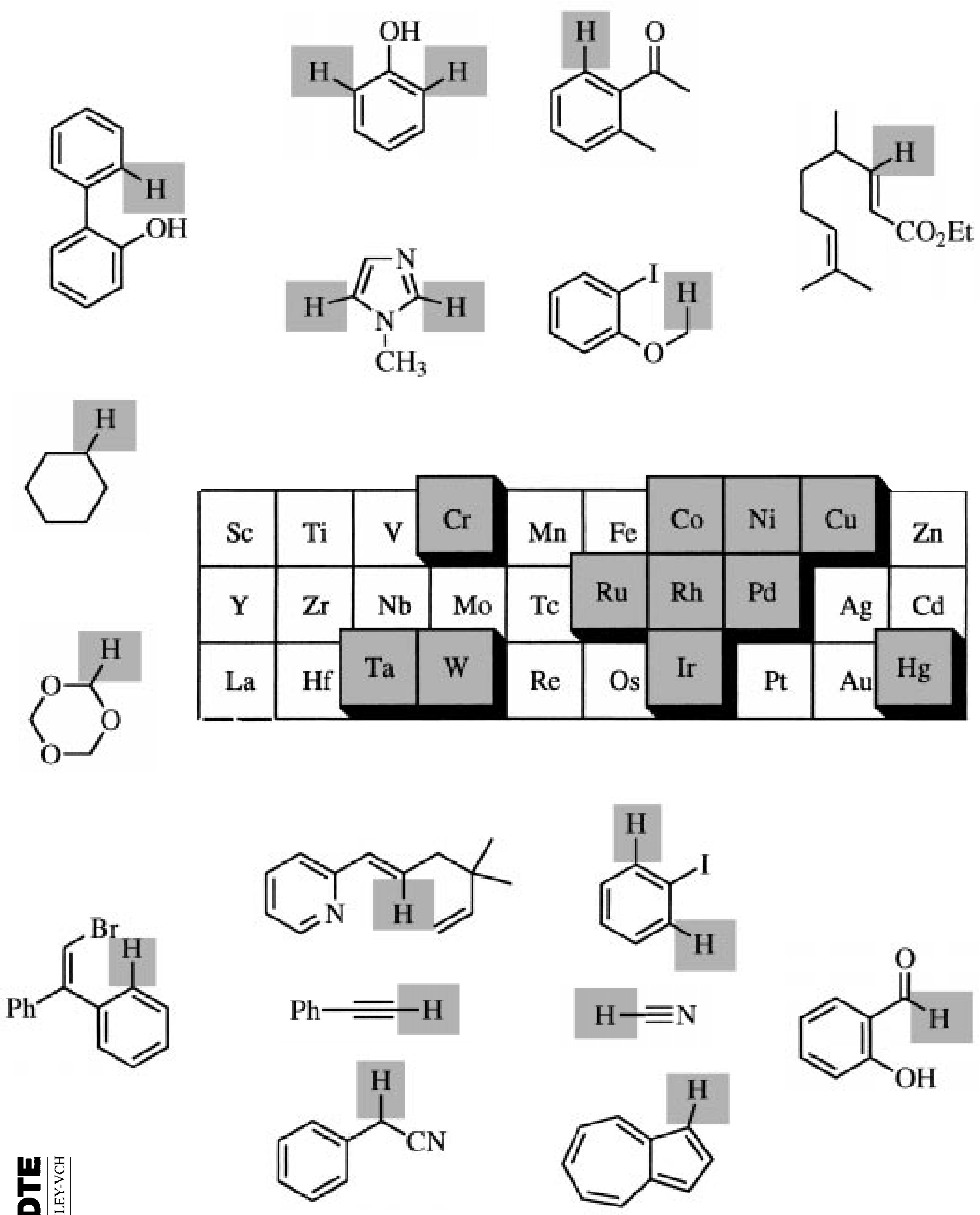

A diverse range of C–H activations can be catalyzed by transition metal complexes.

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Transition Metal Catalyzed Coupling Reactions under C–H Activation

Gerald Dyker*

The activation of C–H bonds is of the same fundamental importance as the formation of C–C bonds for the construction of organic molecules. Particularly in the last ten years, transition metal catalyzed processes have been developed which achieve both these in a single preparative step and hence combine economy, efficiency, and elegance. Palladium and ruthenium catalysts are currently used most frequently, closely followed by rhodium complexes: For instance, ruthenium has proved to be particularly efficient for the C–H activation of arenes, palladium in catalytic processes with metallacycles as intermediates, and rhodium in coupling reactions under C–H activation at the aldehyde function. Mercury displays catalytic activity on photochemical excitation in the gas phase. Iridium and tungsten complexes likewise show potential for economically valuable reactions, but must first prove their worth in catalytic processes.

Keywords: C–H activation · C–C coupling · homogeneous catalysis · transition metals

> *C–H activation means money.*
> *C–H activation begins just below one's own results.*
> Pointed definitions of C–H activation
> (collected at a conference)

1. Introduction

The development of transition metal catalysts for the activation of C–H bonds is one of the major challenges of modern chemistry. The first of the two above-mentioned definitions stresses the economic importance: a coupling reaction of the "greenhouse gases" methane and carbon dioxide to give acetic acid would be of the same enormous commercial interest as the industrially applicable process for the selective oxidation of simple alkanes to give alcohols and carbonyl compounds. The second bon mot illustrates that there is quite a dispute as to which reactions are part of this diverse area of research. Contrary to the widespread opinion that only particularly inert alkanes require activation, it must be mentioned that also in the case of C–H acidic substrates the change from the usual basic reaction conditions to transition metal catalyzed variants can be of great preparative advantage. Murahashi et al. have shown that ruthenium-catalyzed aldol reactions are an illustrative example (see Section 4).

The application of strong organometallic bases for the activation of C–H groups with low acidity offers quite a modern and efficient procedure.[1] Preparative and economic advantages are expected from replacing such stoichiometric metalation reactions by catalytic ones. Particularly for a lack of selectivity under classic conditions or for base sensitivity of the functional groups, transition metal catalysis under mild and neutral conditions offers a promising and superior alternative. Only in recent years have practically applicable examples for transition metal catalyzed coupling reactions under C–H activation become more frequent.

This review focusses on transition metal catalyzed C–H activations that lead to C–C coupling reactions. According to the current understanding of the mechanisms of these reactions, the transition metal catalyst is directly involved in the C–H bond breaking. In Section 2 following this introduction coupling reactions are presented in which the transition metal is precoordinated to a suitable functional group and the C–H bond is cleaved by a cyclometalation step. In the Section 3 sequences are discussed in which the C–H activation occurs intramolecularly by a carbon-bound transition metal atom. This type of reaction is clearly a domain of palladium chemistry. Section 4 introduces the currently still rare examples of "intermolecular" C–H activation, which is taken to cover all reactions of this type that do not require a cyclometalation step. Finally, Section 5 presents an overview of recent stoichiometric C–H activation reactions which are promising candidates for the development of a catalytic reaction.

The Heck reaction[2] and hydrovinylation[3] are not be considered in this review: in these processes C–H activation occurs only after C–C coupling. C–H activations for C–Heteroatom coupling,[4] among them oxidation reactions such as the one with Barton's Gif systems are also not discussed in this review.

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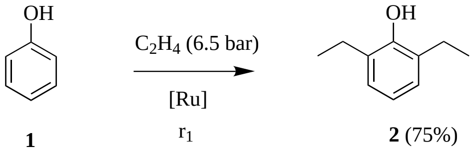
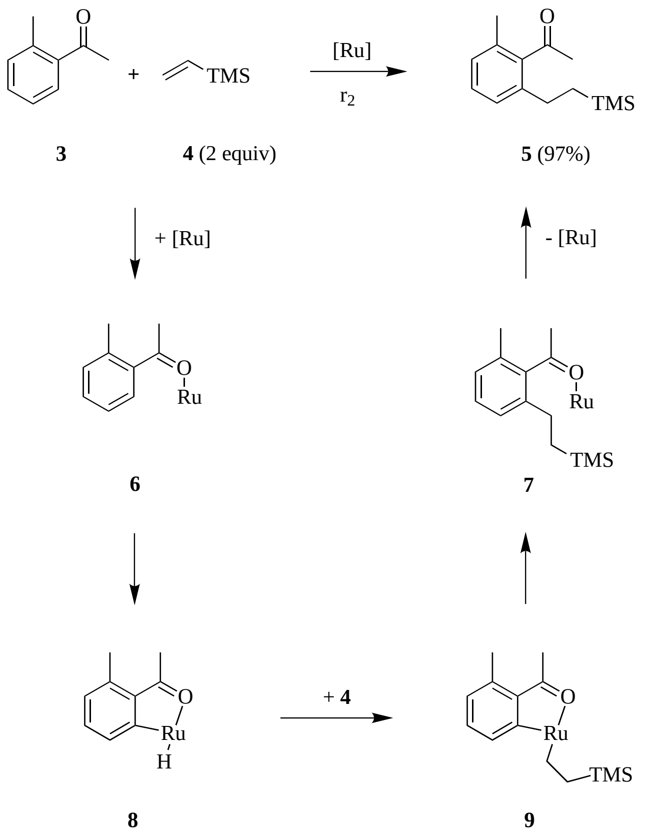
2. Intramolecular C–H Activation by a Precoordinated Transition Metal

Cyclometalation reactions under C–H activation have been known for more than thirty years and represent one of the best developed areas of organometallic chemistry.[5] C–H bond breaking occurs either by oxidative addition at the metal center or by electrophilic substitution; in some cases multicenter reaction paths are discussed.[5a] Cyclometalated transition metal complexes (often referred to as *ortho*-metalated complexes) participate in numerous coupling reactions; however, attempts to integrate such reactions into a catalysis cycle have proven difficult,[6, 7] and it is only recently that a number of catalytic processes been discovered that display remarkable turnover numbers and acceptable yields.

Lewis and Smith achieved an initial success in 1986[8] with the double alkylation of phenol (**1**) with ethylene selectively in the *ortho* positions (Scheme 1) by using an *ortho*-metalated ruthenium phosphite complex. A decisive breakthrough was achieved by Murai et al. in 1993, who reported a highly efficient, ruthenium-catalyzed addition of aromatic C–H bonds to olefins,[6, 9] in which ketones were used as precoordinating functional groups (Scheme 2). This coupling process is easy to carry out (2 mol% ruthenium catalyst in toluene at reflux temperature) and in many cases renders practically quantitative yields. For example, the acetophenone **3** is added to the vinyl silane **4** and yields regioselectively the *ortho* product **5**.[6c] Apparently, the transition metal is precoordinated by the carbonyl function of **3** and thus placed in a favorable position for the cleavage of the C–H bond: cyclometalation leads to the ruthenium hydride complex **8** as the reactive intermediate (additional ligands have been omitted for clarity in Scheme 2). After coordination of the olefin **4** an insertion reaction probably occurs leading to the formation of **9**. The C–C bond is formed by reductive elimination. Subsequent decomplexation of **7** leads to the final product **5** and at the same time liberates the active catalyst.



Scheme 1. Ru-catalyzed double *ortho* ethylation of phenol; reaction conditions r_1: 6 mol% cyclometalated Ru-tetrakisphosphite complex, 9 mol% KOPh, 8.6 equiv ethene, 6.5 bar, THF, 177 °C, 3.5 h. Here and in the subsequent schemes the catalyst is denoted by the symbol for the element in square brackets.



Scheme 2. Reaction conditions r_2: 2 mol% $[RuH_2(CO)(PPh_3)_3]$, toluene, reflux, 2 h.

The Murai reaction is generally applicable with regard to the carbonyl component: aromatic and heteroaromatic ketones such as the compounds **10**, **13**, **19**, and **21**, as well as the six-membered lactone **16** are suitable. (Scheme 3). The coupling reactions with the olefins **11**, **14**, and **17** (also with

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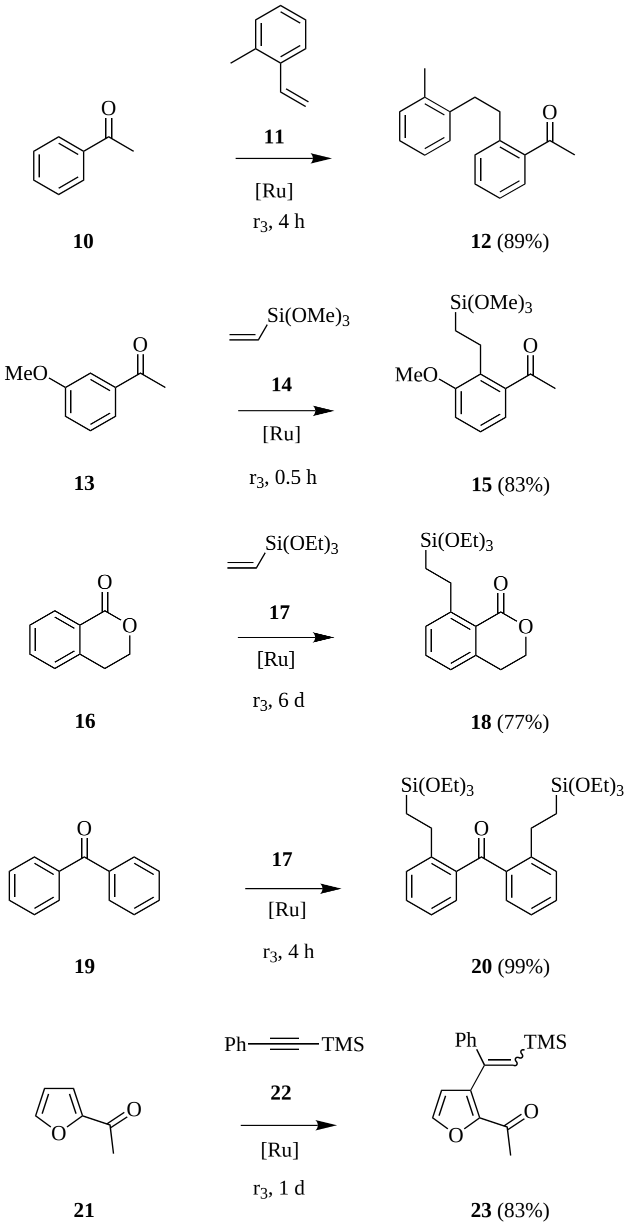
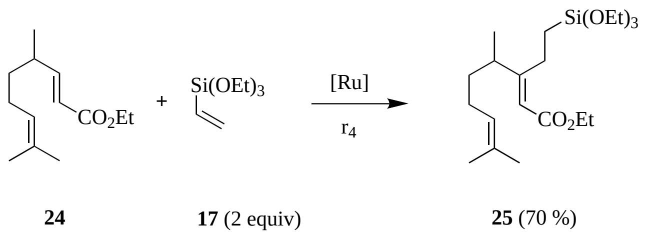


Scheme 3. Reaction conditions r_3: 2 mol% $[RuH_2(CO)(PPh_3)_3]$, 2–4 equiv alkene or alkyne, toluene, reflux, 0.5 h to 6 d.

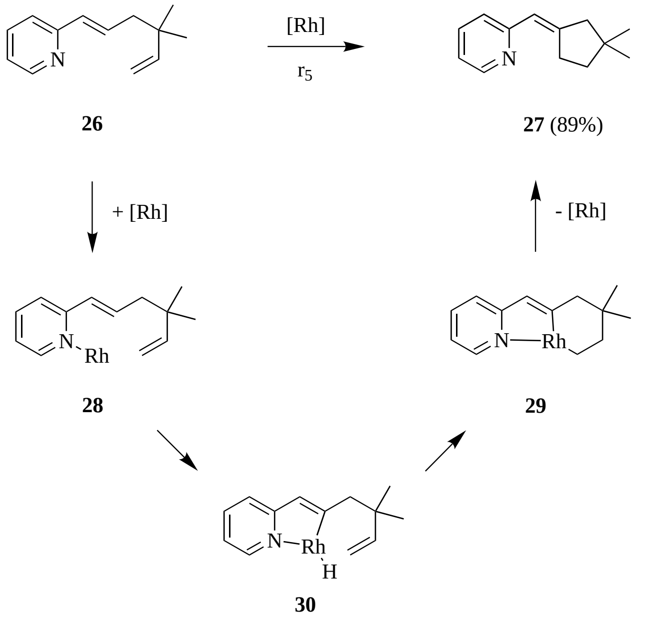
allyl silanes and with norbornene) and with alkynes such as **22**[9c] gives excellent yields of a broad selection of products such as **12**,[6c] **15**,[9b] **18**,[9d] **20**,[6c] and **23**.[9c] Benzoates react in certain cases.[9d] Aryl-substituted aldimines and ketimines are also applicable.[9e, 10] Enol ethers and olefins that can undergo double-bond isomerizations as well as electron-poor olefins such as acrylonitrile have so far been unsuitable for coupling reactions;[6c] a deeper understanding of the mechanistic course and the corresponding modifications of catalyst and reaction conditions should help to overcome these limitations.

The areas of application have been extended by Trost et al.[11a] and by Murai et al.[11b,c] to α,β-unsaturated ketones and esters, as illustrated by the addition reaction of **24** to the vinyl silane **17** (Scheme 4); in this reaction a functionalized side chain is introduced, which opens up interesting possibilities for further transformations.



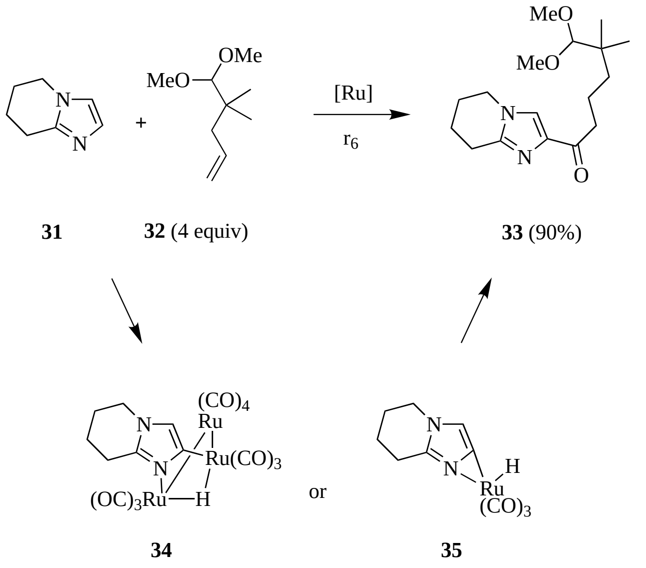
Scheme 4. Reaction conditions r_4: 2 mol% $[RuH_2(CO)(PPh_3)_3]$, toluene/dioxane, reflux, 2 h.

Rhodium seems to be the metal of choice for C−H activation of pyridine derivatives. In this case the pyridyl group is crucial for the precoordination.[12] According to Kim et al.[13] 2-phenylpyridine is alkylated in the 2′-position by terminal alkenes when tris(tricyclohexylphosphane)rhodium chloride is used as the catalyst. Murai et al.[14] reported that Wilkinson's catalyst $[RhCl(PPh_3)_3]$ is suitable for C−H activation at pyridyl-substituted 1,5- and 1,6-dienes. Starting from 1,5-diene **26** a formal 5-*endo-trig*-cyclization is observed. The C−H activation at the vinyl position probably occurs through the intermediates **28** and **30**. The intramolecular insertion of the terminal double bond leads to the metallacycle **29**, which reacts by reductive elimination to give the final product **27** (Scheme 5).



Scheme 5. Reaction conditions r_5: 10 mol% $[RhCl(PPh_3)_3]$, THF, 120 °C, 3 h.

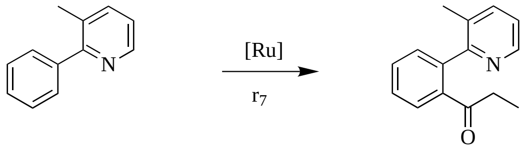
The trinuclear ruthenium cluster $[Ru_3(CO)_{12}]$ metalates nitrogen-hetarenes at the *ortho* position. This reaction step was integrated into a catalytic cycle by Moore et al.:[15a] when carbon monoxide and terminal olefins are employed as coupling components, pyridine is acylated in the 2-position. Murai et al. found that imidazole derivatives are significantly more reactive in coupling processes of this type.[15b] The reaction is highly efficient and selective as illustrated by the synthesis of the functionalized imidazole **33** (Scheme 6). The ruthenium complex **34** with an intact cluster framework is



31 **32** (4 equiv) **33** (90%) **34** **35**

Scheme 6. Reaction conditions r_6: 4 mol% $[Ru_3(CO)_{12}]$, 20 atm CO, toluene, 160 °C, 20 h.

favored as the key intermediate, although the mononuclear ruthenium carbonyl complex **35** so far cannot be ruled out as a possibility. The acylation of the pyridine derivative **36** at the phenyl substituent with ethene and carbon monoxide as coupling components is closely related to this reaction. (Scheme 7).[15c]

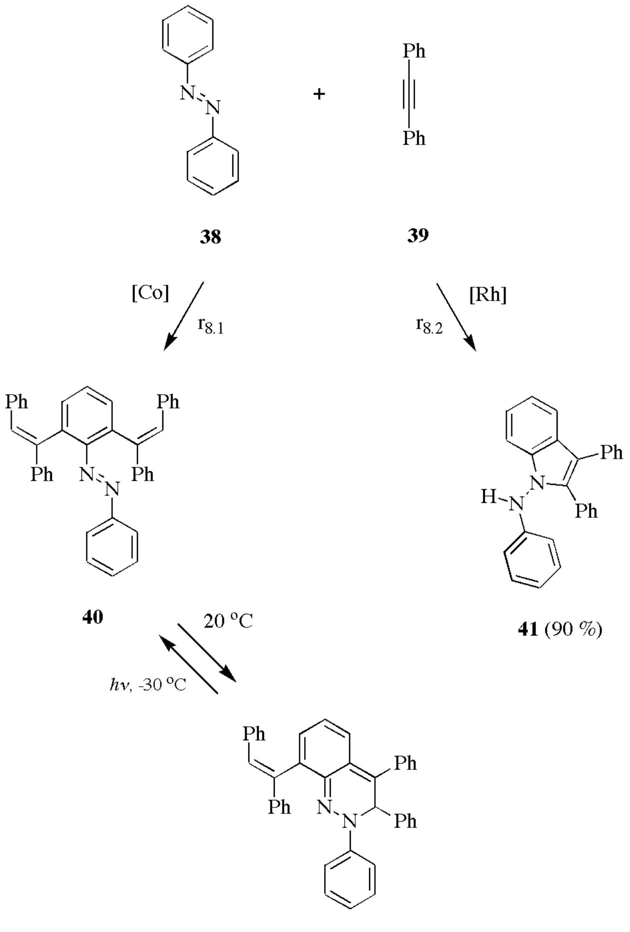


36 **37** (94%)

Scheme 7. Reaction conditions r_7: 2.5 mol% $[Ru_3(CO)_{12}]$, 20 atm CO, 7 atm C_2H_4, toluene, 160 °C, 20 h.

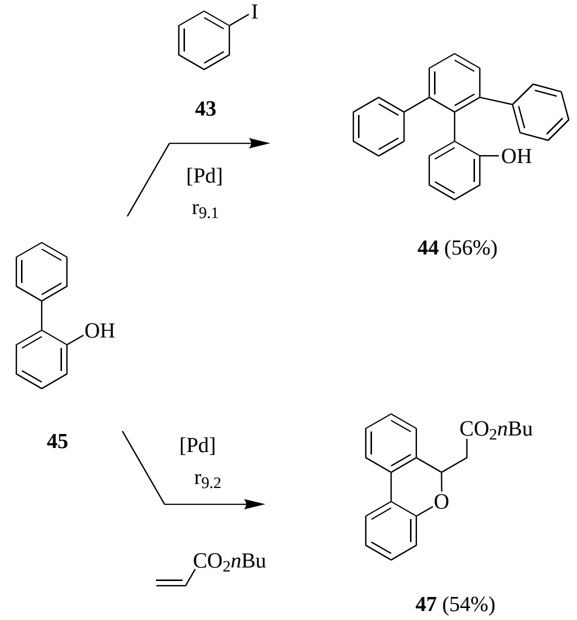
Azobenzene (**38**) reacts with numerous transition metal complexes under cyclometalation.[5] According to Kisch et al. the cobalt-catalyzed coupling reaction of azobenzene with diphenylethyne (**39**) leads to the heterocyclic 1:2 product **42**, which displays photochromic behavior (Scheme 8); the red heterocycle **42** is photochemically transformed at −30 °C to give the orange azo compound **40**, which spontaneously recyclizes at room temperature.[16a] By employing Wilkinson's catalyst under acidic reaction conditions and with equimolar amounts of coupling components, the 1:1 product **41** is obtained in high yields.[16b]

According to Miura et al. phenolates are also suitable as precoordinating group (Scheme 9):[17] 2-hydroxybiphenyl (**45**) is regioselectively arylated in the 2′-position with iodobenzene (**43**) under palladium catalysis. With an excess of **43** a double arylation occurs to give **44**; for both cases oxapalladacycles can be formulated as reactive intermediates.[17a] The variant with the acrylate **46** as coupling component deserves particular attention: The catalysis cycle to give dibenzopyran requires reoxidation of Pd^0 to Pd^{II}.[17b] The aldehydic hydro-



38 **39** **40** **41** (90 %) **42** (70 %)

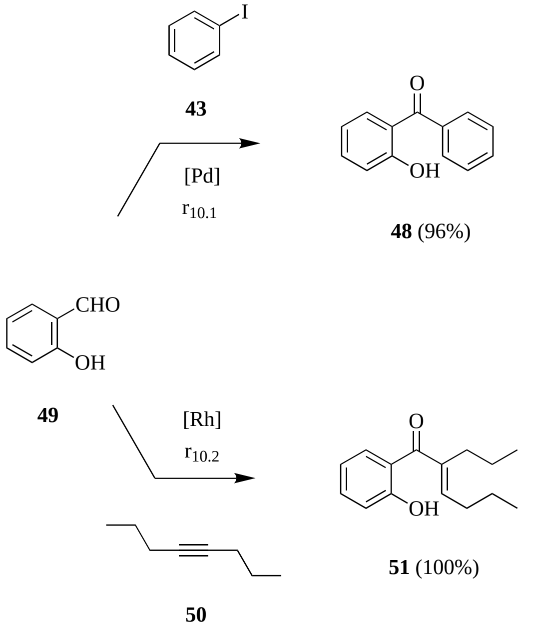
Scheme 8. Reaction conditions; $r_{8.1}$: cat. $[CoH_3(PPh_3)_3]$, 1 equiv **39**, 1-PrOH/HOAc, 110 °C, 24 h; $r_{8.2}$: cat. $[RhCl(PPh_3)_3]$, without solvent, 85 °C, 2 h.



43 **44** (56%) **45** **46** **47** (54%)

Scheme 9. Reaction conditions; $r_{9.1}$: 5 mol% $Pd(OAc)_2$, 4 equiv **43**, Cs_2CO_3, 4 Å molecular sieves, DMF, 100 °C, 44 h. $r_{9.2}$: 5 mol% $Pd(OAc)_2$, 5 mol% $Cu(OAc)_2 \cdot H_2O$, 4 Å molecular sieves, N_2/air (5:1), DMF, 120 °C, 9 h.

gen atom of salicylaldehyde (**49**) can be activated both under palladium[17c] and under rhodium catalysis[17d] (Scheme 10): cyclometalated complexes can be postulated as reactive intermediates in the formation of **48** and of **51**.

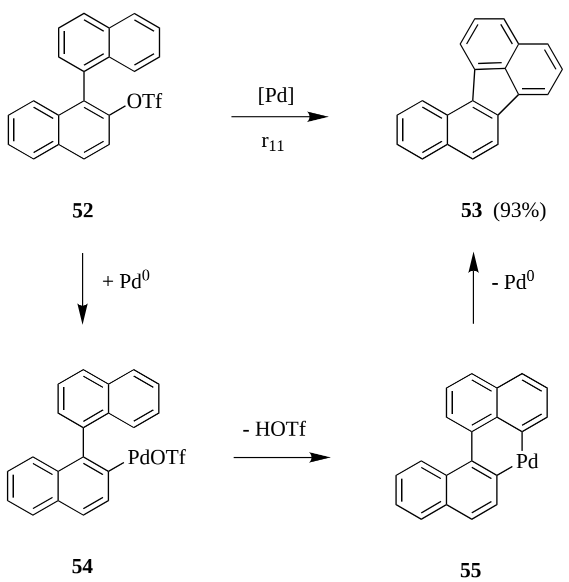


Scheme 10. Reaction conditions; $r_{10.1}$: 5 mol% $PdCl_2$, 2 equiv **43**, Na_2CO_3, DMF, 100 °C, 4 h. $r_{10.2}$: 0.5 mol% $[RhCl(cod)]_2$/dppf, Na_2CO_3, toluene, reflux, 0.5 h. cod = cyclooctadiene, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

The given examples for transition metal catalyzed coupling reactions under C–H activation, which are controlled by a precoordinating functional group, are limited to sp^2-hybridized C–H groups. The development of analogous catalysis cycles for the C–H activation at alkyl groups is a promising undertaking, especially since corresponding stoichiometric cyclometalation ractions are well known.[5a]

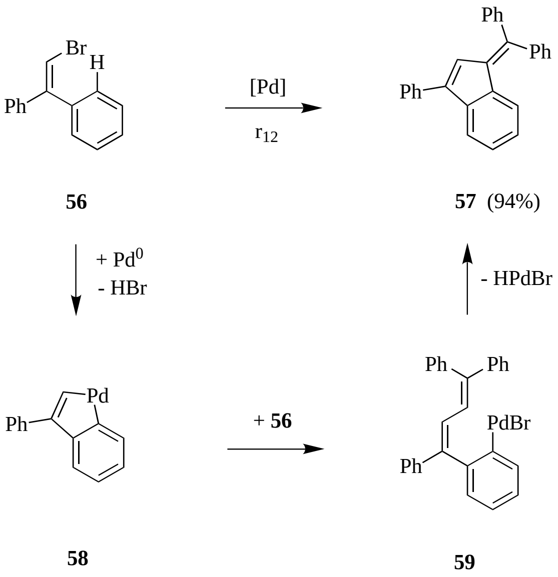
3. Intramolecular C–H Activation through Carbon-Bound Transition Metals

In this section of the review catalytic coupling processes are presented that are initiated by a cyclometalation step. Similar to the examples given in Section 2 the transition metal is directed into the proximity of the C–H bond which is to be broken; however, in these examples by a σ bond between a carbon atom and a transition metal atom. The formation of the fluoroanthene derivative **53** by Rice and Cai illustrates characteristic features of this reaction type (Scheme 11).[18] In general it is assumed that Pd^{II} compounds used for the catalysis are reduced in situ and that the active catalysts are compounds in the oxidation state 0. The first carbon–palladium σ bond is formed by oxidative addition of the Pd^0 catalyst to the aryltriflate **52**. The electrophilic Pd^{II} species **54** is responsible for the intramolecular C–H activation, during which the second palladium–carbon σ bond is formed. This cyclopalladation step can be interpreted as an electrophilic substitution at the arene rings.[19] The intermediate **55** reacts under reductive elimination, a typical reaction step for six-membered and larger palladacycles. In the meantime this type of intramolecular aryl–aryl coupling can be classed as an established method of synthesis and has proven useful for the construction of five- and six-membered carbocyclic and heterocyclic systems.[20]



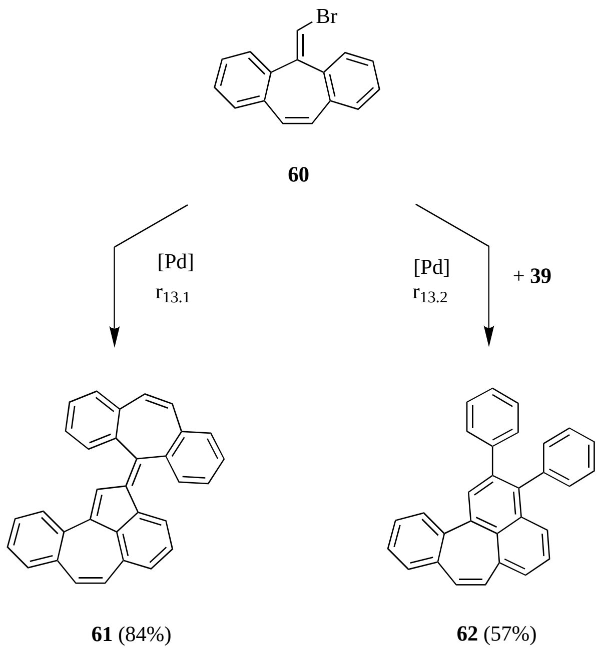
Scheme 11. Reaction conditions r_{11}: 10 mol% $[PdCl_2(PPh_3)_2]$, LiCl, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), DMF, 140 °C, 10 h.

Evidently, six-membered palladacycles react readily under reductive elimination to give the five-membered rings, even when this means the build-up of considerable strain within the ring as for fluoroanthene **53**. Five-membered palladacycles usually react differently: in a reaction sequence comprising oxidative addition and C–H activation the phenyl-substituted bromoethene **56** forms the five-membered palladacycle **58** (Scheme 12).[21a] In this case the reductive elimination of Pd^0 is inhibited because a highly strained and antiaromatic benzo-



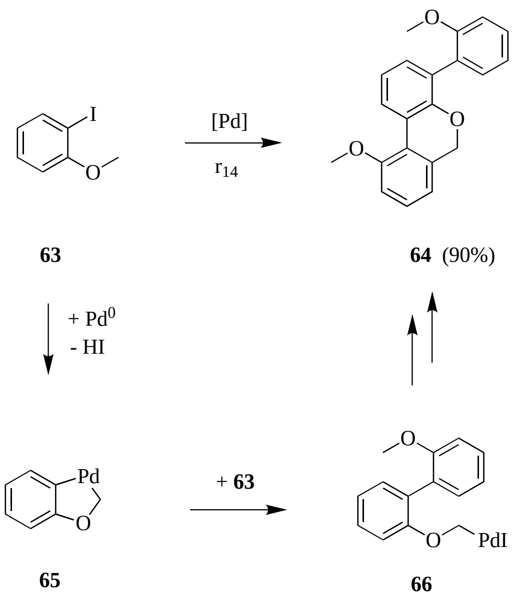
Scheme 12. Reaction conditions r_{12}: 1 mol% $Pd(OAc)_2$, K_2CO_3, $n\mathrm{Bu}_4\mathrm{NBr}$, DMF, 100 °C, 3 d.

cyclobutadiene would be the result. Instead, the palladacycle **58** adds a further equivalent of the starting material **56**, leading to the Pd^{II} intermediate **59**. Ring closure under C–C coupling occurs in the sense of an intramolecular Heck reaction. Tricyclic derivatives of **56** react in the same way; the vinyl bromide **60** with a central seven-membered ring is also condensed to the annelated fulvene **61** (Scheme 13). In the presence of diphenylethyne (**39**) a cross-coupling reaction occurs, leading to the polycyclic hydrocarbon **62**; in this case it can also be assumed that a cyclometalation is crucial for the C–H activation.[21b]

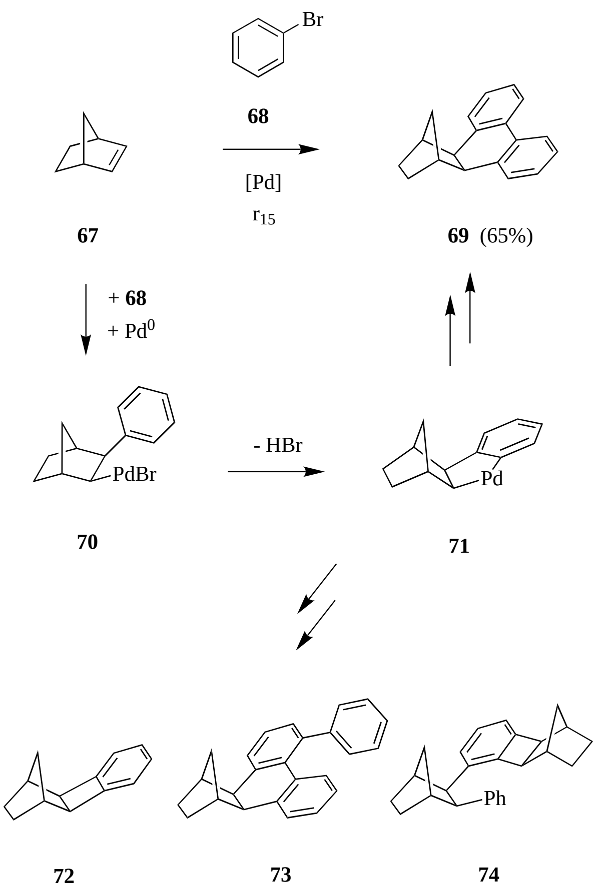


Scheme 13. Reaction conditions; $r_{13.1}$: 1 mol% $Pd(OAc)_2$, K_2CO_3, $n$$Bu_4NBr$, DMF, 100 °C, 3 d. $r_{13.2}$: 1 mol% $Pd(OAc)_2$, 1 equiv diphenylethyne (**39**), K_2CO_3, $n$$Bu_4NBr$, DMF, 100 °C, 3 d.

The coupling reaction of *ortho*-iodoanisole (**63**) to give dibenzopyran **64** is a particularly interesting domino process (Scheme 14).[22] Evidently, three equivalents of the starting material **63** are combined leading to C–H activation at a sp^3-hybridized center, since a methoxy group has been arylated. Once again palladacycles such as **65** are assumed to be the key intermediates. This type of palladium-catalyzed C–H activation at sp^3-hybridized centers is by no means limited to methoxy groups. Similar reactions can also be observed for *tert*-butyl groups.[23]

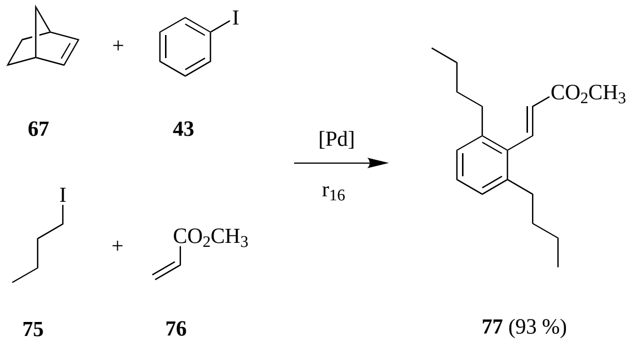


Scheme 14. Reaction conditions r_{14}: 4 mol% $Pd(OAc)_2$, K_2CO_3, $n$$Bu_4NBr$, DMF, 100 °C, 3 d.



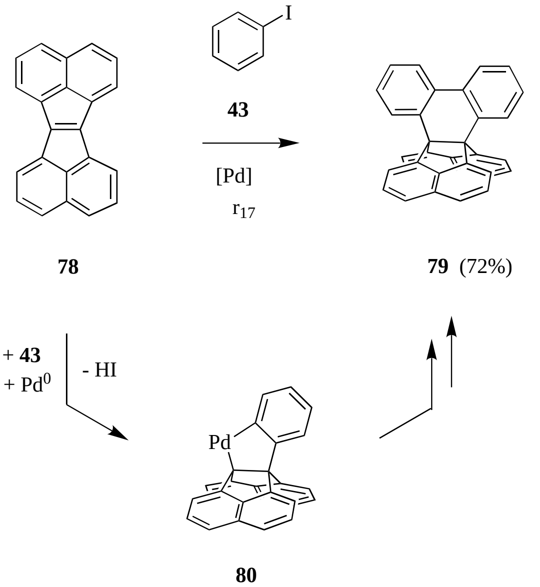
Scheme 15. Reaction conditions r_{15}: 4 mol% $[Pd(PPh_3)_4]$, KOtBu, anisole, 105 °C, 10 h.

The substrates in the examples discussed so far are characterized by a structural unit that allows direct cyclopalladation. In the following examples, such a structural unit first needs to be constructed: carbopalladation at an unsaturated C–C bond preceeds the C–H activation. This reaction type is illustrated by the extensively researched palladium-catalyzed annelation reaction of norbornene (**67**) with bromobenzene (**68**).[24] Depending on the reaction conditions the intermediary five-membered palladacycle **71** leads to at least four different types of products (Scheme 15): the 1:2 product **69**,[24a] the benzocyclobutene derivative **72** as 1:1 product, which is formed directly from the five-membered palladacycle **71** by reductive elimination,[24b] the 1:3 product **73**,[24c,d] and the 2:2 product **74**.[24d] Based on stoichiometric reactions the research group of Catellani has recently been able to present conclusive mechanistic concepts on the formation of these products,[24e] for which the reversibility of the carbopalladation of norbornene **67** plays a decisive role. In the case of steric overloading of the corresponding palladium complexes, the reversibility can already occur at room temperature and it is also a key step in the fascinating multicomponent reaction in Scheme 16.[24f] Norbornene **67** serves as a template to direct the catalytically active palladium center for the necessary C–H activation steps but is not built into the final product **77** itself.

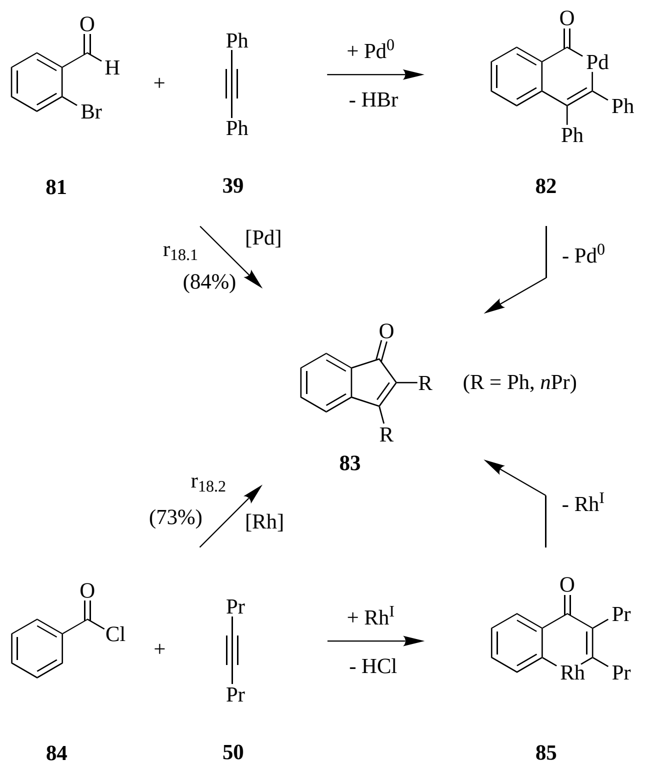


Scheme 16. Reaction conditions r_{16}: 5 mol% Pd catalyst of the isolated structure type **70**, reactants **67**, **43**, **75**, and **76** in the ratio 1:1:4:1.5, K_2CO_3, dimethylacetamide, 20 °C, 30 h.

Similar annelation reactions such as the one at norbornene also occur at disubstituted alkynes[25] and at the hexacyclic hydrocarbon **78**, a strained, tetrasubstituted olefinic coupling component (Scheme 17);[26] the reaction with iodobenzene (**43**) results in the propellane **79** with a hexaarylethane structure.



Scheme 17. Reaction conditions r_{17}: 5 mol% $Pd(OAc)_2$, K_2CO_3, nBu_4NBr, DMF, 100 °C, 14 d.



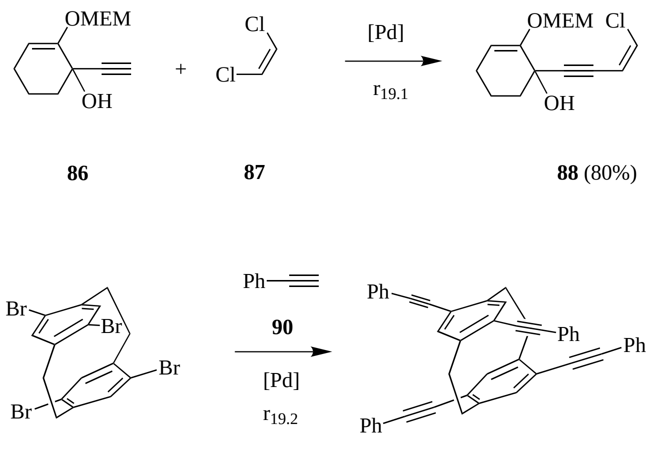
Scheme 18. Reaction conditions; $r_{18.1}$: 1 mol% $Pd(OAc)_2$, NaOAc, nBu_4NCl, DMF, 100 °C, 36 h. $r_{18.2}$: 5 mol% $[RhCl(cod)]_2/PPh_3$, Na_2CO_3, *o*-xylene, 145 °C, 24 h.

Larock et al. also postulate a cyclopalladation as the decisive reaction step in the intramolecular C–H activation at the aldehyde function of **81** (Scheme 18).[27] The coupling of **81** with different disubstituted alkynes provides a general route to indenones **83**. A rhodium-catalyzed coupling reaction starting from aroyl chlorides such as **84** leads to the same result.[28] According to Miura et al. rhodacycles such as **85** can be assumed as intermediates in this process. In comparison to the palladium-catalyzed variant, this method seems to have the advantage that the starting materials are more readily accessible and it illustrates that intramolecular C–H activation through carbon-bound transition metal complexes is by no means limited to palladium.

4. C–H Activation without Cyclometalation

Numerous examples for transition metal catalyzed C–C couplings with the participation of relatively acidic C–H groups are well known and intensively used. The transition metal catalyst can be considered as an organometallic base responsible for the C–H activation. For the Stevens–Castro–Sonogashira reaction[29] (e.g. coupling of **86** with **87** to give **88**, Scheme 19)[30a], additional bases such as amines or carbonates are always present; however, their main purpose is the regeneration of the active Pd^0 catalyst from intermediate hydridopalladium halide complexes. These bases are not absolutely necessary for the C–H activation step. The Sonogashira reaction is of particular interest for the construction of large, conjugated π systems. The fourfold reaction at the paracyclophane **89** provides an indication of the potential synthetic applications.[30b]

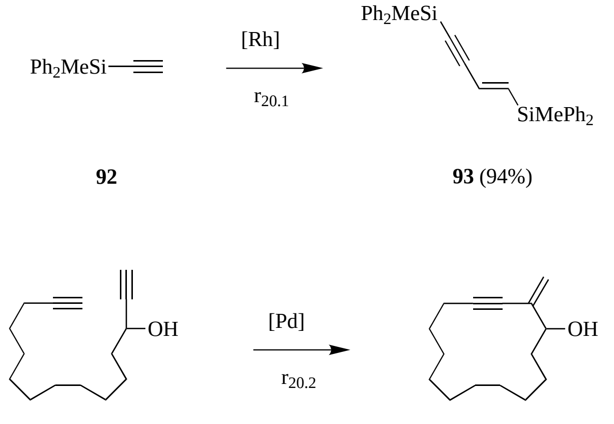
The transition metal is undoubtedly responsible for the C–H activation in the rhodium-catalyzed head-to-head dimerization of the alkynyl silane **92** because in this case no further bases are necessary (Scheme 20).[31] For Ene–yne syntheses[32]



86 **87** **88** (80%)

89 **91** (70%)

Scheme 19. Reaction conditions $r_{19.1}$: 5 mol% $[Pd(PPh_3)_4]$, 15 mol% CuI, nBuNH$_2$, 20 °C. $r_{19.2}$: 10 equiv **90**, 4 mol% $[Pd(PPh_3)_4]$, 9 mol% CuI, NEt$_3$, 3 d, 60 °C.

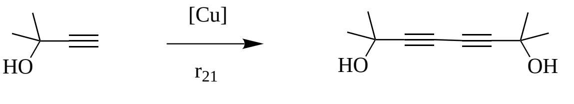


92 **93** (94%)

94 **95** (46%)

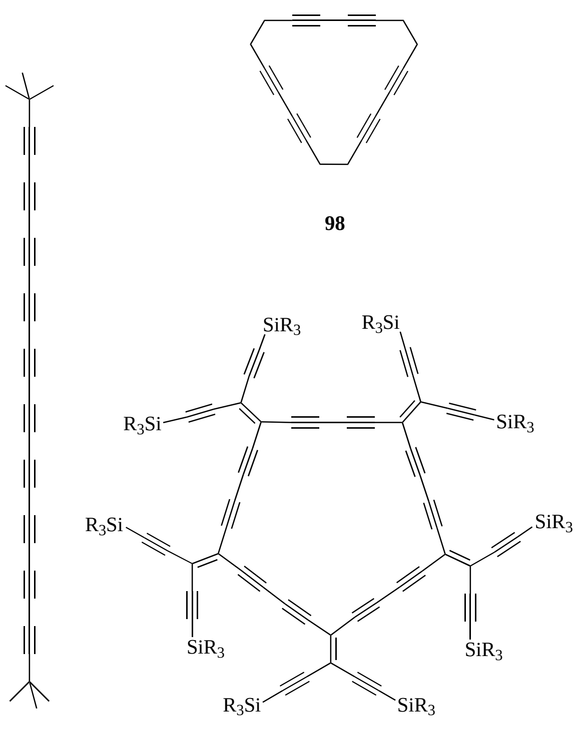
Scheme 20. Reaction conditions $r_{20.1}$: 5 mol% $[RhCl(PPh_3)_3]$, toluene, room temperature, 30 h. $r_{20.2}$: 10 mol% Pd(OAc)$_2$, tris-(2,6-dimethoxyphenyl)phosphane, benzene, reflux.

of this kind the head-to-tail dimerization such as that for the macrocycle **95** is the rule (Scheme 20).[33] In this context a classic among C–H activation reactions, the Glaser coupling,[34] in which terminal acetylenes are coupled under copper catalysis and oxidation to give butadiynes, cannot go unmentioned; the efficient conversion of the butynol **96** serves as a good example (Scheme 21).[34b] A selection of particularly carbon-rich compounds that are accessible by the Glaser coupling are presented in Scheme 22. The potential applications range from macrocycles such as **98**[34c] through polyynes such as **99**[34d] to building blocks for carbon networks **100**.[34e]



96 **97** (90%)

Scheme 21. Glaser coupling; reaction conditions r_{21}: 1.2 mol% Cu$_2$Cl$_2$, pyridine/MeOH, O$_2$, 35 °C, 2.5 h.

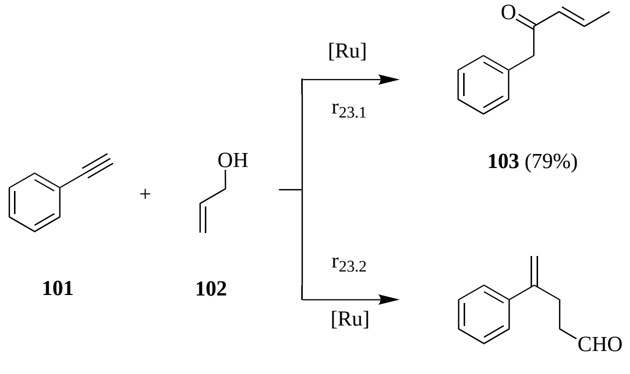


98

99 **100**

Scheme 22. Selection of structures accessible by Glaser coupling. R = iPr.

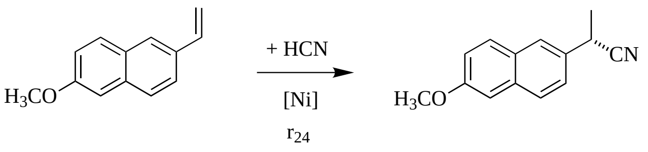
Ruthenium catalysts open up new reaction pathways for terminal alkynes since C–H activation can be used for the formation of cationic vinylidene complexes: with allyl alcohols as the coupling partner a great number of products is selectively accessible.[35] Depending on reaction conditions, substitution pattern, and catalyst, β,γ-unsaturated ketones and α,β-unsaturated ketones such as **103**[35a] or even γ,δ-unsaturated carbonyl compounds[35b] such as **104**[35d,e] are obtained selectively (Scheme 23).



101 **102** **103** (79%) **104** (64%)

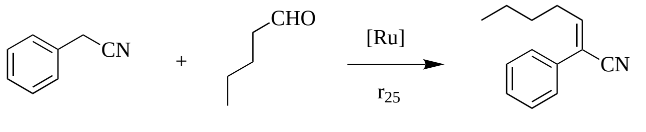
Scheme 23. Reaction conditions $r_{23.1}$: 1. 10 mol% $[CpRuCl(PPh_3)_2]$, NH$_4$PF$_6$, 100 °C, 10 h; 2. RhCl$_3$, THF, reflux. $r_{23.2}$: 5 mol% $[RuCl(cod)(C_5Me_5)]$, water as solvent, 90 °C, 1 h; in addition to the major product **104**, the regioisomer 5-phenyl-4-pentenal was obtained in 21% yield.

Some reactions which fall into the category of transition metal catalyzed C–C couplings with acidic C–H groups are already of commercial interest: the copper acetylide catalyzed synthesis of butynediol from acetylene and formaldehyde[36] as well as hydrocyanation should be emphasized: the enantioselective synthesis of the naproxene-nitrile **106** is a well-known example (Scheme 24).[37] Related coupling reactions of C–H acidic compounds, such as malonates and ketones, with alkenes and alkynes are of particular interest since they are atom-economic addition reactions;[38] however, in many cases the additional bases and not the transition metal catalyst are responsible for the C–H activation. According to Murahashi and Naota the advantages of carrying out a reaction under clearly neutral conditions become particularly apparent for ruthenium-catalyzed aldol reactions (Scheme 25):[39, 40] C–H acidic nitriles such as **107** can be chemoselectively condensed with even stronger C–H acidic aldehydes. In contrast, under classic basic reaction conditions the homocondensation of the aldehydes is the determining reaction path.



105 **106** (100%, 85% *ee*)

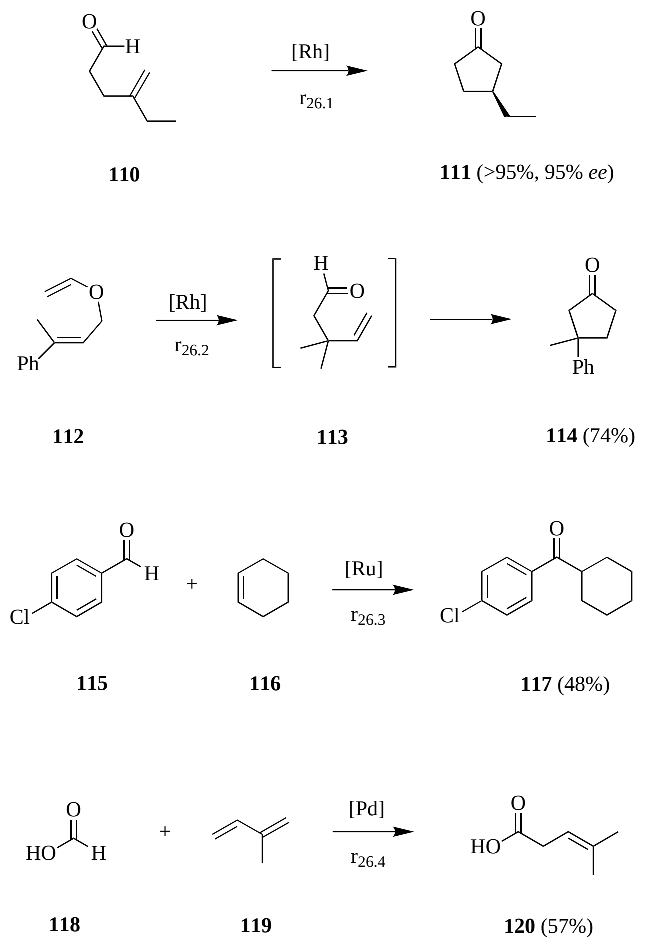
Scheme 24. Reaction conditions r_{24}: 0.1 mol% [Ni(cod)$_2$], chiral bisphosphite ligand, toluene, 25 °C.



107 **108** **109** (98%)

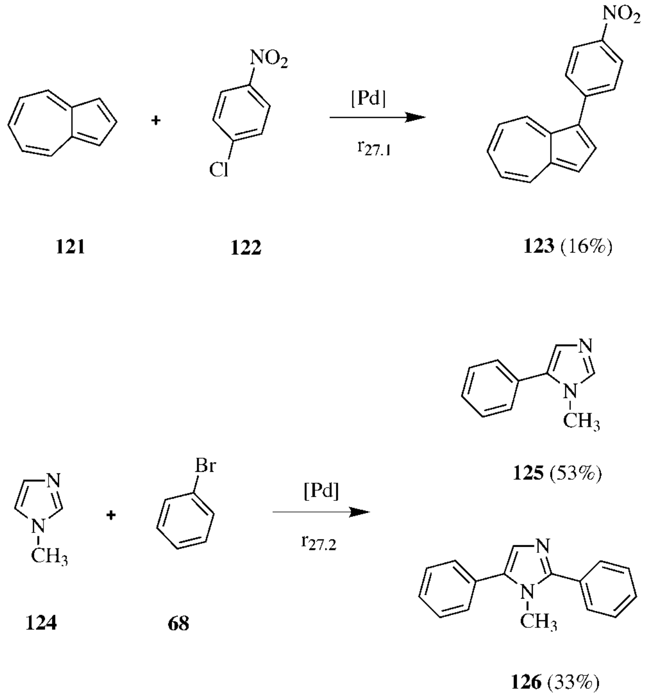
Scheme 25. Reaction conditions r_{25}: 3 mol% [RuH$_2$(PPh$_3$)$_4$], THF, room temperature, 24 h.

Aldehydic hydrogen atoms are classed as more chemically inert with regard to C–H activation, nevertheless ruthenium and rhodium catalysts are particularly successful in this case: Wilkinson's catalyst can efficiently decarbonylate primary aldehydes at room temperature as a result of C–H activation.[41] Under suitable reaction conditions the decarbonylation can be avoided; if necessary the intermediate hydridorhodium acyl complexes can add to alkenes and alkynes. The resulting hydroacylation[42] is a versatile reaction type (Scheme 26): an impressive enantiomeric excess is achieved in the intramolecular hydroacylation of the γ,δ-unsaturated aldehyde **110** by using a rhodium catalyst with chiral bidentate phosphane ligand.[42a] In the synthesis of the cyclopentanone **114** a Claisen rearrangement preceeds the intramolecular hydroacylation.[42c, d] Intermolecular hydroacylations[42e–i] are more difficult to achieve and their yields are usually significantly lower (e.g. synthesis of **117**).[42e] An increase in yields is, for example, achieved by the intermediary formation of pyridylimines on addition of a catalytic amount of 2-amino-3-picoline. Evidently, in this case both the resulting intramolecular C–H activation by cyclometalation and the stabilization of the acyl complexes by the pyridyl ligand have a favorable effect.[42f] The hydroacylation of dienes with formic acid (**118**) is a preparatively valuable special case. In spite of the acidic acid function a palladium-catalyzed C–H activation occurs at the formyl hydrogen atom.[42g]



Scheme 26. Variants of the hydroacylation reaction; reaction conditions $r_{26.1}$: 5 mol% [Rh(*S*,*S*-Me-duphos)(acetone)$_2$]PF$_6$, acetone, 25 °C, < 5 min. $r_{26.2}$: 3 mol% [RhCl(cod)(dppe)], DMF, 140 °C, 20 h. $r_{26.3}$: 1 mol% [Ru$_3$(CO)$_{12}$], 8 equiv **116**, CO, pressure, 200 °C, 48 h. $r_{26.4}$: 10 mol% Pd/C, dppp, PPh$_3$, DME, CO, pressure, 110 °C, 24 h. *S*,*S*-Me-duphos see ref. [42a], dppe = 1,2-bis(diphenylphosphanyl)ethane, dppp = 1,3-bis(diphenylphosphanyl)propane.

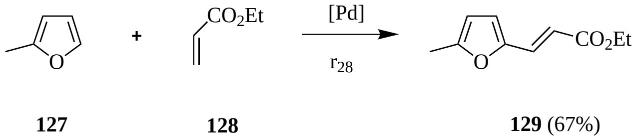
C–C coupling reactions that are based on "intermolecular" catalytic C–H activation on otherwise nonactivated sp^2- and especially sp^3-hybridized centers continue to represent a challenge. Such coupling processes are rare. The few examples known are based on the electrophilicity of Pd^{II} complexes. Whereas the intramolecular coupling reaction of aryltriflates and of aryl halides with a second aryl partial structure has found a considerable number of applications to date[18] (for example the synthesis of **53** as explained in Section 2), the corresponding intermolecular process seems to be limited to specific cases with electron-rich aromatic hydrocarbons and with hetarenes as coupling components. Azulene (**121**) is a suitable substrate for the palladium-catalyzed arylation with 1-chloro-4-nitrobenzene (**122**) and with iodobenzene (**43**) (Scheme 27).[43] The C–C coupling occurs regioselectively at the electron-rich 1-position of azulene (**121**) and is, for example, catalyzed by palladium clusters.[44] Possibly, the



Scheme 27. Reaction conditions, $r_{27.1}$: 5 mol% $Pd(OAc)_2$, 5 equiv **122**, DMF, K_2CO_3, nBu_4NBr, 140 °C, 3 d. $r_{27.2}$: 10 mol% $Pd(OAc)_2$, PPh_3, 2 equiv **68**, DMF, K_2CO_3, 140 °C, 20 h.

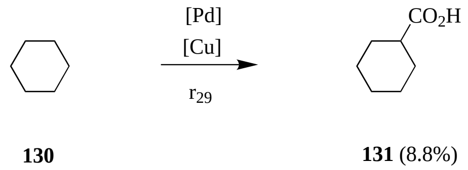
C–H activation occurs according to the pattern of the electrophilic aromatic substitution with an arylpalladium halide as the electrophilic agent. By employing different hetarenes, Miura et al. obtained considerably higher yields in intermolecular aryl–aryl coupling reactions.[45, 46] In the case of the imidazole **124** the first arylation occurs at the electron-rich 5-position; however, a second arylation at the more electron-poor 2-position is evidently also possible (Scheme 27).

These Pd^0-catalyzed coupling reactions must be differentiated from the Pd^{II}-catalyzed biaryl formation under C–H activation: a palladium acetate induced coupling reaction converts benzene oxidatively to give biphenyl. In these cases, reoxidation of Pd^0 intermediates is necessary to close the catalytic cycle. Under an oxygen atmosphere or in the presence of oxidants such as Cu^{II} salts or peroxides, this reaction occurs to a certain extent catalytically.[47] A peracid is used as the oxidant in the related arylation of the acrylate **128** with the furan **127** (Scheme 28).[48] The key step in this reaction is the metalation of **127** at the electron-rich 5-position by the electrophilic palladium benzoate, which finally leads to the Heck-like product **129**.



Scheme 28. Reaction conditions r_{28}: 5 mol% $Pd(OCOPh)_2$, AcOH, $PhCO_3tBu$, 100 °C.

Fujiwara et al. developed a palladium-catalyzed carboxylation of aromatic hydrocarbons and alkanes with carbon monoxide; under suitable reaction conditions turnover numbers of up to 200 are achieved for the formation of cyclohexane carboxylic acid (**131**) (Scheme 29).[49] The analogous reaction proceeds slightly more efficiently with toluene and with *para*-xylene, however slightly worse with methane.

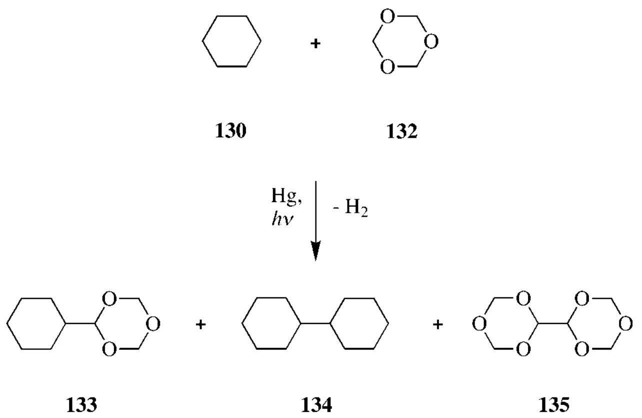


Scheme 29. Reaction conditions r_{29}: 5 mL cyclohexane, 0.02 mmol $Pd(OAc)_2$, 1.0 mmol $Cu(OAc)_2$, 9.0 mmol $K_2S_2O_8$, 3.3 mL CF_3CO_2H, 20 atm CO, 80 °C, 20 h (turnover number ca. 200).

Further investigations into this type of reaction should focus their attention on the role of the cocatalyst copper acetate. Surprisingly, according to Sen and Lin the carboxylation of methane with carbon monoxide and peroxodisulfate can also be achieved without a transition metal catalyst.[50]

Corresponding carbonylations of aliphatic hydrocarbons with carbon monoxide under nonoxidizing conditions are of particular industrial interest since such processes might be able to compete with hydroformylation. Since the early work of Tanaka et al., radical reactions,[51] which in addition to the transition metal catalysis require photochemical activation, have been favored for this. Whereas Tanaka et al.[52] use rhodium–phosphane complexes[53] for the photochemical carbonylation, Hill et al. introduced polytungstates as alternative catalysts.[54, 55] Recent results have shown that the latter are also suitable for the photochemical cyanation of alkanes with cyanoformate.[54c]

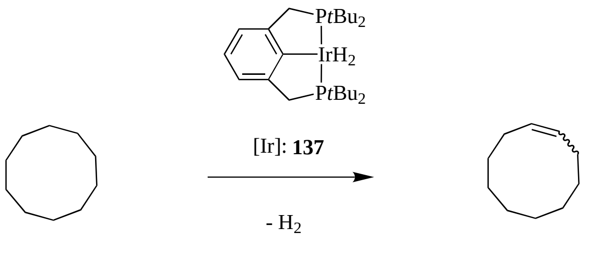
Although these examples of C–C coupling reactions with alkanes are very promising, it is still a long way to industrial applications. One exception is the Mercat process, mainly developed by Crabtree et al.[56] This unique process combines photochemistry with transition metal catalysis in the gas phase, as illustrated by the coupling reaction of cyclohexane (**130**) with the formaldehyde trimer **132** (Scheme 30).[56b] A mixture of the organic substrates and a drop mercury are



Scheme 30. Hg-catalyzed and photochemically induced oxidative dimerization in the gas phase.

heated under reflux and irradiated by UV light: mercury atoms in the excited triplet state cause the homolysis of the C–H bonds. The resulting alkyl radicals can dimerize and the higher boiling coupling products accumulate in the condensed phase, in which they are protected from multiple reactions. The cross-coupling product **133** can easily be separated from the homocoupling products **134** and **135**.

Finally, the transition metal catalyzed dehydrogenation of alkanes as a special case of C–C coupling under C–H activation is discussed briefly.[57] A large number of different transition metal complexes has proven active for this process, including complexes of iridium, rhenium, rhodium, ruthenium, and tungsten as well as heterogeneous catalysts such as palladium on active charcoal. Since the reactions are usually endothermal, sacrificial alkenes are often added to prevent the reverse reaction. The decomposition of the ligands at the often quite high reaction temperatures also presents a problem. Recently the research groups of Kaska, Jensen, and Goldman reported that the cyclometalated iridium complex **137** is sufficiently stable under the required reaction conditions (Scheme 31);[58] for the dehydrogenation of cyclodecane (**136**) no less than 360 catalysis cycles are completed in 24 h.



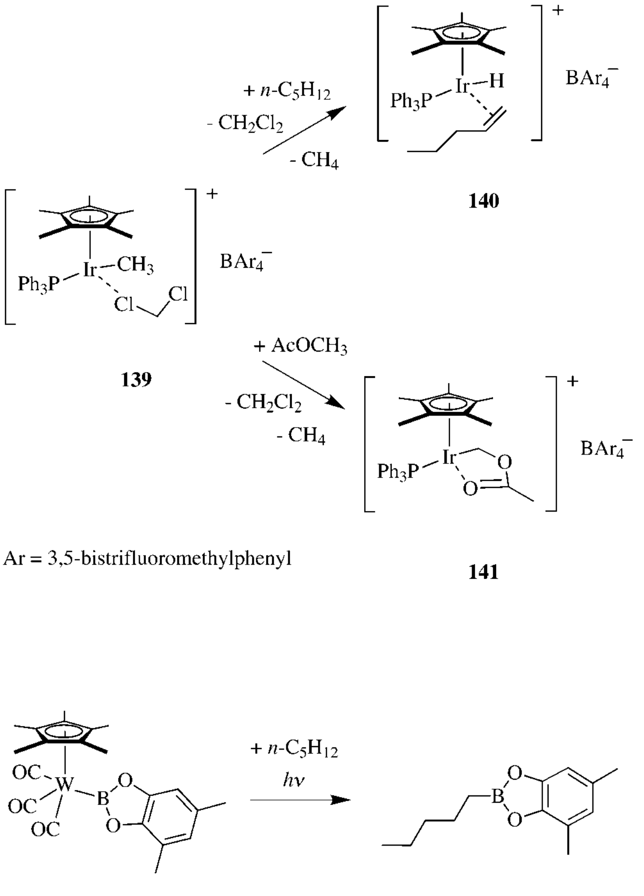
136 **138** (*cis/trans* 3/1)

Scheme 31. Reaction conditions r_{31}: 1.0 mM solution of **137** in **136**, reflux (201 °C).

Shock wave experiments and more recent calculations[59] show that methane disproportionates into hydrogen and higher hydrocarbons at 100 GPa and 4000 K until under pressures of greater than 300 GPa and 5000 K it is finally converted into diamond and hydrogen. Of course, these results are without any industrial relevance because they occur under extreme conditions as anticipated inside the large planets Uranus and Neptune. However, transition metal catalysis can evidently facilitate similar reactions under more moderate conditions: according to Choudhary et al. methane can be converted to higher alkanes below 600 °C, if a special galloaluminosilicate zeolite is used as the catalyst and a sacrificial alkene is employed to couple the hydrogen.[60] Basset et al.[61a] recently reported an alkane metathesis that is catalyzed by tantalum hydrides on a silica gel surface. For example, under normal pressure and at 150 °C ethane disproportionates to methane[62] and propane; however, this is a very slow process (turnover number 46 after more than 50 h reaction time). The C–H and C–C activation steps are part of the catalysis cycle. Corresponding gallium hydrides on silica gel are capable of degrading polyethylene to aromatic hydrocarbons at temperatures of above 500 °C.[61b]

5. From Stoichiometric C–H Activation to Catalytic Reactions?

Since the early 1980s transition metal complexes have been known that are capable of the oxidative addition to alkane C–H bonds.[63] In addition to rhodium, osmium, rhenium, iron, palladium, and platinum complexes, iridium complexes have received particular attention.[63a] Fundamentally, these are electronically unsaturated complexes with vacant coordination sites.[62b] Bergman et al. have recently made significant progress in achieving C–H activation under moderate conditions. The cationic iridium complex **139** proved particularly reactive (Scheme 32).[63c] With benzene, C–H activation already occurs at −30 °C, with *n*-pentane it happens within a few minutes at room temperature, leading to the alkene complex **140**. The selectivity of the C–H activation becomes especially significant during the reaction with methyl acetate: the C–H activation occurs exclusively at the methoxy group and leads to the cyclometalated complex **141**; however, the more acidic acetyl group is not attacked. The development of possibilities for C–H activation under moderate conditions is the first step on the way to useful catalysis cycles. Further investigations should be aimed at searching for reagents which



Ar = 3,5-bistrifluoromethylphenyl

Scheme 32. Stoichiometric C–H activation with cyclopentadienyl complexes of the late transition metals.

regenerate an active transition metal species from complexes such as **140** and **141**, while at the same time liberating a valuable final product.

In the development of new active transition metal complexes Hartwig et al. focussed attention on compounds containing a bond between a transition metal and boron. With alkanes such boryl complexes are capable of forming photochemically induced alkylboronates such as **143** (Scheme 32).[64] In this reaction the boryl group is selectively incorporated in the terminal position. So far, the best results have been achieved with the tungsten complex **142**, however similar iron and ruthenium complexes are also active. The photochemical activation probably eliminates a CO ligand, leading to the formation of a reactive 16-electron complex; an alternative thermal activation would be desirable. The driving force of the reaction is the formation of relatively stable carbon–boron bonds, which makes the development of a catalytic variant look promising.

6. Summary

The presented selection of results illustrates that coupling reactions under C–H activation are an active and current area of research. Most of the literature mentioned is from the 1990s. Noteworthy progress has been made and the first industrial applications are in sight. Thus, the development of new catalytic systems, which improve the selectivity or even open up new reaction paths, is an even more fascinating and rewarding challenge for future research.

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