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Catalytic C–H Bond Functionalization of Cyclopropane Derivatives

Daniela Sustac Roman and André B. Charette

Abstract The present work describes a comprehensive review of the functionalization of cyclopropyl C–H bonds via transition-metal catalysis. Compared to the enormous number of publications related to direct sp^2 and sp^3 bond transformations in the last two decades, the first full account of direct cyclopropyl C(sp^3)–H bond functionalization was only disclosed in 2011. Both intra- and intermolecular transformations are detailed in the review, including asymmetric reactions. In addition, mechanistic aspects of various Pd-catalyzed cyclopropane functionalizations are discussed.

Keywords C–H functionalization · Catalysis · Cyclopropane · Palladium

Contents

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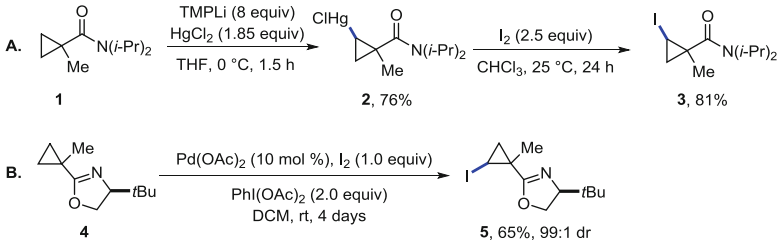
1 Introduction

The cyclopropane ring is a versatile building block in organic synthesis [1]. Cyclopropanes possess unique physical, chemical, and electronic properties as a result of ring strain (27.5 kcal/mol) [2, 3]. Found in numerous natural products, the smallest carbocycle has been both a challenge and an inspiration for synthetic organic chemists [4, 5]. Cyclopropanes are also commonly encountered in current drug targets, where they act as conformational restrictors, thereby orienting a molecule into its bioactive conformation and potentially increasing its potency or providing an improvement in metabolic stability of certain compounds [6]. Recently, the cyclopropane ring was ranked 10th in a top 100 list of the most frequently used rings in the synthesis of small molecule drugs, thus highlighting its continual relevance in medicinally active compounds [7].

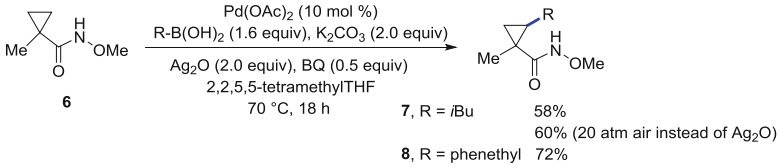
Significant efforts have been dedicated to the syntheses of cyclopropanes in both racemic or enantioenriched forms [8–10]. Cyclopropanes may also act as precursors en route toward accessing more chemical complexity, via involvement in various reactions such as cycloadditions, ring openings, or cross-couplings. In particular, there is ample literature precedence for the functionalization of cyclopropanes via cross-coupling reactions [11]. The cyclopropane can act as either the "nucleophile" (organometallic reagent) or "electrophile" (cyclopropyl halide). Both roles can require numerous synthetic steps to achieve the pre-functionalized partners, resulting in unnecessary waste. One solution to the problem of pre-functionalization would be to use only one pre-functionalized coupling partner and employ the cyclopropyl C–H bond as a functional group. The inherent ring strain of the three-membered ring and orbital rehybridization results in enhanced acidity of cyclopropane C–H bonds, thereby facilitating such transformations. A commonly encountered problem in the activation of alkanes with transition metals is their propensity for β-hydride elimination [12]. In cyclopropanes, β-hydride elimination would result in the formation of a cyclopropene species, which is unfavorable thermodynamically [11]. While C–H bond functionalization at sp^2 and sp^3 centers has been vastly explored in the last decades [13–16], full reports concerning cyclopropanes have only lately appeared in the literature. The current chapter presents a comprehensive review of the direct transformations of the cyclopropane C–H bond via transition-metal catalysis.

2 Early Contributions from the Yu and Sanford Groups

The functionalization of cyclopropanes such as **1** via amide-directed metalation followed by quenching with an electrophile (e.g., iodine) is well known in the literature (Scheme 1a) [17, 18]. However, it was not until 2005 that the first example of a transition-metal-catalyzed direct functionalization process of a cyclopropane C–H bond was disclosed [19]. The use of a chelating oxazoline-based auxiliary (derived from (*S*)-*tert*-leucinol) enabled iodination of primary C(sp^3)–H



Scheme 1 Cyclopropane functionalization via (**a**) amide-directed metalation and (**b**) Pd-catalyzed diastereoselective iodination

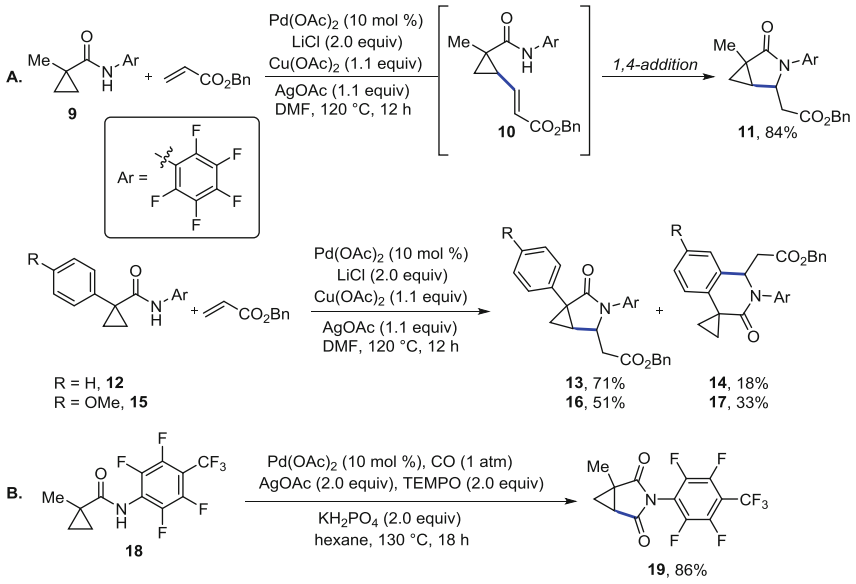


Scheme 2 Yu's Pd-catalyzed alkylation with boronic acids

bonds under Pd catalysis at room temperature. In one example, the secondary C–H group at the β-position of cyclopropyl substrate **4** was exclusively monoiodinated in 65% yield, in preference to the methyl group (Scheme 1b). However, long reaction times (4 days) were required. The oxazoline auxiliary could subsequently be removed under acidic conditions to provide the corresponding cyclopropane carboxylic acid in 99% *ee*.

Later, Yu and coworkers investigated the coupling of C(sp^3)–H bonds with boronic acids, employing $Pd(OAc)_2$ as the catalyst and benzoquinone (BQ)/Ag_2O as oxidants [20] (Scheme 2). The strongly binding, but easily removed, *O*-methyl hydroxamic acid was employed as directing group. The use of 2,2,5,5-tetramethyltetrahydrofuran as solvent was necessary, as it was believed that the bulky solvent not only prevented homocoupling of the boronic acid but also *β*-hydride elimination. Phenethyl and *iso*-butyl boronic acids were employed as coupling partners to provide the corresponding cyclopropyl alkylated products **7** and **8** in 72% and 58% yields, respectively. To improve the practicality of the transformation, the Ag(I) salt could be replaced by air (20 atm) as oxidant.

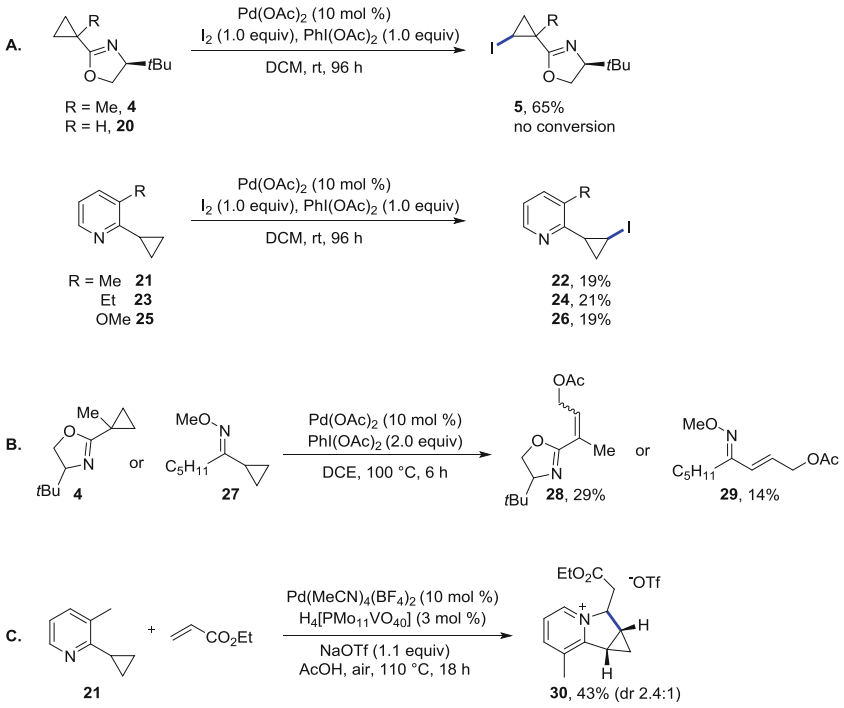
A unique example of direct olefination of a cyclopropane was also disclosed by the Yu lab [21]. An electron-deficient arylamide was employed as directing group, as the previously employed oxazoline or hydroxamic acid was unreactive in the alkenylation. The proposed mechanism for the reaction involves an amide-directed C–H insertion of the Pd(II) catalyst into the cyclopropane methylene C–H bond of **9**, followed by olefin carbopalladation and β-hydride elimination to provide intermediate **10** (Scheme 3a). Pd(0) is re-oxidized back to Pd(II) by Ag(I)/Cu(II), and a tandem 1,4-addition between the amide moiety of **10** and the acrylate provides the corresponding γ-lactam **11** as the sole isolated product. In the presence of an



Scheme 3 Yu's (**a**) direct olefination and (**b**) direct carbonylation of cyclopropanes

α-methyl substituent, the cyclopropane C–H bond is olefinated exclusively in 84% yield to deliver a mixture of *cis*-/*trans*-isomers. However, if an α-aryl substituent is present, significant amounts (18% or 33% yield, respectively) of the competitive sp^2 olefination products **14** and **17** are obtained. Direct cyclopropane carbonylation in the presence of an *N*-arylamide auxiliary is also possible under Pd catalysis [22]. After an amide-directed Pd activation of the cyclopropyl C–H bond of **18**, a migratory insertion of CO takes place, and the subsequent Pd intermediate undergoes C–N reductive elimination to provide a succinimide product **19** in 86% yield (Scheme 3b). More recently, Chatani demonstrated cyclopropyl carbonylation in the presence of an *N*,*N*-bidentate group under $Ru_3(CO)_{12}$ catalysis [23].

Sanford and Kubota investigated the functionalization of cyclopropanes under oxidative conditions, employing directing groups such as oximes or pyridines [24]. Iodination of the cyclopropyl C–H bond was found to be dependent on the steric and electronic environment of the auxiliary; for example, in the absence of the methyl group at the α-position of oxazoline **16**, there was no conversion to product (Scheme 4a). Various substituted pyridines (**21**, **23**, and **25**) could direct the iodination, albeit in low yields, even after long reaction times (Scheme 4a). Attempts at cyclopropane acetoxylation with $PhI(OAc)_2$ using various directing groups, as shown for substrates **4** and **27**, resulted in ring opening of the three-membered ring leading to allylic acetates **28** and **29** (Scheme 4b). In a subsequent communication, Sanford and coworkers disclosed one example of alkenylation of a cyclopropyl C–H bond, resulting in the formation of cyclized pyridinium product **30** in a modest 43% yield (Scheme 4c) [25]. The reaction employed a cationic Pd



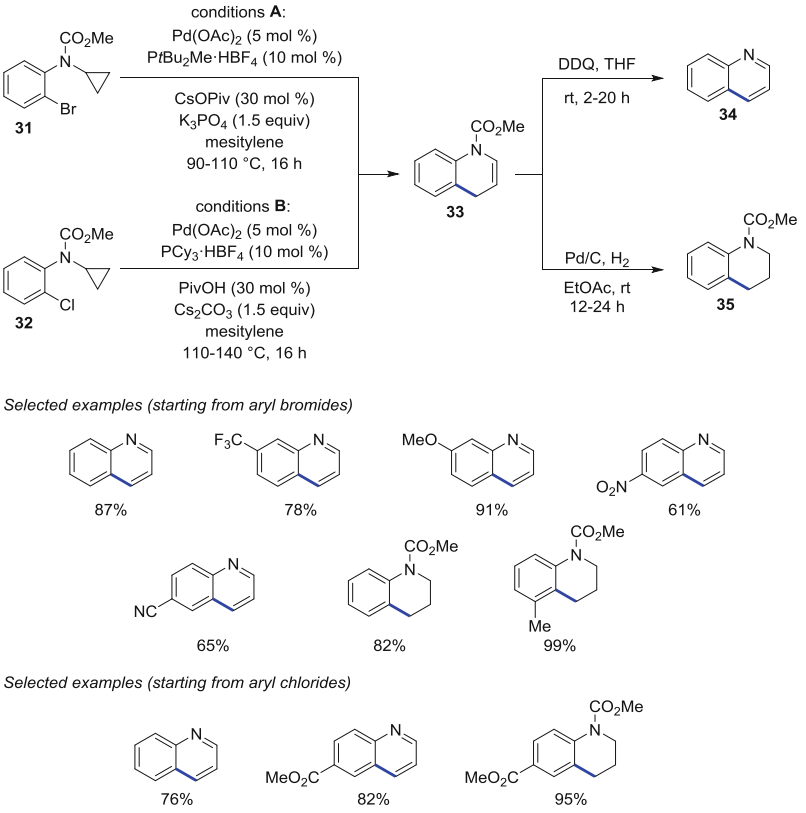
Scheme 4 Cyclopropane functionalization reactions from the Sanford group (**a**) iodination, (**b**) acetoxylation, and (**c**) alkenylation

catalyst, as well as a vanadium-based heteropolyacid ($H_4[PMo_{11}VO_{40}]$) and air as co-oxidants.

3 Intramolecular Direct Functionalization of Cyclopropanes

Similar to the intramolecular functionalization of aryl or alkyl substrates, use of a heteroatom containing-tether not only limits the degree of freedom in the system but also allows for coordination of a transition metal, thus facilitating the reaction.

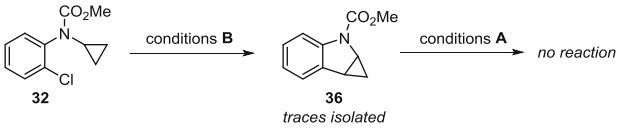
Rousseaux, Liegault, and Fagnou reported the elegant formation of quinoline and tetrahydroquinoline derivatives via a Pd(0)-catalyzed C–H activation of cyclopropane methylene bond [26]. Both bromophenyl and chlorophenyl cyclopropyl carbamates **31** and **32** were found to be suitable substrates for the transformation into dihydroquinoline **33**, albeit under slightly different conditions (Scheme 5). It was found that the resulting dihydroquinolines **33** were prone to decomposition; thus protocols for either oxidation or reduction of the unstable intermediates were developed. A variety of substituents (nitro, cyano, trifluoromethyl, methoxy, ester)



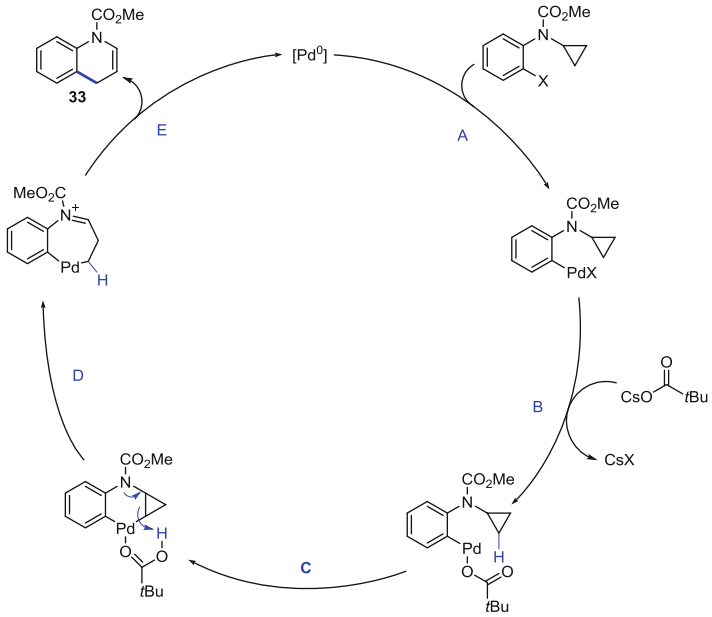
Scheme 5 Synthesis of quinoline and tetraquinoline derivatives via intramolecular cyclopropyl C–H functionalization

were tolerated in the positions *para* and *meta* to the bromide or chloride. A methyl in the *ortho* position provided the corresponding tetrahydroquinoline in 99% yield, demonstrating that the reaction is not sensitive to steric effects.

The authors then investigated the reaction pathway, focusing on whether a concerted metalation–deprotonation (CMD) step occurred prior to the cyclopropane ring opening (recent examples of Pd-catalyzed ring opening of cyclopropanes: [27, 28], [29]). In the absence of a pivalate source, no dihydroquinoline **33** was observed in the cyclization, underlining the involvement of pivalate in the CMD step. Traces of cyclopropyl product **36** were isolated from the reaction of chlorophenyl cyclopropyl carbamate **32**, suggesting the presence of **36** as a possible intermediate in the mechanism (Scheme 6). However, a subsequent control reaction demonstrated that **36** does not undergo ring opening when submitted to the reaction conditions. The result supports the mechanistic proposal that the C–H activation step occurs prior to ring opening and the ring opening of the cyclopropane precedes reductive elimination.



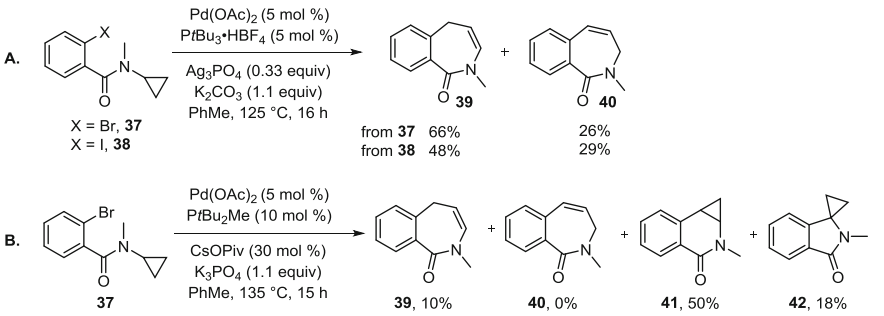
Scheme 6 Control reactions



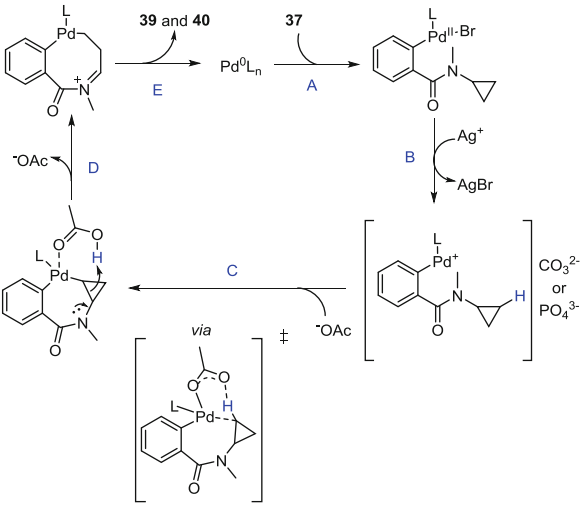
Scheme 7 Proposed reaction mechanism for the formation of dihydroquinoline **33**

Based on the studies, the following mechanism was proposed: oxidative addition of Pd(0) into the aryl halide bond (step A, Scheme 7) is followed by ligand exchange to provide a Pd(II)-pivalate species (step B). Then, pivalate-assisted CMD of the cyclopropyl C–H bond results in the formation of a six-membered palladacycle (step C), which undergoes a cyclopropane ring opening/proton transfer to release ring strain (step D). Deprotonation and reductive elimination (step E) provides the dihydroquinoline **33**.

A further example of cyclopropyl C–H activation followed by ring opening and cyclization was reported by the Charette group in the synthesis of novel seven-membered benzo[*c*]azepine-1-one products [30]. Both bromo- and iodo-cyclopropyl benzamides **37** and **38** were effective substrates for the transformation, providing two isomeric benzazepine-type products **39** and **40** in excellent overall yield (Scheme 8a). When each isomer was separately resubmitted to the reaction conditions, no change was observed for **39**, while **40** slightly isomerized to **39**, suggesting that **40** is the kinetic product and **39** the thermodynamic one. When cyclopropyl benzamide **37** is submitted to Fagnou's reaction conditions with



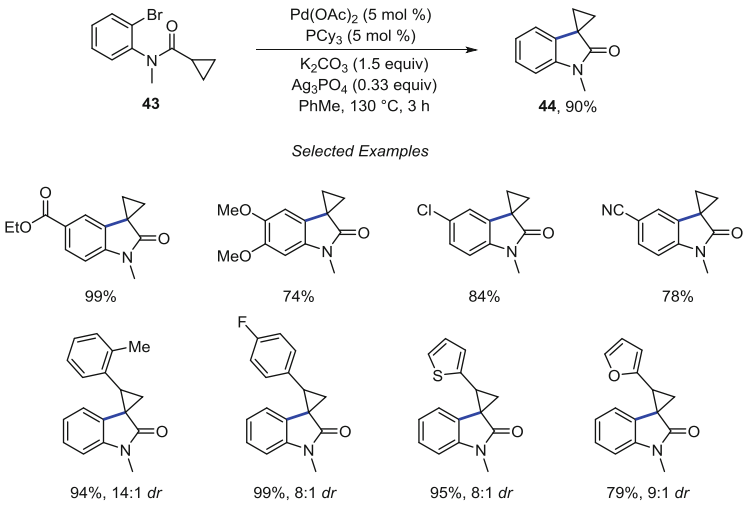
Scheme 8 Synthesis of benzo[*c*]azepine-1-ones, (**a**) optimized reaction conditions, (**b**) pivalate-promoted reaction



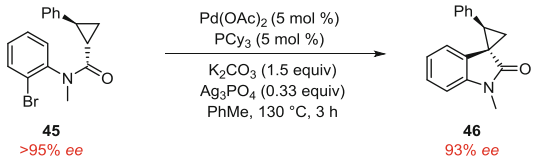
Scheme 9 Plausible mechanism for the formation of benzo[*c*] azepine-1-ones

cesium pivalate, a mixture of spirooxindoles **41** and **42**, as well as benzazepine **39,** is produced, suggesting the intermediacy of **41** in the reaction pathway. However, similar to the control reaction performed in the former Fagnou's report (Scheme 6), **41** was fully recovered when submitted to the optimized reaction conditions. In contrast to other uses of Ag(I) salts as halide sequesters or oxidants, the authors highlight the employment of exactly 1 equiv. Ag^+ as a halide abstractor to provide a reactive cationic Pd species.

The proposed mechanism involves an initial oxidative addition (step A, Scheme 9), followed by halide abstraction by the silver ion to provide a highly reactive cationic Pd species (step B). Acetate-mediated CMD (step C) provides a rare seven-membered ring palladacycle which undergoes ring opening (step D), followed by deprotonation/reductive elimination (step E) to provide the desired products.



Scheme 10 Pd-catalyzed, Ag-mediated synthesis of 3,3′-cyclopropyl spirooxindoles

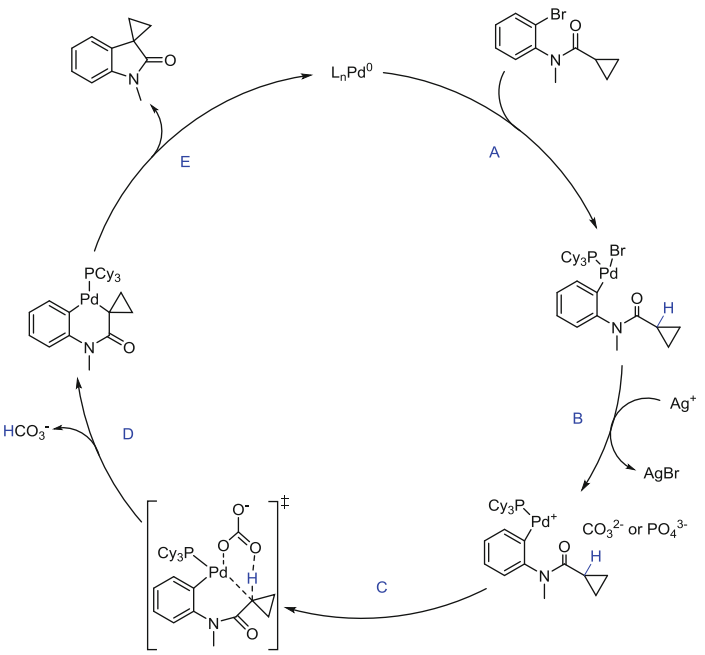


Scheme 11 Epimerization studies of enantioenriched **45**

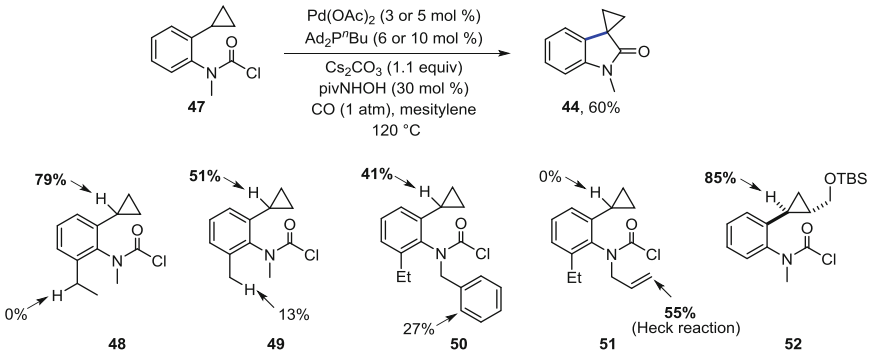
Additionally, Charette and coworkers disclosed the synthesis of biologically active 3,3′-cyclopropyl oxindole **44** via a Pd-catalyzed, Ag-promoted C–H functionalization of cyclopropanecarboxamide **43** derived from 2-bromoaniline (Scheme 10) [31]. Substitution on the aryl ring or on the cyclopropane, including heterocycles such as furan or thiophene, was well tolerated. A mixture of diastereomers was obtained when aryl substitution was present on the cyclopropane. X-ray crystallography confirmed the structure of both diastereomers.

To investigate whether an enolate arylation was occurring, the authors prepared enantioenriched cyclopropane substrate **45** and submitted it to the reaction conditions (Scheme 11). After 3 h, all starting material was consumed, and spirooxindole product **46** showed little erosion of enantioselectivity. Furthermore, the kinetic isotope effect was determined via parallel reactions to be 3.9, identifying C–H cleavage as a rate-determining step. This observation is not consistent with an enolate-like pathway. Furthermore, the use of a weak base (K_2CO_3) makes the enolate pathway quite unlikely.

Based on all the observations, the mechanism shown in Scheme 12 was proposed. An initial oxidative addition step A is followed by bromide abstraction by Ag^+ to give a cationic Pd species (step B), which can undergo a concerted



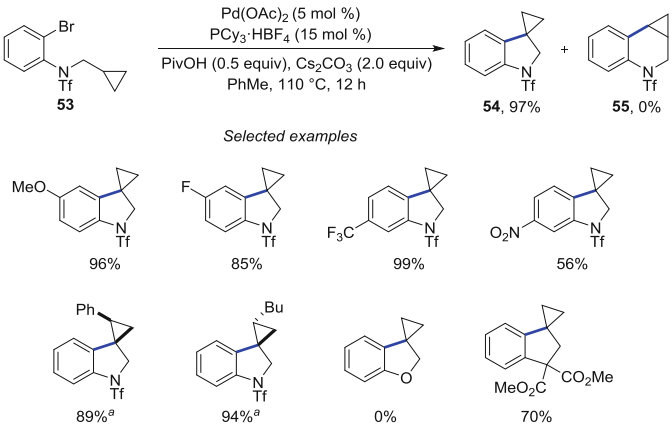
Scheme 12 Proposed reaction mechanism for the synthesis of 3,3′-cyclopropyl spirooxindoles



Scheme 13 Takemoto's synthesis of spirooxindoles and order of reactivity experiments

metalation–deprotonation step mediated by carbonate (or phosphate, C and D). The six-membered palladacycle then undergoes reductive elimination (step E) to give the product and regenerate the Pd^0 catalyst.

A related synthesis of 3,3′-cyclopropyl oxindoles was reported by Takemoto et al. [32]. Carbamoyl chloride **47**, containing a cyclopropyl ring at the *ortho* position, undergoes a Pd-catalyzed cyclization onto the benzylic C–H bond of the cyclopropane to provide the corresponding spirooxindole **44** in 60% yield (Scheme 13). Intramolecular competition reactions investigated the chemoselectivity of the

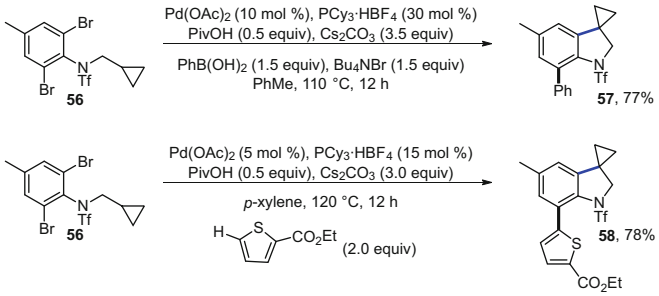


Scheme 14 Pd-catalyzed, pivalate-promoted synthesis of cyclopropyl spiroindolines. [a]With PPh_3 (15 mol%)

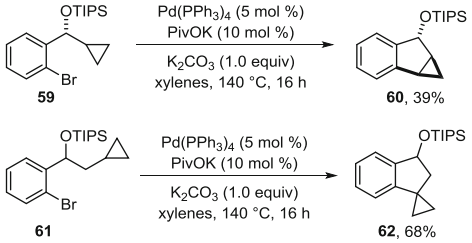
cyclization on the cyclopropane C–H bond versus ethyl (**48**), methyl (**49**), phenyl (**50**), and alkene (**51**). The order of reactivity under the optimized conditions was determined to be the Heck reaction > cyclopropyl C(sp^3)–H activation > C(sp^2)–H activation > methyl C(sp^3)–H activation. In addition, the stereochemistry of the starting material is transmitted to the substrate, as *trans*-substituted **52** provided the corresponding *trans*-spirooxindole in 85% yield.

The Cramer group further reported a synthesis of cyclopropyl spiroindolines [33]. Cyclopropyl substrate **53**, containing a triflyl-protected aniline, undergoes a Pd(0)-catalyzed, pivalic acid-mediated methine C–H activation via a CMD process (Scheme 14). Remarkably, only the five-membered spiroindoline **54** is isolated which can be explained through the easier formation of a six- versus seven-membered palladacycle intermediate. Various functional groups are tolerated in the transformation, including substitution on the cyclopropane with an aryl or alkyl group. In the latter cases, the stereochemistry of the starting material (either *cis* or *trans*) is transferred to the products. A malonate-containing substrate can successfully replace the *N*-triflyl group, but the oxygen analog failed to cyclize to the desired product. In case of 2,6-dibromoaniline **56**, the intramolecular cyclopropane arylation could be followed by a Suzuki coupling to provide **57** in 77% yield or intermolecular C–H arylation to provide **58** in 78% yield in a domino-type reaction (Scheme 15). The triflyl protecting group can be removed by reaction with Red-Al.

Baudoin et al. showed that both methine and methylene cyclopropane C–H bonds can be activated under Pd catalysis to provide the corresponding indanes **60** and **62** (Scheme 16) [34]. The methine functionalization is more efficient (68% vs. 39% yield), due to the formation of a less strained five-membered ring.



Scheme 15 Domino cyclopropane arylation followed by Suzuki coupling or heterocycle arylation

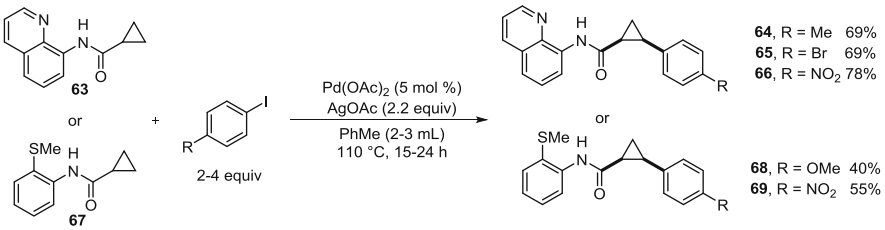


Scheme 16 Intramolecular cyclization onto methylene and methine cyclopropane C–H bonds

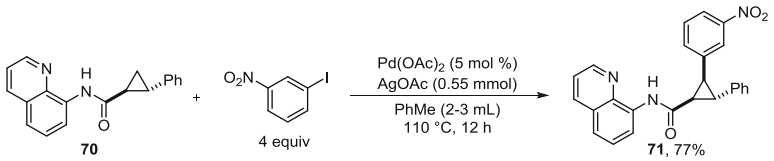
4 Intermolecular Direct Functionalization of Cyclopropanes

The concept of bidentate coordination being able to promote sp^2 or sp^3 C–H activation has been well known in the literature [35]. In comparison to monodentate coordination, bidentate groups maintain a higher degree of stereochemical control around the metal center, which enables the formation of more rigid cyclometalated species. Daugulis et al. introduced the picolinamide and aminoquinolinamide auxiliaries for Pd-catalyzed direct arylation of C(sp^2)–H and C(sp^3)–H centers with aryl iodides [36, 37]. The initial report by Daugulis inspired many other groups to utilize the abovementioned auxiliaries in a wide range of transformations, including C(sp^3)–H arylation or C–heteroatom bond formation [38].

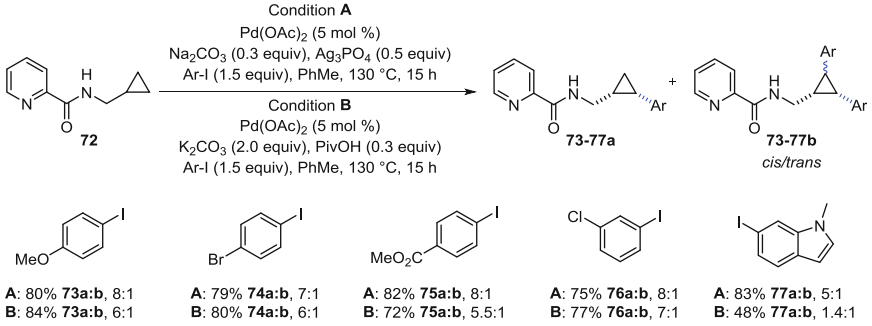
In 2013, Babu et al. [39] and Charette et al. [40] disclosed the direct arylation of cyclopropanes employing the aminoquinolamide and picolinamide auxiliaries, respectively. Thus, the Babu group showed that the methylene C–H bond of cyclopropyl substrate **63** can be functionalized with excess aryl iodide in the presence of catalytic $Pd(OAc)_2$ and stoichiometric AgOAc (Scheme 17) [39]. 2-Methylthioanilide **67** could also be employed as auxiliary; however the arylated cyclopropanes **68** and **69** were obtained in lower yields. Monoarylated cyclopropanes **64–66** and **68–69** were obtained as the *cis*-diastereomer; moreover, *cis*-diarylated cyclopropanes can be obtained when excess (8 equiv.) aryl iodide is employed. It is also possible to access mixed triarylated cyclopropylcarboxamides



Scheme 17 Aminoquinolamide and 2-methylthioanilide-enabled arylation of cyclopropanes



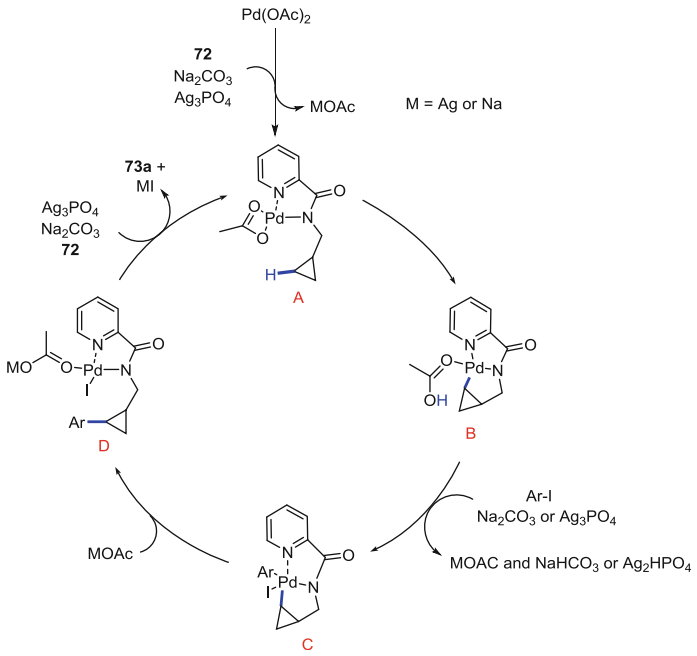
Scheme 18 Synthesis of trisubstituted cyclopropanes



Scheme 19 Picolinamide-directed arylation of cyclopropanes with (hetero)aryl iodides

such as **71** starting from *trans*-disubstituted cyclopropane **70** (Scheme 18). Later, Zeng et al. disclosed one example of the arylation of aminoquinolamide cyclopropane **63** with 4-bromoanisole; however, the yield was only 18% even after 36 h at 140°C [41].

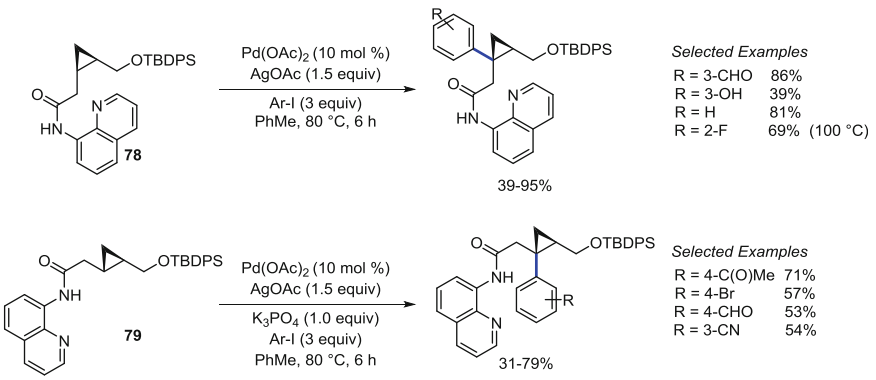
The latter report from the Charette lab disclosed two distinct reaction conditions for the arylation of cyclopropylmethyl picolinamide **72**, employing either excess Ag^+ in the form of Ag_3PO_4 (condition A) or catalytic PivOH (condition B), along with catalytic $Pd(OAc)_2$ (Scheme 19) [40]. The *cis*-diastereomer **73–77a** is obtained exclusively, but in many cases traces of diarylated cyclopropanes **73–77b** (*cis* and *trans*) were observed. The picolinamide group could be transformed into the corresponding *tert*-butylcarbamate by reaction with Boc_2O, followed by oxidative cleavage in the presence of LiOH and H_2O_2. Only aryl iodides were tolerated as coupling partners in the reports from Babu and Charette.



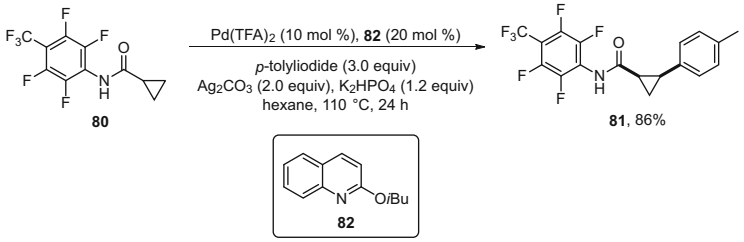
Scheme 20 Proposed mechanism for picolinamide-enabled cyclopropane arylation

Mechanistic evidence from the Daugulis lab [36, 37] and others [42] supports a Pd(II)/(IV) pathway for bidentate-directed C–H functionalization. Sustac and Charette also investigated the mechanism of their cyclopropane arylation [40]. It was determined that an acetate source was necessary for the reaction to proceed, because it is presumably involved in the CMD step. Both Pd(0) and Pd(II) sources could be employed in the Ag-mediated reaction. The silver source is proposed to aid with catalyst regeneration by removing iodide or, in the case of Pd(0) sources, to oxidize them to Pd(II). The proposed mechanism is shown in Scheme 20. Coordination of $Pd(OAc)_2$ to the picolinamide **72** to give complex **A** occurs with loss of one acetate molecule. Then, acetate-mediated concerted metalation–deprotonation provides complex **B**. Oxidative addition of the aryl iodide gives rise to a highly unstable Pd^{IV} complex **C**, which undergoes reductive elimination to provide complex **D**. Loss of iodide mediated by Ag_3PO_4 or Na_2CO_3 and product dissociation and coordination of Pd^{II} to another picolinamide molecule **72** close the catalytic cycle.

The aminoquinolinamide auxiliary was also shown to mediate the construction of 1,1,2-trisubstituted arylcyclopropanes [43]. Substrate **78**, bearing a *cis*-substituted cyclopropyl moiety, reacted smoothly with a variety of (hetero)aryl iodides in a Pd-catalyzed, Ag-mediated transformation (Scheme 21). Notably, substituents such as an aldehyde, a hydroxyl, or an unprotected indole were tolerated under the reaction conditions. Additionally, the reactivity of *trans*-cyclopropyl substrate **79** was investigated (Scheme 21). The challenge here was



Scheme 21 Synthesis of quaternary centers starting from *cis*- or *trans*-substituted cyclopropanes

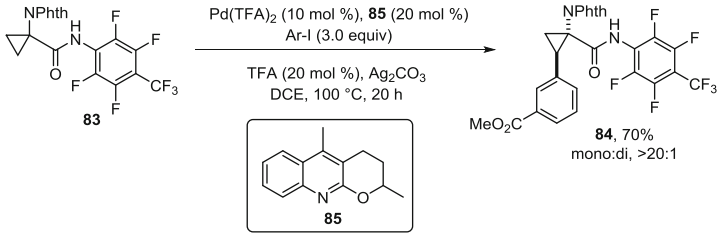


Scheme 22 Pd-catalyzed arylation of cyclopropane **80** enabled by ligand **81**

overcoming the steric effect of the bulky TBDPS group. It was discovered that adding the base K_3PO_4 improved the yield of the reaction (41% without vs. 75% with 1 equiv. K_3PO_4). Various aryl iodides acted as coupling partners in modest to good yields; in general, the yields were lower than in the case of the *cis*-substrate, presumably due to steric effects. Nonetheless, the reaction represents one of the few examples of intermolecular formation of quaternary centers via tertiary C(sp^3)–H functionalization of cyclopropanes.

The Yu group employed a weakly coordinating *N*-arylamide group for the monoarylation of a cyclopropane **80** with *p*-iodotoluene in the presence of 2-isobutoxyquinoline (**82**) as the ligand (Scheme 22) [44]. The ligand had the property of being "mutually repulsive": it allowed for single coordination of Pd to its pyridine portion but also coordination of Pd to the arylamide group of **80**. Such a coordination mode results in an overall lowering the transition state energy of the C(sp^3)–H activation.

Furthermore, selective monoarylation of 1-aminocyclopropane-1-carboxylic acid derivative **83** was achieved in the presence of alkoxy-substituted quinoline **85** in good yield (Scheme 23) [45]. Only one diastereomer of the unnatural amino acid derivative **84** was produced.



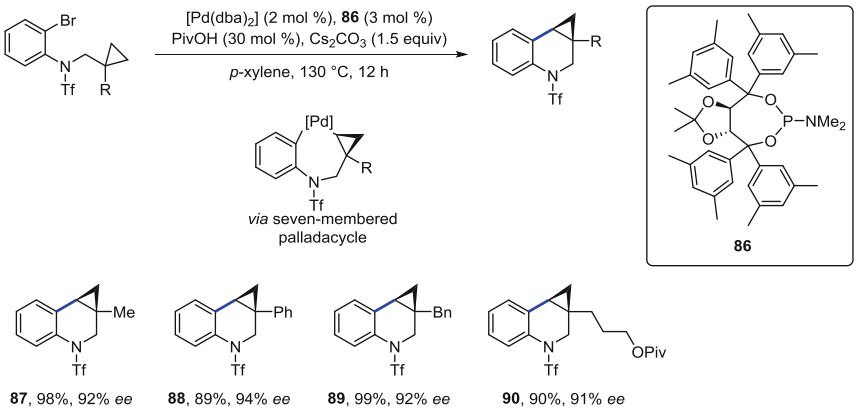
Scheme 23 Selective cyclopropane monoarylation in the presence of alkoxy-quinoline **85**

5 Enantioselective Direct Functionalization of Cyclopropanes

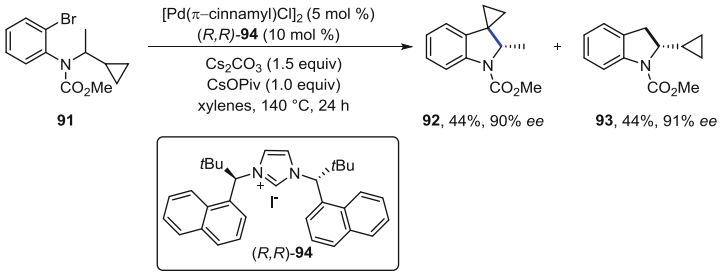
The asymmetric synthesis of cyclopropanes has attracted continual efforts in organic synthesis, due to their relevance in natural products and biologically active compounds. The prevalent methods employed include halomethylmetal mediated processes in the presence of chiral auxiliaries/catalysts (Simmons–Smith-type reactions), transition-metal-catalyzed decomposition of diazoalkanes, Michael-induced ring closures, or asymmetric metalations [8–10, 46]. However, the asymmetric preparation of unfunctionalized cyclopropanes remains relatively undisclosed. The enantioselective activation of unactivated C–H bonds via transition-metal catalysis is an area of active research in organic chemistry [47–49]. Recently, a few groups investigated the enantioselective synthesis of cyclopropanes by direct functionalization reactions.

An intramolecular process for the asymmetric Pd-catalyzed C–H arylation of cyclopropanes was published by the Cramer group [50]. An initial screening of different classes of ligands found TADDOL-type phosphoramidites promising in the synthesis of tetrahydroquinoline **87**. Fine-tuning of the TADDOL structure revealed that ligand **86**, containing 3,5-xylyl substituents, along with the addition of catalytic amounts of pivalic acid to the reaction, provided the best yields and enantiomeric excesses (Scheme 24). The transformation also represented a rare example of the formation of a seven-membered palladacycle as a reaction intermediate. Notably, the cyclization can be performed with catalyst loadings as low as 1 mol%, without affecting the yield or enantioselectivity. Various α-substituted cyclopropanes were tolerated in the reaction to provide the corresponding tetrahydroquinolines **87**–**90**. Of note, the presence of a phenyl or benzyl group in compounds **88** and **89**, respectively, did not result in a competing C(sp^2)–H functionalization. In contrast, the absence of α-substitution led to the synthesis of spiroindolines (Scheme 14, vide supra). The triflyl group of **88** was cleaved by reaction with Red-Al in an excellent 99% yield.

A system consisting of a chiral NHC ligand and a Pd(0) catalyst was shown to activate racemic cyclopropyl substrate **91** in a publication by Kündig et al. [51]. The reaction was not selective as a 1:1 mixture of products arising from the reaction of



Scheme 24 Pd-catalyzed enantioselective aylation of cyclopropanes in the presence of TADDOL-derived ligand **86**

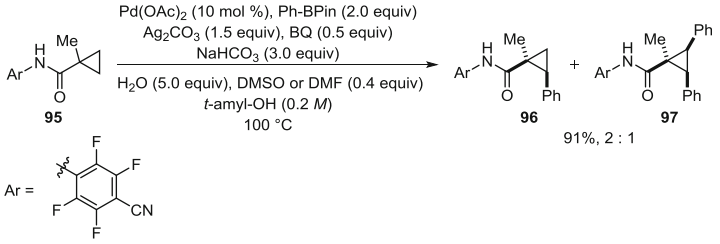


Scheme 25 Enantioselective cyclopropane functionalization promoted by NHC ligand **94**

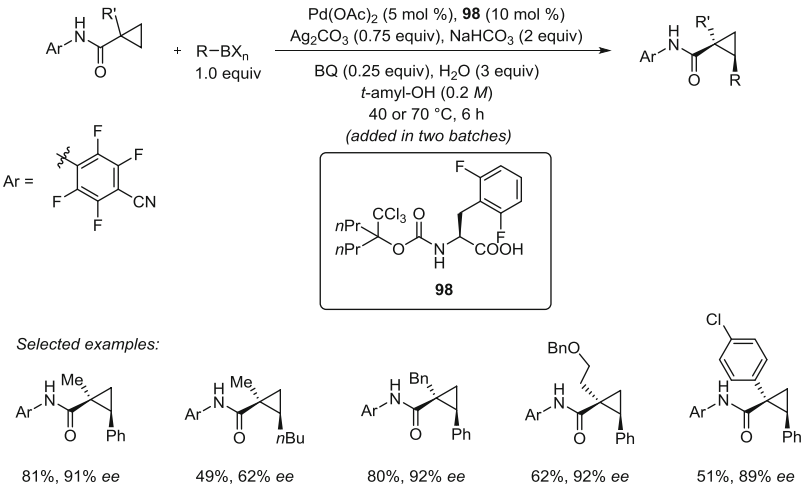
the cyclopropyl methine C–H bond (compound **92**) and methyl C–H bond (compound **93**) was obtained (Scheme 25).

In 2011, the Yu group disclosed the first example of intermolecular enantioselective C–H functionalization of cyclopropanes [52]. Initially, the cross-coupling of amide cyclopropane **95** with phenylboronic acid pinacol ester (Ph-BPin) was investigated in the absence of a chiral ligand. It was established that the transformation takes place at 100°C, in the presence of $Pd(OAc)_2$ as the catalyst, giving rise to a 2:1 mixture of mono- and diarylated *cis*-cyclopropanes **96** and **97**, respectively. Alkyl potassium trifluoroborates were also compatible coupling partners, when the base was changed to Li_2CO_3 (Scheme 26).

A thorough screen of amino acids and their derivatives led to the application of chiral ligand **98** derived from phenylalanine in the intermolecular arylation of cyclopropane derivatives (Scheme 27) [52]. Albeit not practical, the addition of the catalyst and ligand in two batches at 40°C was optimal for the yield and enantioselectivity. Traces of water were also required in the transformation, and it was speculated that water aided in the transmetalation step. Ph-BPin was the best nucleophile, while the employment of alkyl boronic esters required increased



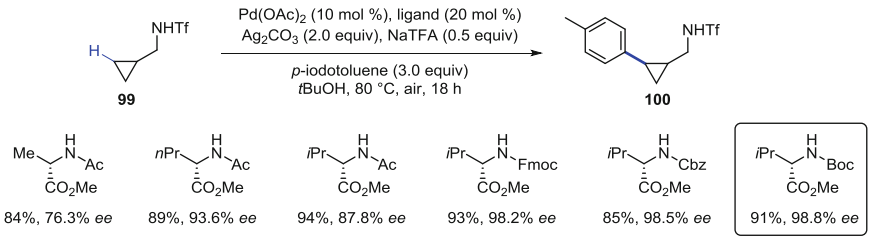
Scheme 26 Optimized conditions for coupling of amide cyclopropane **95** with phenyl boronic ester



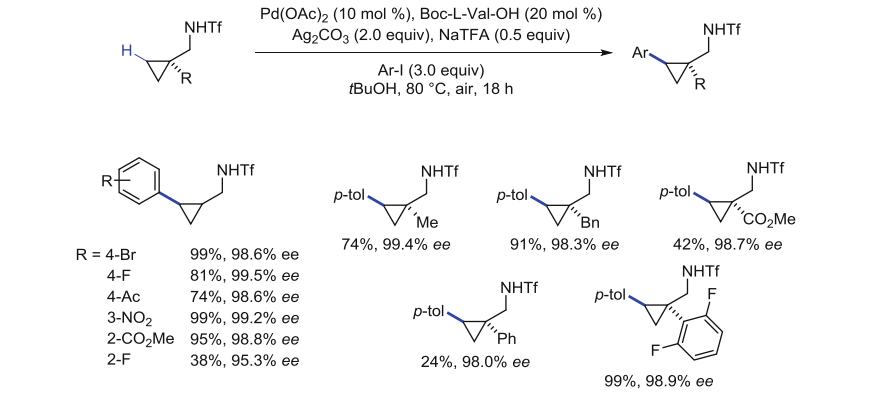
Scheme 27 Enantioselective arylation of cyclopropanes in the presence of mono-protected amino acid ligand **98** and selected examples

temperatures (70°C), leading to slightly lower yields and enantioselectivities. It was also necessary to block the α-position of the cyclopropane in all examples, leading in some cases to lengthy syntheses of the starting materials. Nonetheless, groups such as methyl, isopropyl, cyclopentyl, β-benzyl ethers, γ-protected amines, or even aryls were tolerated in the α-position.

Most recently, the Yu group employed a triflyl-protected amine as a directing group in the asymmetric, intermolecular, and Pd-catalyzed functionalization of cyclopropylmethylamine **99** with aryl iodides (Scheme 28) [53]. Judicious screening of chiral mono-*N*-protected amino acids revealed Boc-L-Val-OH as the ideal ligand. In general, amino acid side chains that were branched (vs. linear) provided better enantioselectivities, while carbamates (e.g., Boc, Fmoc, Cbz) were desirable as *N*-protecting groups. Remarkably, the reaction provided exclusively the monoarylated product **100**, as in all cases the remaining mass balance consisted of unreacted starting material. Furthermore, in contrast to the previous report [52], the presence of a substituent in the α-position of the cyclopropane was not required for reactivity.



Scheme 28 Screen of ligands for the arylation of cyclopropane **99**

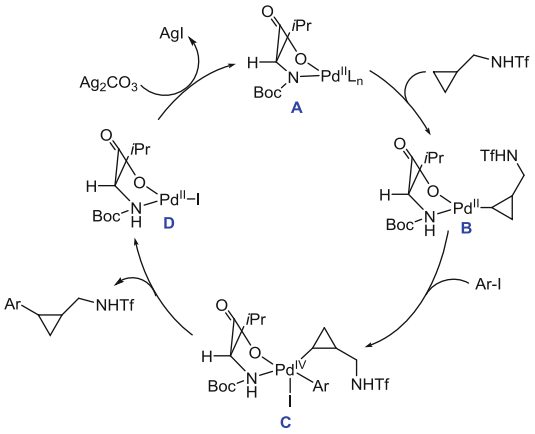


Scheme 29 Enantioselective arylation of cyclopropanes with various aryl iodides

The cyclopropyl methylene C–H bond was exclusively functionalized in the presence of competing aryl, benzyl, or methyl C–H bonds (Scheme 29). Additionally, a wide array of substituted aryl iodides could be employed as coupling partners in excellent yields and enantioselectivities; notably, an ester substituent on the cyclopropane was tolerated, affording the corresponding product in 42% yield. However, heteroaryl iodides were unreactive which represents a limitation to the methodology.

In contrast with the initial report employing boronic esters that follow a Pd(II)/(0) pathway [52], the current methodology is proposed to occur via a Pd(II)/(IV) mechanism. No reaction was observed in the presence of a Pd(0) source or in the absence of the silver salt. A plausible catalytic cycle involves an initial C–H activation step of palladium complex **A** to provide palladacycle **B**, followed by oxidative addition of the aryl iodide to give a highly reactive Pd(IV) complex **C**, which undergoes rapid reductive elimination to provide the desired product and a Pd(II) complex **D** (Scheme 30). The last step is loss of iodide, mediated by the silver salt. The use of the weakly coordinating –NHTf group by the Yu lab has allowed for the development of the first intermolecular and enantioselective C(sp^3)–H activation via a Pd(II)/(IV) catalytic cycle.

Scheme 30 Plausible mechanism for cyclopropane arylation via a Pd(II)/(IV) pathway



6 Conclusion and Outlook

Over the last decade, continued interest in transition-metal-catalyzed C(sp^3)–H bond functionalization reactions has allowed for the development of several methodologies for direct transformations of cyclopropanes. Intramolecular reactions resulted in the synthesis of biologically relevant cyclopropyloxindoles, as well as access to complex quinoline- or benzazepine-type products. Intermolecular transformations employed strongly binding auxiliaries or weakly coordinating directing groups to achieve arylation of cyclopropanes. A significant breakthrough represented the asymmetric direct arylation of cyclopropanes; in particular, contributions from the Yu group have put forward the use of mono-protected amino acids as chiral ligands in Pd(0)/(II) or Pd(II)/(IV) catalysis. Although at the moment the use of Pd salts as catalysts for the activation of cyclopropanes is predominant, it is desirable that less expensive metals such as Cu, Fe, Ni, or Co are also explored for the transformation.

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