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Review

Recent Advances in Acyl Suzuki Cross-Coupling

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Abstract: Acyl Suzuki cross-coupling involves the coupling of an organoboron reagent with an acyl electrophile (acyl halide, anhydride, ester, amide). This review provides a timely overview of the very important advances that have recently taken place in the acylative Suzuki cross-coupling. Particular emphasis is directed toward the type of acyl electrophiles, catalyst systems and new cross-coupling partners. This review will be of value to synthetic chemists involved in this rapidly developing field of Suzuki cross-coupling as well as those interested in using acylative Suzuki cross-coupling for the synthesis of ketones as a catalytic alternative to stoichiometric nucleophilic additions or Friedel-Crafts reactions.

Keywords: Suzuki cross-coupling; acyl cross-coupling; acylation; ketones; acylative cross-coupling; palladium; nickel; phosphine; N-heterocyclic carbene; Suzuki-Miyaura

1. Introduction

The Suzuki cross-coupling represents the most powerful C–C bond forming reaction in organic synthesis [1]. Traditional Suzuki cross-coupling (also referred to as Suzuki–Miyaura cross-coupling) involves the coupling of an organoboron reagent with an aryl halide (pseudohalide), and is most commonly employed for the synthesis of biaryls by a C(sp^2)–C(sp^2) disconnection using a palladium or nickel catalyst (Figure 1A) [2,3]. Since the initial report in 1979, many variants of the Suzuki cross-coupling have been discovered [4]. The ability to systematically apply the cross-coupling of organoboron reagents with high predictability, operational-simplicity, and superb functional group tolerance has contributed to the overwhelming success that this reaction enjoys as the key part of the modern chemistry toolbox. The 2010 Nobel Prize in Chemistry is a fitting testament of its impact [5].

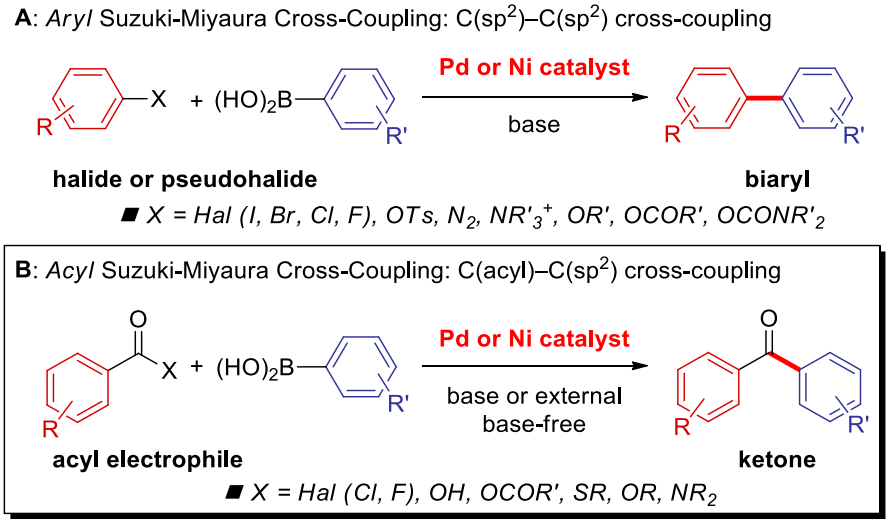


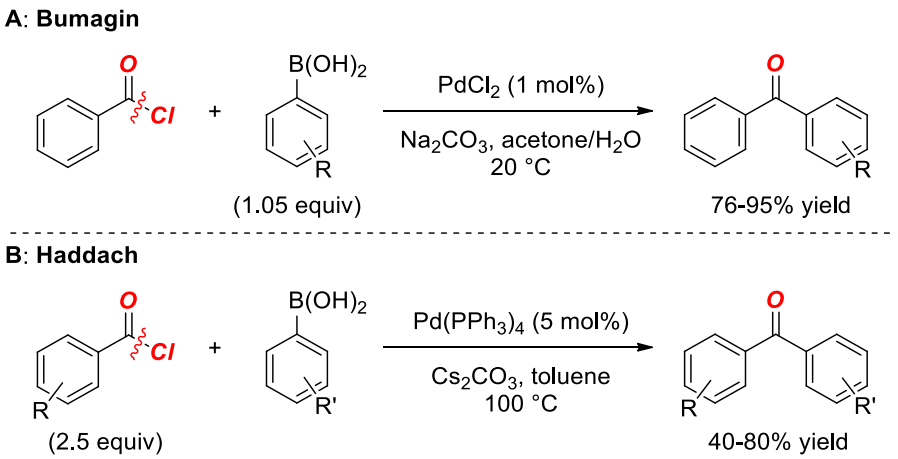
Figure 1. Aryl and Acyl Suzuki-Miyaura Cross-Coupling.

Acyl Suzuki cross-coupling involves the coupling of an organoboron reagent with an acyl electrophile (acyl halide, anhydride, ester, amide) (Figure 1B), and in parallel to the biaryl counterpart typically proceeds by a C(acyl)–C(sp^2) disconnection [6,7]. Since its first discovery in 1999, acylative Suzuki cross-coupling has been established as a new and useful technique for the synthesis of ketones as a catalytic alternative to stoichiometric nucleophilic additions of organometallic reagents or Friedel-Crafts reactions of acyl electrophiles [8-11]. In contrast to the traditional Suzuki cross-coupling, the acylative Suzuki cross-coupling has been much less developed. While this trend is not surprising given the paucity of methods for the synthesis of biaryls other than cross-couplings [2,3], the acylative manifold provides a powerful arsenal of catalytic methods for the C–C bond construction at the acyl group with selectivity, precision and functional group tolerance superseding traditional disconnections. As an added advantage, acyl Suzuki cross-couplings often proceed in the absence of an external base since the leaving group may act as a boron activator facilitating transmetallation [12].

In this review, we will provide a timely overview of the very important advances that have recently taken place in the acylative Suzuki cross-coupling. Particular emphasis is directed toward the type of acyl electrophiles, catalyst systems and new cross-coupling partners. The review is organized by a type of electrophile undergoing cross-coupling in the order of their electrophilic reactivity [13], namely acyl halides, anhydrides, carboxylic acids, esters, and amides. Thioesters are not covered in this review because excellent monographs on C–S activation have been published [14,15], and the acyl coupling of thioesters typically involves co-activation using stoichiometric Cu(I) (Liebeskind-Srogl coupling). We hope that this review will be of value to synthetic chemists involved in this rapidly developing field of acyl Suzuki cross-coupling as well as those interested in using acylative Suzuki cross-coupling for the synthesis of ketones by this catalytic manifold.

2. Suzuki Cross-Coupling of Acyl Halides

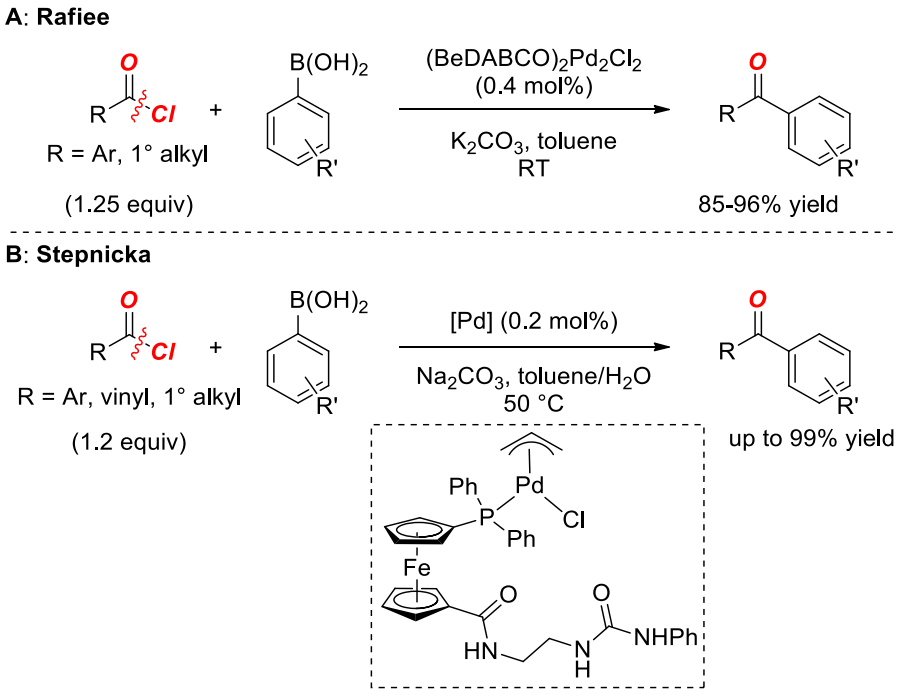
In 1999, Bumagin developed a phosphine-free palladium-catalyzed cross-coupling of boronic acids with acyl chlorides (Scheme 1A) [16]. The biaryl products were generated in high yields under mild, room temperature conditions using water as the key additive. Independently, also in 1999, Haddach discovered an anhydrous Suzuki cross-coupling of acyl chlorides (Scheme 1B) [17]. It is important to note that these anhydrous conditions were possible due to the combined use of cesium carbonate and $Pd(PPh_3)_4$ in refluxing toluene. Both Bumagin's and Haddach's protocols established important precedents in giving practical alternatives to direct acyl additions of organomagnesium or organolithium reagents or the use of less available organozincs or toxic organostannanes [9,10].



Scheme 1. Early Studies in Acyl Suzuki-Miyaura Cross-Coupling: (a) Bumagin; (b) Haddach. For the first cross-coupling of acyl halides with sodium tetrafluoroborates, see, ref. [18].

Suzuki cross-coupling of acyl halides was reviewed in 2013 [19]. For the coverage of the initial studies, the reader is referred to this review. Recent advances in the Suzuki cross-coupling of acyl halides include the development of new ligands, the use of easily-recoverable heterogeneous catalysts and eco-friendly solvents, establishment of new electrophiles and organoboron reagents.

In 2015, in continuation of their studies on 1-benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane chloride-palladium chloride complex [$(BeDABCO)_2Pd_2Cl_6$], Rafiee and co-workers found that this catalyst was highly active for acylative cross-coupling of acyl chlorides with boronic acids (Scheme 2A) [20]. This reaction allowed for the use of various acyl chlorides and arylboronic acids under mild and phosphine-free conditions. At the same time, Stepnicka and co-workers prepared new phosphinoferrocenes with pendant ureas as supporting ligands for palladium(II) η^3-allyl complexes and applied these precatalysts for the synthesis of ketones by Suzuki cross-coupling of acyl chlorides (Scheme 2B) [21]. Phosphinoferrocene ligands have unique structural versatility and, thus, have found several applications in both laboratory and industrial-scale catalytic processes. The catalyst applied to this reaction demonstrated good reactivity at low loading at 50 °C.



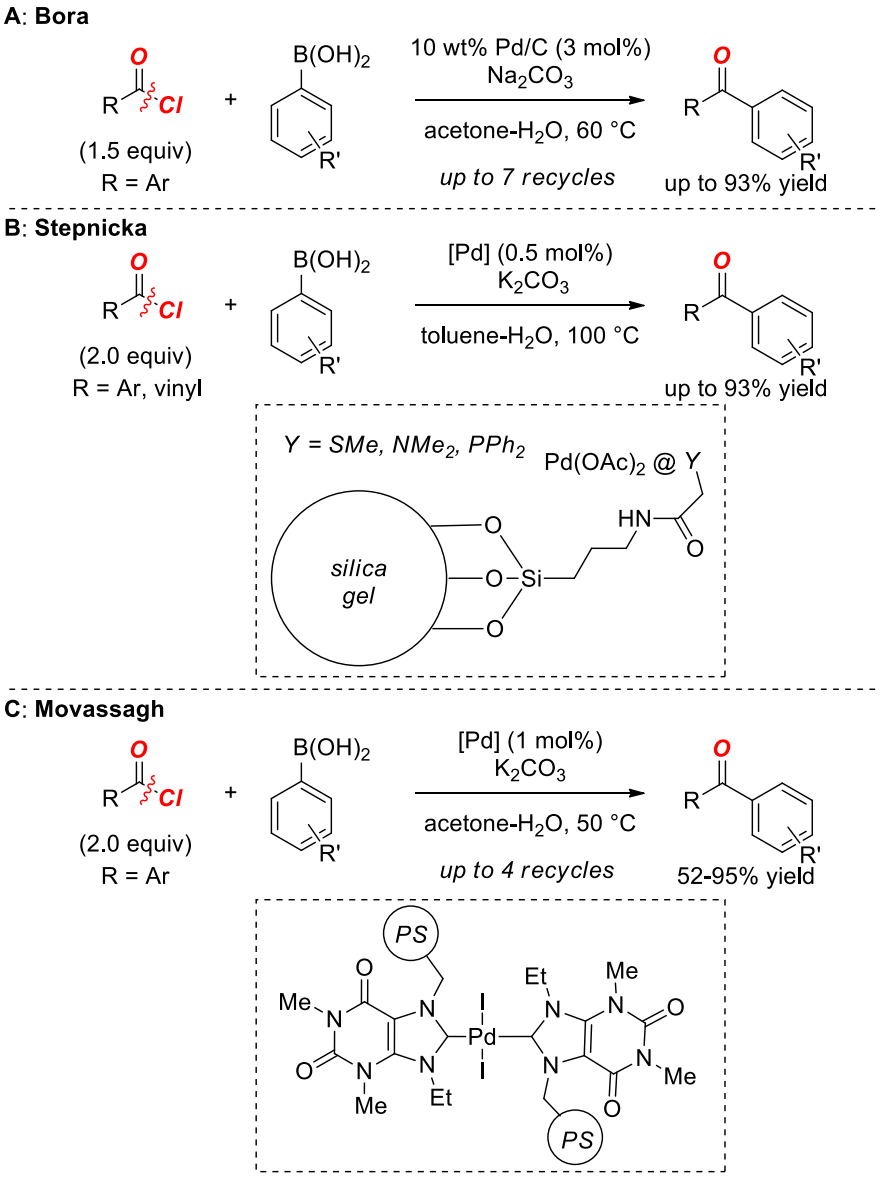
Scheme 2. Synthesis of Ketones from Acyl Chlorides using New Catalysts: (a) $(BeDABCO)Pd_2Cl_6$; (b) [Phosphinoferrocene)Pd(allyl)Cl].

In 2014, Bora described a ligand-free Suzuki-type cross-coupling reaction of aroyl chlorides and arylboronic acids using a Pd/C heterogeneous catalyst (Scheme 3A) [22]. The use of 3 mol% of Pd/C was shown to promote the cross-coupling at 60 °C. Moreover, the heterogeneous catalyst could be recycled up to 7 times without loss of activity.

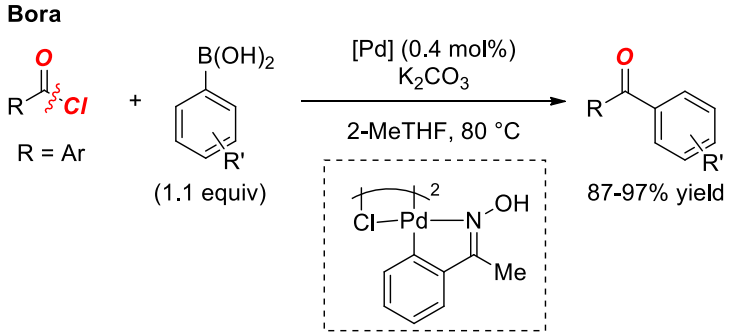
In 2014, Stepnicka prepared immobilized palladium catalysts by the deposition of palladium acetate over functionalized silica gel and applied these heterogeneous catalysts to the reaction of acyl chlorides with boronic acids (Scheme 3B) [23]. In 2017, Movassagh achieved the cross-coupling of aroyl chlorides with arylboronic acids using a polystyrene supported palladium(II) N-heterocyclic carbene complex (Scheme 3C) [24]. This complex allowed for short reaction times, high efficiency under mild aqueous conditions at 50 °C, and ease of isolation. The biaryl ketones synthesized by this method were obtained in high yields and the catalyst could be reused up to 4 times without significant loss of activity.

In 2016, Bora discovered an eco-friendly method relying on the implementation of bio-derived 2-MeTHF as a solvent to make diaryl ketones (Scheme 4) [25]. The developed conditions, applying

an oxime palladacycle, allowed for the use of close to stoichiometric amounts of the coupling partners making the reaction highly atom economic, and gave the products in high yields.



Scheme 3. Synthesis of Ketones from Acyl Chlorides using Heterogeneous Catalysts: (a) Pd/C; (b) Palladium on Silica Gel; (c) Polymer-Supported-Pd-NHC.

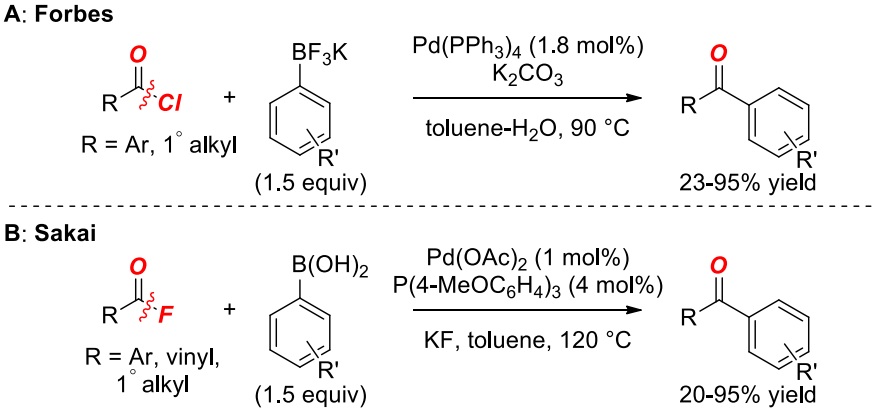


Scheme 4. Synthesis of Ketones from Acyl Chlorides using an Eco-Friendly Solvent.

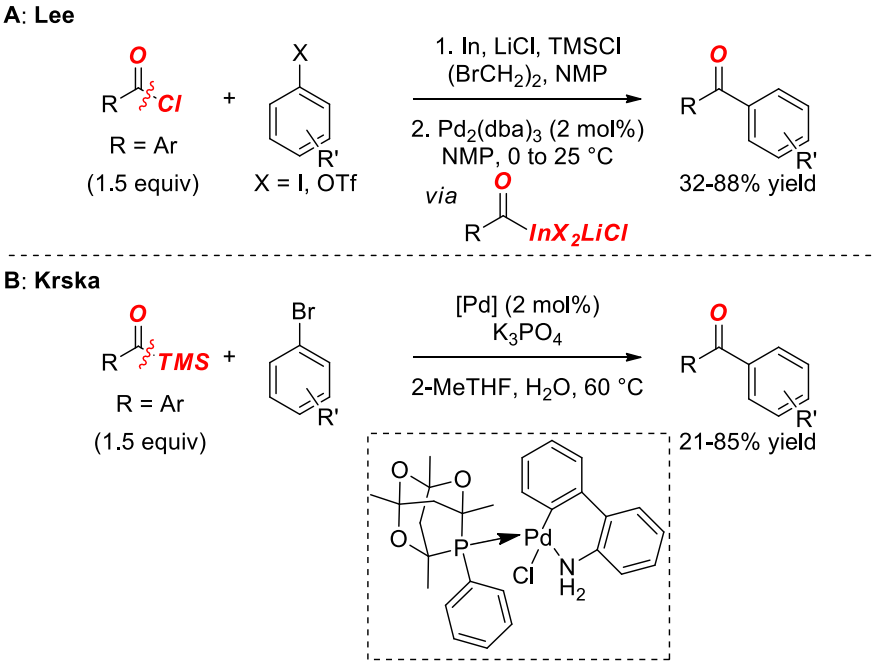
In 2016, Forbes, Magolan and co-workers reported the Suzuki cross-coupling of acyl chlorides using organotrifluoroborates (Scheme 5A) [26]. Organotrifluoroborates offer high functional group tolerance and are moisture-stable making them appealing coupling partners [27]. This coupling offers moderate to excellent yields; however, the reaction appeared to be substrate dependent.

More recently the preparation of ketones using acyl fluorides was reported by Sakai and co-workers (Scheme 5B) [28]. Compared to typical acyl chloride electrophiles, acid fluorides are more stable towards oxidative addition. The use of acyl fluorides allowed for high functional group tolerance and a wide substrate scope with high yields.

An alternative strategy to the cross-coupling of aroyl halides involves a reversed polarity approach (Scheme 6). In 2014, Lee and co-workers developed the cross-coupling of acylindium reagents prepared in situ from aroyl chlorides and indium (Scheme 6A) [29]. This reaction works well using very mild conditions at 25 °C. The tolerance of ketones, esters, and nitriles is advantageous for further functionalization. Krska and co-workers developed a reverse polarity method for the synthesis of biaryl ketones via a Pd-catalyzed cross-coupling between aryl halides and acylsilanes (Scheme 6B) [30]. The use of a bulky phospha-adamantane was identified as an optimal ligand for the reaction.



Scheme 5. (a) Synthesis of Ketones from Acyl Chlorides using Organotrifluoroborates; (b) Cross-Coupling of Acyl Fluorides.



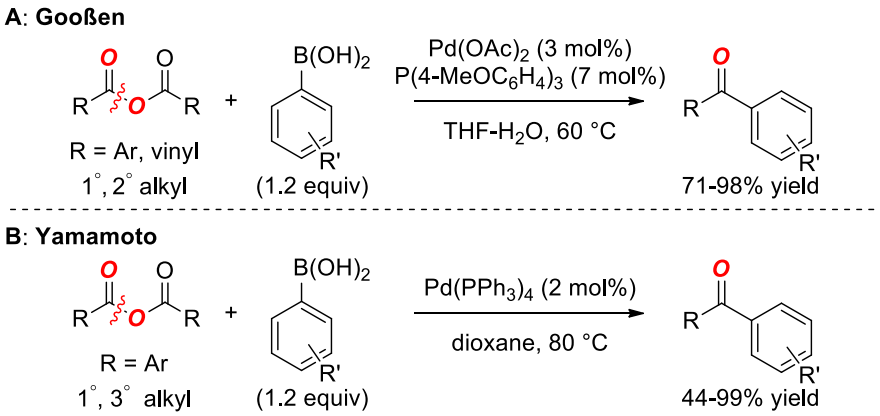
Scheme 6. Synthesis of Biaryl Ketones by Polarity Inversion (a) Acyl Indium; (b) Acyl Silanes.

3. Suzuki Cross-Coupling of Anhydrides

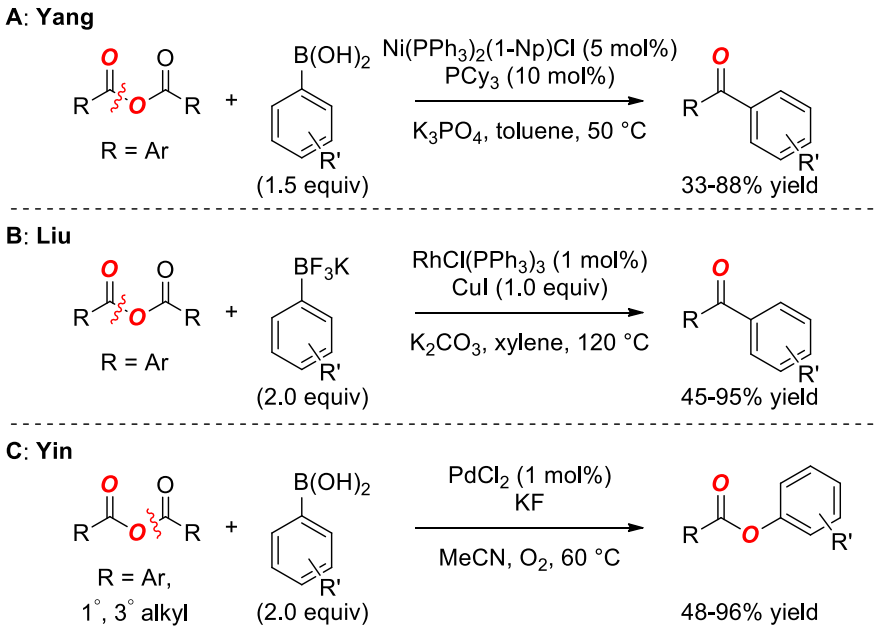
In 2001, Gooßen reported the successful use of anhydrides in acyl Suzuki cross-coupling (Scheme 7A) [31]. This reaction provides a general route to ketones from carboxylic acids using alternative activating reagents to the synthesis from acyl halides. It is important to note that this reaction was not able to support the use of pivalic anhydride. Based on this mechanistic insight, the authors developed in situ protocols for acyl Suzuki cross-coupling of carboxylic acids (see section 4).

Independently, Yamamoto developed an acyl cross-coupling of carboxylic acid anhydrides using readily available $Pd(PPh_3)_4$ to form diverse ketone products (Scheme 7B) [32]. This method permitted for high atom economy and required no base.

Recently, Suzuki cross-coupling of carboxylic acid anhydrides has been developed using Ni, Rh and Pd catalysis (Schemes 8A-C).



Scheme 7. Early Studies in Acyl Suzuki-Miyaura Cross-Coupling of Carboxylic Acid Anhydrides: (a) Gooßen; (b) Yamamoto.



Scheme 8. Synthesis of Ketones and Esters from Carboxylic Acid Anhydrides: (a) Ni; (b) Rh; (c) Pd.

In 2014, Yang developed a mild method to synthesize biaryl ketones using a nickel(II)-σ-aryl precatalyst (Scheme 8A) [33]. This acyl Suzuki cross-coupling provides an efficient, cost-effective and practical route to making ketones in moderate to good yields.

In 2015, Liu developed a Rh(I)-catalyzed acyl Suzuki cross-coupling of carboxylic acid anhydrides and potassium aryltrifluoroborates (Scheme 8B) [33]. It was shown that CuI (1.0 equiv) played an essential role and the reaction could support the use of a wide range of cross-coupling

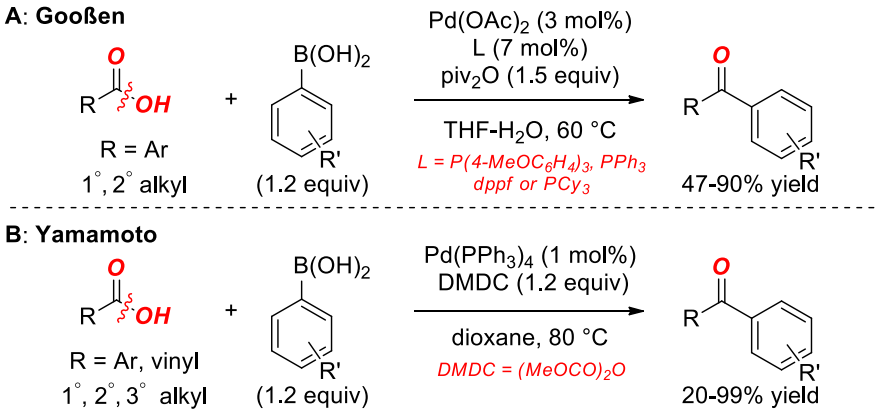
partners. A nice advantage of this coupling includes low catalyst loading, tolerance to air and moisture, and the desired products were obtained in good to excellent yields.

An effective and environmentally-friendly protocol for selective aerobic oxidative coupling of arylboronic acids with carboxylic acid anhydrides in the presence of palladium was developed by Yin (Scheme 8C) [34]. This protocol involves a formal scission of the alternative C–O bond to afford esters by transmetallation of Pd(II) with boronic acid, formation of Pd-carboxylate and reductive elimination. Compared with previous methods this reaction can be conducted using ligandless conditions and low catalyst loading giving good to excellent yields of the ester products.

4. Suzuki Cross-Coupling of Carboxylic Acids

In 2001, Gooßen reported the direct synthesis of ketones from carboxylic acids by Suzuki cross-coupling via an anhydride intermediate generated in situ (Scheme 9A) [31,36]. This methodology allowed for the engagement of an array of functionalized aryl and alkyl carboxylic acids, and, as mentioned previously, relied on the use of an unreactive pivalic anhydride activator.

Independently, Yamamoto developed a related method using dimethyl dicarbonate (DMDC) activator and various carboxylic acids for the synthesis of ketones (Scheme 9B) [37]. It is important to note that these reactions allow for the direct synthesis of ketones from ubiquitous carboxylic acids and are easily compatible with meta-substituted benzoic acids which had previously been problematic in the classical Friedel-Crafts acylation.



Scheme 9. Early Studies in Acyl Suzuki-Miyaura Cross-Coupling of Carboxylic Acids: (a) Gooßen; (b) Yamamoto. DMDC = Dimethyl Dicarbonate. For *N*-Benzoyloxysuccinimide as the Activator, see: Ref. [38,39].

In the past decade, significant progress has been achieved in the development of selective activating reagents for acyl Suzuki cross-coupling of carboxylic acids (Schemes 10-14).

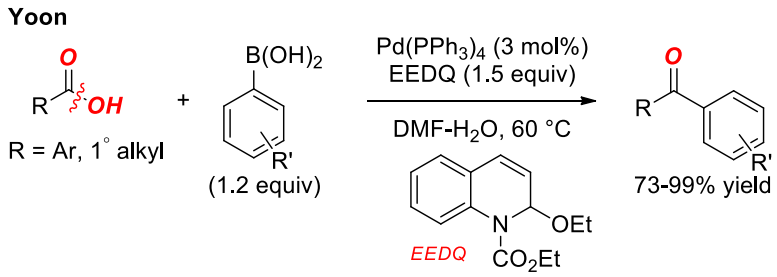
In 2010, Yoon reported the use of EEDQ (*N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) as an activating reagent in the Suzuki cross-coupling of carboxylic acids with arylboronic acids to make the desired ketone products (Scheme 10) [40]. EEDQ is a known coupling reagent and serves in this case to make a mixed carboxylic acid anhydride in situ. This simple and efficient method gave diarylketone products in high to excellent yields.

In 2013, Sharma reported DMC (2-chloro-1,3-dimethyl imidazolidinium chloride) as an activating reagent for the synthesis of biaryl ketones via acyl Suzuki cross-coupling of carboxylic acids (Scheme 11) [41]. This reaction was compatible with electron-donating and withdrawing substituents on both reaction components; however, aliphatic carboxylic acids were not compatible with the reaction conditions.

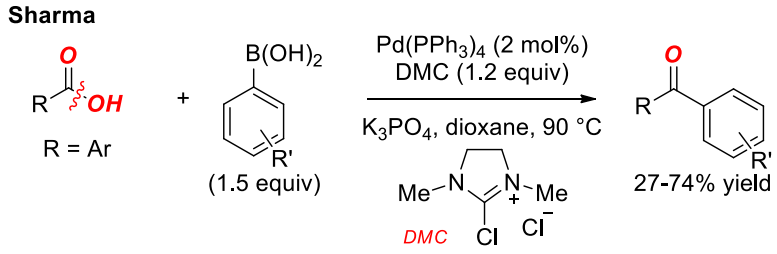
More recently, Lindsley reported the use of PyCUI (1-(chloro-1-pyrrolidinylmethylene) pyrrolidiniumhexafluorophosphate in the synthesis of ketones by acyl Suzuki cross-coupling (Scheme 12) [42]. This highly reactive in situ activating reagent allows for the transformation of carboxylic acids into unsymmetrical ketones. Furthermore, this one-pot reaction can be conducted at room temperature with reaction times of 2 hours or less and gives moderate to high yields.

In 2016, Zeng reported the Suzuki-Miyaura cross-coupling of in situ prepared triazine esters using CDMT (2-chloro-4,6-dimethoxy-1,3,5-triazine) (Scheme 13) [43]. This process is conducted at low catalyst loading and with short reaction times. Moreover, this one-pot, sequential protocol gave moderate to excellent yields using functionalized and sterically-hindered substrates.

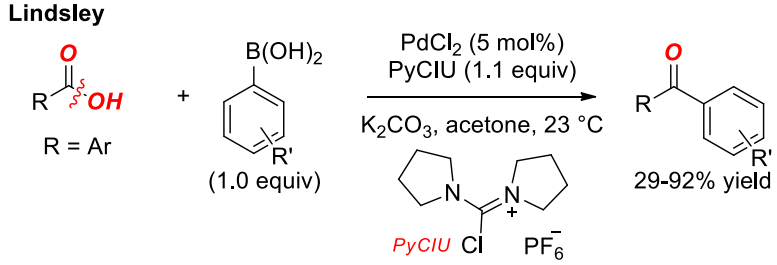
Furthermore, recent progress by Zou in the use of high order aryl boron reagents such as diarylbornic acids and tetra-arylboronates in the acyl Suzuki cross-coupling of carboxylic acids is noteworthy (Scheme 14) [44].



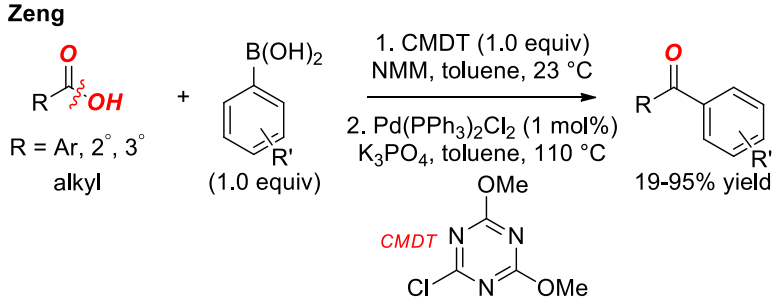
Scheme 10. Synthesis of Ketones from Carboxylic Acids using EEDQ. EEDQ = *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.



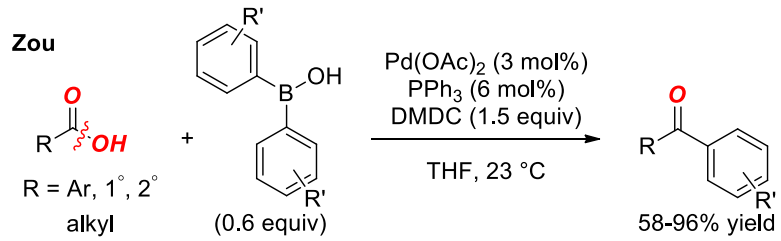
Scheme 11. Synthesis of Ketones from Carboxylic Acids using DMC. DMC = 2-Chloro-1,3-dimethylimidazolinium Chloride.



Scheme 12. Synthesis of Ketones from Carboxylic Acids using PyCIU. PyCIU = 1-(Chloro-1-pyrrolidinylmethylene)pyrrolidinium Hexafluorophosphate.



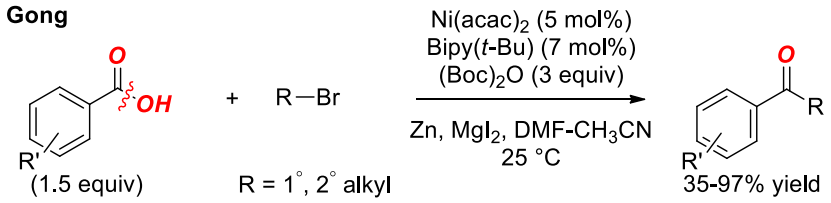
Scheme 13. Synthesis of Ketones from Carboxylic Acids using CDMT. CDMT = 2-Chloro-4,6-dimethoxy-1,3,5-triazine. NMM = *N*-Methylmorpholine.



Scheme 14. Synthesis of Ketones from Carboxylic Acids and Diarylborinic Acids using DMDC.

These reagents are not only more cost effective than conventional boronic acids but also showed increased reactivity in the cross-coupling using DMDC activator. This acylative Suzuki cross-coupling had a remarkably broad substrate scope, affording products bearing hydroxy, bromo, and carbonyl groups in good to high yields.

An interesting application of the Ni-catalyzed reductive cross-coupling of carboxylic acids for the synthesis of ketones was reported by Gong (Scheme 15) [45,46]. The coupling of benzoic acids with primary and secondary alkyl bromides was performed using $Ni(acac)_2$/bipy catalyst system in the presence of Boc_2O activator. Moreover, the group demonstrated the synthesis of functionalized C-glycosides by the direct reductive coupling of 1-glycosyl bromides with carboxylic acids.



Scheme 15. Synthesis of Ketones from Carboxylic Acids by Reductive Coupling.

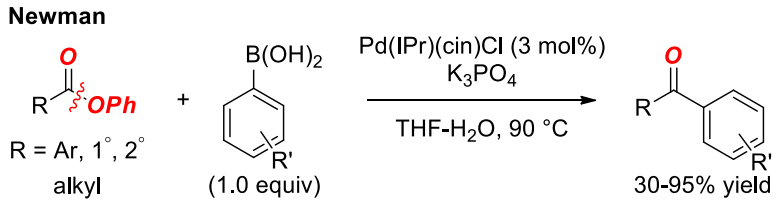
5. Suzuki Cross-Coupling of Esters

Recently, there have been major developments in the acyl Suzuki cross-coupling of aryl esters (Schemes 16-20). There are several key advantages of using ester electrophiles in the acyl Suzuki cross-coupling, including (i) high-stability, (ii) prevalence in organic synthesis, (iii) opportunities for orthogonal cross-coupling strategies, (iv) reduction of toxic waste produced in the cross-coupling step.

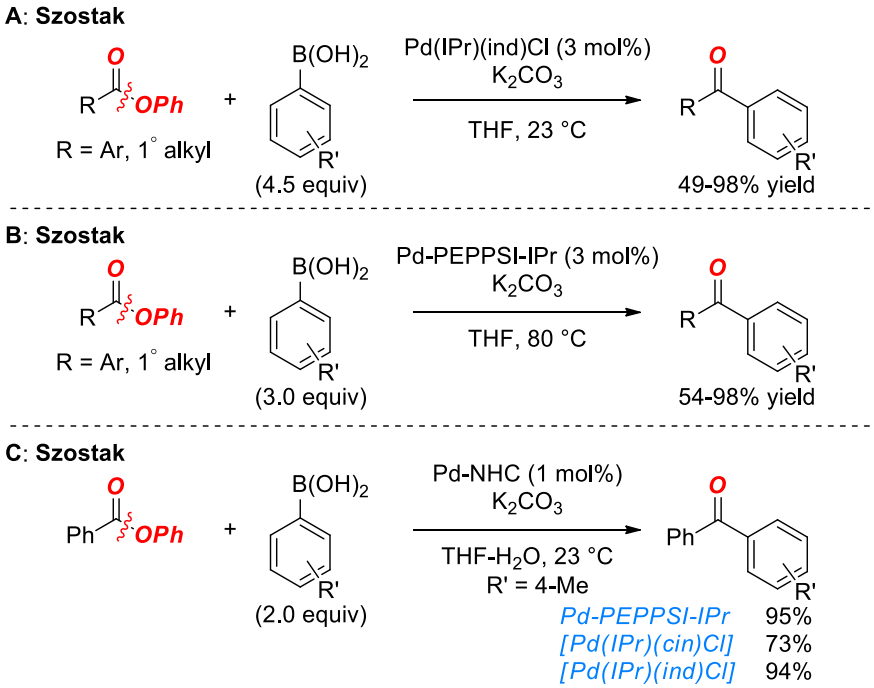
In 2017, Newman demonstrated the first example of Suzuki cross-coupling of aryl esters (Scheme 16) [47]. The Pd-NHC catalyst allows for facile insertion into the unactivated C(acyl)–O ester bond, which had proven challenging using Pd-phosphine catalysts. A broad range of phenolic esters and aryl boronic acids were cross-coupled giving ketones in good to excellent yields.

In 2017, our group demonstrated the Suzuki cross-coupling of phenolic esters by selective C(acyl)–O cleavage under very mild conditions (Scheme 17A) [48]. The use of bench-stable and commercially-available (η^3-1-*t*-Bu-indenyl)Pd(IPr)(Cl) precatalyst was critical to achieve high reactivity, affording a wide range of products in good to high yields. Subsequently, we developed conditions for using practical Pd-PEPPSI precatalysts in the acyl Suzuki cross-coupling of phenolic esters (Scheme 17B) [49]. The pyridine "throw-away" family of ligands render this class of Pd-NHC precatalysts an attractive method due to simplicity of synthesis and high reactivity in C(acyl)–O insertion. Later, we demonstrated that the cross-coupling is effectively promoted at remarkably mild room temperature conditions (Scheme 17C), while supporting various Pd-NHC precatalysts as well as Pd(II)-NHC hydroxide dimers (Figure 2) [50].

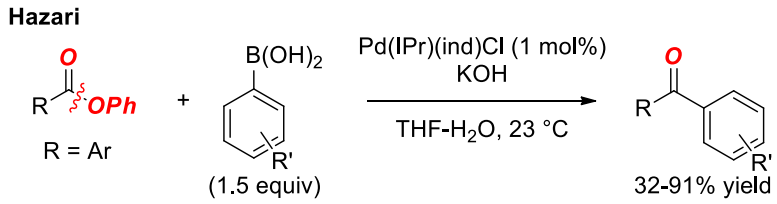
The preparation of ketones using (η^3-1-*t*-Bu-indenyl)Pd(IPr)(Cl) in the presence of a strong base was reported by Hazari (Scheme 18) [51]. This Pd-NHC effectively coupled esters with aryl boronic acids in good to high yields at room temperature using non-toxic reagents.



Scheme 16. Synthesis of Ketones from Phenolic Esters by Newman and co-workers.



Scheme 17. Synthesis of Ketones from Phenolic Esters by Szostak and co-workers.



Scheme 18. Synthesis of Ketones from Phenolic Esters by Hazari and co-workers.

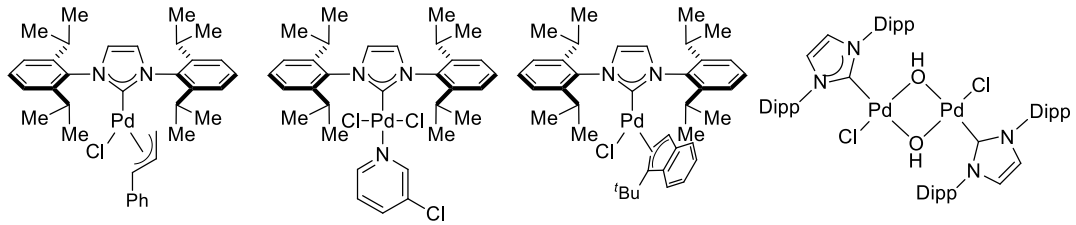
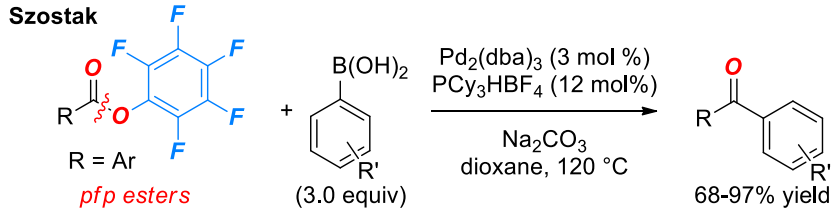


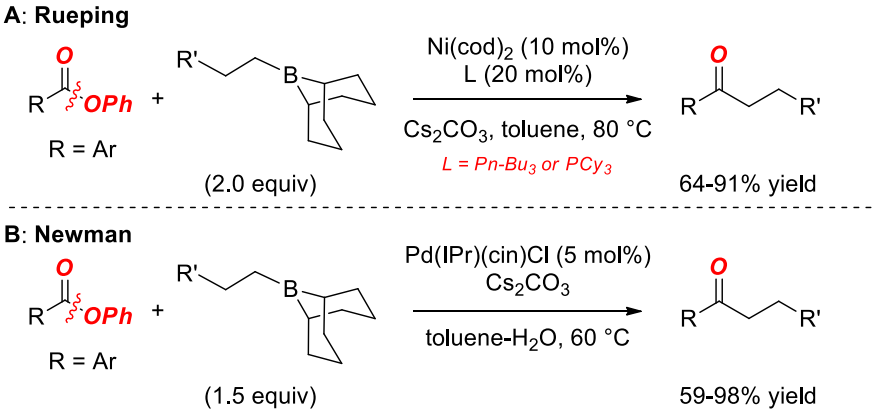
Figure 2. Structures of Air-Stable Pd-NHC Precatalysts in Cross-Coupling of Phenolic Esters.

In 2018, to further explore the reactivity of phenolic esters in the acyl Suzuki cross-coupling reaction, we have reported the Pd-phosphine-catalyzed cross-coupling of pentafluorophenyl esters (pfp) (Scheme 19) [52]. Due to the activating effect of the fluorine substituents, a mild $Pd_2(dba)_3/PCy_3$ catalyst was able to effectively activate the C(acyl)–O bond giving products in high yields without the need for a more reactive, albeit less selective, Pd-NHC precatalyst.

Recently, Rueping and Newman groups reported Ni- and Pd-catalyzed B-alkyl acyl Suzuki cross-coupling of phenolic esters (Scheme 20) [53,54]. Both groups have shown that the catalyst type and reaction conditions dictate whether the process is a decarbonylative or acyl coupling. This novel approach gives alkyl ketones in good to high yields, while also demonstrating the importance of ligand selection to promote cross-coupling/decarbonylation of the acyl-metal intermediate.



Scheme 19. Synthesis of Biaryl Ketones from Pentafluorophenyl Esters.



Scheme 20. B-Alkyl Suzuki-Miyaura Cross-Coupling of Phenolic Esters: (a) Rueping; (b) Newman.

6. Suzuki Cross-Coupling of Amides

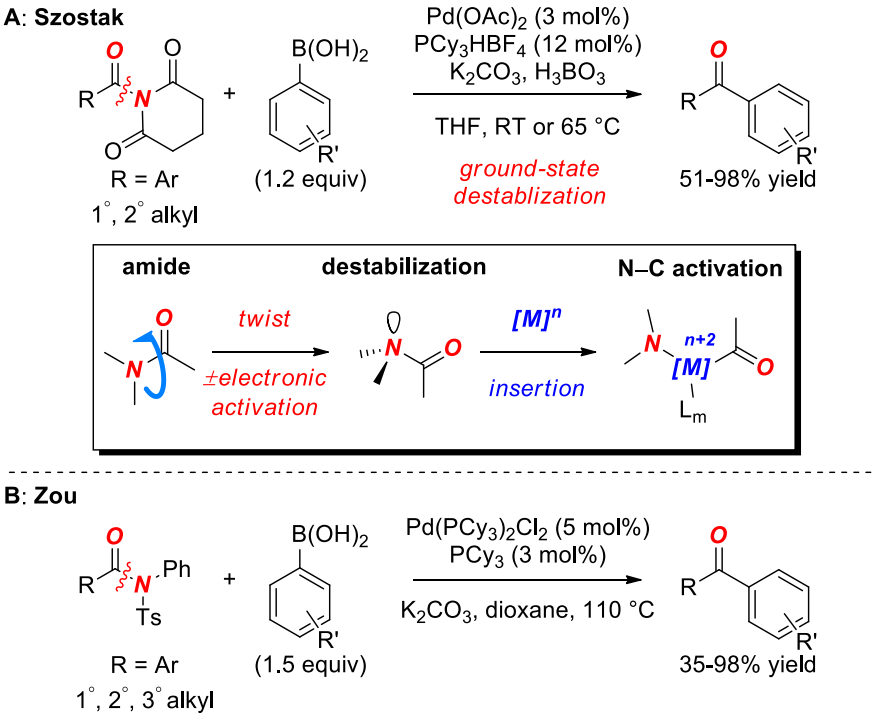
The ability of transition-metals to catalyze activation of the acyl N–C(O) amide bond was first reported in 2015. Traditionally, the amide bond is the most challenging carboxylic acid derivative to achieve metal insertion due to $n_N \rightarrow \pi^*_{C=O}$ conjugation (15-20 kcal/mol) [55], rendering the classical amide bond approximately 40% double bond in character.

To tackle the challenge of selective metal insertion into the acyl N–C(O) amide bond, we designed a concept of ground-state-destabilization of the amide bond in transition-metal-catalysis (Scheme 21A) [56,57]. We demonstrated a highly chemoselective, Pd(0)-catalyzed, direct acyl Suzuki cross-coupling between boronic acids and geometrically activated amides. A twisted glutarimide diminishes amidic resonance, thus destabilizing the amide ground-state and giving access to versatile ketone products in good to excellent yields. Since the initial report, amide ground state destabilization is considered a prevalent theme in amide bond cross-coupling [58], and all amides thus far have been shown to undergo cross-coupling due to resonance activation [59-62].

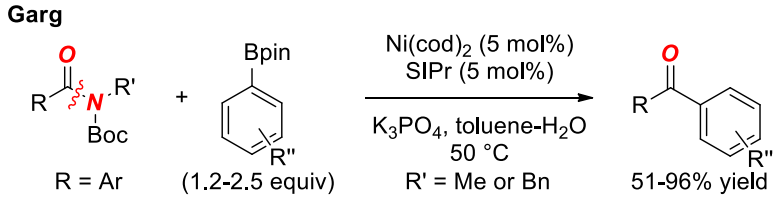
Independently, a new methodology for the synthesis of aryl ketones by acyl Suzuki coupling was developed by Zou, in which amides are used to react with arylboronic acids (Scheme 21B) [63]. Amide bond activation was achieved by using modifiable activating groups on the nitrogen atom. The reaction gave good to excellent yields, and allowed access to sterically-hindered ketones.

At the same time, Garg reported the Ni-catalyzed Suzuki cross-coupling of amide derivatives (Scheme 22) [64]. This coupling is tolerant to significant changes on both amide and boronate

substrates, and tolerates both heterocycles and epimerizable stereocenters. The scaffolds produced are diverse and the reaction was applied to the synthesis of an antiproliferative agent.



Scheme 21. Studies in Suzuki Cross-Coupling of Amides: (a) Szostak; (b) Zou.



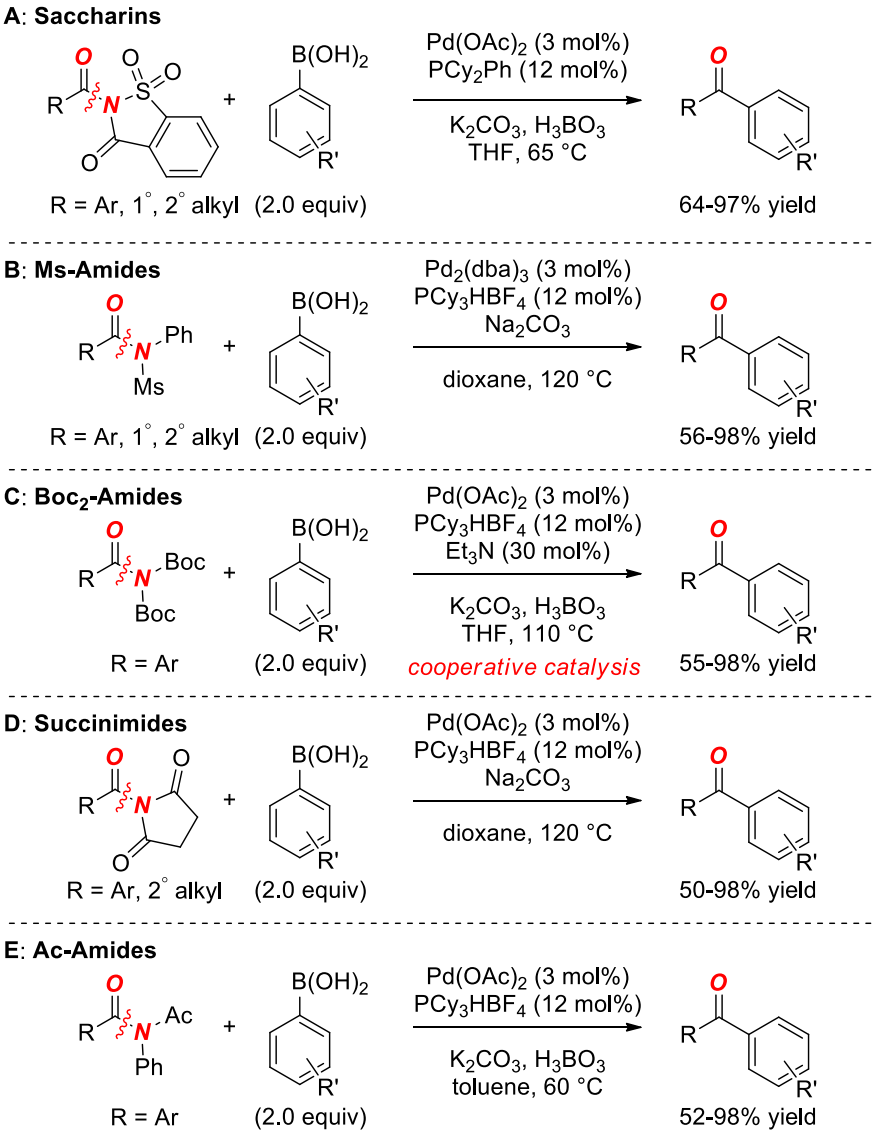
Scheme 22. Studies in Suzuki Cross-Coupling of Amides: Garg. SIPr = 1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine.

Given the indispensable role of the amide bond in chemistry and biology, the amide bond cross-coupling is one of the most rapidly expanding areas of acyl Suzuki coupling [65-72]. The key advances enabling the routine use of this methodology include (1) the development of new amide precursors, (2) the establishment of new catalysts, and (3) the discovery of new types of acyl cross-coupling of amides. These developments are summarized below.

To enable a better control of the insertion step and participation of common amides, we have developed a number of activating groups for acyl Suzuki cross-coupling of amides, including saccharin, Ms, Boc_2, succinimide, and Ac functional groups (Scheme 23A-E).

N-Acylsaccharins are of interest as bench-stable, highly reactive, and easily prepared amides from low-costing saccharin (Scheme 23A) [73]. Independently, Zeng and co-workers reported acyl Suzuki cross-coupling of N-acylsaccharins [74]. We have also explored the activating effect of the mesyl group, and found it to be advantageous to the synthesis of biaryl ketones using highly atom-economical mesyl activation (Scheme 23B) [75].

On the other hand, N,N-Boc_2-activation of amides was shown to be successful with a combination a Lewis base and palladium catalysis, establishing a new concept for activation of amide bonds by cooperative catalysis (Scheme 23C) [76]. Crucially, this method enables the use of primary amides as starting materials. Since primary amides are among the most common amide derivatives in pharmaceuticals and biologically active intermediates, this approach constitutes a powerful method for the synthesis of ketones from common amides [77].



Scheme 23. Synthesis of Ketones from Amides using Pd-Phosphine Catalysts: (a) Saccharins; (b) Ms-Amides; (c) Boc2-Amides; (d) Succinimides; (e) Ac-Amides.

Furthermore, "half-twisted" N-acylsuccinimides (τ = 46.1°) were also demonstrated as versatile acyl transfer reagents in Suzuki cross-coupling (Scheme 23D) [78]. This reaction relies on the increase in reactivity of the amide bond due to the half-twist of the amide bond caused by the succinimide moiety (cf. "fully perpendicular" N-acylglutarimides, τ = 88.6°), which coupled with high efficiency. Low cost and commercial availability of succinimides make this process a viable candidate for the formation of biaryl ketones. Other catalysts have also been reported for the acyl cross-coupling of N-acylsuccinimides [79,80].

More recently, we have reported "mono-twisted" N-Ac-amides as highly reactive acyclic amides in acyl Suzuki cross-coupling (Scheme 23E) [81]. In this work, it was demonstrated that catalyst selection dictates an acyl or decarbonylative mechanism. Due to selective mono-twist destabilization mechanism of the amide bond (τ = 46.1° vs. τ = 5.1°), Ac-amides represent the most reactive acyclic amides developed thus far for amide bond cross-coupling.

Our group reported the structural characterization and acyl Suzuki cross-coupling of the most twisted N-acyclic amides prepared to date (Figure 3) [82]. We found that a combined N-carbamate and N-Ts or N-Ac activation results in a near perpendicular twist of the amide bond in simple acyclic amides (τ = 87.2°). These amides for the first time matched the distortion achieved in bridged lactams [83], and represent another class of reactive amides for acyl Suzuki cross-coupling.

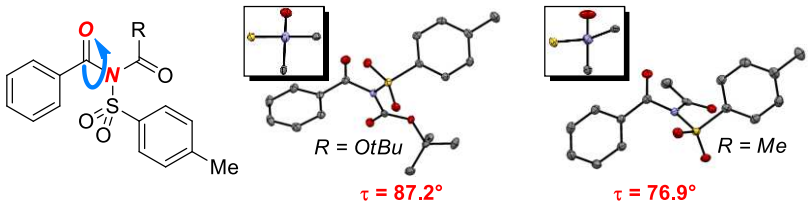
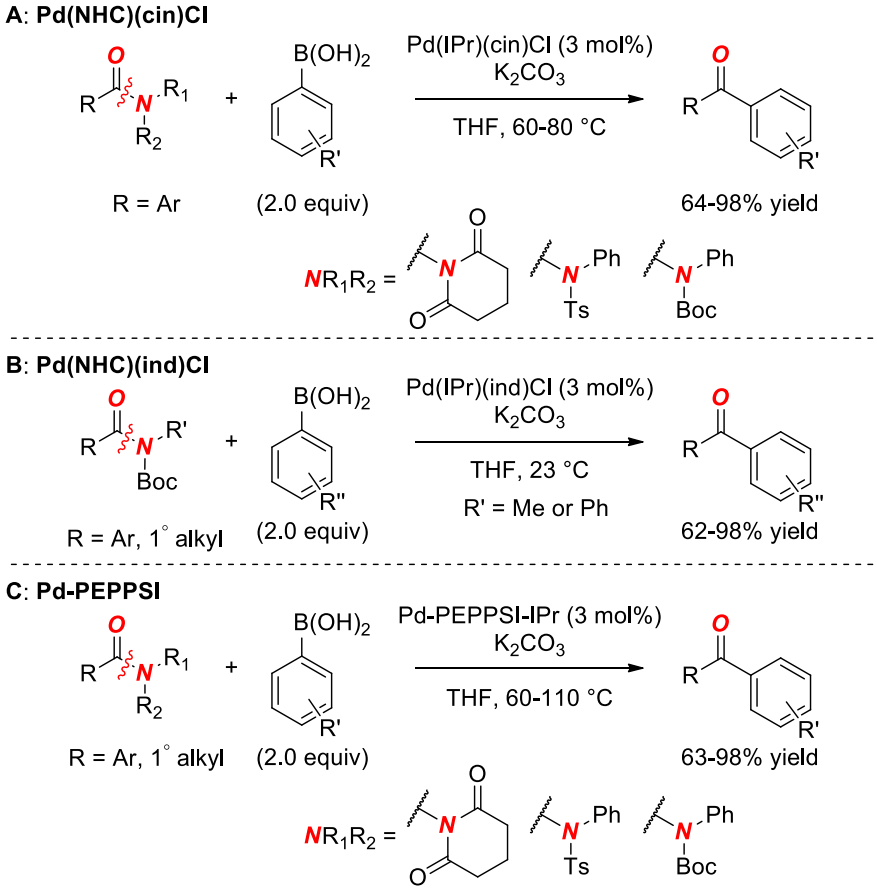


Figure 3. Structures of the Most Twisted N-Acyclic Amides.



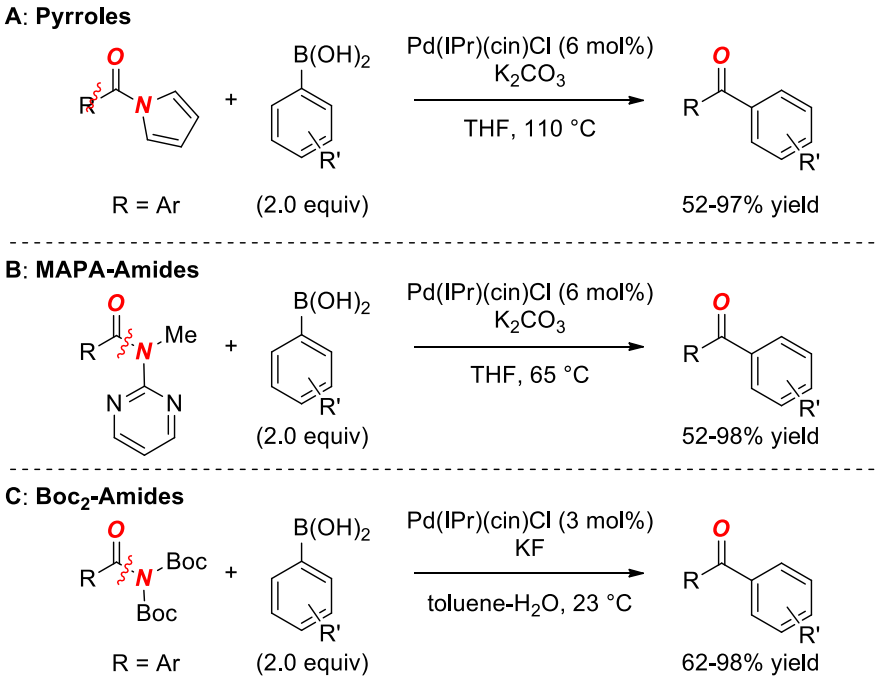
Scheme 24. Synthesis of Ketones from Amides using Pd-NHC Catalysts: (a) Pd(NHC)(cin)Cl; (b) Pd(NHC)(ind)Cl; (c) Pd-PEPPSI. For a study using IPr*-type catalysts, see, ref. [85].

A mechanistically distinct approach to improving reactivity of amides in acyl Suzuki cross-coupling involves the development of new catalyst systems (Scheme 24-28).

Over the past years, we have made significant contributions to the use of strongly σ-donating Pd-NHCs for ketone synthesis by acyl Suzuki cross-coupling of amides. In 2017, we have reported (IPr)Pd(cinnamyl)Cl to demonstrate its superior reactivity to all current Pd-phosphine-based catalysts (Scheme 24A) [84,85]. This catalyst supported a wide range of substrates for ketone synthesis in good to excellent yields. Subsequently, we found that (IPr)Pd(η^3-1-*t*-Bu-indenyl)Cl precatalyst not only showed unprecedented reactivity, but it also allowed for very benign reaction conditions (Scheme 24B) [48]. Of further significance, Pd-PEPPSI-IPr was used in the acyl Suzuki cross-coupling of an array of amides, showing both excellent catalyst performance and a highly diverse substrate scope (Scheme 24C) [86]. The ease of synthesis and high air- and moisture-stability of Pd-NHC precatalysts [87-89] are important factors in considering widespread applications in organic synthesis.

In 2017, we were able to apply (IPr)Pd(cinnamyl)Cl to previously unreactive N-acylpyrroles and N-acylpyrazoles (Scheme 25A) [90]. The cross-coupling of these electronically-activated (RE ca. 10 kcal/mol, RE = resonance energy) planar amides is attributed to the strong σ-donation of the

Pd-NHC catalyst platform. Furthermore, this method demonstrates the potential for catalytic cross-coupling of unactivated primary amides.



Scheme 25. Synthesis of Ketones from Amides using Pd-NHC Catalysts: (a) Pyrroles; (b) MAPA-Amides; (c) Boc_2-Amides.

We further went on to demonstrate the use of N-methylaminopyrimidyl-amides (MAPA) for the acyl Suzuki cross-coupling (Scheme 25B) [91]. With the use of (IPr)Pd(cinnamyl)Cl precatalyst this reaction occurs with high acyl N–C activation chemoselectivity. Of significance, this work provides MAPA as resonance-controlled (RE = ca. 7 kcal/mol) practical alternative to anilides.

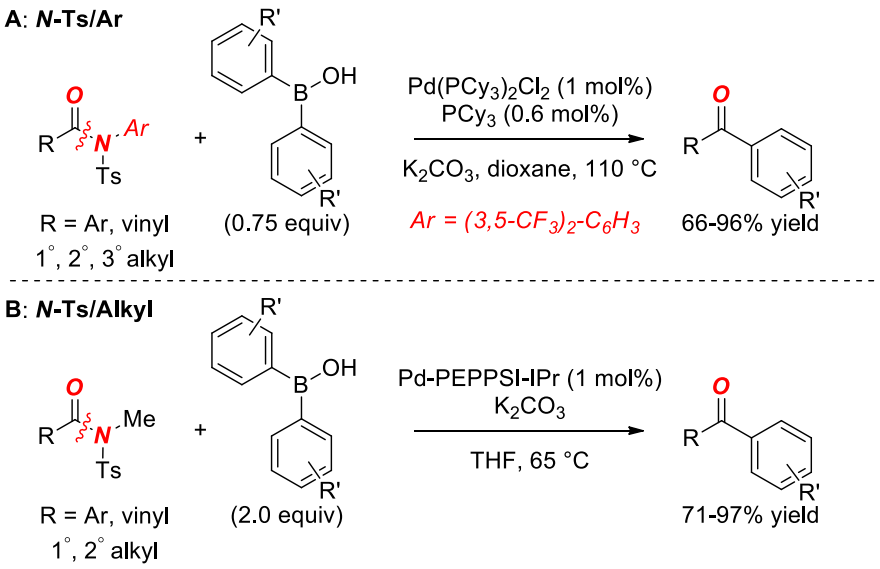
More recently, N-Boc_2 amides also proved to be highly reactive with the application of (IPr)Pd(cinnamyl)Cl (Scheme 25C) [92]. This reaction demonstrated the synthesis of biaryl ketones under exceedingly mild conditions, achieving a TON of >1000 for the first time in amide acyl Suzuki cross-coupling.

The acyl Suzuki cross-coupling of higher order aryl boron reagents with amides was reported by Zou (Scheme 26) [93]. With the use of N-3,5$(CF_3)_2C_6H_3$ activating group and $Pd(PCy_3)_2Cl_2/PCy_3$ catalyst system they were able to overcome the electronic and steric factors for the cross-coupling of amides with diarylborinic acids or tetra-arylborates to synthesize ketones (Scheme 26A). Later, they reported the use of Pd-PEPPSI-IPr for the cross-coupling of N-alkyl-amides with diarylborinic acids (Scheme 26B) [94]. The method is characterized by a broad substrate scope, affording ketones in good to excellent yields, while it also uses a commercially-available Pd-NHC.

Zeng reported the acyl Suzuki cross-coupling of N-acylsuccinimides (Scheme 27A, see also Schemes 23D and 28) [79]. This reaction gave moderate to good yields in a short reaction time. More recently, they used structurally-related N-acyl-5,5-dimethylhydantoins in the acyl Suzuki cross-coupling with aryl boronic acids (Scheme 27B) [95]. The use of commercially-available, air- and moisture-stable (IPr)Pd(allyl)Cl precatalyst as well as good tolerance to several functional groups are important features of this protocol. Our group independently studied the structural features of the amide bond in N-acyl-hydantoins [96], demonstrating that replacement of the carbon atom in the succinimide ring with nitrogen to give hydantoin results in a substantial increase of the amide bond distortion (additive Winkler-Dunitz parameter of 70°).

In 2018, Liu developed the acyl Suzuki cross-coupling of N-acyl-succinimides with aryl boronic acids using benzothiazole-supported Pd-NHC PEPPSI-type precatalyst (Scheme 28) [97]. This Pd-NHC is easily prepared [98], and provides biaryl ketones in high yields. In 2018, Rhee developed the first example of using N,N-bis(methanesulfonyl)amides as acyl-transfer reagents in

399 Suzuki cross-coupling (Scheme 29) [99]. In addition to using new class of substrates, this reaction
400 works under mild conditions to provide a wide range of unsymmetrical ketones.



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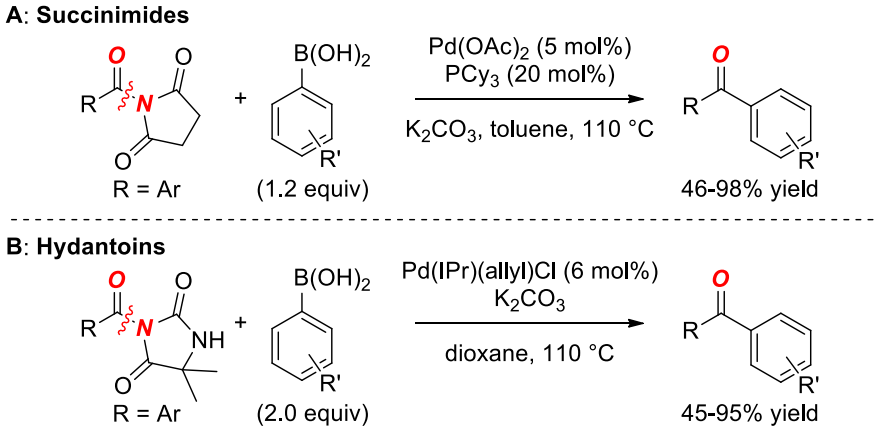
402 **Scheme 26.** Synthesis of Ketones from Amides using Diarylborinic Acids: (a) *N*-Ts/Ar Amides; (b)
403 *N*-Ts/Alkyl Amides.



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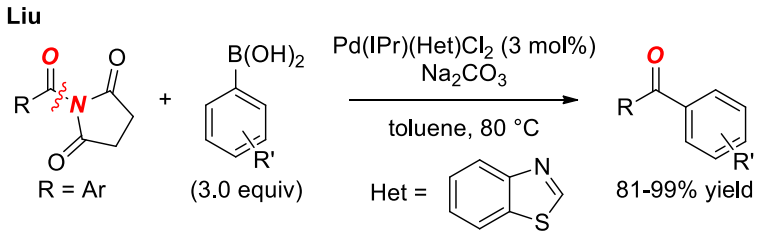
405 **Scheme 27.** Synthesis of Biaryl Ketones from Amides: (a) Succinimides; (b) Hydantoins.



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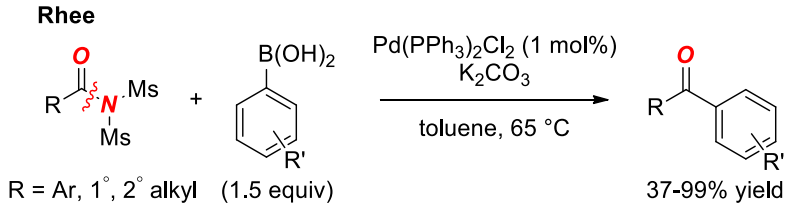
407 **Scheme 28.** Synthesis of Biaryl Ketones from Amides using Benzothiazole-Supported Pd-NHCs.

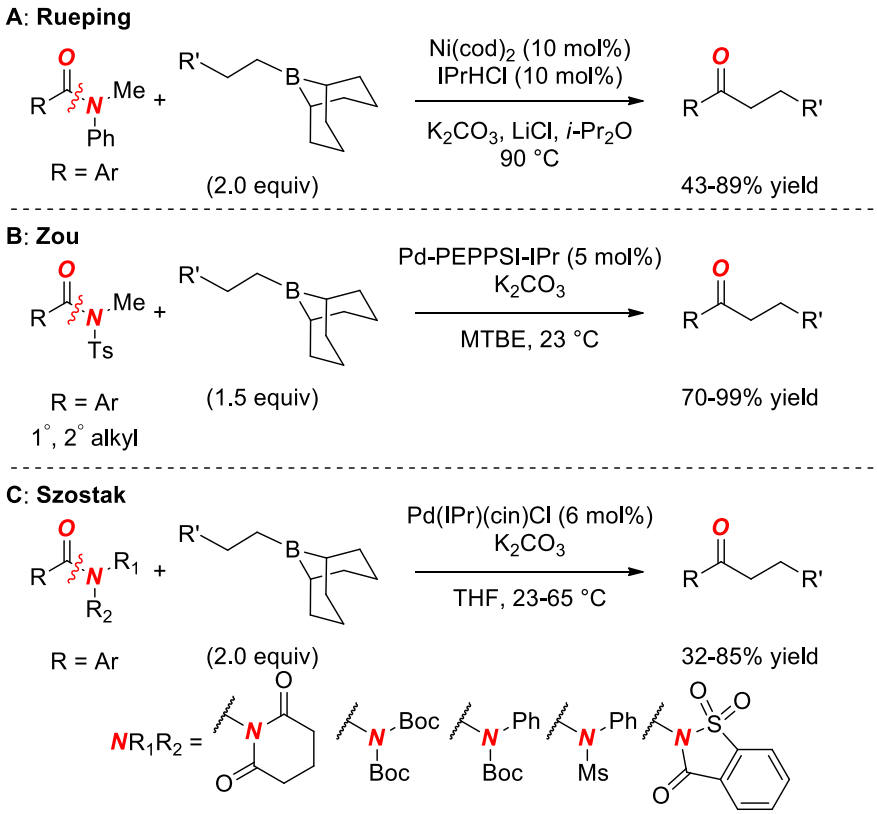


408

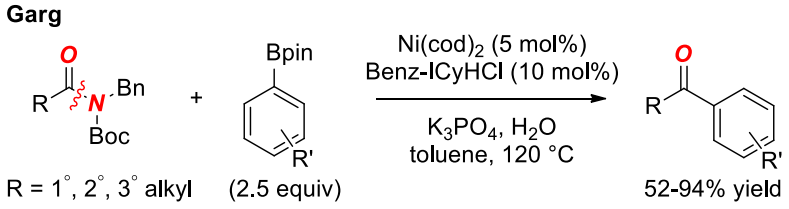
409 **Scheme 29.** Synthesis of Ketones from Di-Sulfonyl Amides by Rhee and co-workers.

In 2018, three groups reported independently B-alkyl Suzuki cross-coupling of amides by selective N–C(O) acyl cleavage (Scheme 30). The Rueping group explored the alkyl ketone synthesis from anilides with the use of alkylboranes and a nickel catalyst (Scheme 30A) [100]. This process allows comparatively mild reaction conditions and supports various functional groups. The Zou group reported the use of Pd-PEPPSI-IPr in the cross-coupling of N-tosylamides with trialkylboranes or alkyl-9-BBN reagents (Scheme 30B) [101]. This highly efficient acylative cross-coupling method gives also access to unsymmetrical di-alkyl ketones. Our group reported (IPr)Pd(cinnamyl)Cl-catalyzed cross-coupling of alkyl-9-BBN reagents with different types of amides, including even the more challenging Boc$_2$-amides derived directly from common primary amides (Scheme 30C) [102]. The efficiency of this process was highlighted in a sequential C(sp^2)–C(sp^2)/C(acyl)–C(sp^3) cross-coupling of common amides.

In a complementary approach, the Garg group reported Ni-catalyzed cross-coupling of α-C-aliphatic amides with arylboronic acid pinacol esters (Scheme 31) [103]. This methodology relies on an electron-rich N-alkyl-NHC supporting ligand, and successfully addressed the difficulty of using α-C-aliphatic amide derivatives. Furthermore, the method was highlighted in the synthesis of a bioactive spiroindolenine precursor.

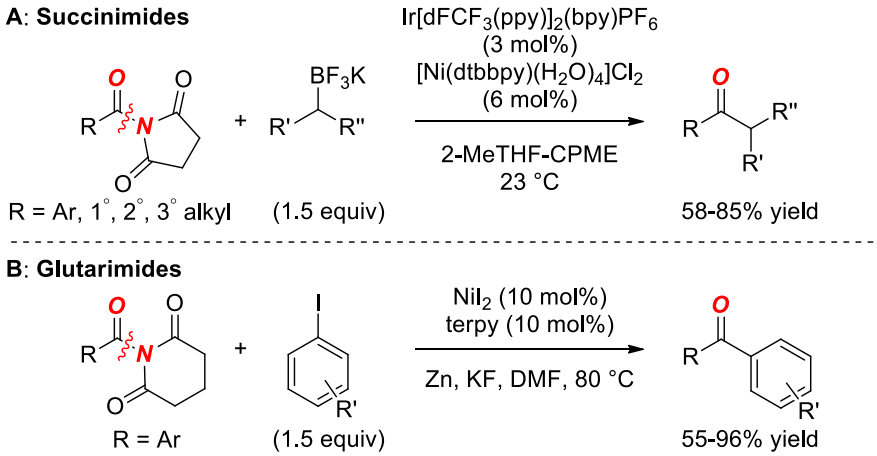


Scheme 30. B-Alkyl Suzuki-Miyaura Cross-Coupling of Amides: (a) Anilides; (b) Tosylamides; (c) *N*-Boc Amides, Glutarimides and Saccharins.



Scheme 31. Synthesis of Ketones from Aliphatic Amides by Garg and co-workers.

The groups of Molander and Pan developed the synthesis of ketones by acyl-type cross-coupling of amides (Scheme 32). The Molander group developed a photoredox/Ni-catalyzed cross-coupling of N-acyl-succinimides with alkyl trifluoroborates for the synthesis of aliphatic ketones (Scheme 32A) [104]. This reaction provides mild conditions and tolerance for a wide variety of functional groups on both coupling partners. The Pan group demonstrated the first example of a reductive cross-coupling of amides by acyl cleavage (Scheme 32B) [105]. The reaction is mechanistically significant because Ni-catalyst allowed for selective activation of the amide bond instead of the C–I bond, preventing self-coupling under reductive conditions. Additional methods for the synthesis of ketones by cross-coupling of amides have been reported [106,107].



Scheme 32. Synthesis of Ketones from Amides: (a) Ir/Ni-Cooperative Catalysis; (b) Ni-Catalyzed Reductive Coupling.

7. Conclusions

In summary, significant advances have recently taken place in the field of acylative Suzuki cross-coupling. This is highlighted by a rapid discovery of new acyl electrophiles, catalyst systems and cross-coupling partners. In a broader perspective, the acyl Suzuki cross-coupling allows for the synthesis of ketones as a catalytic alternative to stoichiometric nucleophilic additions and Friedel-Crafts reactions, but also to using less available or toxic organometallic reagents such as organozincs or organostannanes. The major advance has undoubtedly been the development of previously considered as unreactive common ester and amide electrophiles in the cross-coupling. This allows for utilization of bench-stable carboxylic acid electrophiles that are prevalent in organic synthesis. The ubiquity of the amide bond in natural products, pharmaceuticals and biomolecules provides a strong motivation for the further development of acyl cross-couplings of carboxylic acid derivatives of major practical importance.

Despite progress being considerable, numerous challenges remain. Future research will need to address the development of more reactive catalyst systems, expansion of the substrate scope, development of new sustainable protocols and application to the synthesis of natural products and pharmaceuticals. Future mechanistic studies together with a better understanding of the underlying elementary steps could potentially lead to the general acyl Suzuki platform that is routinely considered for the construction of key structural motifs.

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