Invited paper

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The mechanism of palladium(II)-mediated C–H cleavage with mono-*N*-protected amino acid (MPAA) ligands: origins of rate acceleration

DOI 10.1515/pac-2015-0902

Abstract: It has long been known that transition metals are capable of interacting with, cleaving, and mediating the functionalization of activated and unactivated carbon–hydrogen (C–H) bonds. Broadly speaking, a basic underlying principle in the fields of inorganic and organometallic chemistry is that the primary and secondary coordination spheres around a metal affect its reactivity and selectivity in elementary reactions. Hence, ligand design in transition metal catalysis has been a captivating area of research for over half a century. The discovery and development of novel ligands to promote and control otherwise recalcitrant C–H functionalization reactions is now at the forefront of organic and organometallic chemistry. Central to this line of inquiry is the interplay between ligand, substrate, metal, and reaction mechanism. This Review highlights the mechanistic details of palladium(II)-mediated C–H cleavage with mono-*N*-protected amino acid (MPAA) ligands. Relevant historical background is discussed, the key discoveries in catalysis with MPAAs are examined, experimental and computational studies to elucidate reaction mechanisms are presented, and possible future directions are described.

Keywords: C–H bond reactivity; C–H functionalization; catalysis; concerted metalation/deprotonation (CMD); cross-coupling; cyclometalation; IUPAC-SOLVAY International Award for Young Chemists; ligand design; mono-*N*-protected amino acid (MPAA); organometallic chemistry; palladium.

Dedication: This article is written in memory of Kristína Csatayová.

Introduction

Carbon–hydrogen (C–H) bond functionalization has attracted a great deal of attention from the organometallic [1–4], organic [5–10], medicinal [11–14], and materials [15–19] chemistry communities during the past several decades. Many transition metal species are capable of performing inner-sphere C–H cleavage; among them, palladium(II) has proven to particularly versatile in enabling a range of different catalytic carbon–carbon (C–C) and carbon–heteroatom (C–Y, Y=N, O, S, F, Cl, Br, I, etc.) bond–forming reactions [20–31]. Several long-standing challenges have persisted in this field since its inception [32–34], including poor catalytic efficiency, limited substrate scope, and inability to control site- and stereoselectivity. These deficiencies point to the

Article note: A collection of peer-reviewed articles by the winners of the 2014 IUPAC-SOLVAY International Award for Young Chemists.

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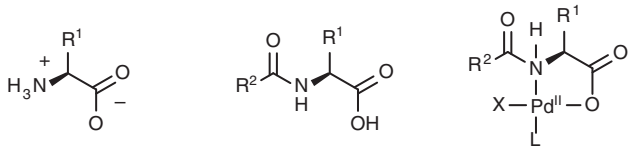


Fig. 1: General structures of an α-amino acid, a mono-*N*-protected amino acid (MPAA), and a representative [Pd(II)–MPAA] complex.

need for ancillary ligands to facilitate the palladium(II)-mediated C–H cleavage step during catalysis [35]. Among ligands that have been used for this purpose, mono-*N*-protected amino acids (MPAAs), introduced by the Yu laboratory in 2008, have proven to be particularly effective (Fig. 1).

This Review focuses on the mechanistic details of C–H cleavage at palladium(II) centers with bound MPAA ligands. First, relevant background is briefly summarized to provide the reader with a broader context for this topic. Second, the initial discoveries of MPAA ligands in Pd(II)-catalyzed stereoselective and non-stereoselective reactions are presented. Third, a comprehensive summary of recent literature reports addressing the mechanism of MPAA ligands in C–H cleavage is presented. Lastly, future directions in ligand design, reaction development, and catalysis are discussed.

Historical background

Cyclometalation reactions are organometallic transformations that serve as elementary steps in many catalytic, directed C–H functionalization reactions. These reactions are inner-sphere processes that can proceed by different mechanisms depending on the metal (and its oxidation state), the ancillary ligands, the organic substrate, and the reaction conditions; these mechanisms include electrophilic activation, σ-bond metathesis, concerted metalation/deprotonation (CMD) and oxidative addition [1–4, 36].

Originally pioneered by Kleiman and Dubeck in 1963 and Cope and Siekman in 1965 [37, 38], cyclometalation reactions involving both C(sp^2)–H and C(sp^3)–H cleavage have since been extensively studied [39–41]. One intriguing subclass of cyclometalation reactions consists of those that are stereocontrolled and generate

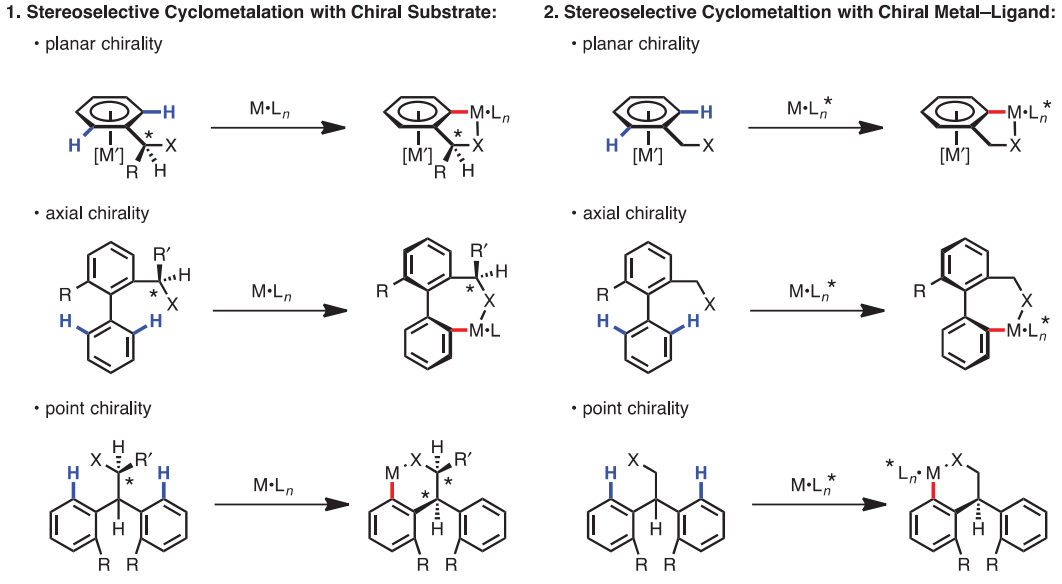


Fig. 2: Classes of stereoselective cyclometalation involving C(sp^2)–H cleavage. M, M′ = metal; L_n = ancillary ligands; R, R′ = substituents; X = coordinating atom. Analogous categories can be envisioned for C(sp)–H or C(sp^3)–H cleavage.

chiral, enantioenriched metalacycles (Fig. 2) [42, 43]. Approaches to achieve stereoinduction in stoichiometric cyclometalation include using (1) a chiral organic substrate that contains either a removable or permanent element of stereochemistry and (2) using an enantiopure, chiral [M–L_n^*] species.

Major advancements in both substrate and metal–ligand control were made by Sokolov and coworkers in the late 1970s and early 1980s [42, 44–48]. This work built upon earlier contributions of Shaw, who documented that stoichiometric quantities of inorganic acetate salts promoted otherwise problematic cyclometalation reactions [49–52]. Gaunt and Shaw took advantage of this finding to carry out a previously unsuccessful cyclopalladation of (dimethylamino)methylferrocene (**1**) (Fig. 3) [53, 54]. Shaw had previously observed a similar effect with acetate promoting cyclometalation with other metals [49]. Sokolov later postulated the involvement of what is now commonly referred to as a CMD mechanism (*vide infra*) involving a carboxylate ligand serving as internal base for abstracting an *ortho*-proton concomitant with Pd–C bond formation (Fig. 4) [47].

The Sokolov group's first foray into stereoinducing cyclometalation involved the use of enantiopure substrate (*R*)-**4**, a chiral analog of ferrocene **1** (Fig. 5). Under the conditions developed by Shaw [54], acetate-promoted cyclopalladation proceeded in 84 % yield and 85:15 d.r. Sokolov's report was a major advance at the time, demonstrating that stereochemical control is possible in cyclometalation reactions.

Given the hypothesis that a CMD mechanism was involved in the acetate-promoted cyclopalladation of **1** and (*R*)-**4**, Sokolov and Troitskaya next postulated the use of a prochiral substrate with a chiral internal base would provide an alternative approach to stereoinduction. Thus, a series of chiral carboxylates were examined in the cyclopalladation of **1** to provide modestly enantioenriched planar chiral products (Table 1)

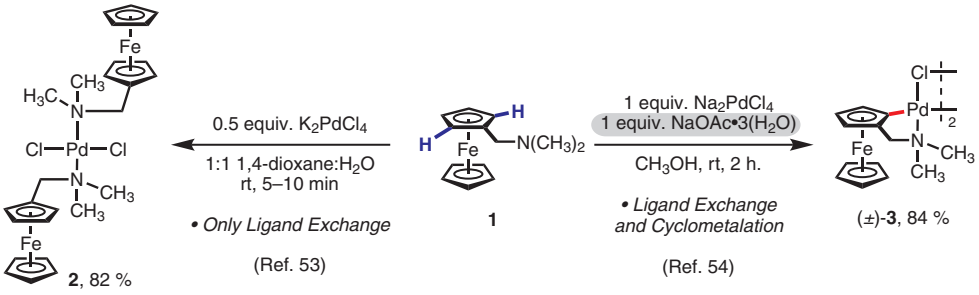


Fig. 3: The effect of acetate counterions in promoting cyclometalation of **1**.

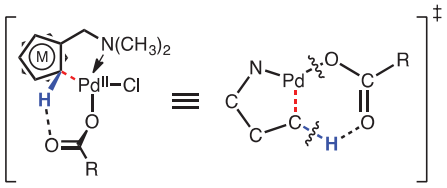


Fig. 4: Proposed mechanism for C–H cleavage (cyclometalation) promoted by acetate, as originally drawn by Sokolov [47]. Using modern nomenclature, this is now commonly referred to as "concerted metalation/deprotonation" (CMD). (Color added for emphasis.).

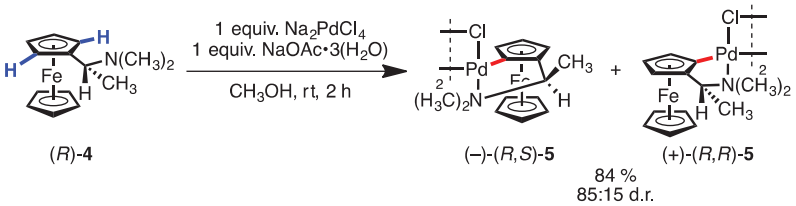
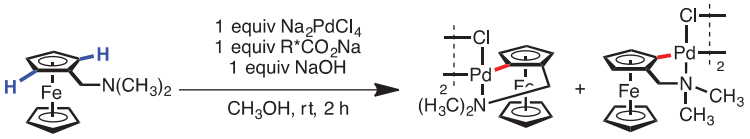
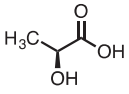
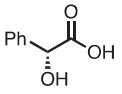
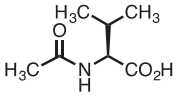
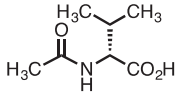
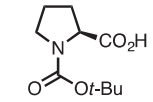


Fig. 5: Diastereoselective cyclopalladation of enantiopure (*R*)-**4** [44, 45].

Table 1: Early application of chiral carboxylates, including protected amino acids, in enantioselective cyclopalladation [46].



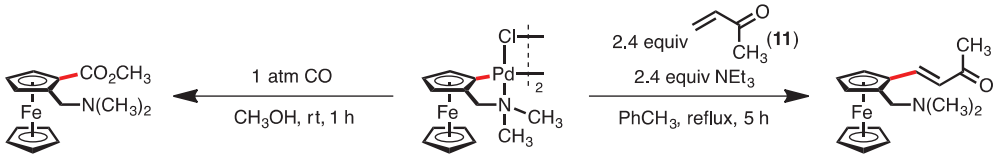
1 (*S*)-**2** (*R*)-**2**

Entry[a]	R*CO_2H	% ee (major enantiomer)[c]
1[b]	 (*S*)-**6**	2.3 (*S*)
2[b]	 (*R*)-**7**	5.8 (*R*)
3	 (Ac-Val-OH, (*S*)-**8**)	8.3 (*R*)
4	 (Ac-D-Val-OH, (*R*)-**8**)	7.5 (*S*)
5[b]	 (Boc-Pro-OH, (*S*)-**9**)	10.9 (*S*)

[a]Experimental procedure: a solution of equimolar NaOH, R*CO_2Na, and Na_2PdCl_4 was added to a solution of **1** in MeOH. After 2 h, **2** was filtered, washed with MeOH, and dried. [b]Average of two trials. [c]ee determined by optical rotation of the corresponding acac complex.

[46]. Of the chiral carboxylates tested, protected amino acids gave the highest ee values, though the overall effectiveness was limited. In particular, with the sodium carboxylate salts of Ac-Val-OH (**8**) and Boc-Pro-OH (**9**), modest ee values were obtained of optically enriched palladacycle **2**. This initial series of experiments led to a detailed investigation into the effect of pH on the yield and enantioselectivity using Ac-Val-OH ((*S*)-**8**) as the source of chirality (Table 2) [47]. Palladacycle **2**, enriched in the *R* enantiomer was obtained in up to 79 % ee when the reaction was carried out at an optimal pH of 7.95. It was also established that the new Pd(II)–C bond could subsequently be coupled with electron-poor olefins or CO (Fig. 6) [55, 56].

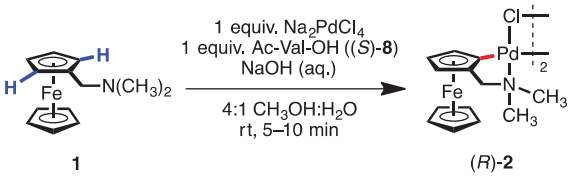
These cases represented the first reports of enantioselective cyclometallation (i.e., enantioselective C–H cleavage) [57, 58]. As discussed above, in the initially proposed model, Sokolov hypothesized that the amino acids serve as simple chiral carboxylates, with the carbonyl group functioning as an internal base and the α-carbon stereocenter acting as the source of chiral information during the CMD process (Fig. 4). Sokolov's



(*R*)-**10**, 70 % (*R*)-**2** (*R*)-**12**, 80 %

Fig. 6: Stoichiometric reactivity of (*R*)-**2** [55].

Table 2: Early application of Ac-Val-OH (**5**) in enantioselective cyclopalladation [47].



1 (*R*)-**2**

Entry[a]	pH[b]	pH[c]	Yield (%)[d]	ee (%)[e]
1	5.48	6.28	46	8.0
2	6.00	7.35	73	24.5
3	6.45	7.90	83	40.5
4	6.70	8.75	89	65.0
5	7.60	9.30	85	73.0
6	7.95	9.82	50	78.8
7	8.50	10.30	37	56.0

[a]Experimental procedure: an aqueous solution of equimolar NaOH and Ac-Val-OH was added to a solution of Na_2PdCl_4 in MeOH. The pH was adjusted to appropriate value *via* addition of 50 % NaOH (aq.); a solution of **1** in MeOH was then added, and after 5–10 min, **2** precipitated. [b]pH measured before addition of **1** solution. [c]pH measured after addition of **1** solution. [d]Isolated yield. [e]ee determined by optical rotation of the isolated complex.

notion of using chiral carboxylates in this way was invaluable in triggering these early exploratory studies in enantioselective C–H cleavage. Indeed, this chiral carboxylate idea was revisited again three decades later in the development of *catalytic* transformations. While the exact mechanism in Sokolov's reaction and the relationship between this stoichiometric system and the catalytic examples discussed in the next section remain the topic of ongoing study, the most recent data from the literature suggests that in addition to the carboxylate–palladium bond, an interaction between the metal and a second coordinating atom, namely a mono-protected amine, is vital for reactivity and selectivity in most (if not all) cases.

Beginning with work from Yu laboratory in 2008, the realization that amino acids function through coordination of both the carboxylate and the amine ushered in array of new applications and mechanistic insights, culminating in the development of mono-*N*-protected amino acids (MPAAs) as general ligand scaffold in palladium(II)-catalyzed C–H functionalization (*vide infra*).

Discovery and development of MPAA ligands in palladium(II)-catalyzed C–H functionalization

The stoichiometric organometallic reactions that were discovered and studied from the 1960s to 1980s provided a firm intellectual foundation for contemporaneous and future findings in catalytic C–H functionalization. Pd(II)-catalyzed C–H functionalization reactions, in particular, have been actively investigated since the pioneering work on Pd(II)-catalyzed C(sp^2)–H olefination of simple arenes by Fujiwara and Moritani in the late 1960s [32–34]. Key contributions in this area of research have been the development of different catalytic manifolds (including most notably Pd(II)/Pd(0) and Pd(II)/Pd(IV) catalysis (Fig. 7)), the diversification of coupling partners for new modes of bond construction, the expansion of reactivity to new substrates classes (particularly electron-rich heterocycles and compounds containing Lewis basic directing groups), and strategic applications of new reactions in the synthesis of complex targets. Much of this chemistry has been thoroughly reviewed elsewhere [20–34, 36]. More recently, the identification of ancillary ligands to control the activation energy of the C–H cleavage step to achieve stereoinduction, site selectivity, and ligand-accelerated catalysis has been at the forefront of research in Pd(II)-catalyzed C–H functionalization [35]. This section highlights key discoveries regarding the efficacy of MPAA ligands in these different contexts.

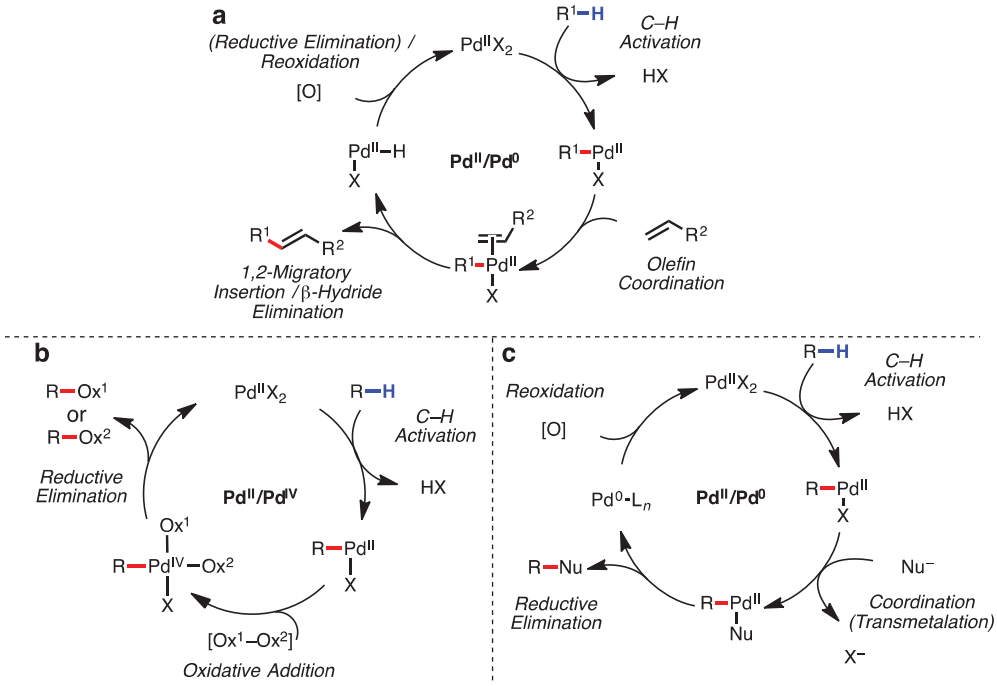


Fig. 7: General depiction of different catalytic cycles that are prevalent in Pd(II)-catalyzed C–H functionalization: (a) olefination via a Pd(II)/Pd(0) manifold, (b) oxidation via a Pd(II)/Pd(IV) manifold, or (c) oxidative coupling with a nucleophile via a Pd(II)/Pd(0) manifold.

Since 2005, the Yu group has sought to understand and exploit stereochemical control in inner-sphere Pd(II)-mediated C–H cleavage [43]. At the outset, this line of inquiry was motivated not only by a desire to improve the mechanistic understanding of C–H cleavage at palladium(II) centers but also by an interest in developing novel catalytic, stereoselective C–H functionalization reactions for use in organic synthesis. The first successful demonstration of Pd(II)-catalyzed diastereoselective C–H functionalization by the Yu group employed a removable, chiral oxazoline directing group (**13**, Fig. 8) [59–62]. Using this approach, reactions were found to take place at room temperature and provide high levels of stereoinduction (>99:1 d.r. in some cases). Diastereoselective C–H iodination and acetoxylation along a Pd(II)/Pd(IV) catalytic cycle could thus be achieved with various oxazoline substrates containing α,α-*gem*-dimethyl groups (**13** → **14**), α,α-*gem*-diphenyl groups, or cyclopropanes.

In parallel to the oxazoline work, the Yu group questioned whether similarly high levels of stereoinduction could be achieved with a substrate that did not contain preexisting chirality using a chiral [M–L$_n^*$] species (see Fig. 2) [63, 64]. Having first validated catalytic, non-stereoselective pyridine-directed C(sp^2)–H/R–B(OH)$_2$ cross-coupling with substrate **15** containing prochiral α,α-*gem*-diphenyl substituents (Fig. 9), the next task was to identify an appropriate chiral ligand. In particular, the ligand would need to bind to create a steric and electronic environment at the metal center that was compatible with C–H cleavage and effective in inducing enantiocontrol to favor C–H cleavage at one of the two possible *ortho*-C(aryl)–H bonds. Hypothesizing the involvement of a CMD mechanism with acetate serving as an inner-sphere base, the Yu group reasoned

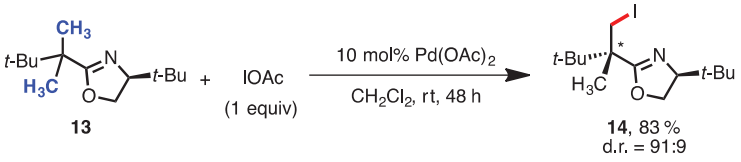


Fig. 8: Pd(II)-catalyzed diastereoselective C(sp^3)–H iodination using a removable chiral oxazoline auxiliary [59, 60].

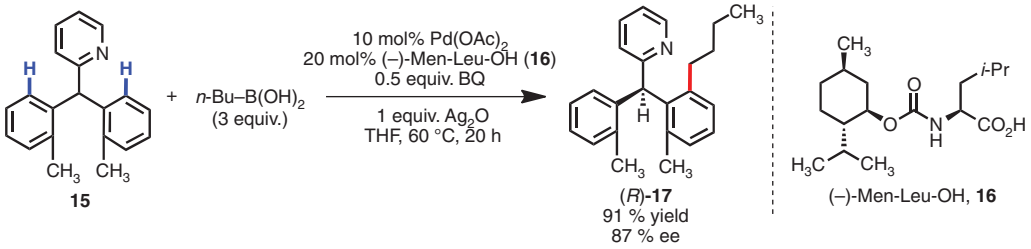


Fig. 9: Pd(II)-catalyzed enantioselective C(sp^2)–H/R–B(OH)$_2$ cross-coupling promoted by MPAA ligand (–)-Men-Leu-OH (**16**) [63, 64].

that chiral carboxylates could influence the activation energy of the two otherwise degenerate C–H cleavage events to favor formation of one of the two enantiomeric products [35]. After surveying a range of commercially available chiral carboxylates, mono-*N*-protected amino acids (MPAAs) were identified as effective ligands for this asymmetric transformation [35, 63]. Importantly, mono-*N*-protection was critical for the performance of the ligands. Unprotected amino acids completely suppressed catalysis, while di-*N*-protection resulted in <10 % ee. These results strongly implicated an important role of the nitrogen atom (and the N–H bond) in the catalytic cycle, likely through coordination to palladium(II). By carefully tuning the amino acid backbone and the *N*-protecting group, (–)-Men-Leu-OH (**16**) was identified as the optimal ligand, providing good yield and high enantiomeric excess of the product, (*R*)-**17**.

Importantly, in the same manuscript, the Yu group reported preliminary results in which enantioselective C(sp^3)–H/R–B(OH)$_2$ cross-coupling of substrate **18** containing enantiotopic *gem*-dimethyl groups (**18** → **20**) took place in the presence of cyclopropyl MPAA ligand **19** (Fig. 10) [63]. In this case, it is believed that the lower yield and enantioselectivity and the need for higher reaction temperature (100 °C) is due to the increased activation energy for the C(sp^3)–H cleavage step compared to the C(sp^2)–H case in Fig. 9. The need for more rigid ligand **19** is believed to be due to the greater conformational flexibility of the starting material **18** (compared to **15**). Though the reported yield and ee were low, this results provided important evidence that stereoinducation in both C(sp^2)–H and C(sp^3)–H cleavage could be achieved using the MPAA ligand scaffold.

Since this seminal report, MPAA ligands have been applied to achieve stereoinduction with a variety of different substrates in Pd(II)-catalyzed C–H functionalization (Fig. 11) [63–77]. In addition to C–H/R–BX$_n$ cross-coupling, these enantioselective transformations have included olefination, oxygenation, iodination, and arylation with aryl iodides.

The discovery that MPAA ligands promoted high levels of stereoinduction suggested that the MPAA ligand was bound to the palladium(II) center and was intimately involved during C–H cleavage. It was thus reasoned that MPAA ligands could be used to affect the activation energy of other non-stereoselective reactions involving C–H cleavage. To this end, the Yu group found that MPAA ligands could be used to control site selectivity of an otherwise unselective C(aryl)–H olefination of phenylacetic acid substrate **21** (Fig. 12) [78]. In particular, use of For-Ile-OH (**22**) as the ligand gave a 20:1 ratio of **23-A** to **23-B**, favoring olefination at the C–H bond adjacent to the methoxy group.

Furthermore, based on this line of thinking, the Yu laboratory reasoned that MPAA ligands could potentially accelerate C–H functionalization with otherwise poorly reactive substrates [78–80]. Indeed,

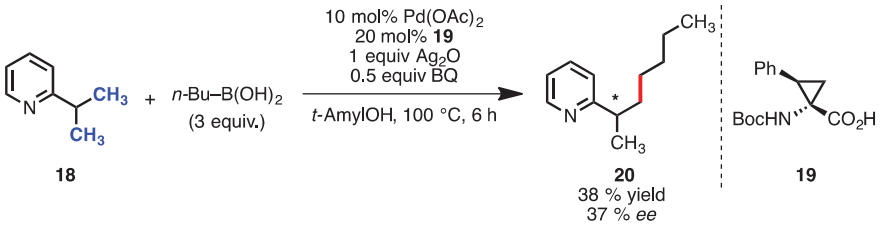


Fig. 10: Pd(II)-catalyzed enantioselective C(sp^2)–H/R–B(OH)$_2$ cross-coupling promoted by MPAA ligand (–)-Men-Leu-OH (**16**) [63].

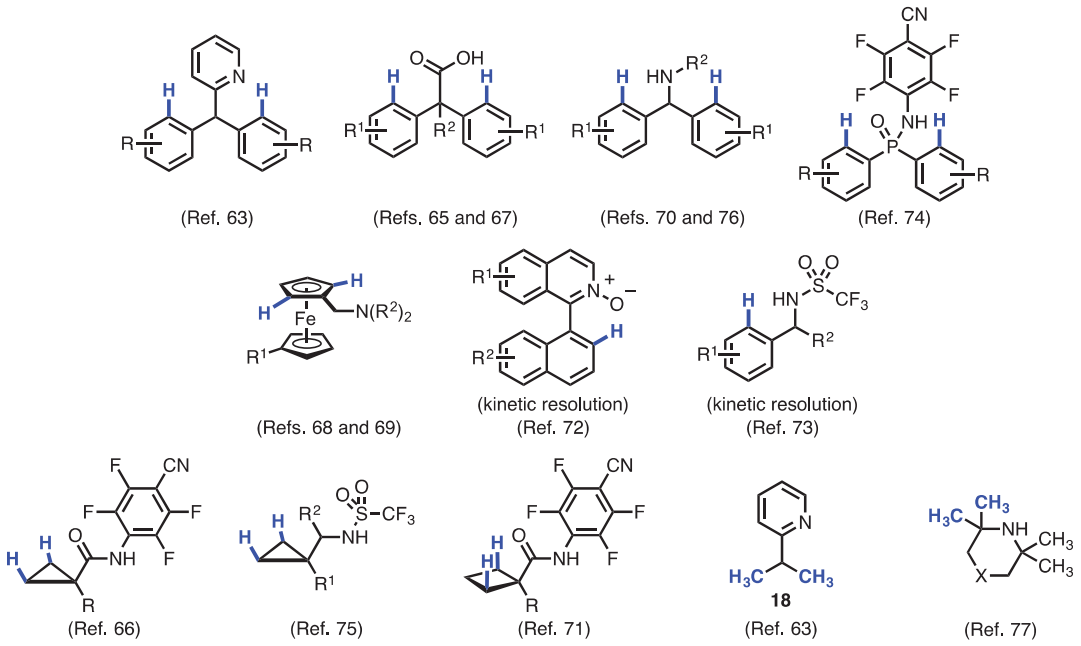
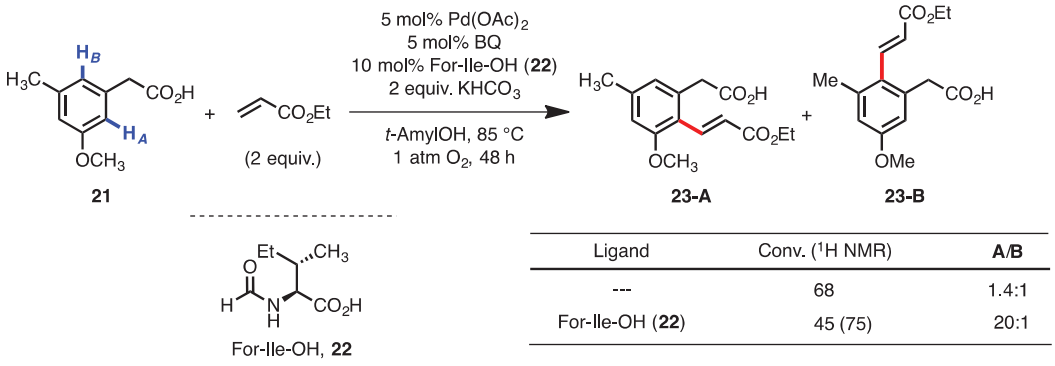


Fig. 11: Substrate classes for which enantioselective Pd(II)-catalyzed C–H functionalization has been reported using MPAA ligands [63–77].



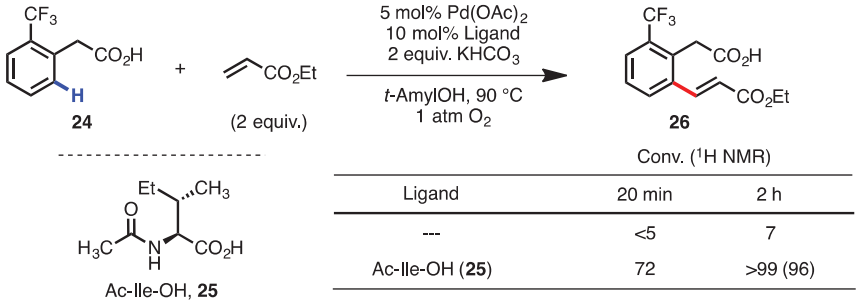
Ligand	Conv. (^{1}H NMR)	A/B
---	68	1.4:1
For-Ile-OH (**22**)	45 (75)	20:1

Fig. 12: Pd(II)-catalyzed site-selective C(sp^2)–H olefination promoted by MPAA ligand For-Ile-OH (**22**) [78]. The value in parentheses corresponds to a reaction performed using 7 mol % $Pd(OAc)_2$ and 14 mol % For-Ile-OH (**22**) under otherwise identical conditions.

this turned out to be the case, and in the first proof-of-concept experiments, phenylacetic acid substrates with electron-poor aromatic rings, such as **24**, were found to give drastically faster reaction rates and higher overall yields in *ortho*-C–H olefination using MPAA ligands (Fig. 13) [78–82]. Systematic modification of the amino acid backbone and the *N*-protecting group led to the identification of Ac-Ile-OH (**25**) as optimal in terms of initial rate and final yield, providing product **26** in nearly quantitative yield. With MPAA ligand Ac-Ile-OH (**25**), reduced reaction time, temperature, and $Pd(OAc)_2$ catalyst loading (as low as 0.2 mol %) could be employed [80–82].

The mechanism of this reaction system has been extensively studied [80, 81], and the finding from these mechanistic experiments have helped elucidate the role the MPAA ligand plays in the C–H cleavage step, as discussed in more detail below. Moreover, this Pd(II)/MPAA-catalyzed C–H olefination reaction has been applied in the synthesis of several natural products and analogs (Fig. 14) [83–86].

During the past 5 years since this initial series of reports involving phenylacetic acid substrates, MPAA ligands have been applied to achieve enhanced reactivity and/or selectivity in Pd(II)-catalyzed C–H



Ligand	Conv. (^{1}H NMR) 20 min	2 h
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Ac-Ile-OH (**25**)	72	>99 (96)

Fig. 13: Pd(II)-catalyzed MPAA-accelerated C(sp^2)–H olefination with Ac-Ile-OH (**25**) [34, 79]. The values in the table correspond to averages of three independent experiments, except in the case of the data point with Ac-Ile-OH (**25**) at 2 h, which corresponds to the result from a single trial. Isolated yield is shown in parentheses.

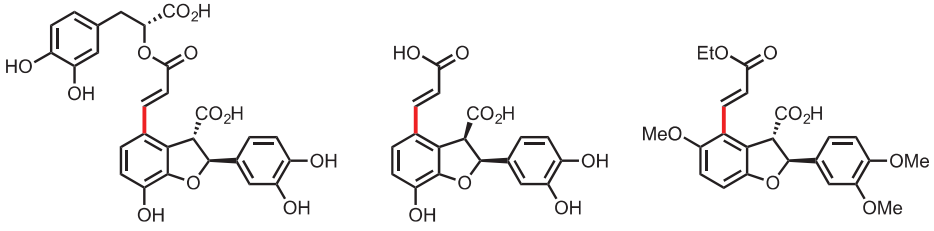


Fig. 14: Natural products and analogs synthesized using Pd(II)/MPAA-catalyzed C(sp^2)–H olefination [83–86]. The C–C bonds formed through C–H olefination are drawn in red.

functionalization with many different substrate classes (Fig. 15) [78–113]. A diverse array of coupling partners have proven to be compatible with MPAA ligands, enabling many new C–C and C–Y bond-forming reactions via Pd(II)/Pd(0) and Pd(II)/Pd(IV) catalysis.

The last line of inquiry that will be highlighted in this section is the use of MPAA ligands to enable *meta*-selective C(aryl)–H functionalization of substrates such as **30** that contain an end-on nitrile template (Fig. 16) [114–125]. The first report from the Yu laboratory described *meta*-C–H olefination of substituted toluene derivatives and hydrocinnamic acids [114]. For each class of substrates, a unique nitrile-containing template was developed to coordinate to palladium(II) and position it above the *meta*-C–H bond. In the case of hydrocinnamic acid amides, the use of Ac-Gly-OH (**31**) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent was a key for achieving high *meta* selectivity and synthetically useful yields.

Since the Yu group's first report, the use of end-on templates to achieve *meta* selectivity in Pd(II)-catalyzed C(aryl)–H functionalization has quickly become an active research area, now covering many different substrate classes (Fig. 17) [114–125]. MPAA ligands have proven to be critical for reactivity and selectivity in these systems. The combination of Ac-Gly-OH (**31**) and HFIP, in particular, has proven to be widely applicable across many examples. In contrast to classical cyclometalation, these reactions are presumed to proceed via a macrocyclic, cyclophane-like palladacycle. The transition state en route to this arylpalladium(II) species is conformationally flexible, which makes C–H cleavage entropically unfavorable. Hence, in these *meta*-selective C–H functionalization reactions, MPAA ligands play a critical role by lowering the activation energy of C–H cleavage, which would otherwise be prohibitively high.

This diverse collection of examples in which MPAA ligands [63–130] have been used points to a fundamental role of MPAAs during the C–H cleavage step of the catalytic cycle. During the past several years, different mechanistic models have been proposed on the basis of reactivity data, stereochemical outcomes,

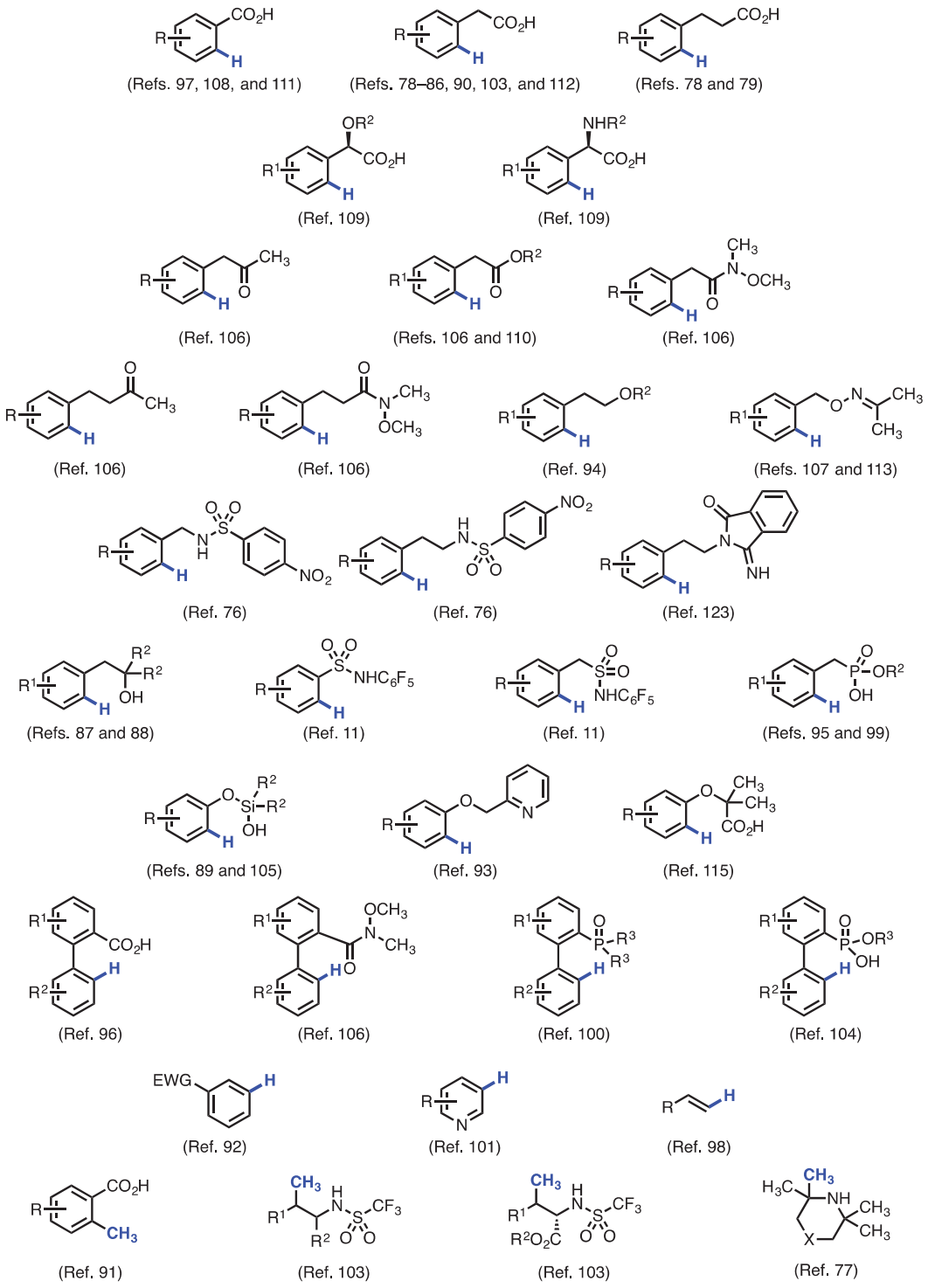


Fig. 15: Substrate classes for which MPAA ligands have been used to promote reactivity and/or site-selectivity in non-stereoselective Pd(II)-catalyzed C–H functionalization [78–113].

physical organic studies, computation, NMR spectroscopy, and mass spectrometry. The ensuing section discusses these different mechanistic models in light of historical precedents in the Pd(II)-mediated C–H functionalization literature and summarizes the current understanding of the topic.

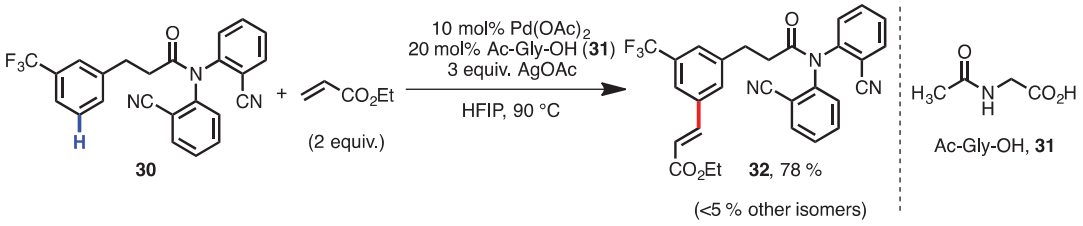


Fig. 16: Pd(II)-catalyzed *meta*-selective C(aryl)–H olefination using a removable end-on nitrile template [114].

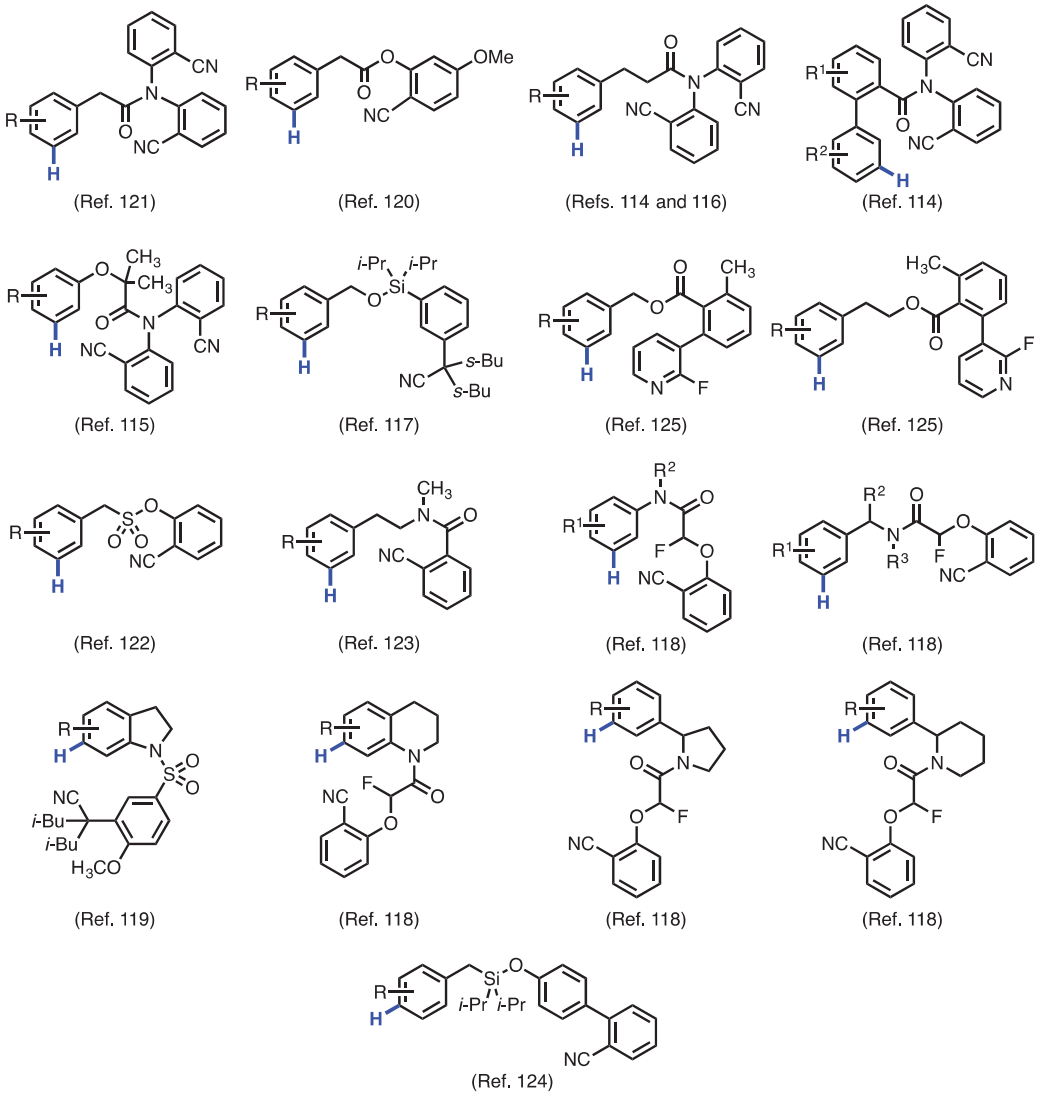


Fig. 17: Substrate classes for which MPAA ligands have been used to promote *meta*-selective Pd(II)-catalyzed C(sp^2)–H functionalization in conjunction with an end-on template [114–125].

Mechanistic models for C–H cleavage at palladium(II) centers with bound MPAA ligands

During the past several decades, many mechanistic proposals for C(sp^2)–H cleavage at Pd(II) centers have been put forward, with the operative mechanism being highly system-dependent. These mechanisms roughly

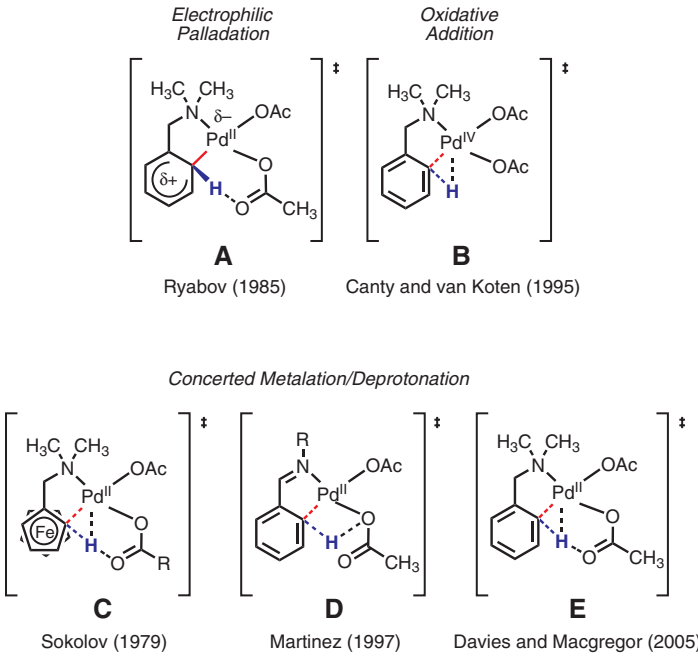


Fig. 18: Mechanistic models for C(sp²)–H cleavage, represented in the form of plausible transition state structures [47, 80, 133–146].

fall into three general categories: electrophilic palladation (**A**) [131], oxidative addition (**B**) [132], and concerted metalation/deprotonation (CMD) (**B**) (Fig. 18) [47, 80, 133–145]. While these are often viewed distinct entities, it is likely that these categories are in fact more accurately described as apexes on a continuum of possible mechanisms, depending on how early or late the transition states are with respect to C–H bond breaking and Pd–C bond making [35].

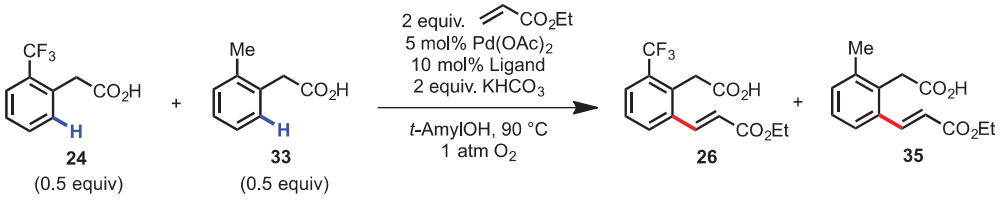
Much of the discussion in the literature surrounding the mechanism of C(sp²)–H cleavage at palladium(II) centers has focused on systems containing directing groups. This is due to the fact that the products are often stable, isolable metalacycles, making these systems easier to study using reaction kinetics, spectroscopy and other techniques. In the case of C(sp³)–H bonds, oxidative addition and CMD mechanisms analogous to those proposed for C(sp²)–H cleavage can be envisioned. On the other hand, there is no clear analogy in the case of electrophilic palladation due to the absence of a π-bonding orbital to coordinate palladium(II).

Electrophilic palladation (**A**) was described by Ryabov and coworkers in 1985 based on a physical organic study of a model cyclopalladation reaction of *N*,*N*-dimethylbenzylamine [131]. Ryabov's study revealed that the rate-limiting step was electrophilic in character. Based on this result and the observation of a small kinetic isotope effect (KIE, $k_H/k_D = 2.2$), the system was proposed to proceed via an early transition state in which partial positive charge build up on the arene occurs concomitant with coordination of palladium(II) to the π-bonding orbital of the *ipso*-carbon atom. The intermediate can be viewed as a Wheland-type arenium species, from which deprotonation to internally bound acetate leads to rearomatization. Oxidative addition (**B**) was proposed in a review article in 1995 by Canty and van Koten based on the many examples of stable palladium(IV)–aryl and –alkyl complexes in the literature as well as reports implicating the possible intermediacy of a [Pd(IV)–H] species supported by a tris(pyrazol-1-yl)borate ligand [132]. In an oxidative addition mechanism, the transiently formed [Pd(IV)–H] would undergo rapid reductive elimination with bound acetate to give the palladacycle intermediate. Lastly, concerted metalation/deprotonation (CMD) (**C**) with palladium(II) was first put forward by Sokolov in 1979 (*vide supra*) [47]. The characteristic feature of this mechanism is minimal charge build-up during the transition state. Since that time, carboxylate-mediated CMD has been revisited and studied using physical organic and computational techniques [133–137], notably by the groups of Martinez in 1997 [133] and by Davies and Macgregor in 2005 [136]. It should be noted that in the latter paper, the authors computed that formation of the intramolecular [C–H···Pd(II)] agostic interaction is electrophilic in character and is predicted to be rate-limiting. Subsequent deprotonation by bound acetate,

which must take place in order for the reaction to be productive, was computed to have almost no energy barrier. Overall, the preponderance of evidence in the literature to date suggests that oxidative addition is not a commonly encountered mechanism for C–H cleavage at a palladium(II) center. Thus, the remaining discussion will focus on the other two types of mechanism [146].

Qualitatively speaking, reactions that proceed by electrophilic palladation would be expected to be accelerated by electron-donating substituents on the aromatic ring, whereas reactions involving CMD would be expected to be minimally affected by the electronic properties of the arene or accelerated by electron-withdrawing substituents. Dating back to the early work of Fujiwara and Moritani [32–34], reactivity trends consistent with electrophilic palladation have been commonly observed when simple palladium salts (e.g., $Pd(OAc)_2$) are used as catalysts.

Based on the high levels of stereoinduction observed in stoichiometric cyclopalladation and catalytic C–H functionalization, it was evident that MPAA ligands were bound to the palladium(II) center during the C–H cleavage process. From these results alone, however, the precise mechanism by which the MPAA ligand was involved remained unclear. During the course of the aforementioned investigation on MPAA-accelerated C–H functionalization of phenylacetic acids (Fig. 13) [78–82, 90], the Yu laboratory made a series of observations suggesting that the MPAA ligands were altering the mechanism of C–H cleavage. In the absence of MPAA ligands, electron-rich arylacetic acids reacted with higher rates and gave greater overall yields than those bearing electron-withdrawing substituents in both C–H olefination and C–H/R–BX_n cross-coupling, reactivity trends consistent with electrophilic palladation [78–82, 90, 147]. In contrast, when MPAA ligands were added, the reactivity pattern inverted, such that electron-deficient substrates were preferentially reactive, consistent with a CMD mechanism (Fig. 19). In an extreme case, 2-nitrophenylacetic acid was completely unreactive in the absence of ligand but provided 70 % yield after 2 h in the presence of Ac-Ile-OH (**25**) [80]. In the same study, it was found that in the absence of MPAA ligand, a large primary KIE ($k_H/k_D = 6.1$) was observed. In the presence of MPAA ligands, the KIE became smaller, with faster ligands leading to lower values, for example Ac-Ile-OH (**25**) gave the smallest KIE of ligands that were studied ($k_H/k_D = 1.7$). The variation of the KIE as a function of MPAA ligand structure was suggestive of a switch in mechanism in the presence of MPAA ligands.



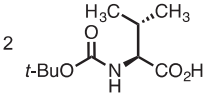
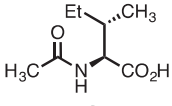
Entry	Ligand	Time (min)	% Conv. **26**	% Conv. **34**	k_1/k_2
1	—	120	3	14	0.22
2	 Boc-Val-OH, **34**	10	18	30	0.58
3	 Ac-Ile-OH, **25**	10	40	21	1.87

Fig. 19: Single-pot competition experiment data suggest a change in mechanism. The conversion was determined by ^{1}H NMR analysis. The data from the corresponding single-component reactions showed the same trend [80].

With mounting evidence, for a CMD-type mechanism in the presence of MPAA ligands, at this stage, general depictions of different possible CMD mechanisms (**F**–**I**) were proposed by the Yu group (Fig. 20) [80, 90, 146].

The ambiguity surrounding the mechanism of C–H cleavage at palladium(II) centers with MPAA ligands stems in large part from uncertainty regarding the coordination mode of these ligands under the reaction conditions. In particular, due to the fact that both the amide and carboxylate functional groups have relatively weak coordination strength (compared, for example, to a phosphine ligand), many different coordination modes can be envisioned (Fig. 21).

The research groups of Beck and Navarro shed light on the coordination chemistry of palladium(II) with MPAAs through structural studies (Fig. 22) [148, 149]. The authors reacted pre-formed palladacycles with unprotected and mono-*N*-protected amino acids and observed bidentate coordination, with the amino group occupying the site *trans* to the directing group. Furthermore, it was found that in these complexes the carboxylate was coordinated as an anionic donor and that the N–H bond of the amino moiety remained intact, even in the case of an electron-withdrawing acetyl protecting group (i.e., R^2 = Ac), making the amide a neutral donor (overall, a LX-type ligand). While these results are important for establishing the stability and isolability of palladacycle–MPAA complexes, the question of whether or not the observed LX coordination mode is relevant in catalysis remained unclear given the potential for both groups to undergo protonation/deprotonation or dissociation under catalytic C–H functionalization conditions.

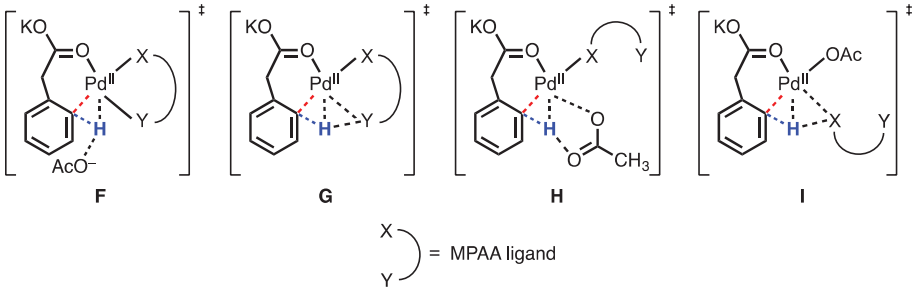


Fig. 20: General depiction of possible base-assisted CMD-type mechanisms involving bound MPAA ligands, where X and Y represent the carboxylate and amide/carbamate groups [80, 90, 146].

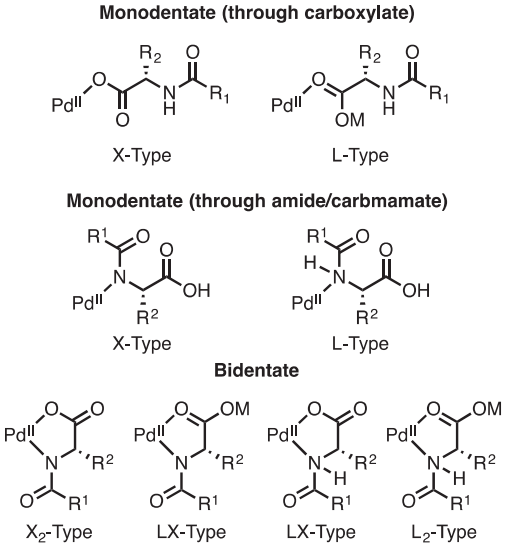


Fig. 21: Possible binding modes of MPAA ligands to palladium(II). The substrate is not drawn for simplicity; in principle, the directing group could be coordinated *cis* to the carboxylate or to the amide with the C(sp^2)–H bond coordinated to the final vacant site of the square planar palladium(II) center.

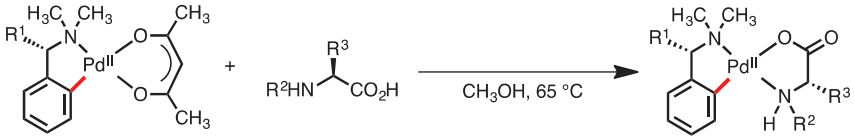


Fig. 22: Ligand exchange between acetylacetonate (acac) and amino acids on benzylamine-derived palladacycles [148].

Since Sokolov's initial reports using MPAAs to promote stereocontrol in cyclometalation, the mechanism of C–H cleavage at palladium(II) centers with bound MPAAs has been the topic of discussion in the literature (Fig. 23). As discussed previously, Sokolov proposed a mechanism analogous to acetate-assisted CMD (**J**), wherein the carboxylate group of the MPAA initially coordinates in a κ^2 fashion, and the carboxylate carbonyl then partially dissociates and serves as internal base to deprotonate the *ortho*-C–H bond. Asymmetric induction comes through remote conformational biasing via the stereocenter at the α position of the MPAA. In recent years, Richards has extended this proposal through additional work [57, 58, 150]. With this model, however, it is difficult to rationalize how MPAA ligands would promote reactivity in ligand-accelerated, non-stereoselective reactions (particularly with electron-poor substrates that are unreactive with $Pd(OAc)_2$), especially given the pronounced effects that the electronic properties of the *N*-protecting group have on reactivity.

In Yu's pioneering early work on Pd(II)-catalyzed stereoselective C(sp^2)–H and C(sp^3)–H functionalization, a different model was proposed (**K**) [63, 65], inspired by the ligand exchange results of Beck and Navarro and based on the Yu group's own NMR experiments. In particular, it was envisioned that the MPAA ligand coordinates in an LX bidentate fashion, with an acetate ligand positioned adjacent to the directing group. Presumably, the next steps involve dissociation of acetate to give a cationic complex, followed by formation of an *ortho*-C–H agostic interaction, and deprotonation by external acetate. Yu proposed that the stereochemical information at the α position is "geared" through space, by way of the intervening chiral protonated N atom, to the *N*-protecting group, and thus to the site of the reaction. One issue with model **K** is that one would expect the N–H bond (particularly when bound to palladium(II)) to be more acidic than the *ortho*-C–H bond, so it is difficult to rationalize why deprotonation by external acetate would take place at the C–H bond.

Based on subsequent computational and experimental work on the system shown in Fig. 9 [64], Yu and Musaev proposed model **L**. In this model, following substrate binding to the [Pd(II)(MPAA)(OAc)] complex, the lowest energy pathway involves N–H deprotonation/activation as the first step, which renders the MPAA a bidentate X_2-type ligand. The resulting palladium(II) center is comparatively electron-rich and nucleophilic. Thus, formation of the *ortho*-C–H agostic interaction, followed by deprotonation by exogenous acetate forms an anionic palladacycle–MPAA complex. Lastly, protonation takes place to give

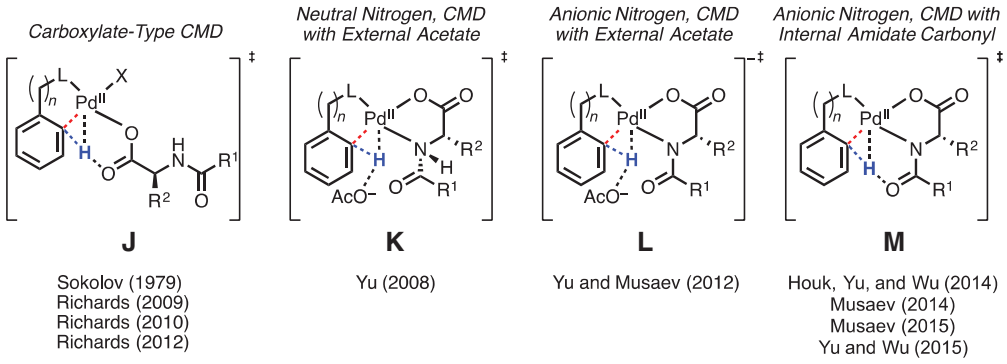


Fig. 23: General depiction of possible base-assisted CMD-type mechanisms involving bound MPAA ligands [57, 58, 80, 90, 146, 150–154].

isolable complexes of the type shown in Fig. 22, containing an intact N–H bond. If model **L** were correct, it would stand to reason that increasing the electron-withdrawing character of the *N*-protecting group would increase the rate of N–H activation and downstream C–H cleavage. However, it was previously observed that replacement the acetyl group of the MPAA ligand with a trifluoroacetyl group completely suppresses the reaction shown in Fig. 13 [80].

In more recent collaborative work between the laboratories of Houk, Yu, and Wu investigating remote, nitrile-directed C–H functionalization, results from mass spectrometry (MS) and density functional theory (DFT) were consistent with mechanism **M**. In this model, N–H activation takes place and subsequently the carbonyl group of the resulting amidate group, rather than external acetate, serves as the internal base for proton abstraction in an overall ligand-assisted CMD process [151]. In mechanism **M**, C–H cleavage with the [Pd(II)–MPAA] is promoted by several factors: (1) the greater basicity of the carbonyl group of the amidate compared to acetate, (2) a less sterically hindered environment for coordination of the directing group due to the smaller bite angle of the MPAA ligand compared to two acetate ligands, and (3) the favorable coplanar orientation of the *N*-acyl carbonyl group and the C–H bond stemming from the planar geometry of the X_2-type MPAA ligand and the square planar palladium(II) center. These authors also highlighted the important role that the MPAA ligand plays in stabilizing the active monomeric palladium species in solution. Model **M** was supported by additional computational and experimental data from Musaev [152, 153] and Yu and Wu [154]. Moreover, model **M** is consistent with the significant impact of the electronic properties of the *N*-protecting group on reactivity. In particular, the nature of the protecting group affects both the N–H acidity and the resulting amidate's C=O Brønsted basicity, creating a delicate interplay. Thus in the example discussed in the preceding paragraph, presumably the trifluoromethyl amidate is insufficiently basic to abstract the *ortho*-C–H bond. Figure 24 depicts a representative reaction pathway for enantioselective C–H cleavage (specifically, the example shown in Fig. 9) via mechanism **M**.

During the past few years, a combination of stereochemical information, kinetic investigations, computation, solid-state characterization, NMR spectroscopy, and mass spectrometry, has helped to elucidate a mechanistic framework to explain the role of MPAA ligands in C–H cleavage at palladium(II) centers. Among the four leading mechanistic proposals **J**–**M** that have been put forward, model **M** appears to be most consistent with all of the reactivity and selectivity data reported to date. That said, it is entirely possible that the operative mechanisms could be a function of substrate, conditions, MPAA ligand, or unappreciated nuances of C–H cleavage with MPAA ligands that have yet to be uncovered.

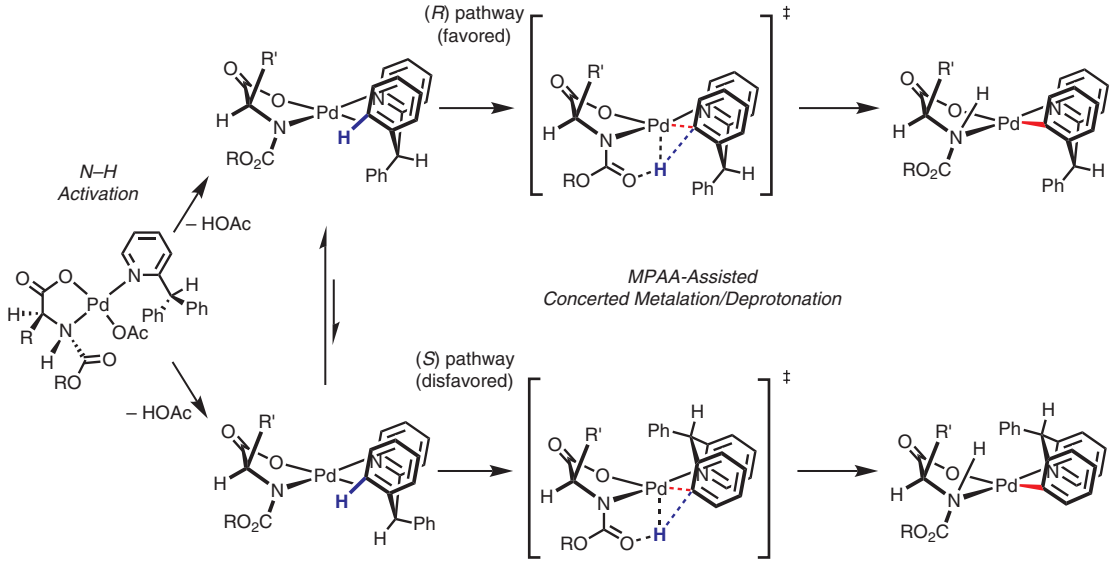


Fig. 24: Stereomodel for the reaction in Fig. 9, involving mechanistic model **M** for the C–H cleavage step, as supported by computational evidence [152, 153].

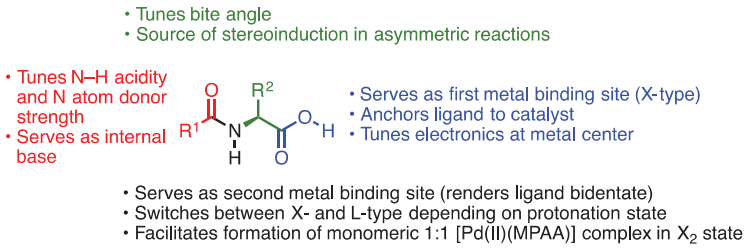


Fig. 25: Structure–activity relationships of MPAA ligands.

Outlook and perspective

MPAA ligands have been essential in the development of a large and growing number of novel palladium(II)-catalyzed C–H functionalization reactions during the past few years. Applications include enantioselective functionalization of prochiral C–H bonds, ligand-accelerated reactions with otherwise problematic substrates, and site-selective C–H cleavage in systems containing several potentially reactive C–H bonds. Many complementary factors engender MPAA ligands with the capacity to facilitate C–H cleavage (Fig. 25): (1) the nitrogen and oxygen atoms are of appropriate donor strength to still allow substrate binding while maintaining an electrophilic palladium(II) center, (2) the MPAA ligand favors formation of the monomeric, 1:1 [Pd(MPAA)] complex where the ligand is dianionic (X_2-type), (3) the N–H bond is sufficiently acidic to be deprotonated, allowing the nitrogen atom to toggle between an L- and X-type donor, (4) the carbonyl of the amidate formed upon N–H activation lies in the appropriate geometric orientation and is sufficiently basic to deprotonate the adjacent C–H bond.

It is anticipated that MPAA ligands will continue to find widespread use in enabling novel reactivity and selectivity in palladium(II)-catalyzed C–H functionalization in the coming years. At the same time, many long-standing problems persist in this area. These include stereoselective and ligand-accelerated C(sp^3)–H cleavage [63, 66, 71, 75, 77, 155] (particularly of less reactive methylene and methine positions), higher turnover numbers (i.e., TON > 1000) for large-scale industrial applications, more efficient reoxidation with environmentally friendly terminal oxidants (e.g., air), and improved control of site-selectivity in the absence of a classical *ortho* directing group.

To this end, improved knowledge of the mechanism by which MPAA ligands function provides the opportunity to rationally tune the MPAA scaffold and design entirely new ligand architectures for improved function. As a representative example, replacement of the carboxylate group with an *N*-methoxy amide was found to enable moderate yield and high enantioselectivity in the asymmetric C(sp^3)–H/R–BX_n cross coupling of cyclobutanes, whereas the parent MPAA containing a carboxylate offered low yield and poor enantioselectivity [71]. Presumably the improved performance stems from tighter binding of the *N*-methoxy amide to the palladium(II) center, which would become increasingly important in more conformationally flexible transition states, as seen in C(sp^3)–H cleavage. In an alternative design strategy, one could envision replacing the carbonyl of the *N*-protecting group with a more Brønsted basic functional group to facilitate proton transfer with less acidic C–H bonds. More generally, combining structural elements from MPAA ligands and blending them with other established ligand motifs in palladium(II) catalysis, such as sulfoxides, thioethers, pyridines, and bipyridines offers a broad scope of structural space to explore. Finally, given that the mechanism of Pd(II)-mediated C–H cleavage with MPAA ligands does not involve any chemistry unique to palladium(II), it is anticipated that MPAAs could find applications with other metals that proceed via carboxylate-assisted CMD, including rhodium(III), iridium(III), and ruthenium(II). Indeed, a few examples using MPAAs in Rh(III)- and Ru(II)-catalyzed C–H functionalization have recently been reported [128–130].

Collectively, this body of work serves an exciting platform for the continued development and application of MPAAs and related motifs as ligands for promoting synthetically enabling C–H functionalization. As interest in designing ligands to promote C–H cleavage continues to mount, the mechanistic lessons that have emanated from investigations of [Pd(MPAA)] catalysts will provide fuel for the engine of discovery.

Acknowledgments: I thank Prof. Jin-Quan Yu at The Scripps Research Institute (TSRI) and Véronique Gouverneur and John M. Brown at the University of Oxford for their unwavering support during my graduate studies. Without their inspiration and guidance, my thesis research would not have been possible. Similarly, I acknowledge Prof. Robert H. Grubbs for his mentorship during my postdoctoral work at Caltech. I am deeply grateful to my coworkers and collaborators, whose individual names are mentioned in the references. Among them, Dong-Hui Wang deserves special mention for his early contributions working together with me on MPAA-accelerated reactions. Dr. Alexander A. Kislukhin (Tsien Lab, UCSD) is acknowledged for translation of Refs. 45 and 55 from Russian to English. Prof. Jin-Quan Yu (TSRI), Dr. Kin Yang (Engle Lab, TSRI), and Dr. Will R. Gutekunst (Hawker Lab, UCSB) are acknowledged for helpful discussions and for proofreading this manuscript. While writing this review, K. M. E. was supported by a National Institutes of Health Postdoctoral Fellowship at Caltech (F32GM108145) and start-up funds from TSRI.

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