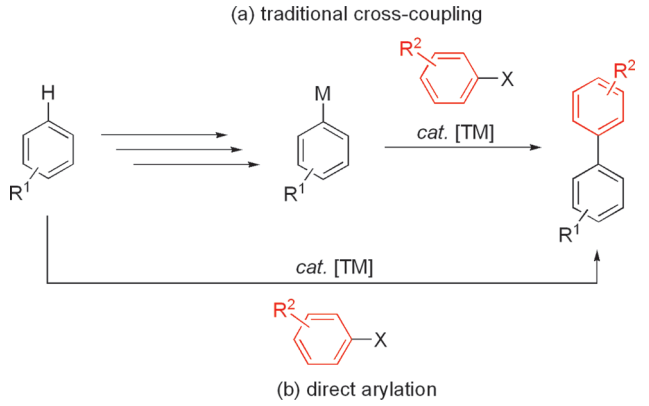
on the nature of the substituents on the arenes.[146] While products **24** were predominantly formed due to steric interactions, a *meta*-fluoro-substituted arene provided regioisomer **25** as the major product (Scheme 18). Originally, two distinct mechanisms were put forward to account for this observation, namely, a σ-bond metathesis and an intermolecular deprotonation by a noncoordinated carbonate base.

Comparable observations were made for intermolecular direct arylations in that electron-deficient (hetero)arenes could be efficiently converted despite their insufficient nucleophilicity required for electrophilic activation reactions. Hence, electron-deficient azine *N*-oxides were site-selectively arylated with a palladium catalyst derived from an electron-rich tertiary phosphine (Scheme 19).[147,148] Notably, intermolecular competition experiments unravelled the increased reactivity of pyridine *N*-oxides bearing electron-withdrawing groups, indicating a non-S_EAr reaction manifold. As to the scope of this transformation, the palladium catalyst proved also applicable to direct arylations of various diazine *N*-oxides with aryl halides.[149,150] Moreover, the use of an electron-rich biphenyl monophosphine ligand allowed Ackermann and Fenner to use challenging aryl and alkenyl tosylates or mesylates as coupling partners for direct C−C bond formations on (di)azine *N*-oxides and electron-deficient arenes.[151] In more general terms, these palladium(0)-catalyzed C−H bond functionalizations represent valuable alternatives to the use of often unstable 2-pyridyl organometallics[152,153] in traditional cross-coupling chemistry.[154,155]

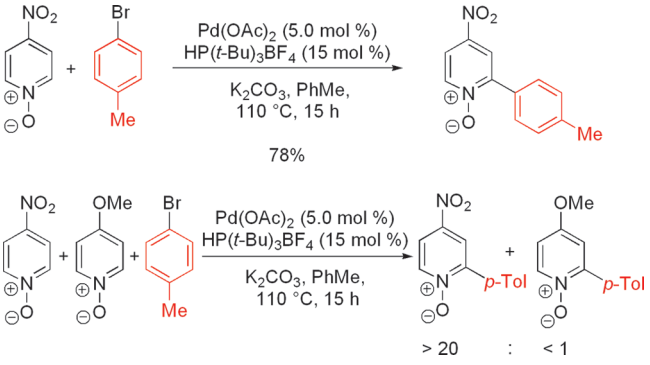
Scheme 17. Traditional Cross-Coupling (a) versus Direct Arylation (b)



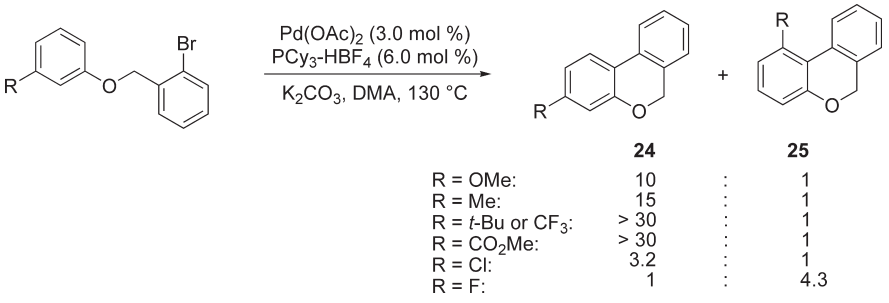
The high reactivity of palladium catalysts in intermolecular direct arylations was not restricted to electron-deficient heteroarenes but enabled C−H bond functionalizations of oligofluoroarenes as well.[151,156] Hence, a complete inversion of reactivity as compared to reactions via traditional S_EAr-type mechanisms was noted in that the less electron-rich arene reacted preferentially. A KIE of k_H/k_D = 3.0 was experimentally determined, being indicative of a kinetically relevant C−H bond cleavage.[156] As arylating reagents, aryl bromides or chlorides could be employed under the optimized reaction conditions while aryl iodides called for the use of AgOTf as additive. Moreover, heteroaromatic fluoroarenes and heteroaryl bromides turned out to be viable substrates (Scheme 20). Subsequent optimization studies revealed that more efficient catalysis was accomplished through the use of electron-rich biphenyl monophosphine ligand S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl),[157,158] along with isopropyl acetate as solvent, thereby allowing direct arylations to proceed at a lower reaction temperature of 80 °C.[159] Moreover, biphasic reaction conditions enabled palladium-catalyzed direct arylations of electron-poor fluorinated arenes at ambient reaction temperature.[160] The site selectivity of these reactions was originally attributed to the increased C−H bond acidity, but recent DFT calculations suggested that a correlation with Pd−C bond energies provides more satisfactory results.[161,162]

In independent studies on the mechanism of intramolecular palladium-catalyzed direct arylations of (hetero)arenes Echavarren and co-workers experimentally found a KIE of k_H/k_D = 5.0, which was again not in agreement with an electrophilic C−H bond activation manifold.[163−167] Further, intramolecular competition experiments with Dave-Phos (2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl) as the ligand highlighted a

Scheme 19. Intermolecular Competition Experiment



Scheme 18. Intramolecular Competition Experiments



	24		25
R = OMe:	10	:	1
R = Me:	15	:	1
R = *t*-Bu or CF_3:	> 30	:	1
R = CO_2Me:	> 30	:	1
R = Cl:	3.2	:	1
R = F:	1	:	4.3

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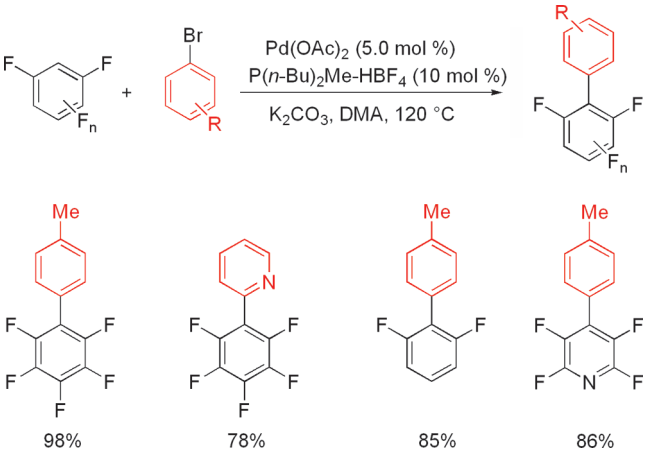
significant rate acceleration by electronegative groups exerting a negative inductive effect, such as fluorine (Scheme 21), chlorine, or trifluoromethyl substituents.

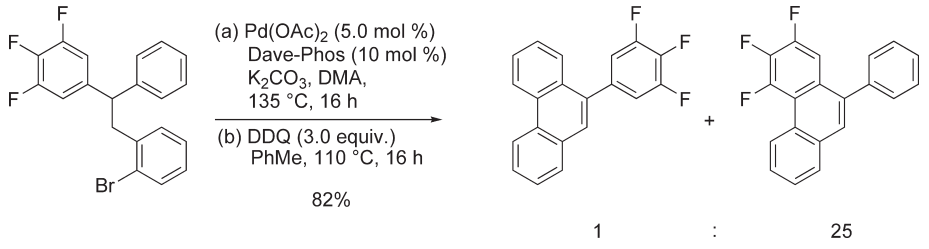
Scheme 20. Palladium-Catalyzed Direct Arylations of Electron-Deficient Oligofluoro-Substituted (Hetero)Arenes



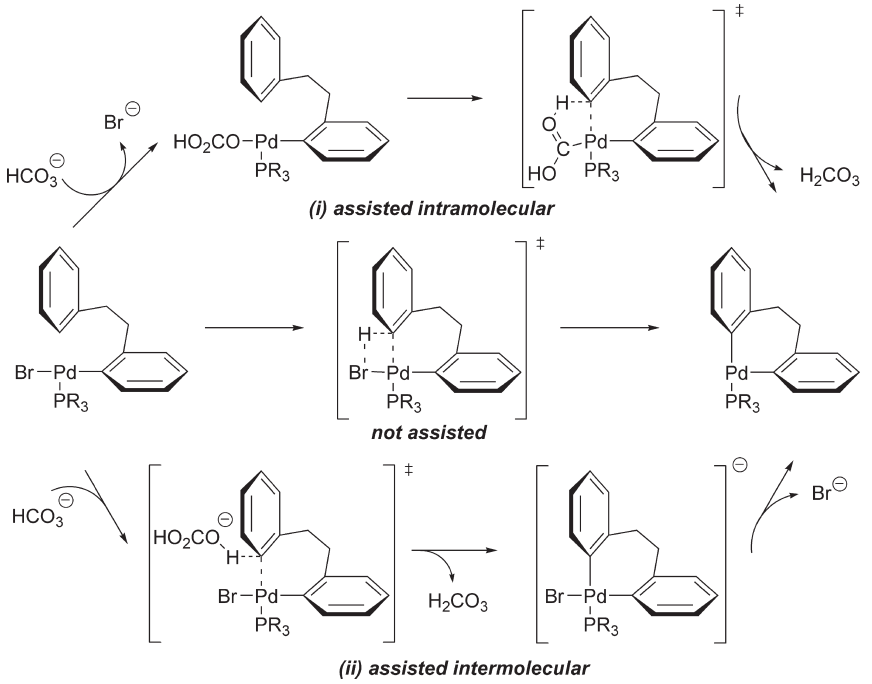
These experimental observations, along with DFT calculations reported by Echavarren, Maseras, and co-workers, suggested a concerted deprotonative C−H bond metalation via carbonate assistance to be operative.[20,163−166,168] For palladium catalysts derived from monodentate phosphine ligands, two mechanisms were calculated to be viable, namely, (i) a concerted deprotonation through a coordinated carbonate in an intramolecular fashion or (ii) an intermolecular deprotonation through the action of an external noncoordinated carbonate base (Scheme 22).[166] On the contrary, a HBr elimination was calculated to be far less accessible.

Interestingly, subsequent optimization studies revealed bidentate phosphine ligands, such as dppf, dppm, dppe, or Xantphos, to be superior in intramolecular palladium-catalyzed direct arylations with aryl bromides, as illustrated by the functionalization of fluorene derivative **26**[169] to deliver benz[*e*]acephenanthrylene (**27**) (Scheme 23).[165] Contrary to various direct arylations with monodentate phosphine ligands, the use of pivalic acid as cocatalytic additive (vide infra) proved not to be beneficial when employing bidentate ligands. As a consequence, the authors proposed direct arylations with bisphosphines to occur by the action of the external carbonate base to avoid the

Scheme 21. Intramolecular Competition Experiment



Scheme 22. Computed Mechanisms for C−H Bond Palladation in Intramolecular Direct Arylations



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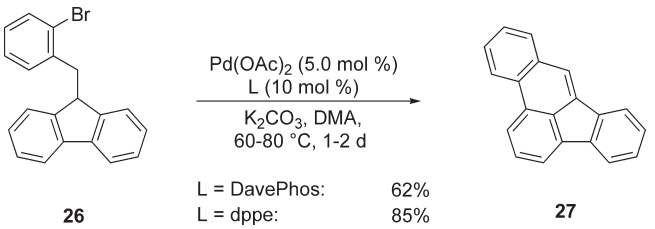
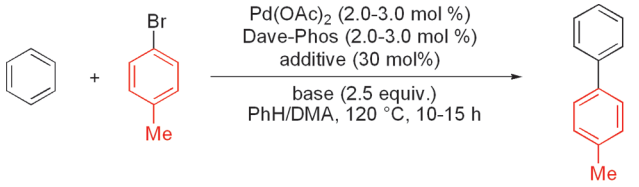
Scheme 23. Monodentate versus Bidentate Phosphine Ligands in Palladium-Catalyzed Intramolecular Direct Arylations

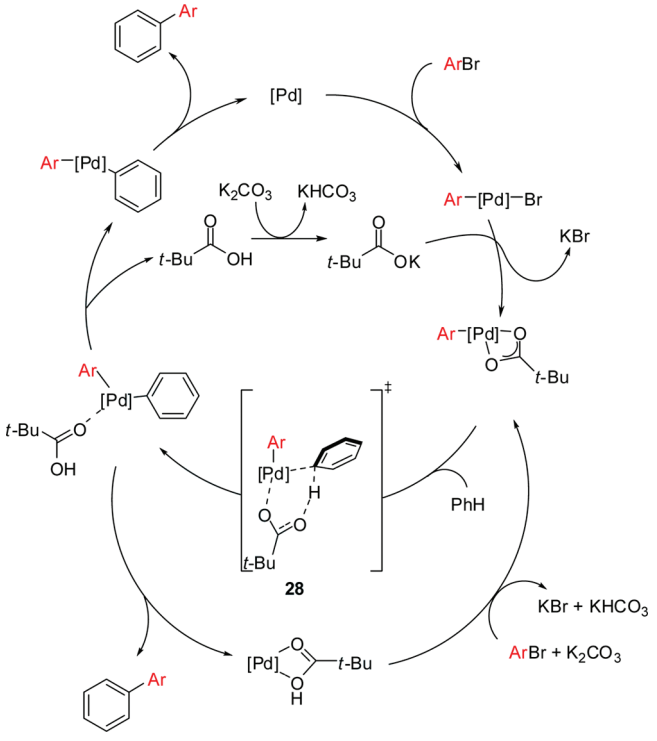


Scheme 24. Effect of Base and Additive on an Intermolecular Palladium-Catalyzed Direct Arylation



base	additive	yield (GC-MS)
K_2CO_3	---	0%
KOPiv	---	41%
K_2CO_3	AcOH	11%
K_2CO_3	*i*-$PrCO_2H$	13%
K_2CO_3	PivOH	82%

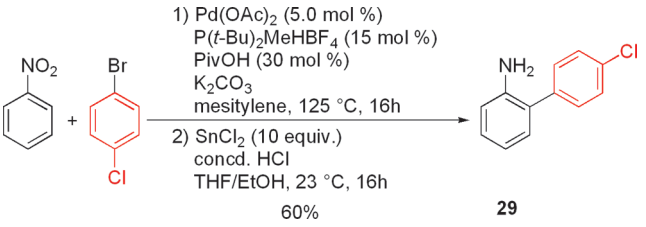
Scheme 25. Proposed Mechanism for Pivalate-Assisted Palladium-Catalyzed Direct Arylations



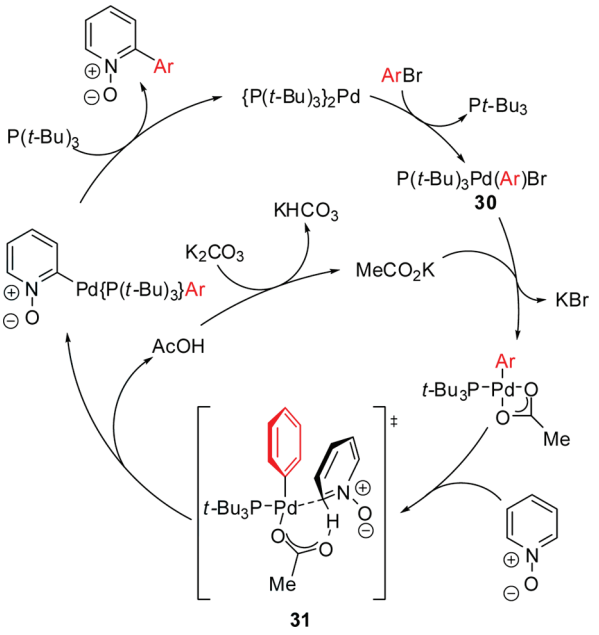
otherwise required formation of a pentacoordinate palladium(II) species.

3.2.1.2. Direct Arylations with Carboxylic Acids as Cocatalysts. C(sp^2)−H Bond Functionalizations. With the aim of increasing the amount of available soluble base, Fagnou and Lafrance probed different carboxylic acids as cocatalysts in

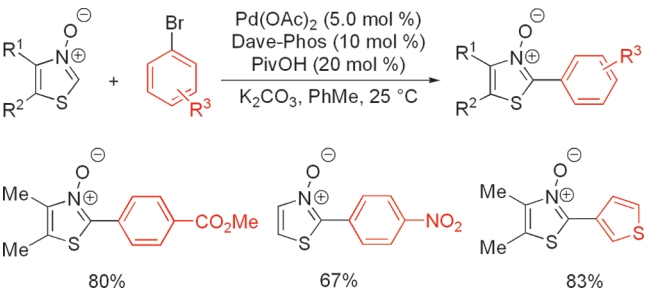
Scheme 26. Carboxylate-Assisted Palladium-Catalyzed Direct Arylation To Produce Biphenyl 29



Scheme 27. Proposed Catalytic Cycle of Palladium-Catalyzed Direct Arylations of Pyridine *N*-Oxides with $Pd(OAc)_2$ as Precatalyst



Scheme 28. Palladium-Catalyzed Direct Arylation of Azole *N*-Oxides



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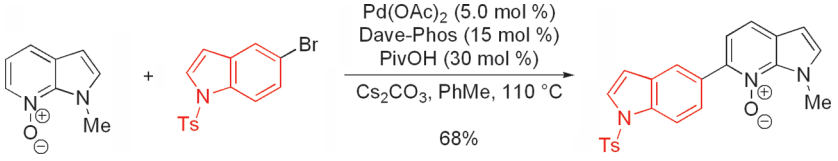
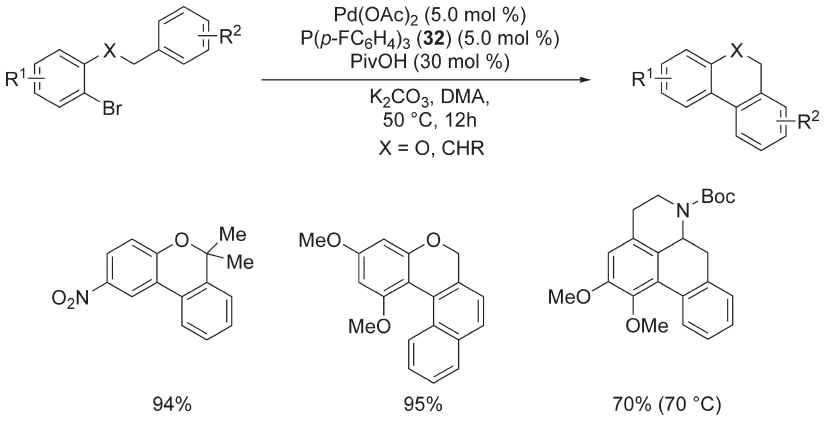
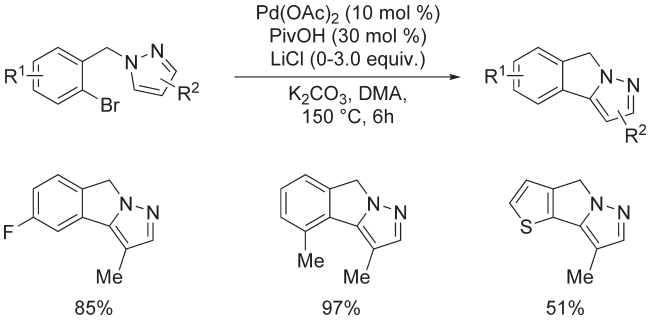
Scheme 29. Palladium-Catalyzed Direct Arylation of Azaindole *N*-Oxides



Scheme 30. Palladium-Catalyzed Intramolecular Direct Arylations in the Presence of Electron-Deficient Phosphine Ligand 32



Scheme 31. Phosphine Ligand-Free Palladium-Catalyzed Intramolecular Direct Arylations



palladium-catalyzed direct arylations of unactivated arenes (Scheme 24).[170] Here, both the quantity and the nature of the acid strongly affected the yield of the desired products.

To rationalize the remarkable reactivity of the palladium catalyst derived from PivOH,[171] the authors suggested that the potassium pivalate acts as a proton shuttle within concerted metalation−deprotonation (CMD) transition state **28** (Scheme 25).[170]

An illustrative application of carboxylate-assisted palladium-catalyzed direct arylations of arenes is represented by the efficient reaction of nitrobenzenes with aryl halides, which set the stage for an atom-economical preparation of biaryl **29**, an intermediate in the synthesis of the commercial agrochemical product Boscalid (Scheme 26).[172]

Very recently, the mechanism of palladium-catalyzed direct arylations of electron-deficient azine *N*-oxides was revisited by detailed kinetic and computational studies, which highlighted the critical role of the acetate in the frequently used precursor $Pd(OAc)_2$.[173] Thus, a catalytic cycle was proposed to commence with a fast oxidative addition of the aryl halide to a palladium(0) complex (Scheme 27). While the resulting palladium(II) species **30** might exist in an equilibrium with inactive dimeric species, a salt metathesis with the acetate sets the stage for six-membered inner-sphere CMD transition state **31**. Subsequently, the acetic acid is likely deprotonated by the stoichiometric carbonate base, and the desired product is finally obtained by reductive elimination.

While palladium-catalyzed direct arylations of electron-deficient azine *N*-oxides were thus far mostly accomplished in the absence of pivalic acid (vide supra),[150,151] C−H bond functionalizations on azole *N*-oxides proceeded often more efficiently through carboxylate assistance.[174,175] For instance, thiazole *N*-oxides were directly arylated in the presence of a catalyst derived from ligand Dave-Phos, a transformation that occurred under exceedingly mild reaction conditions (Scheme 28).[175] The optimized protocol was furthermore employed for the selective assembly of fully substituted azoles.

Additionally, the pivalate-modified palladium catalyst proved applicable to general direct arylations of 6- or 7-azaindole *N*-oxides (Scheme 29).[176] Notably, products originating from more typical C-3[177] or C-2 direct arylations[107,178] were only observed as minor byproduct under the optimized reaction conditions.

The increased reactivity of the pivalic acid-modified palladium catalyst was further exploited for entropically favored intramolecular direct arylations.[144] Interestingly, most efficient reactions with aryl bromides were achieved with an in-situ-generated complex of electron-deficient phosphine $P(p\text{-}FC_6H_4)_3$ (**32**).

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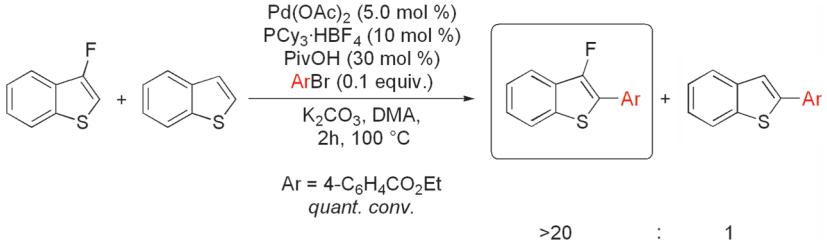
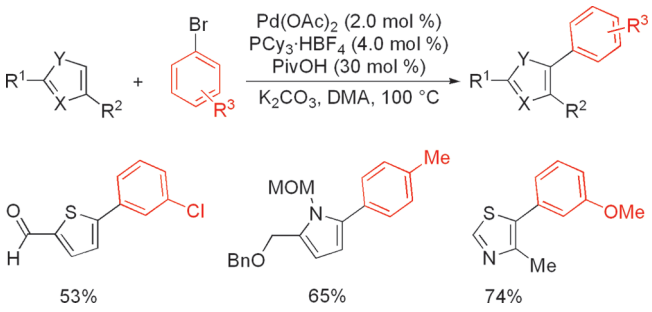
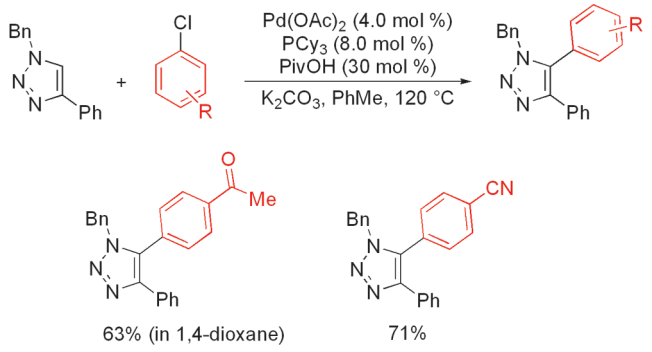
Scheme 32. Competition Experiment for the Palladium-Catalyzed Direct Arylation of Electron-Rich Heteroarenes



Scheme 33. Pivalate-Assisted Direct Arylations of Electron-Rich Heteroarenes



Scheme 34. Palladium-Catalyzed Direct Arylations with Aryl Chlorides

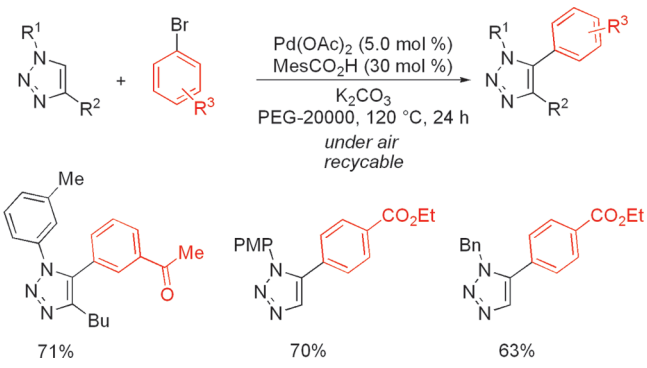


Again, the nature of the stoichiometric base was of prime importance, with K_2CO_3 ensuring optimal yields (Scheme 30).

Intramolecular direct arylations of pyrazoles were viable under phosphine ligand-free conditions with pivalic acid as a cocatalyst.[179,180] However, stoichiometric amounts of LiCl were found to be required to guarantee generality in direct arylations with aryl iodides and bromides. Conversely, aryl triflates, tosylates, or mesylates unfortunately provided only unsatisfactory results. The phosphine ligand-free catalytic system displayed remarkable functional group tolerance, enabling effective direct arylations with among others thiophene (Scheme 31) or pyridine derivatives.[179a] An additional example of using pivalic acid in palladium-catalyzed intramolecular direct arylations is represented by a recent microwave-assisted synthesis of aporphine alkaloid analogs.[181]

Until recently, pivalic acid was primarily used for carboxylate-assisted direct arylations of electron-deficient heteroarenes. Yet, electron-rich derivatives turned out to be useful substrates for

Scheme 35. Palladium-Catalyzed Direct Arylations in Polyethylene Glycol (PEG) with a Recyclable Palladium Catalyst (PMP = 4-$MeOC_6H_4$)



palladium(0)-catalyzed intermolecular C−H bond arylations under comparable reaction conditions as well.[161,182] Notably, heteroarenes bearing electron-withdrawing substituents reacted again preferentially, as showcased by the competition experiment depicted in Scheme 32.[161] These results indicated that a non-S_EAr-type mechanism is likely operative even with these electron-rich substrates, and DFT calculations supported a CMD working mode to be most favorable.

The optimized catalytic system displayed a remarkable wide substrate scope, thereby enabling site-selective direct arylations of various electron-rich heteroarenes, such as thiazoles, furans, pyrroles, triazoles, or oxazoles, when employing aryl bromides (Scheme 33).[182] On the contrary, the use of aryl iodides, triflates, or chlorides as arylating reagents provided here only unsatisfactory yields.

Intermolecular direct arylations of electron-rich 1,2,3-triazoles[183,184] with inexpensive[185,186] aryl chlorides[187,188] proceeded with high efficacy in toluene as solvent even in the absence of carboxylic acids as cocatalysts for the vast majority of substrate combinations.[189] An exception was found by reactions with aryl chlorides displaying an enolizable ketone or a cyano substituent, which were more effectively converted when using a pivalic acid-modified palladium catalyst (Scheme 34).[189]

As of yet, pivalic acid was almost exclusively employed as a cocatalytic additive in base-assisted palladium(0)-catalyzed direct C−H bond functionalizations. Yet, palladium-catalyzed direct arylations in polyethylene glycol (PEG) as reaction medium proceeded highly efficiently with carboxylic acid $MesCO_2H$ (Scheme 35).[190] Notably, the catalytic system was found to be highly robust, as evidenced by reactions being conducted under an atmosphere of air with substrates bearing a variety of

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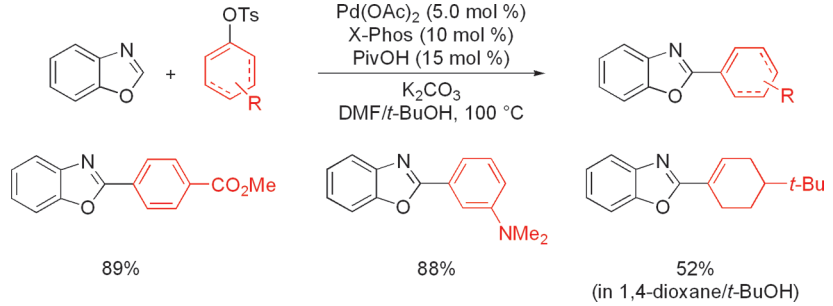
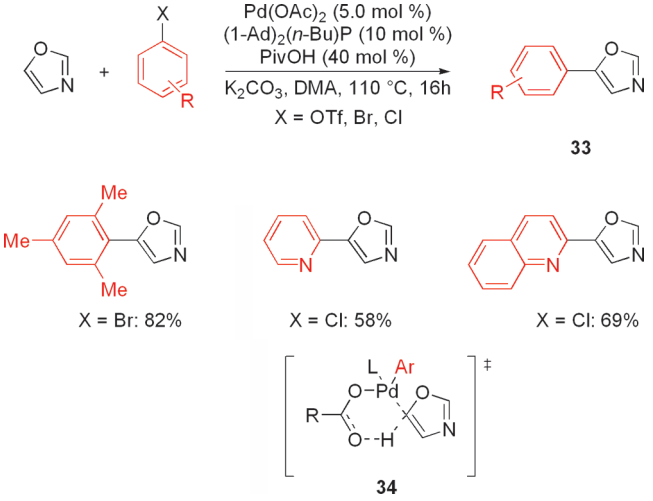
Scheme 36. Palladium-Catalyzed Direct Functionalizations with Aryl and Alkenyl Tosylates



Scheme 37. C-5-Selective Palladium-Catalyzed Direct Arylations of Oxazole



valuable electrophilic functional groups.[171,190,191] Moreover, the palladium(0) catalyst derived from $MesCO_2H$ could be conveniently recycled[192] when employing PEG-20000 as a user-friendly reaction medium.[190]

Challenging intermolecular direct arylations of heteroarenes with inexpensive yet easily accessible aryl tosylates or mesylates[193] could generally be achieved in the absence of a carboxylic acid additive, with the exception being transformations of more acidic benzoxazole (Scheme 36, X-Phos = (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl).[151,194,195] On the contrary, direct arylations of 1,2,3-triazoles, caffeine, or simple oxazoles with aryl tosylates proceeded more efficiently without pivalic acid as cocatalytic additive.[194]

Unusual site selectivity was recently observed in carboxylate-assisted direct arylations of oxazole, providing predominantly the C-5-substituted products **33** with $P(1\text{-}Ad)_2(n\text{-}Bu)$ (cataCXium A) as the ligand, along with pivalic acid as cocatalytic additive in DMA as solvent (Scheme 37).[196] This rather unexpected selectivity was rationalized with transition state **34**, while optimized reaction conditions for C-2-selective direct arylations involved the use of S-Phos as the ligand and cocatalytic amounts of pivalic acid in toluene as solvent.

Electronegative chloride substituents exerted an activating effect[197] on heteroarenes being reminiscent of the one previously observed in reactions of oligofluoroarenes.[166] Thus, the reactivity of easily accessible chloro-substituted heteroarenes was shown to be superior in palladium-catalyzed direct arylations under pivalate assitance. Intermolecular competition experiments clearly revealed the non-S_EAr-type nature of this transformation, which resulted in inverted product ratios as compared to traditional Vilsmeier−Haack formylations (Scheme 38). Moreover, this protocol gave direct access to otherwise difficult to prepare heteroarenes, such as 3-arylated benzothiophenes. The improved reactivity of chloroheteroarenes was rationalized through computational DFT studies in terms of a CMD reaction mechanism.

Most studies on carboxylate-assisted palladium-catalyzed direct arylations had until recently focused on the use of electron-rich phosphines as stabilizing ligands,[144] which set the stage for the use of less expensive aryl bromides or chlorides as arylating reagents. Unfortunately, these reaction conditions only met with limited success when employing aryl iodides as coupling partners.[198] However, René and Fagnou recently illustrated that these substrates are more efficiently converted in direct arylations of electron-rich hetereoarenes provided that an electron-deficient tertiary phosphine was used as the ligand, along with Ag_2CO_3 as the base.[199] Hence, particularly sterically encumbered phosphine **35** proved to give rise to optimal results in direct functionalizations of among others (benzo)thiophenes, furans, pyrroles, pyrazoles, or imidazoles (Scheme 39).

Additionally, palladium-catalyzed direct arylations of electron-rich heteroarenes under phosphine ligand-free reaction conditions with aryl bromides were recently shown to proceed efficiently with catalytic amounts of pivalic acid (Scheme 40).[200]

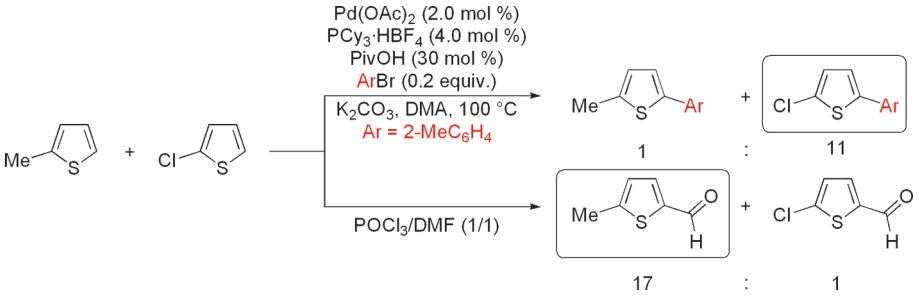
$C(sp^3)$−H Bond Functionalizations. Fagnou and co-workers accomplished general palladium-catalyzed intramolecular direct arylations of alkanes[201,202] through the use of CsOPiv in cocatalytic amounts.[203,204] The nature of both the stoichiometric base as well as the additive proved to be of prime importance for achieving satisfactory results (Scheme 41).[204] Thus, the use of either Cs_2CO_3 or CsOPiv as the sole stoichiometric base did not meet with success. Moreover, cocatalytic amounts of PivOH were found to be superior as compared to AcOH.

More recent studies on palladium-catalyzed direct arylations of alkanes revealed Rb_2CO_3 to be the stoichiometric base of choice for robust intramolecular alkane functionalizations (Scheme 42).[204]

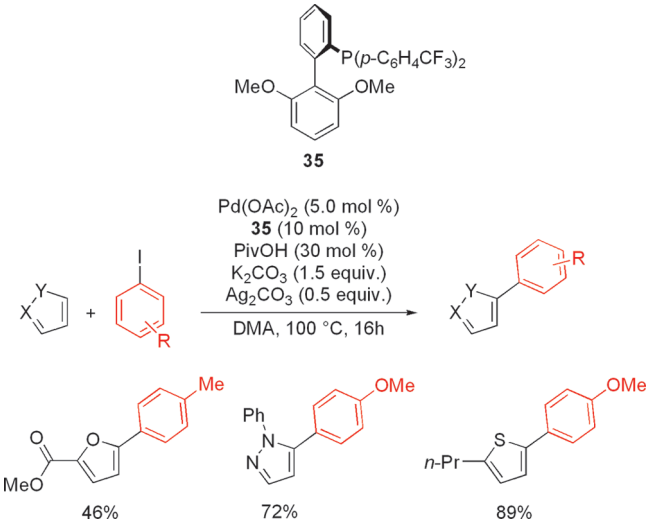
However, 2,2-dialkyldihydrobenzofurans **36** were efficiently prepared when using Cs_2CO_3 as the base and PivOH as cocatalytic additive (Scheme 43).[203] This catalytic system proved applicable to direct alkane arylations with aryl bromides as well as less expensive aryl chlorides as arylating reagents. Moreover, a

dx.doi.org/10.1021/cr100412j |Chem. Rev. 2011, 111, 1315–1345

Scheme 38. Competition Experiments for a Direct Arylation and a Vilsmeier−Haack Formylation



Scheme 39. Intermolecular Direct Arylations with Aryl Iodides and Electron-Deficient Ligand 35



KIE of k_H/k_D = 5.4 was suggestive of a kinetically relevant C−H bond metalation event.

Further, *N*-methylsulfonamides turned out to be suitable substrates when Cs_2CO_3 was used as stoichiometric base (Scheme 44).[204] The chemoselective synthesis of sulfonamide **37** within an intramolecular competition clearly revealed the functionalization of a C(sp^2)−H bond to be more facile as compared to the arylation of a C(sp^3)−H bond (Scheme 44, R = Ph).

Intramolecular direct C(sp^3)−H bond arylations were exploited for the synthesis of indoline derivatives by Fujii, Ohno, and co-workers.[205] Here, a palladium complex of an electron-rich tertiary phosphine proved most effective when using PivOH as additive, which enabled cyclization reactions of substrates not displaying a geminal disubstitution[206] in the backbone (Scheme 45).[205]

Experimental mechanistic studies by Fagnou and co-workers resulted in the synthesis of fully characterized palladium complex **38**, which was shown to be catalytically competent (Scheme 46).[204,207] Stoichiometric experiments with this well-defined complex showed that both the stoichiometric base Cs_2CO_3 as well as the additive PivOH are mandatory for achieving high-yielding cyclizations.[204]

DFT calculations as well as ^{31}P NMR spectroscopic studies suggested that the pivalate promotes the dissociation of one phosphine ligand. Further, kinetic analysis showed the initial rate dependence on concentration of substrate and catalyst to be zeroth and first order, respectively. The reaction is further first order in pivalate until a palladium/pivalate ratio of 1:3, thus revealing saturation kinetics. On the basis of these mechanistic studies Fagnou and co-workers proposed a catalytic cycle consisting of (a) initial oxidative addition of the aryl halide to a palladium(0) species, (b) facile ligand exchange and phosphine dissociation, (c) rate-limiting CMD, (d) irreversible deprotonation, and (e) fast reductive elimination (Scheme 47).[204] The irreversible deprotonation thus rationalizes the strong dependence of the reaction outcome on the nature of the stoichiometric base.

Baudoin and co-workers developed reaction conditions for efficient intramolecular direct arylations of alkanes to yield cyclobutarene,[208,209] and more recently indanes, indolines, dihydrobenzofurans, or indanones.[201,208−212] Less reactive but more easily accessible aryl chlorides could generally be employed as arylating reagents provided that electron-rich tertiary phosphines were present as stabilizing ligands.[213] Irrespective of the substrate, experimental and computational studies by Baudoin, Clot, and co-workers indicated the reaction to proceed by rate-limiting C−H bond metalation within a CMD manifold.[209,213] Particularly, the importance of C−H agostic interactions was revealed through DFT calculations,[213] which increase the acidity of the geminal C−H bonds, also highlighting the dependence of the exact reaction mechanism on the nature of the phosphine ligand and the base.[214] In terms of carboxylate assistance, a palladium catalyst derived from cocatalytic amounts of pivalic acid provided improved isolated yields only in the formation of heterocycles or indanones (Scheme 48).[213] Moreover, C−H bond functionalizations occurred site selectively at primary C−H bonds, leaving secondary or tertiary C−H bonds unchanged.

3.2.1.3. Direct Alkylations. Direct alkylations of (hetero)arenes through C−H bond cleavages under basic reaction conditions represent attractive alternatives to traditional Friedel−Crafts-type alkylations or conventional cross-coupling with alkyl halides.[215] Notable features of this approach include excellent chemoselectivities, thus providing access to mono-*n*-alkylated products, without the interference of undesired cationic rearrangements. With respect to the development of base-assisted C−H bond benzylations, Chang and co-workers disclosed an intramolecular direct benzylation for the preparation of condensed pyrroloindoles **39** (Scheme 49).[216] Interestingly, substrates with electron-withdrawing substituents on the heteroaromatic moiety initially reacted faster (R = CHO > Ac > Me). These experimental observations could not be explained with a conventional electrophilic activation process. Instead, the authors suggested

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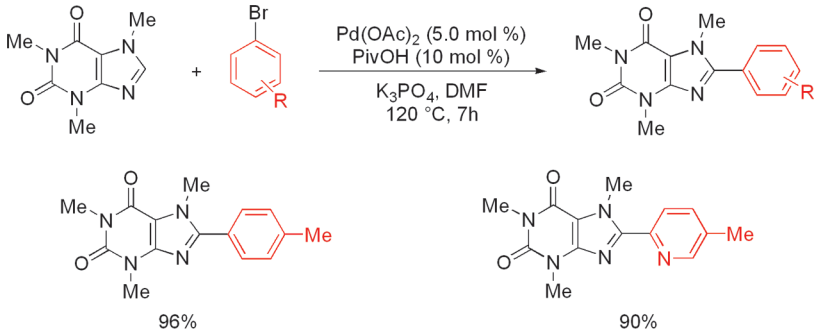
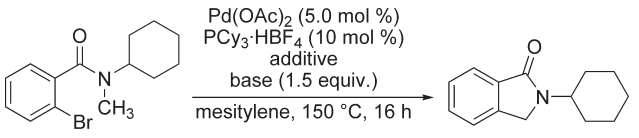
Scheme 40. Phosphine Ligand-Free Palladium-Catalyzed Direct Arylations through Pivalate Assistance

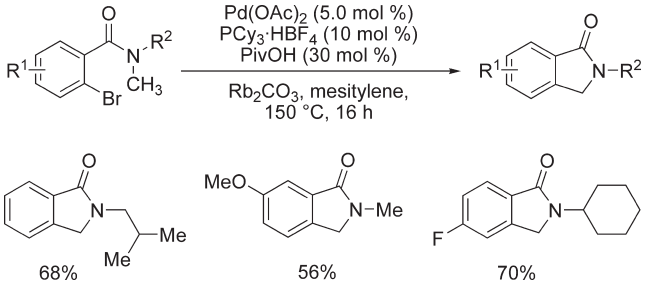


Scheme 41. Effect of Carboxylic Acids and Bases on Intramolecular Alkane Arylation

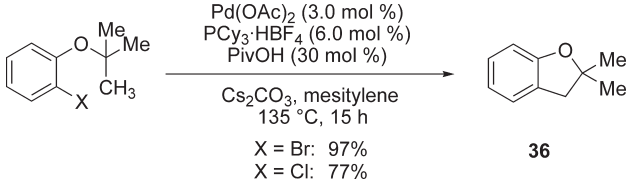


base	additive	yield
Cs_2CO_3	---	14% (GC-MS)
CsOPiv	---	5% (GC-MS)
Cs_2CO_3	AcOH (30 mol %)	27% (GC-MS)
Cs_2CO_3	PivOH (30 mol %)	83%

Scheme 42. Scope of Pivalate-Assisted Intramolecular Direct Arylations with Rb_2CO_3 as the Base



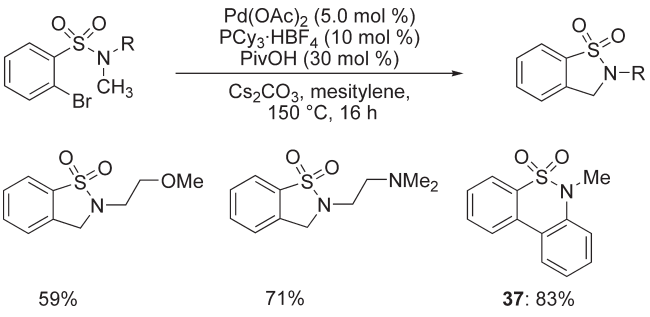
Scheme 43. Intramolecular Direct Alkane Arylation for the Synthesis of Dihydrobenzofuran 36



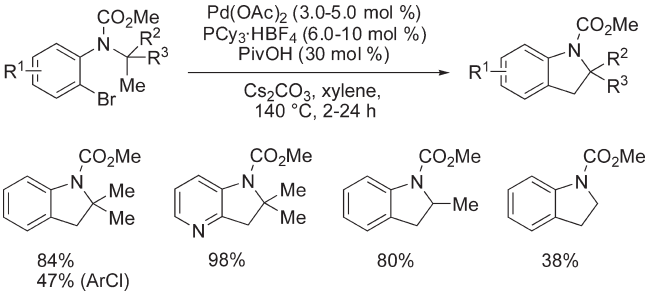
a deprotonative metalation to be operative through four-membered transition state **40**.

An extension to arenes as substrates revealed less electron-rich phosphines and inorganic base Cs_2CO_3 to be superior for the synthesis of fluorenes **42** (Scheme 50).[216,217] Hammett studies with differently substituted substrates **41** as well as an intermolecular KIE of k_H/k_D = 2.1 led the authors to suggest a six-membered transition state **43**, in which the coordinated carbonate assists the cyclopalladation.[217]

Scheme 44. Intramolecular Direct Arylations with Sulfonamides



Scheme 45. Pivalate-Assisted Direct Arylation for the Synthesis of Indolines



Intermolecular palladium-catalyzed direct benzylations of various five-membered heteroarenes through carboxylate assistance were reported by Fagnou and Lapointe.[218] Thus, a system relying on cocatalytic amounts of pivalic acid allowed for challenging direct functionalizations on thiophene derivatives with reduced[219] nucleophilicity (Scheme 51).[218] The reactions were proposed to proceed by a deprotonative C−H bond metalation paradigm, which offers a complementary substrate scope to classical S_EAr-type reactions.

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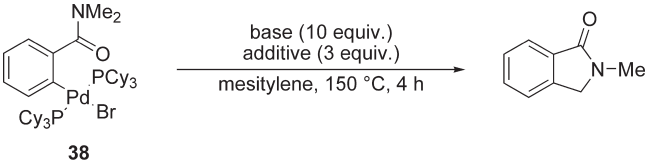
The use of challenging alkyl halides for intermolecular C−H bond alkylations could be circumvented through a reaction sequence comprising an intramolecular Mizoroki−Heck reaction[121] along with an intermolecular direct alkylation.[220] Here, five-membered heterocycles were functionalized in an intermolecular[221] fashion through the in-situ formation of alkylpalladium(II) intermediates **44** (Scheme 52).[220] Notably, addition of cocatalytic amounts of pivalic acid turned out to be beneficial, which was rationalized in terms of a CMD mechanism.

Generally applicable intermolecular direct alkylations of arenes with unactivated alkyl halides were, on the contrary, accomplished through the use of 8-aminoquinoline as an auxiliary and pivalic acid as cocatalytic additive (Scheme 53).[222] Thereby, primary unactivated alkyl and benzyl iodides or bromides could be employed for *ortho*-selective[223] direct C−H bond functionalizations. Importantly, alkylations were not limited to C(sp^2)−H bond functionalizations but occurred at challenging unactivated C(sp^3)−H bonds as well. Experimental mechanistic studies led the authors to propose an oxidative addition of the alkyl halides to a palladium(II) species, presumably yielding a palladium(IV) intermediate, although formation of palladium(III)[224,225] complexes could not be ruled out.[222]

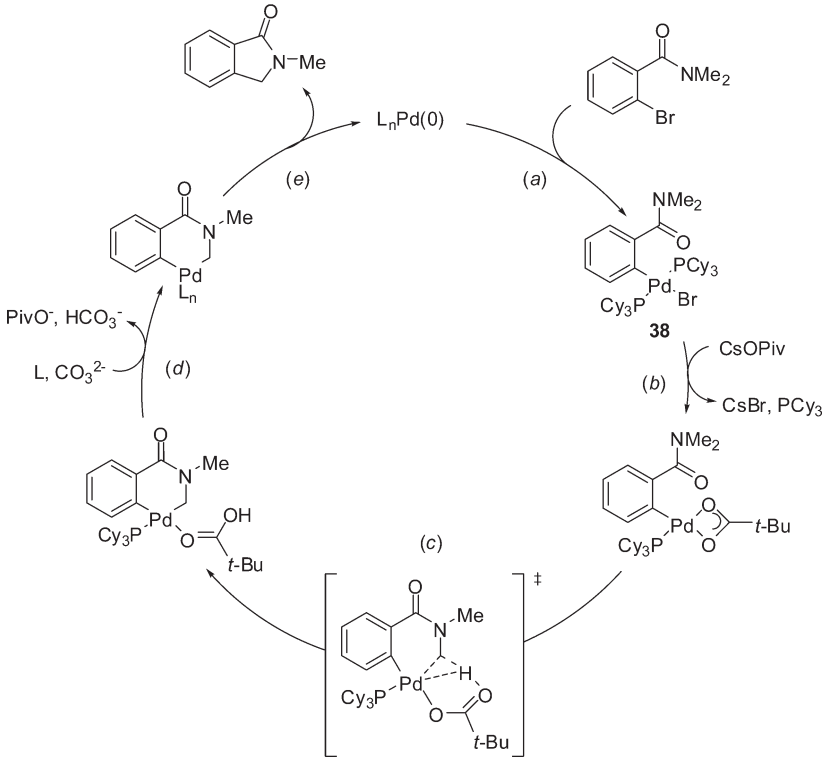
Scheme 46. Stoichiometric C(sp^3)−H Bond Activation with Isolated Complex 38



base	additive	yield
---	---	0%
Cs_2CO_3	---	0%
CsOPiv	---	28%
Cs_2CO_3	CsOPiv	96%

3.2.2. Ruthenium. *3.2.2.1. Direct Arylations.* Generally applicable methods for ruthenium-catalyzed syntheses of bi(hetero)aryls through traditional cross-coupling reactions between easily accessible aryl halides and organometallic reagents have proven elusive,[226] a striking contrast to well-established palladium-, nickel-, or copper-catalyzed processes.[1,227−229] Additionally, knowledge on the stoichiometric formal oxidative addition of aryl halides to ruthenium complexes is comparably underdeveloped.[230] Despite this lack in mechanistic understanding, ruthenium-catalyzed direct arylations of arenes with aryl halides[231] were accomplished, however, until recently only[232] with complexes derived from phosphine- or N-heterocyclic carbene[68−70] (NHC) ligands.[9,67,233,234] Notably, all of these reactions required the use of highly polar *N*-methylpyrrolidinone (NMP) as solvent, which led to catalytic systems with lower robustness, particularly when being applied to more challenging substrate combinations.[9,72] Since stoichiometric C−H bond metalations were previously shown to benefit from the presence of acetate additives (vide supra),[49−51,59] the Ackermann group probed carboxylates as potential cocatalysts for general phosphine ligand-free ruthenium-catalyzed direct arylations.[235] In 2008, we thus disclosed a comparison of the efficacy of various cocatalytic additives in direct arylations using toluene as inert solvent and *N*-aryl-substituted 1,2,3-triazoles[183,184] as substrates

Scheme 47. Proposed Mechanism for Palladium-Catalyzed Intramolecular Direct Arylations of Alkanes



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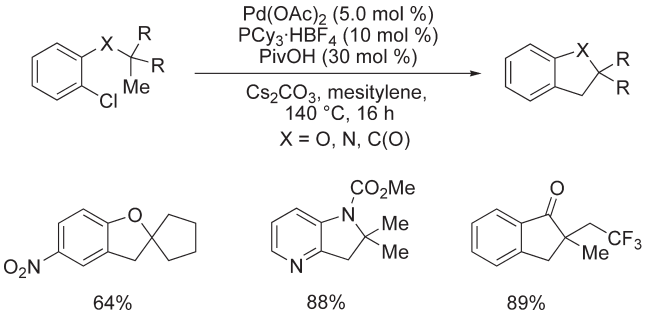
(Scheme 54).[235] Interestingly, complexes of previously used ligands, such as tertiary phosphines or NHC precursors, only performed poorly.[235] On the contrary, a ruthenium complex derived from bifunctional sterically hindered SPO preligand[22−25,27,236] $(1\text{-Ad})_2P(O)H$ enabled more efficient catalysis.[9,235] Interestingly, acids as cocatalysts were found to be superior, with optimal results being obtained with sterically hindered derivative $MesCO_2H$.[72,235]

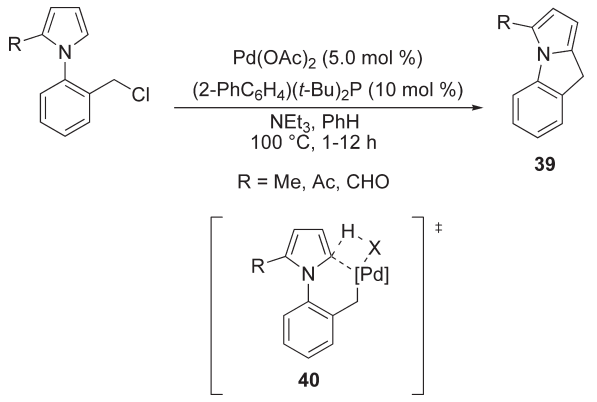
The remarkable catalytic activity accomplished with these bifunctional (pre)ligands was rationalized with a facile base-assisted C−H bond metalation reaction mechanism, proceeding through five- or six-membered transition state **45** or **46**, respectively (Figure 4).[235]

Importantly, the carboxylate-assisted ruthenium catalyst displayed a remarkable broad scope in the direct functionalization of

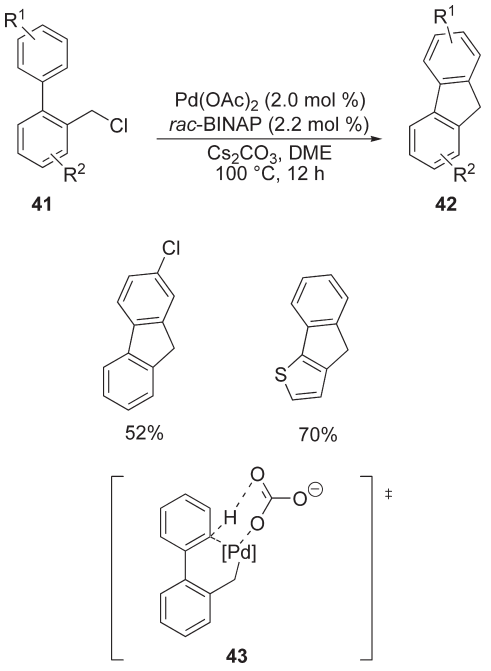
Scheme 48. General Intramolecular Direct Alkane Arylation with Aryl Chlorides



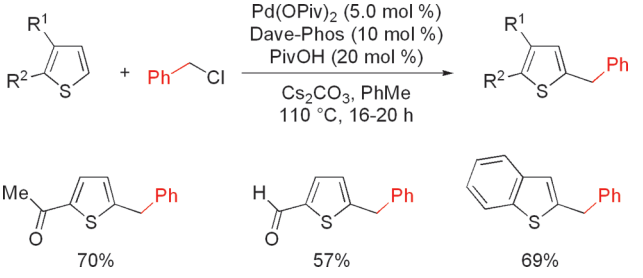
Scheme 49. Palladium-Catalyzed Intramolecular Benzylation and Proposed Transition State 40



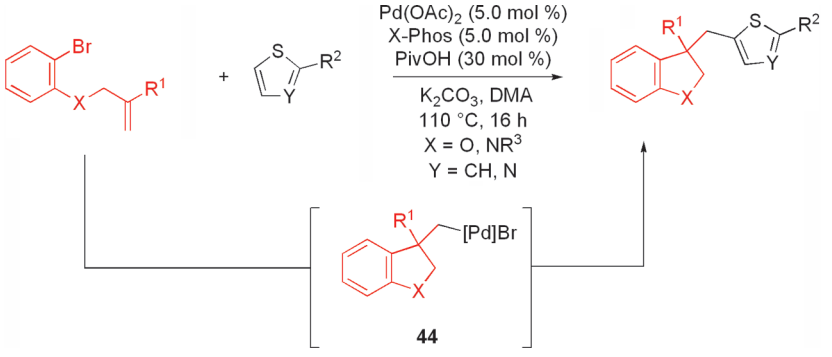
Scheme 50. Intramolecular Direct Benzylation with Arenes 41 and Proposed Six-Membered Transition State 43



Scheme 51. Intermolecular Direct Benzylations of Thiophenes



Scheme 52. Sequential Palladium-Catalyzed Direct Alkylations



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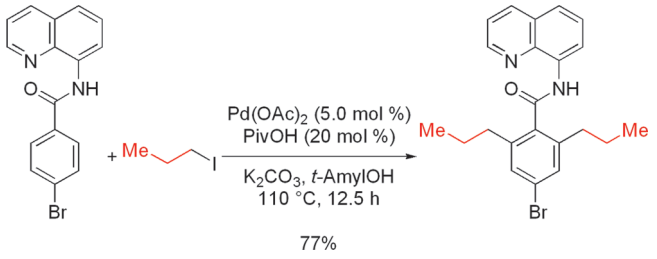
differently substituted 1,2,3-triazoles (Scheme 55).[235] Hence, valuable functional groups, such as enolizable ketones, esters, or heteroarenes, were well tolerated. As is generally observed in ruthenium-catalyzed direct arylations, intramolecular competition experiments revealed that aryl bromides reacted preferentially as compared to aryl chlorides and thus enabled the chemoselective synthesis of biaryl **47** from 4-bromochlorobenzene as the sole product.[235,237]

4-Aryl-substituted 1,2,3-triazoles also underwent efficient direct arylations with various arylating reagents.[238] Among a variety of cocatalysts, carboxylic acid $MesCO_2H$ again proved to be superior for the desired transformation (Scheme 56).

The scope of the carboxylate-assisted ruthenium catalysis included a variety of differently substituted arenes.[238] When

Scheme 53. Auxiliary-Assisted Intermolecular Direct Alkylation of Arenes



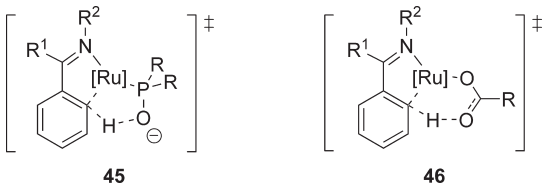
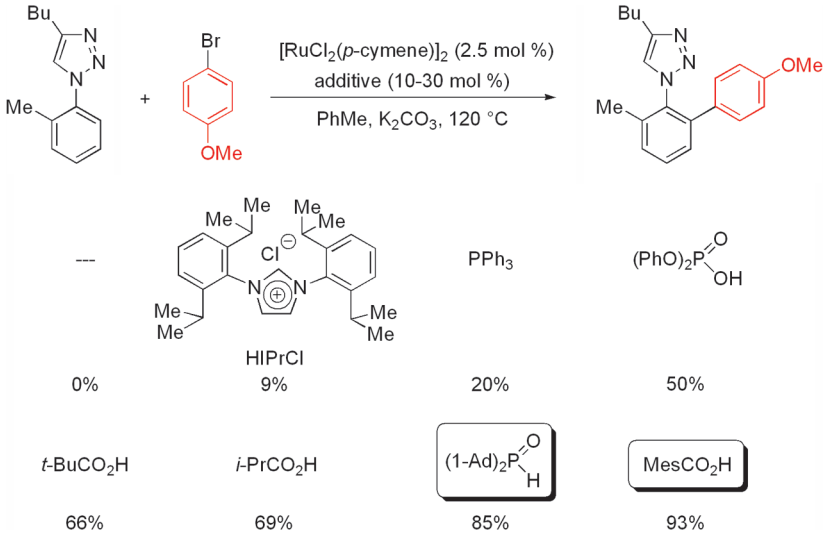
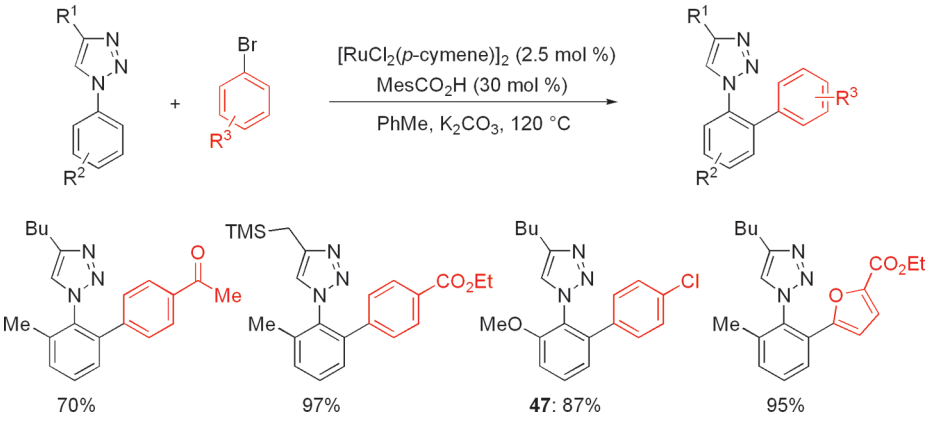


Figure 4. Proposed transition states **45** and **46** for base-assisted cycloruthenations.

Scheme 54. Effect of Cocatalytic Additives on Ruthenium-Catalyzed Direct Arylations in Toluene as Solvent



Scheme 55. Scope of Ruthenium-Catalyzed Direct Arylations with $MesCO_2H$ as Cocatalyst



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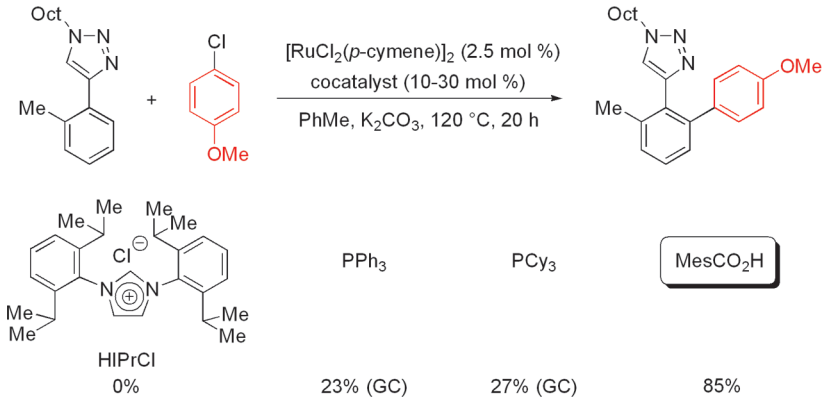
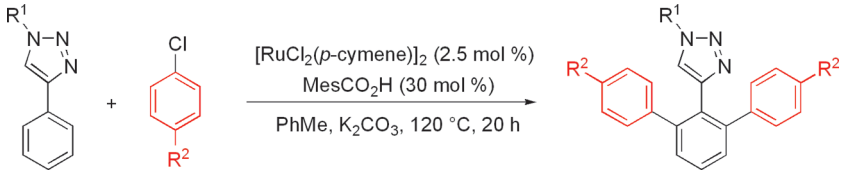
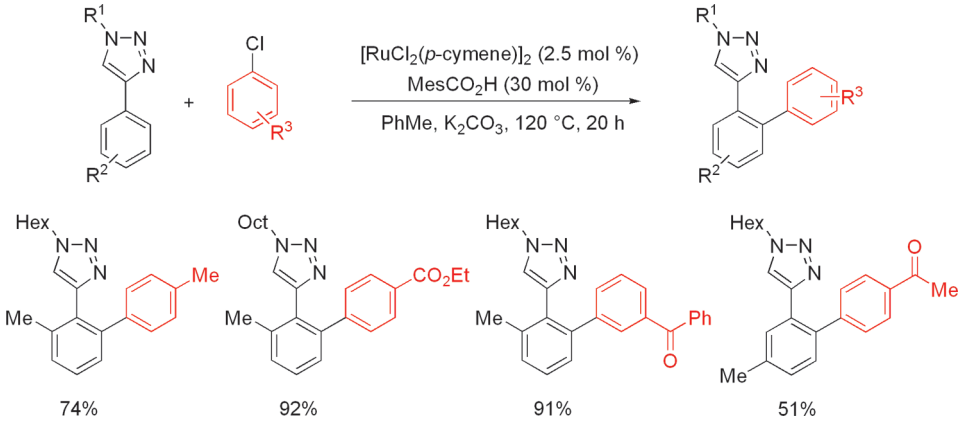
Scheme 56. Catalytic Additives in Ruthenium-Catalyzed Direct Arylations



Scheme 57. Carboxylate-Assisted Direct Diarylation of 4-Aryl-Substituted 1,2,3-Triazoles



Scheme 58. Monoarylation of Triazol-4-yl-Substituted Arenes



using an excess of the aryl chlorides, these reactions delivered predominantly diarylated products (Scheme 57).[238]

On the contrary, monoarylated products can generally be prepared in a chemoselective fashion when *ortho*- or *meta*-substituted arenes are employed as substrates (Scheme 58)[238] or often simply by changing the ratio of starting materials. The site selectivity in direct arylations of arenes bearing *meta*-alkyl-substituents was controlled by steric interactions.

Interestingly, the chemoselectivity of the C−H bond functionalization altered when specific *ortho*-disubstituted arenes were reacted with *ortho*-substituted aryl halides in that oxidative homocouplings[239,240] occurred preferentially (Scheme 59).[238] Detailed optimization studies demonstrated that most effective dehydrogenative arylations took place with sterically hindered *ortho*-chlorobenzotrifluoride (**48**) as the terminal oxidant.

The carboxylate-derived ruthenium catalyst was found not to be restricted to arenes displaying 1,2,3-triazoles as directing groups. Hence, substrates bearing oxazolines, pyridines, or pyrazoles as Lewis-basic functionalities could be directly functionalized in toluene as solvent with comparable efficacy.[235] Notably, C−H bond functionalizations of oxazolinyl-substituted arenes with aryl bromides were conveniently accomplished at reaction temperatures as low as 80 °C (Scheme 60).[235]

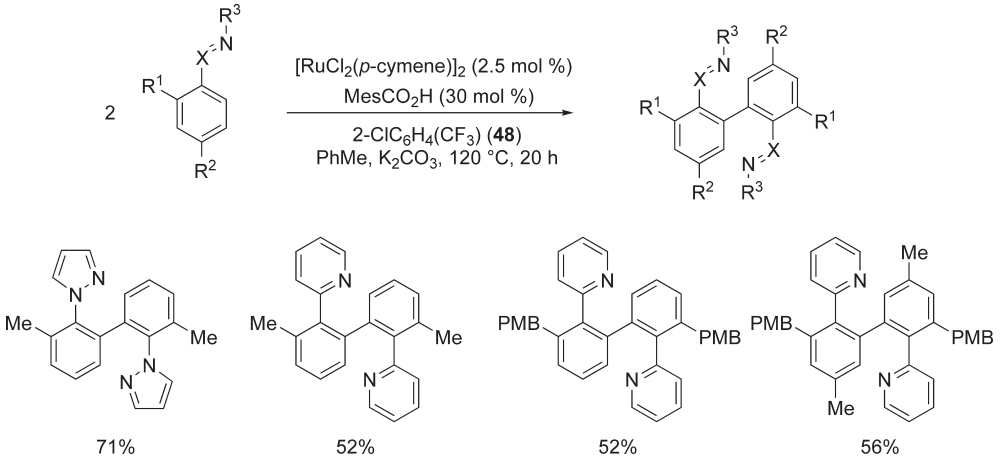
Also, pyrazolyl-substituted arenes were successfully employed in direct arylations with both functionalized electron-deficient as well as electron-rich aryl halides (Scheme 61).[235]

The ruthenium catalyst further enabled the diastereoselective preparation of alkenes through direct arylations of C−H bonds,[241] as illustrated with the synthesis of trisubstituted olefin **49** (Scheme 62).[235]

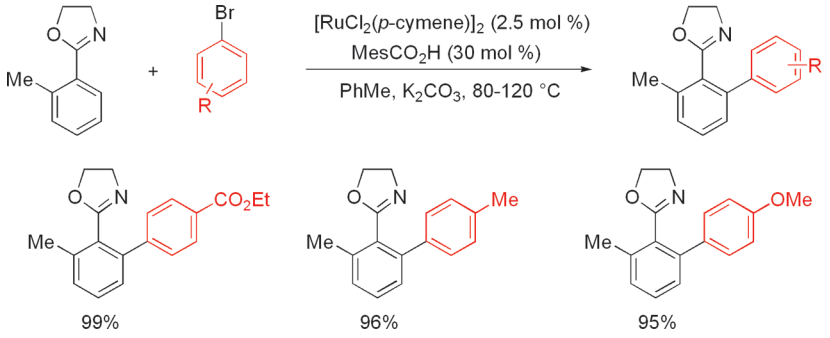
Direct arylations of arenes with different Lewis-basic functional groups, such as oxazolines or pyridines, with convenient

dx.doi.org/10.1021/cr100412j |*Chem. Rev.* 2011, 111, 1315–1345

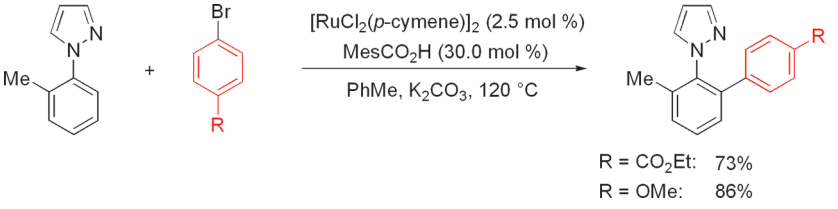
Scheme 59. Dehydrogenative Arylations with Aryl Chloride 48 as Terminal Oxidant (PMB = 4-MeOC$_6$H$_4$CH$_2$)



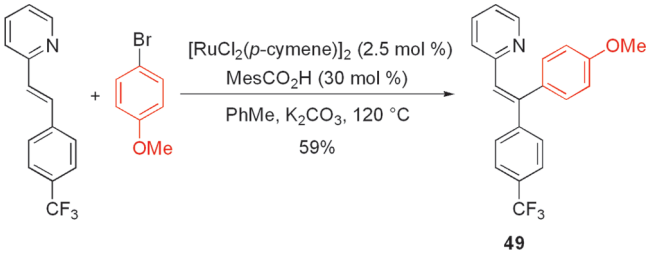
Scheme 60. Carboxylate-Assisted Ruthenium-Catalyzed Direct Arylations



Scheme 61. Ruthenium-Catalyzed Direct Arylations of Pyrazolyl-Substituted Arenes



Scheme 62. Carboxylate-Assisted Ruthenium-Catalyzed Direct Arylation for the Synthesis of Alkene 49



aryl chlorides furnished the desired products with yields being comparable to the ones obtained with aryl bromides (Scheme 63, cf. Scheme 60).[235]

Despite this significant recent progress in ruthenium-catalyzed direct arylations with aryl halides, detailed experimental mechanistic studies on the working mode of these catalysts were unfortunately until very recently not available. Thus, several distinct reaction manifolds continued to be considered for these transformations. To address this lack in mechanistic understanding we prepared ruthenium(II) biscarboxylate complexes, which turned out to be catalytically competent for C−H bond functionalizations, also when using apolar toluene as inert solvent (Scheme 64).[72] Notably, well-defined complex **50** displayed a broad substrate scope in that various arenes were directly functionalized with differently substituted (hetero)aryl chlorides in a highly regioselective fashion. Generally, transformations with electron-deficient aryl halides proceeded more efficiently, and reactions with *meta*-substituted arenes occurred with excellent site selectivities at the less hindered C−H bond. Further, direct

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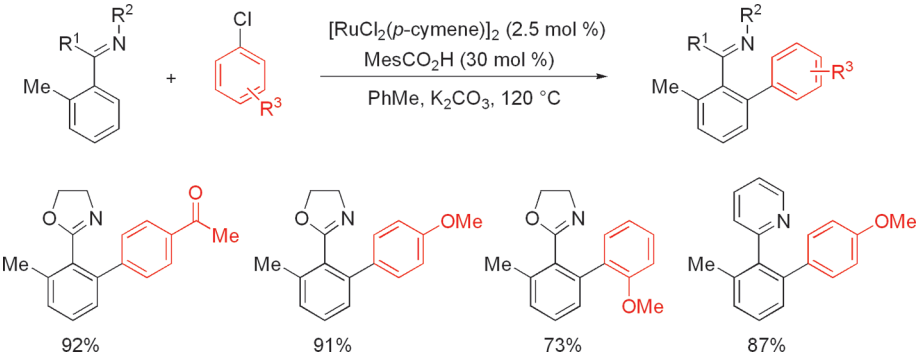
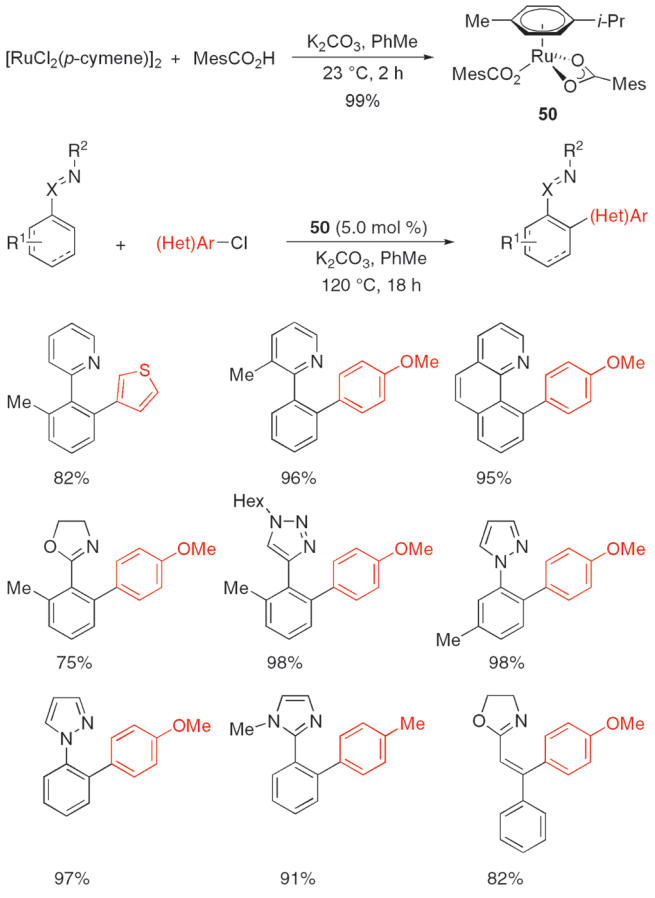
Scheme 63. Carboxylate-Assisted Ruthenium-Catalyzed Direct Arylations with Aryl Chlorides



Scheme 64. Direct Arylations Catalyzed by Ruthenium(II) Biscarboxylate 50



arylations of alkenes enabled the diastereoselective formation of olefins as well.

On the contrary, intramolecular competition experiments with *meta*-fluoro-substituted arenes delivered predominantly the 2-arylated products (Scheme 65),[72] which can be rationalized by the increased C−H bond acidity[242] or the stronger[243] Ru−C bond.[72]

Further, experiments with isotopically labeled starting materials clearly revealed a D/H-exchange reaction.[72,244] Contrary to previous proposals, these results suggested the C−H bond metalation step to be reversible in nature.[72] Moreover, competition experiments with an excess of differently substituted electrophiles showed that electron-deficient aryl halides reacted preferentially (Scheme 66a) and that electron-rich arenes displayed an increased reactivity (Scheme 66b).[72] The observed chemoselectivities were independent of the nature of the leaving group or solvent, and optimal isolated yields were obtained in toluene.

Given the high catalytic activity of complex **50**, we thereafter tested its mode of action through stoichiometric experiments (Scheme 67).[72] Hence, ruthenium(II) carboxylate **50** was found to be inert in the presence of aryl chlorides, even at elevated reaction temperatures. In contrast, cyclometalation occurred readily, thereby yielding catalytically competent cyclometalated complex **51**.

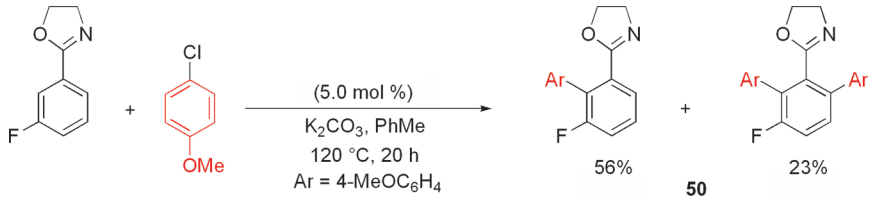
On the basis of these experimental studies we proposed an initial reversible cyclometalation through a carboxylate-assisted deprotonation (Scheme 68).[72] Thereafter, complex **51** reacts in the rate-limiting step with aryl halide to yield intermediate **52**. Finally, reductive elimination regioselectively gives rise to the desired product and thereby regenerates the active catalyst. Therefore, the carboxylate has overall at least a dual role in ruthenium-catalyzed direct arylations. First, it enables an almost barrierless cycloruthenation, as illustrated by stoichiometric experiments (vide supra), and second, it accelerates the formal oxidative addition of the aryl halide onto the cyclometalated ruthenium complex.

In 2009, Dixneuf and Požgan reported a ruthenium-catalyzed direct arylation of one 2-phenylpyridine with KOAc as additive.[245] The in-situ-generated catalyst yielded predominantly the diarylated products (Scheme 69). In this context it is noteworthy that these reactions were again performed in NMP as solvent (vide supra).

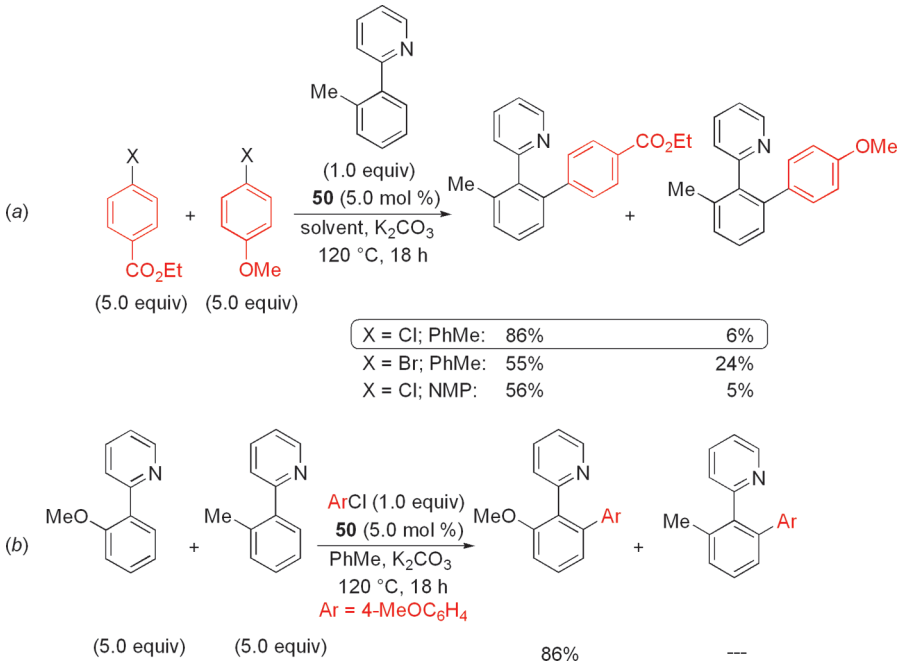
The use of aryl tosylates in transition-metal-catalyzed arylations is highly desirable, since they can be prepared from readily available phenols using inexpensive reagents and because they are usually highly crystalline as well as stable toward hydrolysis.[185] Unfortunately, the remarkable stability of these user-friendly compounds translates into a significantly diminished reactivity in metal-catalyzed arylation reactions. As a result, palladium-catalyzed traditional cross-coupling reactions of electronically unactivated aryl tosylates mainly called for the use of specifically designed electron-rich stabilizing ligands.[193] On the contrary, Ackermann and co-workers found that ruthenium-catalyzed biaryl formation can be accomplished from differently substituted aryl

dx.doi.org/10.1021/cr100412j |*Chem. Rev.* 2011, 111, 1315–1345

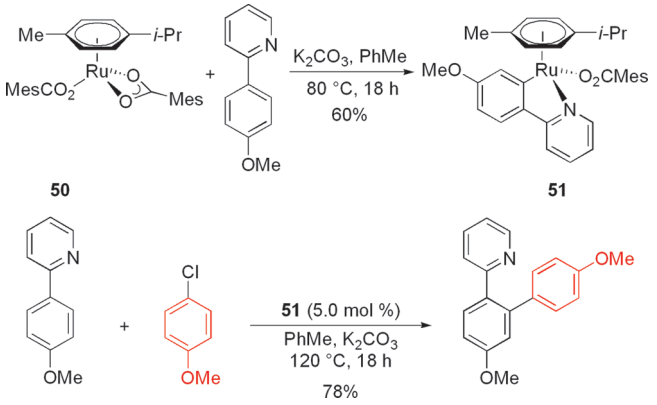
Scheme 65. Intramolecular Competition Experiments with a *meta*-Fluoro-Substituted Arene



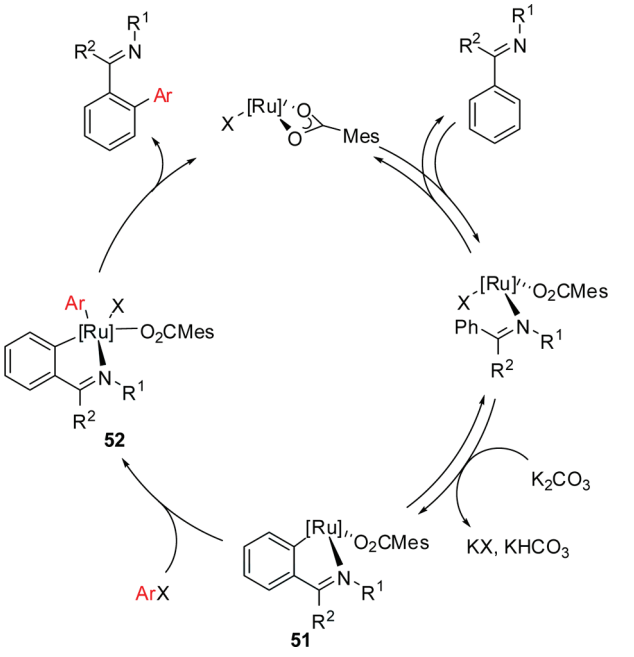
Scheme 66. Intermolecular Competition Experiments



Scheme 67. Synthesis of and Catalysis with Cyclometalated Complex 51



Scheme 68. Proposed Mechanism for Ruthenium-Catalyzed Direct Arylations



tosylates with a phosphine ligand-free ruthenium complex derived from a simple carboxylic acid (Scheme 70),[235,246] which, in more general terms, represented a first example of ruthenium-catalyzed coupling reactions with challenging aryl tosylates.[235,247]

Whereas direct C−H bond arylations (Scheme 71b) were recognized as ecologically benign and economically sound alternatives

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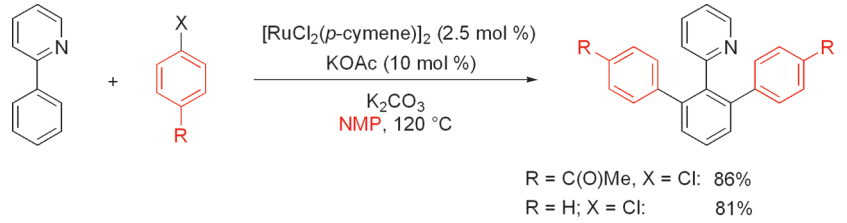
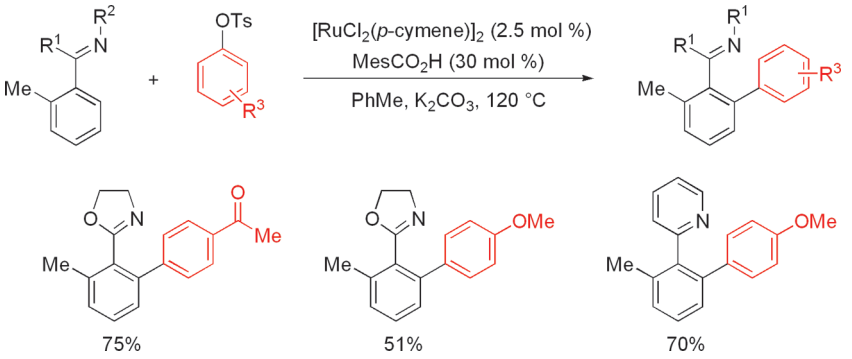
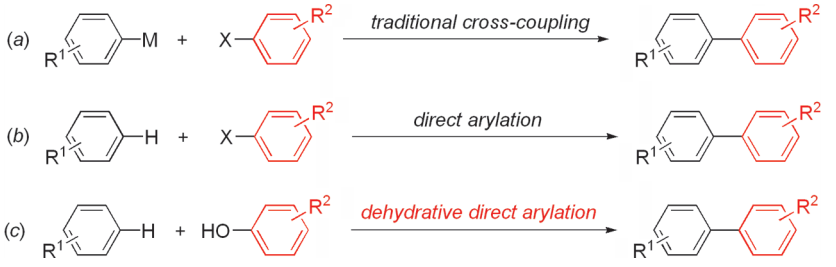
Scheme 69. Ruthenium-Catalyzed Direct Arylations in NMP as Solvent



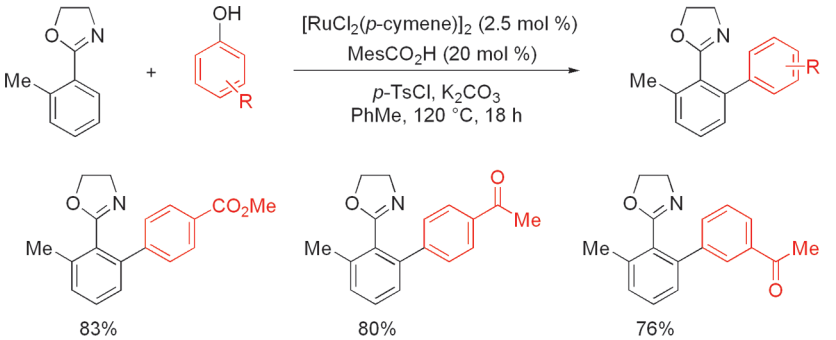
Scheme 70. Ruthenium-Catalyzed Direct Arylations with Aryl Tosylates



Scheme 71. Strategies for Catalytic Biaryl Syntheses



Scheme 72. Ruthenium-Catalyzed Formal Dehydrative Direct Arylation



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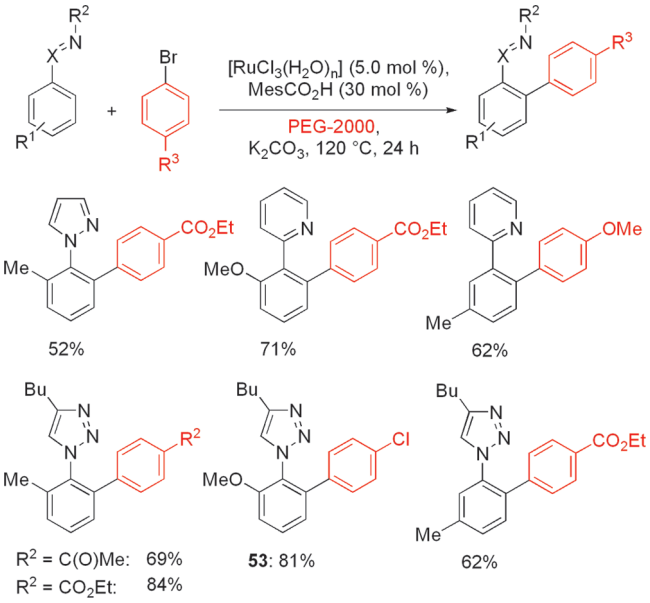
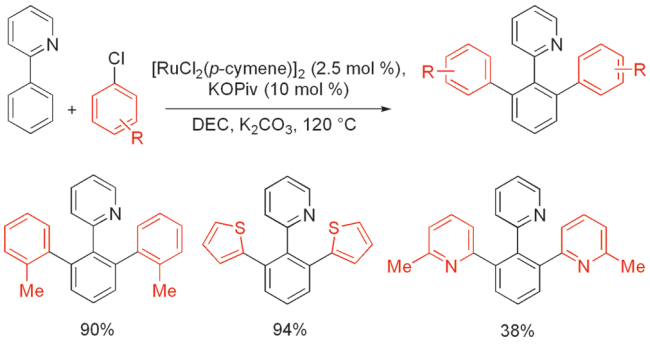
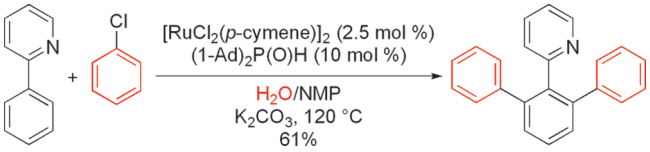
Scheme 73. Ruthenium-Catalyzed Direct Arylations in Polyethylene Glycol (PEG)



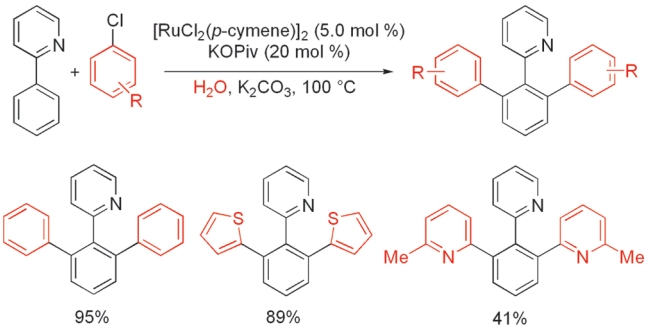
Scheme 74. Carboxylate-Assisted Ruthenium-Catalyzed Direct Arylations in Diethyl Carbonate (DEC)



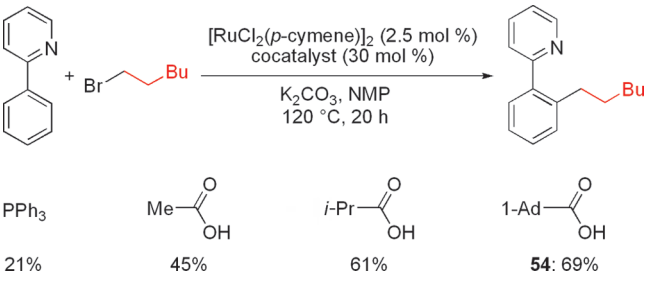
Scheme 75. Ruthenium-Catalyzed Direct Arylation in the Presence of H_2O



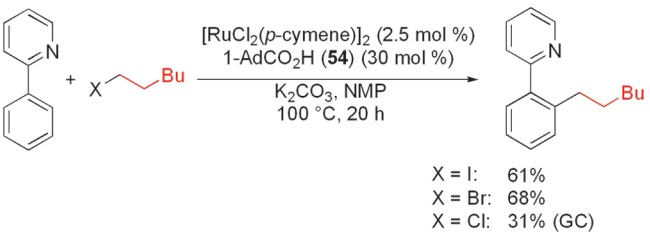
Scheme 76. Pivalate-Assisted Ruthenium-Catalyzed Direct Arylations in the Presence of H_2O



Scheme 77. Cocatalysts in Ruthenium-Catalyzed Direct Alkylations



Scheme 78. Influence of the Leaving Group in Direct Alkylations



to conventional cross-coupling strategies (Scheme 71a),[129] the direct use of widely available, inexpensive phenols as proelectrophilic reagents for biphenyl syntheses was previously not reported. As a consequence, we became interested in developing formal dehydrative direct arylations within the context of further streamlining biaryl syntheses (Scheme 71c).

In 2008, Ackermann and Mulzer disclosed a protocol for formal dehydrative couplings between simple arenes and inexpensive phenols, which was realized with a chemo- and regioselective ruthenium catalyst derived from either a HASPO preligand[23,24,27] or from $MesCO_2H$, along with sulfonyl chlorides as additive (Scheme 72).[248] The outstanding chemoselectivity of the ruthenium[249] catalyst was reflected by the fact that formation of undesired byproduct originating from a nucleophilic reactivity of phenols[250] or from desulfinylative coupling reactions[251] was not observed.[248] Notably, this operationally simple dehydrative arylation was accomplished through the functionalizations of both C−H as well as C−OH bonds.

Thus far, most protocols for metal-catalyzed direct arylations through C−H bond cleavages were lacking operational simplicity in that potentially hazardous organic solvents and/or vigorous anaerobic reaction conditions were required. During studies on the use of more sustainable reaction media for C−H bond functionalizations, Ackermann and Vicente found that a

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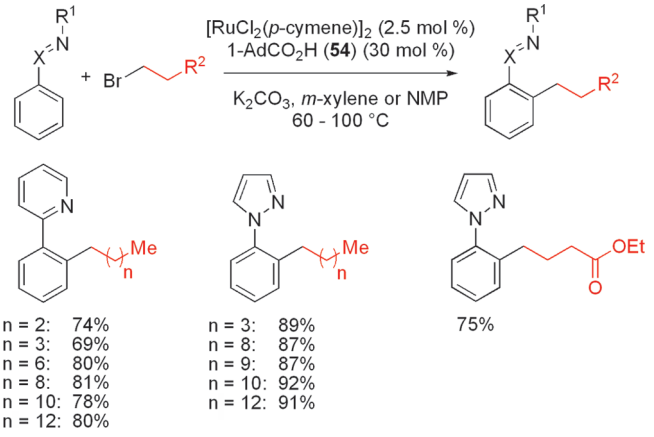
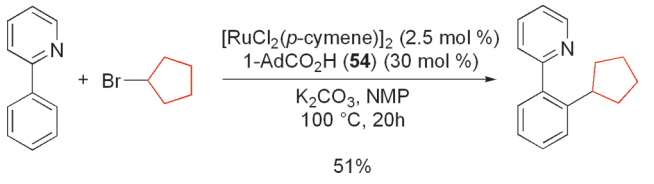
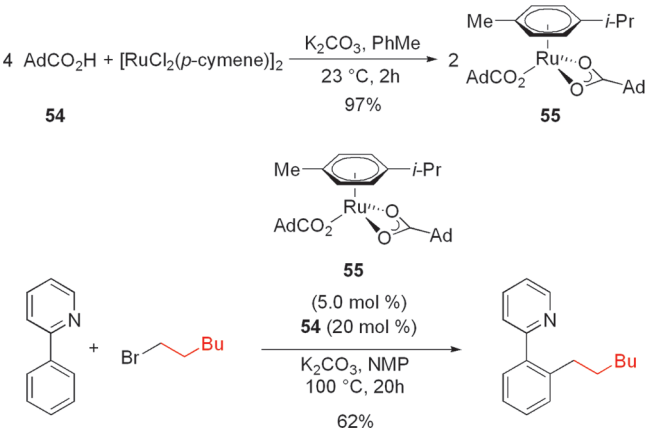
Scheme 79. Scope of Carboxylate-Assisted Ruthenium-Catalyzed Direct Alkylations



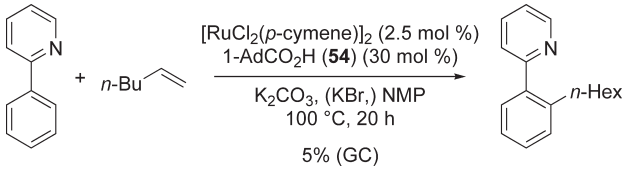
Scheme 80. Direct Alkylations with Secondary Alkyl Bromides



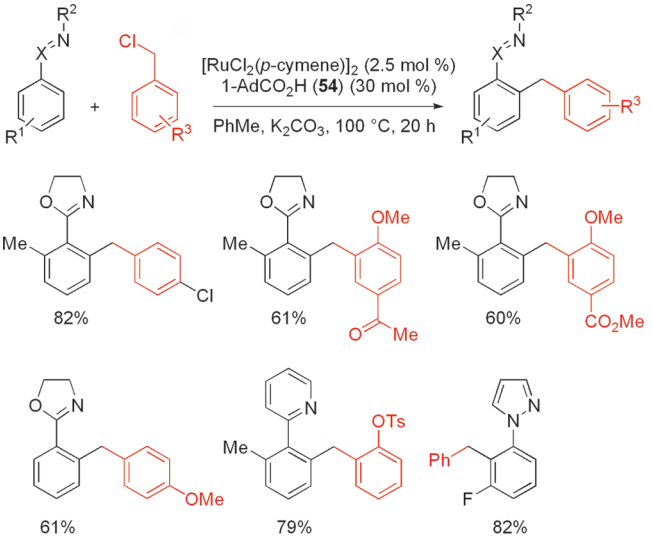
Scheme 81. Preparation of and Catalysis with Complex 55



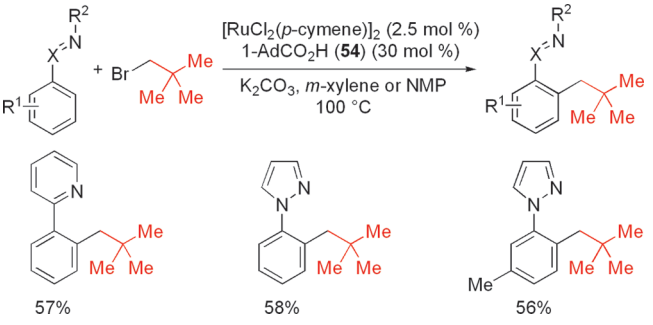
Scheme 82. Attempted Catalytic Hydroarylation



Scheme 83. Ruthenium-Catalyzed Direct Benzylations of Arenes



Scheme 84. Carboxylate-Assisted Ruthenium-Catalyzed Direct Neopentylation



ruthenium catalyst derived from carboxylic acid $MesCO_2H$ enabled direct arylations of arenes displaying 1,2,3-triazoles[183] in nontoxic polyethylene glycol (PEG).[190] Specifically, PEG-2000 turned out to be optimal for ruthenium-catalyzed direct arylations (Scheme 73). Arenes with various Lewis-basic directing groups could be regioselectively arylated with $[RuCl_3(H_2O)_n]$[232] as inexpensive ruthenium precursor.[190] An intramolecular competition experiment with a dihaloarene clearly revealed once more that bromides react preferentially to deliver exclusively product **53**. Moreover, the transformation of *meta*-substituted arenes occurred with excellent site selectivities, which were controlled through steric interactions.[190]

Furthermore, Dixneuf, Fischmeister, and co-workers reported on valuable ruthenium-catalyzed direct arylations in nontoxic diethyl carbonate (DEC)[252,253] as reaction medium.[254,255] While preliminary studies revealed a beneficial effect of amides, a more generally applicable catalytic system was found with cocatalytic amounts of KOPiv (Scheme 74).[254]

The remarkable chemoselectivity and stability of ruthenium(II) catalysts[256] was highlighted by the Ackermann group in 2005

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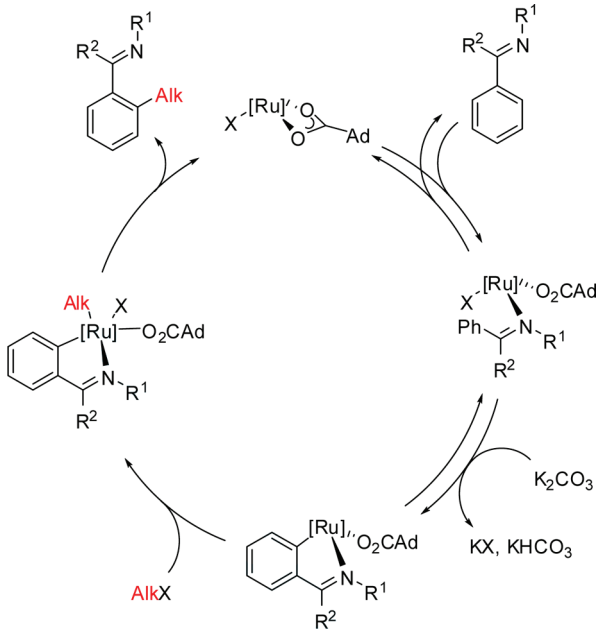
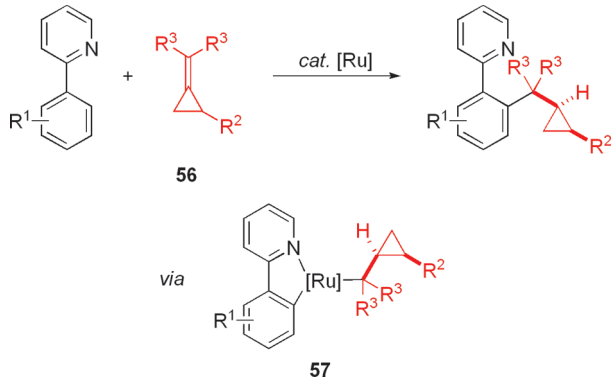
Scheme 85. Proposed Mechanism for Ruthenium-Catalyzed Direct Alkylations



Scheme 86. Ruthenium-Catalyzed Hydroarylation of Methylenecyclopropanes 56



by performing ruthenium-catalyzed direct arylations with aryl chlorides in the presence of H_2O (Scheme 75).[257]

Subsequently, a ruthenium complex derived from pivalate was elegantly exploited in 2010 for direct arylations on[258] water (Scheme 76).[259] The authors obtained higher isolated yields when using aryl chlorides as compared to the reactions with aryl bromides or iodides. Isolated yields proved mostly to be comparable to reactions being performed in organic solvents, although a higher than typical catalyst loading was employed.

3.2.2.2. Direct Alkylations. Given the remarkable activity accomplished through carboxylate assistance in ruthenium-catalyzed direct arylations, we explored unprecedented intermolecular direct alkylations[215] with unactivated β-hydrogen-containing alkyl halides. As was observed in ruthenium-catalyzed direct arylations, NHC precursors or tertiary phosphines provided only unsatisfactory results (Scheme 77).[260] Fortunately, carboxylate assistance was found to be key to success, with highest yields being realized with sterically hindered acid **54**. The direct alkylations proceeded with remarkable site selectivity through chelation assitance and yielded the *n*-alkylated products chemoselectively under basic reaction conditions as the sole products.

Direct alkylations could be performed with unactivated alkyl iodides, bromides, or chlorides. Yet, alkyl bromides gave rise to optimal results, whereas alkyl chlorides led to diminished yields (Scheme 78).[260]

The scope of the optimized catalytic system turned out to be broad, which enabled site-selective direct *n*-alkylations on among others pyridinyl- or pyrazolyl-substituted arenes (Scheme 79) as well as ketimines.[260]

More challenging secondary alkyl bromides could be employed as well for direct alkylations under basic reaction conditions, which bears great potential for further applications of carboxylate-assisted C−H bond functionalizations (Scheme 80).[260]

With regard to the working mode of the ruthenium(II)-catalyzed transformation, it is noteworthy that independently prepared ruthenium(II) biscarboxylate complex **55** was found to be catalytically competent as well (Scheme 81).[260]

Importantly, a potential working mode involving a reaction sequence consisting of β-elimination and hydroarylation[261−264] was proven unlikely to be operative by among others unsuccessful hydroarylations with 1-alkenes under otherwise identical reaction conditions (Scheme 82).[260]

Direct benzylations of differently substituted arenes were accomplished under the optimized reaction conditions likewise (Scheme 83),[265] rendering an initial elimination reaction less likely to be of importance in carboxylate-assisted ruthenium-catalyzed direct alkylations.

Moreover, the unprecedented use of neopentyl halides in transition-metal-catalyzed arene functionalizations proved viable (Scheme 84).[260] Thereby, site-selectively neopentylated products were obtained through C−H bond cleavage reactions, without formation of undesired byproducts stemming from cationic rearrangements. Again, the use of neopentyl halides excludes a reaction mechanism relying on an initial β-elimination event.

On the basis of these experimental findings as well as on our mechanistic studies on carboxylate-assisted ruthenium(II)-catalyzed direct arylations,[72,235] we proposed a working mode for direct alkylations, which initiates with a reversible carboxylate-assisted cycloruthenation (Scheme 85).[215,260] Subsequently, the thus formed cyclometalated complex undergoes a formal oxidative addition with the alkyl halide. Thereby, a ruthenium(alkyl)(aryl) complex is formed as precursor for a final reductive elimination, which regenerates the catalytically active ruthenium species and provides the desired product.

The final reductive elimination is proposed to proceed fast,[215] since inter alia ruthenium-catalyzed hydroarylation reactions of methylenecyclopropanes **56** were found to occur with conservation of the cyclopropane moieties while involving (cyclopropylcarbinyl)metal intermediate **57** (Scheme 86).[266]

4. CONCLUSIONS

Transition-metal-catalyzed direct functionalizations of otherwise inert C−H bonds represent an attractive approach for the development of more sustainable chemical processes. The significant rate acceleration of stoichiometric cyclometalations by

carboxylates along with detailed experimental and computational studies have provided strong evidence for various C−H bond metalations to proceed by base-assisted deprotonations. For instance, stoichiometric cyclometalations with palladium, iridium, ruthenium, or rhodium complexes were found to follow this reaction paradigm. Here, C−H bond metalation is frequently facilitated by both base assistance and increased electrophilicity of the metal center. This mechanistic insight has set the stage for efficient late transition-metal-catalyzed C−H bond transformations with aryl halides through the use of sterically hindered carboxylates as cocatalysts. Specifically, carboxylate assistance enabled efficient palladium-catalyzed direct arylations or alkylations of (hetero)arenes to occur at mild reaction conditions and set the stage for challenging C−H bond functionalizations of alkanes. Furthermore, the remarkable chemoselectivity of ruthenium(II) carboxylate complexes allowed for intermolecular direct arylations with challenging substrates, such as aryl chlorides or tosylates. Ruthenium complexes derived from sterically demanding carboxylic acids were also employed for unprecedented direct alkylations under basic reaction conditions with unactivated primary and secondary β-hydrogen-containing alkyl halides. Hence, in recent years, carboxylate assistance has overall expanded the scope of direct C−H bond functionalizations significantly beyond the limits of traditional S_EAr-type transformations. Considering the highly sustainable nature of direct C−H bond functionalizations, along with the improved mechanistic understanding of base-assisted metalations, further exciting developments are expected in this rapidly evolving research area.

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BIOGRAPHY

Lutz Ackermann studied Chemistry at the Christian-Albrechts-University Kiel, Germany, and obtained his Ph.D. degree 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 fellow in the research group 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 within the Emmy Noether-programme of the DFG. In 2007, he became Full Professor at Georg-August-University Göttingen. His recent awards and distinctions include an ORCHEM-price (2006), a Dozentenstipendium (2007), a JSPS visiting professor fellowship (2009), an Alphora Lectureship at the University of Toronto (2010), as well as visiting professorships at the Università degli Studi di Milano, Italy (2007), and the University of Wisconsin at Madison (2008). The development of sustainable catalytic C−H bond functionalizations for organic synthesis constitutes one of his major current research interests.

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