

Increasing Catalyst Efficiency in C–H Activation Catalysis

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C–H activation · catalysis · methane · palladium · rhodium · turnover

C–H activation reactions with high catalyst turnover numbers are still very rare in the literature and 10 mol % is a common catalyst loading in this field. We offer a representative overview of efficient C–H activation catalysis to highlight this neglected aspect of catalysis development and inspire future effort towards more efficient C–H activation. Examples ranging from palladium catalysis, Cp*Rh^{III}- and Cp*Co^{III}-catalysis, the C–H borylation and silylation to methane C–H activation are presented. In these reactions, up to tens of thousands of catalyst turnovers have been observed.

1. Introduction

The direct functionalization of C–H bonds is a highly desirable and expedient way to increase molecular complexity from simple, readily available starting materials.^[1] In particular, metal-catalyzed C–H activation has become one of the most rapidly growing fields of organic chemistry by offering novel retrosynthetic disconnections and streamlining synthesis.^[2] While research has initially focused on identifying metal compounds suitable for the formation of organometallic complexes by reaction with C–H bonds,^[3] there is now a clear trend towards the development of methods with highly active catalyst systems.^[4] Still, the majority of catalytic methods employing C–H activation are reported as requiring high catalyst loading, with 10 mol % being common in many of these reactions. Thus, even at full conversion, the maximum turnover number (TON) of these catalysts is merely 10. Most C–H activation catalysts are based on rare metals such as palladium or rhodium and/or specialized ligands such as Cp* (1,2,3,4,5-pentamethylcyclopentadienyl). Considering the high cost of these compounds, high catalyst loadings are detrimental to the widespread uptake of C–H activation into synthetic or industrial applications. Although methods attain-

ing TONs of up to 100 with 1 mol % of the catalyst are regularly published, reports of higher TONs are still very rare. Nevertheless, remarkable exceptions of catalysts reaching ten thousands of turnovers have been reported.

Herein, we present an overview of transformations that have achieved very high catalyst turnover and identify underlying trends aiding catalyst development. Currently, the factors controlling catalyst lifetime in C–H activation reactions are not clearly understood. While generally catalyst stability, the absence of catalyst poisons, and an overall high activity of the catalyst are beneficial for high TONs, the rational design of systems with such properties is still in its infancy. We hope an increased awareness of the community for this crucial and neglected part of C–H activation will inspire future work towards highly efficient catalysts and encourage the utilization of C–H activation in general.

The catalyst turnover number equals the yield divided by the catalyst loading [Eq. (1)]. However, if the precatalyst is a dimer and the mechanism involves only mononuclear species, as is generally the case with precursors such as [Pd₂(dba)₃] or [Cp*RhCl₂]₂, the catalyst loading is conventionally considered as twice the amount of the dimer, thus halving the TON.

$$TON = \frac{n_{\text{product}}}{n_{\text{catalyst}}} \quad (1)$$

We have selected representative examples of high-turnover C–H activation catalyses, depicting the conditions resulting in the highest TON reported in a publication, usually applying to a single example in that report. We wish to point out that in the majority of the presented works, higher yields than those shown have been obtained under different conditions.

For the purpose of this Minireview, we include those reactions that are proposed by the authors or later work to proceed via the formation of organometal intermediates by

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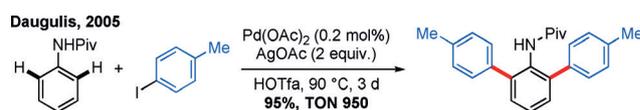
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the metal-mediated cleavage of a C–H bond. Considering that the exact mechanisms are sometimes unclear, disputed or dependent on the precise conditions, we will not discuss finer mechanistic details and refer the reader to Reviews specialized on this aspect.^[5]

2. Palladium Catalysis

Molecules with the biaryl motif are ubiquitous, with applications ranging from pharmaceuticals to functional materials. The tremendous impact palladium-catalyzed (hetero)arene cross-coupling methods has had on the synthesis of biaryl compounds, and synthetic chemistry in general, is a result of their overall reliability and defined regioselectivity.^[6] Research on catalyst efficiency in cross-coupling has led to the development of very active catalysts achieving millions of turnovers.^[7] However, both the regioselectivity and reactivity are a consequence of the required substrate prefunctionalization. This necessitates extra synthetic steps and leads to the generation of stoichiometric amounts of metal salts as byproducts. To overcome these limitations, intense research efforts have been devoted to finding ways of introducing either one or both of the coupling partners by reaction with a C–H bond.^[8]

In particular, highly efficient protocols have been developed for the direct arylation of (hetero)arenes with (hetero)aryl halides.^[9] Daugulis and co-workers presented a twofold arylation of anilides by C–H activation and coupling with aryl iodides under oxidative conditions (Scheme 1). While the scope of this transformation was demonstrated with 5 mol % of the catalyst, a reaction performed with 0.2 mol % achieved

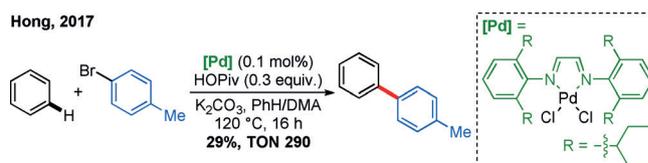


Scheme 1. Directed palladium-catalyzed direct arylation of arenes.^[10a]

a TON of 950.^[10a] A similar efficiency was observed later by the same group in a related direct arylation of aminoquinoline benzamide.^[10b]

Amides and other Lewis-basic functional groups can aid a C–H activation event by coordinating to the catalyst, thus increasing the local catalyst concentration at the substrate and stabilizing the organometal intermediates.^[11] Conversely, C–H activation of unactivated substrates lacking such “directing groups” is often associated with more forcing reaction conditions and higher catalyst loadings. The Hong group recently presented a procedure for the intermolecular direct arylation of simple arenes at low catalyst loadings (Scheme 2).^[12] The use of a diimine ligand enabled a TON of 290 with 0.1 mol % of catalyst.

The relative inertness of simple arenes in direct arylations is contrasted by a much higher reactivity of electron-rich heteroarenes. Most notably, the group of Doucet reported



Scheme 2. Undirected palladium-catalyzed direct arylation of arenes.^[12]



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Toryn Dalton read Natural Sciences at Trinity College, Cambridge, working in the laboratory of Prof. Steven V. Ley in his final year. He then joined the GSK R&D Future Leaders Programme at the Medicines Research Centre, Stevenage, UK, where he completed a Postgraduate Certificate in Professional Development. He will shortly begin a Ph.D. with Prof. F. Glorius at the Westfälische Wilhelms-Universität Münster.



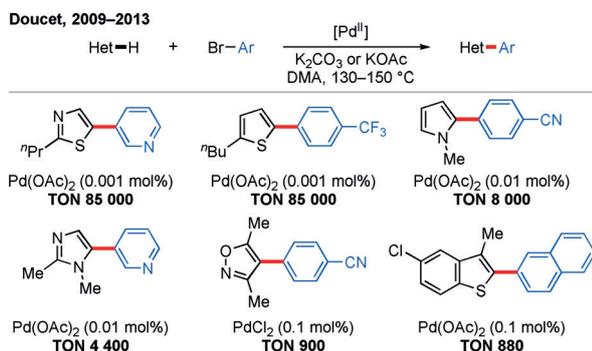
Michael J. James carried out his undergraduate studies and obtained an MChem degree at the University of York (including a one-year industrial placement at GlaxoSmithKline, Stevenage). He stayed in York to undertake his doctoral studies, working on catalytic dearomatisation reactions under the joint supervision of Prof. Peter O'Brien & Prof. Richard J. K. Taylor. Currently, he is working as an Alexander von Humboldt postdoctoral research fellow in the group of Prof. Frank Glorius at the Westfälische Wilhelms-Universität Münster.

His current research is focused on the development of photocatalytic cross-coupling reactions.



Frank Glorius is a Full Professor of Organic Chemistry at the Westfälische Wilhelms-Universität Münster. His research program focuses on the development of new concepts for catalysis in areas such as C–H activation, photocatalysis, screening technologies, N-heterocyclic carbenes (NHCs) in organocatalysis, as surface modifiers, and in (asymmetric) arene hydrogenation.

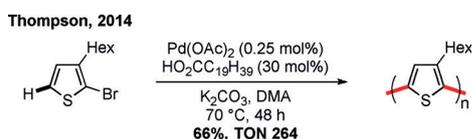
a series of methods for highly efficient direct arylation of a range of heteroarenes reaching impressive TONs up to 85 000 (Scheme 3).^[13] The mechanism in these reactions is the subject of ongoing research and may be dependent on the



Scheme 3. Representative examples from Doucet's program on efficient palladium-catalyzed direct arylation of heteroarenes.^[13]

exact substrate, as well as catalyst composition.^[14] Likely, the arene coupling partner is introduced to the heterocycle by means of a carbopalladation as in the Heck olefin arylation.^[15] Thus, these reactions might not involve actual C–H activation. Nevertheless, we include them here to aid the discussion in relation to other examples.

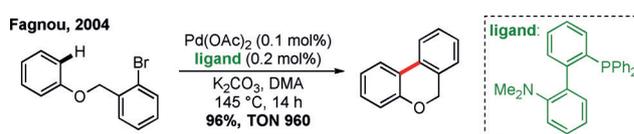
The palladium-catalyzed direct arylation of heteroarenes has found several interesting applications, such as multikilogram-scale syntheses of synthetic intermediates in the pharmaceutical industry.^[16] Polythiophenes are an important class of organic semiconductor materials and recently their synthesis by direct arylation polymerization (DARp) has been popularized,^[17] as exemplified by a protocol from the Thompson group (Scheme 4) at low catalyst loadings.^[18]



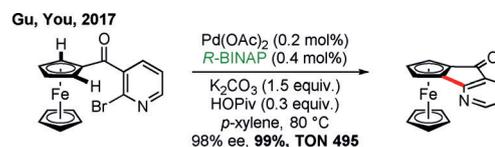
Scheme 4. Palladium-catalyzed direct arylation polymerization (DARp).^[18]

In molecules containing an aryl halide and another suitably positioned arene moiety, intramolecular direct arylation generates polycyclic products.^[19] After oxidative addition of palladium to the aryl halide, the intramolecular C–H activation is facilitated analogous to the use of a directing group. The group of Fagnou presented the efficient use of palladium in syntheses of benzochromenes and other polycyclic heterocycles, demonstrating TONs up to 960 (Scheme 5).^[20]

The group of Gu and You extended this concept to the synthesis of planar chiral ferrocenylpyridine derivatives with high enantioselectivities (Scheme 6).^[21] In a gram-scale experiment, a TON of 495 was obtained at full conversion using 0.2 mol% of $Pd(OAc)_2$ and a chiral bisphosphine ligand.

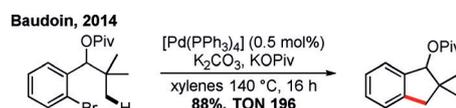


Scheme 5. Pd-catalyzed cyclization by intramolecular direct arylation.^[20]



Scheme 6. Enantioselective intramolecular Pd-catalyzed direct arylation.^[21]

Baudoin and co-workers found an intriguing conformational effect enabling a rare efficient activation of a Csp^3 -H bond (Scheme 7).^[22] A TON of 176 was observed for the C–H activation at a *tert*-butyl group with 0.5 mol% of a Pd^0 catalyst precursor. As little a change as using a substrate bearing an isopropyl group led to a decreased catalytic efficiency.

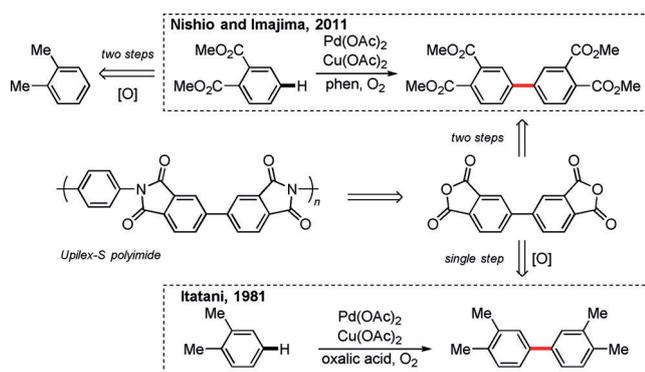


Scheme 7. Pd^0 -catalyzed Csp^3 -H activation.^[22]

Cross-dehydrogenative coupling (CDC) involves the activation of two C–H bonds and subsequent coupling of the fragments. With no need for prefunctionalization of either species, this atom- and step-economical transformation is of significant industrial potential. The first example of palladium-mediated CDC, reported by van Helden and Verberg in the 1960s, generated isomeric mixtures of biphenyls using stoichiometric $PdCl_2$.^[23] Substantial progress has since been made in catalytic CDC.^[24] A major limitation of the catalyst efficiency in these reactions is the agglomeration and deposition of Pd^0 formed by reductive elimination of the product. Thus, the oxidant used for recycling to Pd^{II} plays a crucial role for the catalyst lifetime. While silver- or copper-based oxidants are commonly employed for this purpose, much progress has been made in the use of oxygen or air as terminal oxidant.^[25]

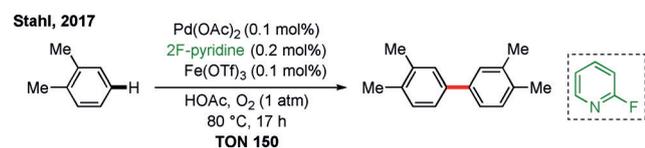
The Pd-catalyzed CDC of arenes is well-established in industrial processes for the synthesis of precursors to the polyimides Upilex (Scheme 8).^[26] Since the terminal oxidant is molecular oxygen, water is the only byproduct of this reaction. To avoid over-oxidation, these reactions are typically halted at low conversion, the unconverted feedstock recycled and the catalysts regenerated. The use of copper salts increases the longevity of the active Pd species and facilitates lower oxygen pressures.^[27] The ton-scale CDC of dimethylphthalate, with a TON of approximately 300, is run in preference to *o*-xylene, which suffers poorer chemo- and regioselectivity.

Based on mechanistic investigations, the group of Stahl devised an improved, highly active catalyst system, enabling



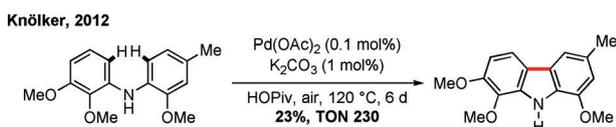
Scheme 8. Ube Industries syntheses of Upilex polyimide.^[26,27]

a highly regioselective CDC of *o*-xylene and a shorter, viable route to Upilex.^[28] Triflate and 2-fluoropyridine are introduced as weakly coordinating ligands, increasing the electrophilicity of the metal center. Optimizing the source of triflate counter ions revealed that the addition of Fe(OTf)₃ increases the TON above 150 (Scheme 9).^[28c] These efficiency improvements appear to have been adopted already in industry.^[29]



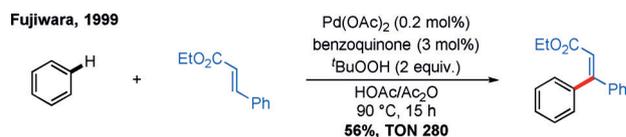
Scheme 9. Pd-catalyzed CDC of *o*-xylene.^[28]

Dehydrogenative cyclizations in biaryl compounds^[30] can benefit from the intramolecular nature of the second C–H activation and the stabilization of the diarylpalladium intermediates.^[31] In the synthesis of the carbazole alkaloid Murrayastine, the group of Knölker demonstrated efficiency of the palladium catalyst in an oxidative cyclization with TONs up to 230 (Scheme 10).^[32]



Scheme 10. Murrayastine synthesis by Pd-catalyzed oxidative cyclization.^[32]

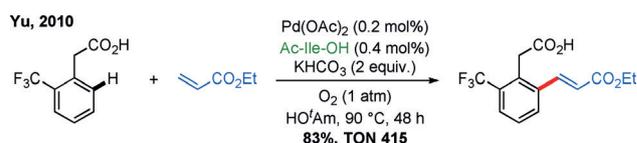
The oxidative olefination of arenes catalyzed by palladium, also known as the Fujiwara–Moritani or oxidative Heck reaction, is one of the most prominent C–H functionalization reactions.^[33] Originally discovered in the 1960s as a transformation stoichiometric in palladium,^[34] many developments have since been reported to render this a highly efficient reaction. A marked improvement in catalyst efficiency was observed by the group of Fujiwara when ^tBuOOH was used as the oxidant, enabling TONs up to 280 (Scheme 11).^[35] Later, the Jacobs group demonstrated even higher catalyst efficiency by adding benzoic acid, using an excess of the arene substrate as solvent, and running the reaction under a pressure of O₂.^[36]



Scheme 11. Palladium-catalyzed undirected oxidative arene olefination.^[35]

The highest TON reported under these conditions is 762, although the authors indicate that an unspecified mixture of products is formed.

One strategy to avoid the generation of regioisomeric products in arene C–H activation is the use of directing groups.^[11] Investigating the directed olefination of phenylacetic acids, the Yu group discovered that the addition of a monoprotected amino acid ligand significantly increased the TON and reaction scope of the overall process (Scheme 12).^[37a,b] Thus, using 0.2 mol% of Pd(OAc)₂ and 0.4 mol% of *N*-acetyl isoleucine, the olefination of a substituted phenylacetic acid proceeded with a TON of 415, an efficiency that was further extended to a gram-scale reaction. Detailed kinetic studies revealed the origin of this increased reactivity in the presence of the ligand. The formation of less active palladium species by coordination with carboxylates derived from the substrate or product is therefore suppressed by the introduction of suitable ligands.^[37c]



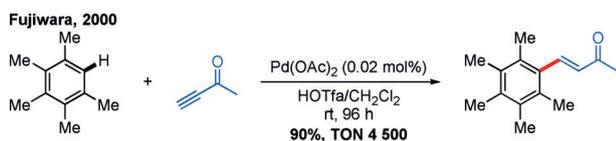
Scheme 12. Palladium-catalyzed directed oxidative arene olefination.^[37]

Further exploring the use of carboxylates as directing groups in conjunction with mono-*N*-protected amino acid ligands in Pd-catalyzed C–H activation,^[38] the group of Yu developed a synthesis of dihydroisocoumarins from benzoic acids and epoxides (Scheme 13).^[39] Under the standard conditions, this reaction proceeds with 1 mol% of Pd(OAc)₂ and in a gram-scale experiment, a TON of 186 was observed with 0.5 mol% of the catalyst.



Scheme 13. Palladium-catalyzed dihydroisocoumarin synthesis.^[39]

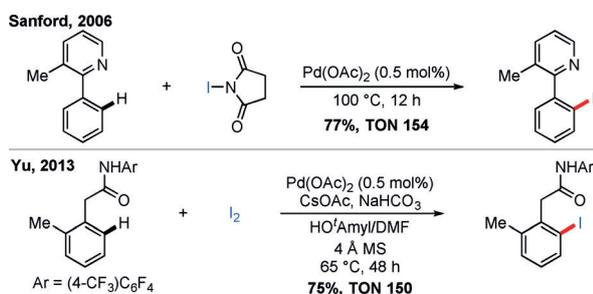
Another efficient method for olefination of arenes is the redox-neutral alkyne hydroarylation. The Fujiwara group demonstrated the ability of Pd(OAc)₂ to catalyze this reaction with TONs up to 4500 (Scheme 14) in strongly acidic media using trifluoroacetic acid (HOTfa) as cosolvent.^[40] Of note, the mechanism of this reaction is disputed and may not proceed via C–H activation, but rather via electrophilic



Scheme 14. Palladium-catalyzed alkyne hydroarylation.^[40]

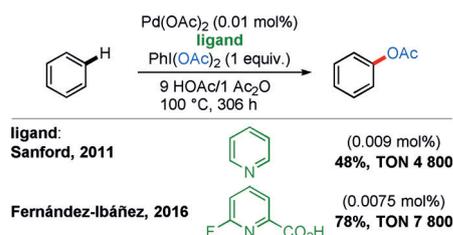
aromatic substitution by an alkyne that is activated by Lewis-acidic palladium species.^[41]

The directed C–H iodination of arenes can proceed under highly efficient palladium catalysis. The Sanford group presented the halogenation of arenes bearing directing groups using *N*-halosuccinimides as reaction partners.^[42a] A TON of 154 was observed with 0.1 mol % of catalyst in the iodination of 2-methyl-3-phenylpyridine (Scheme 15). The group of Yu developed a directed iodination with molecular iodine as reaction partner, using 2 mol % of Pd(OAc)_2 under the standard conditions and TONs of up to 150 were observed in gram-scale syntheses using 0.5 mol % of the catalyst (Scheme 15).^[42b]



Scheme 15. Palladium-catalyzed directed C–H iodination.^[42]

Another prominent palladium-catalyzed transformation on C–H bonds is the acetoxylation of arenes.^[43] The first truly efficient catalyst system for this transformation was presented by the group of Sanford in 2011 (Scheme 16).^[44a] In this work, they noted a crucial influence of pyridine as coligand with Pd(OAc)_2 on the efficiency of the catalyst system. The scope of this reaction was demonstrated with 2 mol % of Pd(OAc)_2 and a maximum TON of 4800 was observed in an experiment with 0.01 mol % of catalyst. At the optimal pyridine: Pd ratio of nearly 1:1, a dinuclear complex is the catalyst resting state, which is in equilibrium with a highly active mononuclear species.^[44b] Under the reaction conditions, the formation of



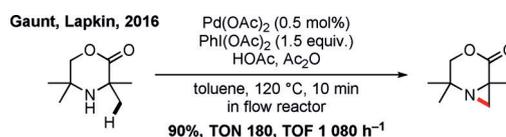
Scheme 16. Palladium-catalyzed arene acetoxylation.^[44]

palladium black and thus catalyst deactivation only occurs after full consumption of the oxidant.

The group of Fernández-Ibáñez investigated the pyridine substitution, finding an even more efficient catalyst system for this reaction.^[44c] Based on the assumption that carboxylates facilitate C–H activation, they focused on picolinic acid derivatives. Using 6-fluoropicolinic acid in a 1:0.75 ratio of Pd to ligand, they observed a TON of 7800 under otherwise identical reaction conditions to those reported by Sanford (Scheme 16).

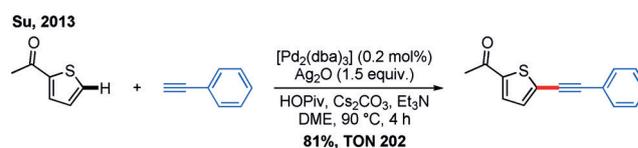
The group of Stahl demonstrated the influence of NO_x -based redox mediators such as NaNO_3 or $^t\text{BuONO}$ on the efficiency of palladium-catalyzed C–H acetoxylation of benzene with oxygen as terminal oxidant in the absence of iodine(III)-based oxidants and pyridine ligands.^[44d] The highest TON observed, with fuming HNO_3 as redox mediator, is 136. This work shows the potential for further increased catalyst efficiency by the use of redox mediators.^[45]

The palladium-catalyzed reaction of aliphatic amines to afford aziridines by intramolecular $\text{Csp}^3\text{–H}$ amination was originally reported using 5 mol % of Pd(OAc)_2 under the standard conditions by the Gaunt group (Scheme 17).^[46a] In a collaboration with Lapkin, this transformation was optimized for catalyst efficiency using flow reactors.^[46b] Careful kinetic analyses and in silico modelling of the entire reaction mechanism allowed the development of a flow process using 0.5 mol % of the catalyst that produces 90 % product yield within 10 minutes, which corresponds to a TON of 180 and an exceptional turnover frequency (TOF) of 1080 h^{-1} .



Scheme 17. Palladium-catalyzed aziridine synthesis.^[46]

High catalyst efficiency was observed by the group of Su in a palladium-catalyzed/silver-mediated CDC of heteroarenes with terminal alkynes.^[47] Under the standard conditions, 0.2 mol % of $[\text{Pd}_2(\text{dba})_3]$ was used together with superstoichiometric amounts of Ag_2O to achieve TONs up to 202 (Scheme 18). The authors propose that the alkyne is initially converted into a silver acetylide with very low solubility. They argue this precipitate might serve as a support for palladium species, inhibiting agglomeration and deactivation.

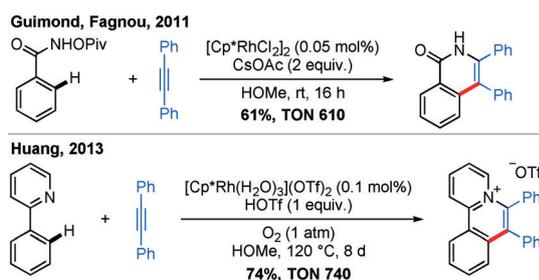


Scheme 18. Pd-catalyzed dehydrogenative alkyne-heteroarene coupling.^[47]

3. Cp*Rh^{III} and Cp*Co^{III} Catalysis

Cp* complexes of the Group 9 metals Ir, Rh, and Co are highly versatile catalysts for C–H activation.^[48] The wide range of transformations with electrophilic reagents and/or oxidizing directing groups have drawn attention to this class of C–H activation catalysts.^[49] In particular, exceptionally mild transformations have resulted from the use of directing groups that simultaneously serve as internal oxidants.^[4a,b] Nevertheless, the majority of transformations with the Cp*Rh^{III} and Cp*Co^{III} catalysts proceed with catalyst loadings of 5–10 mol%. However, a few examples with remarkably low catalyst loadings have been reported.

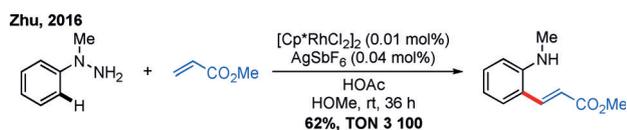
An oxidative annulation of alkynes forming isoquinoline derivatives can proceed with high efficiency of the rhodium catalyst with a number of substrates. In 2011, the group of Guimond and Fagnou presented the rhodium-catalyzed reaction of *O*-pivaloyl benzhydroxamates with alkynes to isoquinolones (Scheme 19).^[50a] Under the standard conditions, this transformation proceeds with 1 mol% of the Rh precatalyst. In a separate experiment, the TON was demonstrated to reach 610 with 0.05 mol% [Cp*RhCl₂]₂. The use of the directing group as an internal oxidant greatly facilitates the oxidation of rhodium and is probably linked with the efficiency of this transformation.



Scheme 19. Rhodium-catalyzed alkyne annulations.^[50]

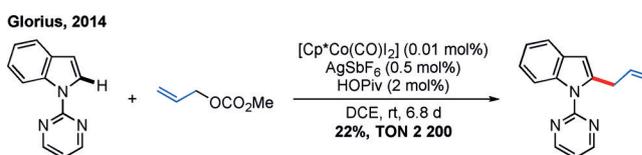
The group of Huang reported conditions for the rhodium-catalyzed synthesis of isoquinolinium salts by oxidative alkyne annulation.^[50b] Again, 1 mol% of catalyst was used under the standard conditions (Scheme 19) and with 0.1 mol% of [Cp*Rh(H₂O)₃](OTf)₂, a TON of 740 was observed.

In another example of increased catalyst efficiency by the use of oxidizing directing groups, Zhu and co-workers observed very high TONs in the rhodium-catalyzed C–H olefination of phenyl hydrazines (Scheme 20).^[51] In gram-scale experiments, TONs of 370 and 3100 were observed using 0.1 and 0.01 mol% of the precatalyst [Cp*RhCl₂]₂, respectively.



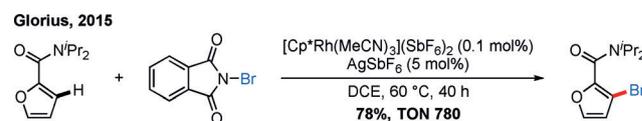
Scheme 20. Rh-catalyzed C–H olefination with an oxidizing directing group.^[51]

The Cp*Co^{III}-catalyzed allylation of pyrimidylindoles with allyl carbonates reported by the Glorius group proceeds with remarkable efficiency (Scheme 21).^[52a] Under the standard conditions, 0.5 mol% of the precatalyst [Cp*Co(CO)I₂] was sufficient to obtain near quantitative yields within four hours at room temperature, translating to TONs of up to 194. In a series of experiments, the catalyst loading was decreased while increasing the reaction time to elucidate the maximum TON of the cobalt catalyst in this transformation. Finally, with 0.01 mol% of the precatalyst, a TON of 2200 was observed after a reaction time of one week. A further study indicated that pyrimidyl indoles might be privileged substrates for the exceptional efficiency of this transformation, as other substrates required a higher catalyst loading of 5 mol% [Co] to promote conversion.^[52b]



Scheme 21. Cobalt-catalyzed directed C–H allylation.^[52]

Cp*Rh^{III} complexes catalyze directed C–H halogenation with electrophilic halogenating agents such as *N*-halosuccinimides.^[53] In 2015, the group of Glorius presented a study of the selective halogenation of electron-rich heteroarenes (Scheme 22).^[54] The standard conditions of this transformation utilize 2 mol% of the precatalyst [Cp*Rh(MeCN)₃](SbF₆)₂. An even more efficient reaction was developed by analysis of the reaction mechanism, revealing a secondary role of the rhodium catalyst as halide scavenger. While this role suppresses the uncatalyzed electrophilic halogenation of the substrate, it also deactivates the rhodium catalyst for the desired directed halogenation. Thus, by the addition of a silver salt as halide scavenger, the loading of the rhodium catalyst could be decreased to 0.1 mol%, achieving a TON of 780 in a directed bromination.



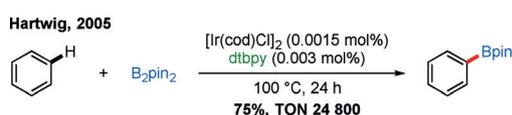
Scheme 22. Rhodium-catalyzed directed heteroarene halogenation.^[54]

4. Ir-, Rh-, and Ru-Catalyzed C–H Borylation and Silylation

Unlike the majority of the aforementioned areas of catalysis, ligand design has featured more prominently in high TON-Ir^I, and Rh^I- and Ru^{II}-catalyzed C–H activation. Primarily, these catalysts have been employed in borylation reactions of unactivated arenes. In particular, arylboronic acid pinacol esters have been targeted due to their application in a number of well-established diversification reactions, such as

Suzuki–Miyaura cross-coupling.^[6] Methods for the synthesis of borylated arenes utilizing C–H activation are highly valuable processes as they subvert the need for air-sensitive reagents with poor chemoselectivity and the wasteful pre-functionalization of substrates.^[55]

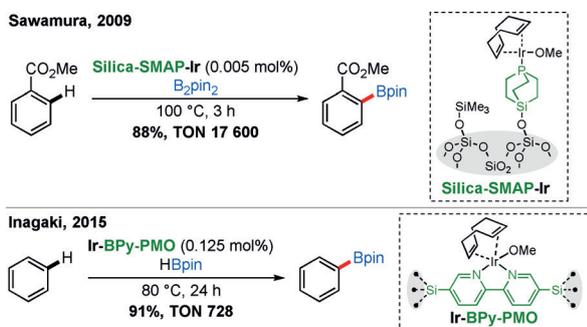
Major advances in the efficiency of Ir^I-catalyzed borylation reactions began when Smith and co-workers reported the regioselective borylation of arenes using HBpin and a bisphosphine-ligated Ir^I complex.^[56] Simultaneously, Ishiyama, Miyaura, Hartwig and co-workers disclosed B₂pin₂ could also be used in conjunction with a bipyridyl-ligated Ir^I complex to more efficiently borylate arenes, even at room temperature.^[57] Further mechanistic studies by the Hartwig group revealed the true efficiency of this process, when benzene was borylated using 0.0015 mol% [Ir(cod)Cl]₂, 0.003 mol% 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbpy) and B₂pin₂ to afford the borylated product in 75% yield with an outstanding TON of 24 800 (Scheme 23).^[58] Part of the efficiency of this process was attributed to the relatively mild conditions, the lack of major byproducts, and the absence of a coordinating solvent that could block the catalytically active coordination site. The active catalyst species forms in situ from the air-stable precatalyst, which may help to prevent catalyst deactivation prior to reaction.



Scheme 23. Ir^I-catalyzed C–H borylation of benzene.^[58]

The group of Hartwig implemented the iridium-catalyzed borylation into the total syntheses of (–)-Taiwaniaquinone H and (–)-Taiwaniaquinol B. In the first step, a brominated resorcinol derivative was obtained by a sequence of borylation with a TON of ≥ 150 and subsequent copper-mediated substitution of the boronate with bromide.^[59]

Later, Sawamura and co-workers performed the directed *ortho* borylation of arenes with a highly efficient heterogeneous iridium catalyst system, enabled by a solid-supported phosphine ligand (silica-SMAP, Scheme 24).^[60] The compact and constrained nature of the phosphine is proposed to selectively form a monocoordinated Ir^I complex, which allows the directing group to interact with the coordinatively

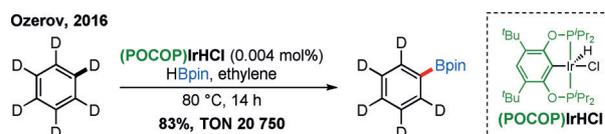


Scheme 24. Heterogeneous Ir^I-catalyzed C–H borylation reactions.^[60,62]

unsaturated catalyst species. The regioselectivity in this work is complementary to the sterically controlled selectivity of previous systems. The efficiency of this reaction was demonstrated on a 20 mmol-scale with methyl benzoate, in which the borylated product was formed in three hours with an impressive TON of 17 600. Again the authors note an improvement in catalyst efficiency by performing the reaction without additional solvent.

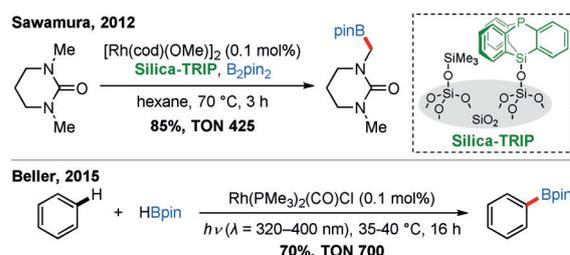
Other solid-supported catalyst systems based on tethered bipyridyl ligands were later reported by both the Jones^[61] (not shown) and Inagaki groups (Scheme 24).^[62] Inagaki's Ir-bpy-PMO catalyst system can utilize HBpin as an inexpensive borylating agent instead of B₂pin₂. The efficiency of this system was demonstrated by the borylation of benzene with 0.125 mol% of the catalyst and a TON of 728. Furthermore, the catalyst could be recovered and reused effectively another three times.

More recently, Ozerov and co-workers presented a catalyst for the borylation of arenes with HBpin at levels of efficiency comparable to the aforementioned work of Hartwig and co-workers.^[63] This was enabled by a POCOP pincer-ligated precatalyst, using ethylene as a hydrogen acceptor to form the active catalyst species in situ. Benzene-d₆ was borylated in 83% yield using just 0.004 mol% of the precatalyst, resulting in a TON of 20 750 (Scheme 25) and a range of substrates were borylated under similar conditions with an average TON of ≈ 3000 .



Scheme 25. Pincer-ligated Ir complex-catalyzed C–H borylation.^[63]

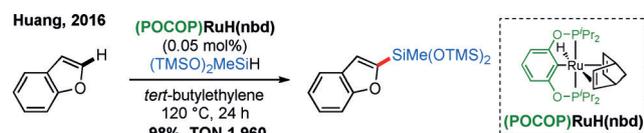
Relative to the efficiency of iridium catalysis in C–H borylation reactions, rhodium catalysis is still in its infancy. However, Sawamura and co-workers have shown that Rh^I catalysts can be utilized for challenging C(sp³)–H activation by using a solid-supported phosphine ligand framework (silica-TRIP, Scheme 26).^[64] One example was performed on a gram-scale to afford the product in 85% yield with a TON of 425. Other notable Rh^I-catalyzed borylation reactions include the work of Beller and co-workers,^[65] who used UV light irradiation to activate the precatalyst [Rh(PMe₃)₂(CO)Cl] via the extrusion of CO (Scheme 26). This system was used to prepare PhBpin with a TON of 700. The efficiency



Scheme 26. Rh^I-catalyzed C–H borylation reactions.^[64,65]

of this reaction is perhaps enhanced through the use of light irradiation as opposed to more forcing thermal conditions.

Huang and co-workers demonstrated the power of a pincer-ligated Ru^{II} hydrido complex for C–H silylation (Scheme 27).^[66] Previous work in the C–H silylation of arenes has required, for the purpose of this Minireview, relatively high catalyst loadings (> 1 mol %).^[67] Here, the Ru^{II} catalyst was capable of silylating a range of arenes at < 1 mol % catalyst loading; one example was also performed on multi-gram scale to produce 33 g of a silylated benzofuran with 0.05 mol % catalyst loading and a TON of 1960. Five other examples attained similar TONs, albeit on a smaller scale. The efficiency of this catalyst was in part proposed to be derived from the high thermal stability of the Ru^{II} complex. Also, the active catalyst system was only formed in situ by reaction with the hydrogen acceptor *tert*-butylethylene.



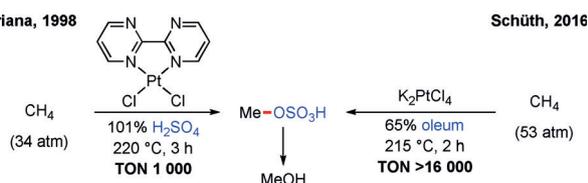
Scheme 27. Ru^{II}-catalyzed C–H silylation.^[66]

5. C–H Activation at Methane

At first glance, methane may appear an unlikely substrate for C–H activation. The pK_a value of methane is ≈ 50 , with a bond dissociation enthalpy of 105 kcal mol⁻¹. Nevertheless, processes for the direct, wholesale conversion of methane feedstocks into functionalized derivatives are of great economic and environmental importance.^[68] Building on the pioneering work of Shilov,^[69] the Catalytica–Periana system converts methane to methyl bisulfate (Scheme 28).^[70] A Pt^{II} catalyst activates the C–H bond by electrophilic addition. The catalyst is then proposed to be oxidized to Pt^{IV} by the disproportionation of the solvent sulfuric acid.^[71]

The methyl bisulfate product is hydrolyzed to afford methanol; the net process is the oxidation of methane to methanol. The TON for the process is limited to around 1000, owing to difficulties with sulfur dioxide reoxidation in situ.

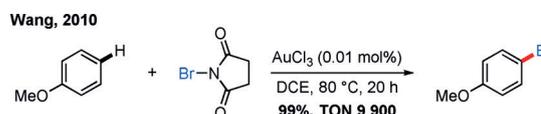
Recently Schüth published a substantially improved system, with TONs of > 16000 using the highly active catalyst K₂PtCl₄ in oleum (Scheme 28),^[72] which contains a higher effective concentration of SO₃. No precipitation of inactive PtCl₂ or “Pt black” was detected under these conditions, and the catalyst was still active when the reactions were terminated.



Scheme 28. Pt-catalyzed systems for the oxygenation of methane.^[70, 72]

6. Emerging Catalyses

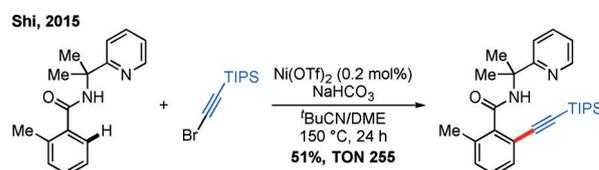
Other areas of catalysis which do not align into established categories and have only just begun to show potential for efficiency in the field of C–H activation will be covered here, for example, the AuCl₃-catalyzed C–H halogenation of arenes reported by Wang and co-workers (Scheme 29).^[73]



Scheme 29. Au^{III}-catalyzed C–H halogenation.^[73]

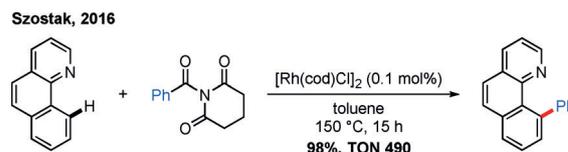
Under these conditions anisole was selectively brominated with 0.01 mol % AuCl₃ and NBS to afford the *para*-brominated product with a TON of 9900. The efficiency of this reaction was attributed to a dual role of the Au^{III} catalyst, which was tentatively proposed to both promote C–H activation by electrophilic auration to form arylgold intermediates and to activate NBS as a Lewis acid. This system was most efficient with electron-rich substrates, with two other examples attaining similarly high TONs. A solid-supported variant of this system was later disclosed by Bian, Yu and co-workers.^[74]

Other notable work includes that of Shi and co-workers,^[75] who used a Ni^{II} catalyst for the directed C–H alkylation of arene derivatives (Scheme 30). A variety of substrates were alkylated with 0.5 mol % Ni(OTf)₂. A single example using 0.2 mol % Ni(OTf)₂ was also reported, achieving a TON of 255.



Scheme 30. Ni^{II}-catalyzed C–H alkylation.^[75]

Other than the previously described C–H borylation reactions, Rh^I catalysis has also been efficiently used for the formation of C–C bonds, as reported by the Szostak group (Scheme 31).^[76] A range of biaryls were prepared by using benzamides as coupling partners in a sequence involving both directed C–H activation as well as amide C–N cleavage and CO-extrusion. In one example 0.1 mol % of the dimeric precatalyst was utilized to form the arylated product in 98 % yield, corresponding to a TON of 490.



Scheme 31. Rh^I-catalyzed C–H arylation by amide decomposition.^[76]

7. Summary and Outlook

In this Minireview, the current state of the art in efficient, high TON C–H activation has been described. Early examples of high catalyst efficiency were observed primarily in simple ligand-free palladium-catalyzed transformations, such as the olefination of arenes or the direct arylation of heteroarenes as described by the groups of Fujiwara and Doucet, respectively. However, the TONs of later systems were heavily dependent on the inclusion of an appropriate ligand, as exemplified by Sanford/Fernández-Ibáñez and co-workers in the acetoxylation of arenes. Furthermore, the development of privileged ligand systems (Cp* or POCOP pincer ligands etc.) has enabled a range of other metals to participate in increasingly efficient transformations. Other than choice of ligand, a general understanding of what fundamentally improves the efficiency of a catalyst often remains elusive. It is hoped that this Minireview will aid the future identification of such catalyst performance indicators, such as thermal or oxidative stability or immunity to impurities, which may be incorporated into the design of superior systems.

Aside from advancing the efficiency of Csp²–H activation catalysis, the development of more efficient Csp³–H activation processes, of which this Minireview has only three examples, will undoubtedly become an area of high interest. Gaunt, Lapkin and co-workers have shown the power of flow chemistry to improve efficiency in this area. The combination of these flow techniques with a solid-supported catalyst, as used by Sawamura and co-workers, could prove highly efficient.

Overall, we hope that this Minireview will encourage scientists to look into catalyst efficiency, and thus to enable C–H activations to find further wide-spread industrial relevance.

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Conflict of interest

The authors declare no conflict of interest.

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