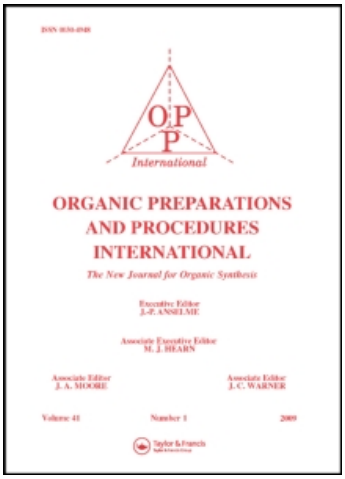

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Online publication date: 03 February 2010

To cite this Article Gagnon, Alexandre , Duplessis, Martin and Fader, Lee(2010) 'Arylcyclopropanes: Properties, Synthesis and Use in Medicinal Chemistry', Organic Preparations and Procedures International, 42: 1, 1 — 69
To link to this Article: DOI: 10.1080/00304940903507788
URL: http://dx.doi.org/10.1080/00304940903507788

Organic Preparations and Procedures International, 42:1–69, 2010

ISSN: 0030-4948 print
DOI: 10.1080/00304940903507788

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Introduction

The cyclopropyl group is commonly found in natural products and in biologically active synthetic compounds.[1] Because of its unique steric, electronic and conformational properties, this smallest cyclic alkyl group is frequently utilized in medicinal chemistry in the context of structure activity relationship (SAR) studies. Due to its prevalence in organic and medicinal chemistry, numerous reviews covering the preparation and reactivity of cyclopropanes have appeared.[2] Arylcyclopropanes (also called cyclopropylarenes) are compounds where the cyclopropyl group is directly attached to an aryl moiety. The introduction of small cyclic groups on aryl scaffolds of medicinally relevant compounds allows the exploration of lipophilic binding pockets and the optimization of hydrophobic interactions with a biological target.[3] In some cases, the cyclopropyl group also provides an improvement in metabolic stability over linear alkyl groups, resulting in a superior pharmacokinetic profile. In addition, cyclopropanes can be used to "lock" a molecule into its bioactive conformation, potentially leading to a significant increase in potency.[4] The broad utility of cyclopropanes and the ubiquity of the aryl moiety thus make the arylcyclopropane a very attractive motif to the medicinal chemist.

In the first part of this review, the conjugative, physical and conformational properties associated with arylcyclopropanes are discussed. The microsomal metabolism of this class of compounds and their use in medicinal chemistry is then addressed. In the second part, the synthesis of arylcyclopropanes through coupling reactions involving cyclopropyl fragments is reviewed. The cyclopropanation of alkenes has been extensively covered elsewhere and is therefore not included in the present review.

Received July 17, 2009; in final form November 16, 2009.

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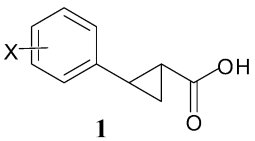
1. Conjugative, Physical and Conformational Properties

The ring strain associated with the cyclopropyl group results in unique physical, chemical and electronic properties. In arylcyclopropanes, the cyclopropyl group acts as a competent electron donating group,[5] thus resulting in the activation of the phenyl ring. This behavior can be explained by the fact that the molecular orbitals of the cyclopropyl group can enter into conjugation with adjacent p orbitals or π systems. This conjugative property of the cyclopropyl ring was first investigated more than ninety years ago through UV spectroscopic experiments on arylcyclopropanes.[6] In this seminal study, a comparison of the absorption spectra of benzoyl cyclopropanes and their ethylenic and saturated analogs showed a shift towards the visible region for the cyclopropyl compounds, similarly but to a lesser extent than the unsaturated compounds, supporting the fact that the cyclopropyl group can enter into conjugation with π-systems. This conjugative effect was later confirmed in experiments where the UV absorption bands for compounds containing a cyclopropyl group adjacent to a double bond were found to have a λ_{max} between their alkyl and unsaturated analogs.[7,8] This hyperconjugation was also observed in the UV spectra of 2-cyclopropylpyridine[9] and 2,4-dinitrophenylhydrazones derived from cyclopropyl ketones[10] where a shift in the λ_{max} was also detected in comparison with the saturated analogs.

In order to evaluate the capacity of the cyclopropyl group to transmit electronic effects from a phenyl ring to a carboxylic acid, the pK_a of different substituted *trans*-2-phenylcyclopropane carboxylic acids **1** (*Figure 1*) was measured potentiometrically.[11] In this study, little variation in pK_a values was observed for compounds with electron withdrawing and electron donating groups, suggesting that, contrary to the spectroscopic experiments, the cyclopropyl group is incapable of transmitting electronic effects through conjugation.

The comparison of the Hammett ρ value for the dissociation of *trans*-cinnamic acid **2**, *trans*-2-phenylcyclopropane carboxylic acid **3**, and β-phenylpropionic acid **4** provided further evidence against the conjugative properties of the cyclopropyl ring (*Figure 2*). The conclusions put forward following these studies were again in strong contradiction with previous reports and therefore served as impetus to other research groups to further explore the conjugative properties of the cyclopropyl group.



1

X	pK_a (H_2O, 25°C)
1a : *m*-NO_2	4.408 ± 0.004
1b : *p*-NO_2	4.448 ± 0.006
1c : *m*-Cl	4.514 ± 0.005
1d : *p*-Cl	4.529 ± 0.003
1e : H	4.570 ± 0.002
1f : *p*-NHCOMe	4.570 ± 0.002
1g : *p*-Me	4.597 ± 0.003
1h : *p*-OMe	4.617 ± 0.002

Figure 1

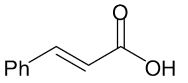
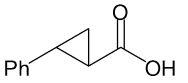
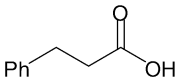
Series		Hammett ρ value
	(**2**)	0.466
	(**3**)	0.182
	(**4**)	0.212

Figure 2

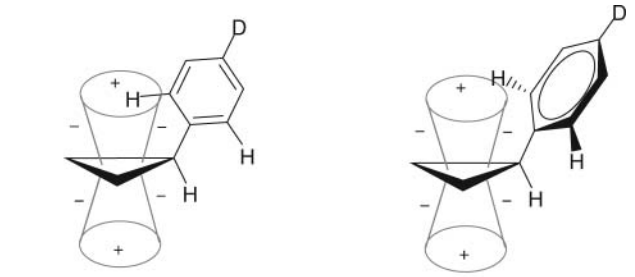
In order to evaluate the competence of the cyclopropyl group in transmitting electronic effects from a phenyl ring, kinetic experiments on the rates of hydrolysis of 2-phenylcyclopropane carboxylic esters were conducted.[12] These experiments showed a significant difference in the rate of hydrolysis depending on the electronic nature of the aryl moiety, indicating that the cyclopropane is in fact better than a saturated ethyl linker in transmitting electronic effects. Additionally, the determination of ionization constants of *trans*-2-phenylcyclopropane carboxylic acids in ethanol rather than water provided further evidence of the conjugative effect of the cyclopropyl ring.[13–15]

The conjugative interaction between cyclopropanes and π-systems in arylcyclopropanes results in important conformational effects. Two limiting low-energy conformations, which can be characterized by the angle θ between the plane of the aromatic ring and the benzylic hydrogen of the cyclopropane, have been proposed for cyclopropylarenes (*Figure 3*). In the bisected conformation **5** ($\theta = 0^\circ$), the benzylic hydrogen is in the plane of the phenyl ring, thus allowing optimal electronic interaction between the π-system of the aromatic ring and the e_a and $e_a{}^*$ frontier Walsh-type orbitals of the cyclopropyl group. In the perpendicular conformation **6** ($\theta = 90^\circ$), the benzylic hydrogen of the phenylcyclopropane is orthogonal to the aromatic ring, resulting in poor molecular overlap between both fragments. Based on calorimetric studies, the thermodynamic stabilization provided by the interaction between the cyclopropyl group and the aromatic system was calculated to be 1.9 kcal/mol.[16] Following molecular mechanics calculations on phenylcyclopropane, a barrier of 1.2 kcal/mol was predicted for the interconversion from the bisected to the

5
bisected
conformation
θ = 0°

6
perpendicular
conformation
θ = 90°

Figure 3



7
shielding of *ortho* protons in the bisected conformation

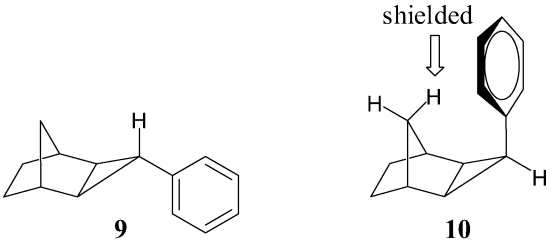
8
deshielding of *ortho* protons in the perpendicular conformation

Figure 4

perpendicular conformation and a difference in energy of 1.1 kcal/mol between both conformers was calculated.[17] These values thus predict that the cyclopropyl group can freely rotate at room temperature, but with a slight preference for the bisected conformation.

Nuclear magnetic resonance (NMR) studies on *p*-deuteriophenylcyclopropane have revealed a high shielding for the *ortho* protons of the aromatic ring, as indicated by their chemical shifts in the proton spectra (*Figure 4*).[18–20] Since protons located above the plane of the ring experience shielding (conformer **7**) and protons located near the plane of the ring experience deshielding (conformer **8**), the upfield shift observed for the *ortho* protons indicates a higher population of the bisected conformation. In this conformation, the *ortho* protons are directly in the anisotropic shielding area of the cyclopropyl ring and are therefore shifted upfield compared to *meta* and *para* protons. While the chemical shift of the *meta* protons is only slightly affected by a decrease in temperature, an increase in the shielding of the *ortho* protons is observed. Therefore, contrary to toluene where conjugation is not possible, a temperature dependence is observed for $\nu(\delta_o - \delta_m)$, supporting the fact that phenylcyclopropane preferentially adopts the bisected conformation.[21,22]

In order to further study the anisotropic effects present in arylcyclopropanes, Creary prepared the norbornene derivatives **9** and **10** which can preferentially adopt one of the two extreme conformations (*Figure 5*).[23] In the case of the *exo* isomer **9**, an upfield shift (shielding) was observed for the *ortho* protons of the phenyl ring, suggesting that this molecule



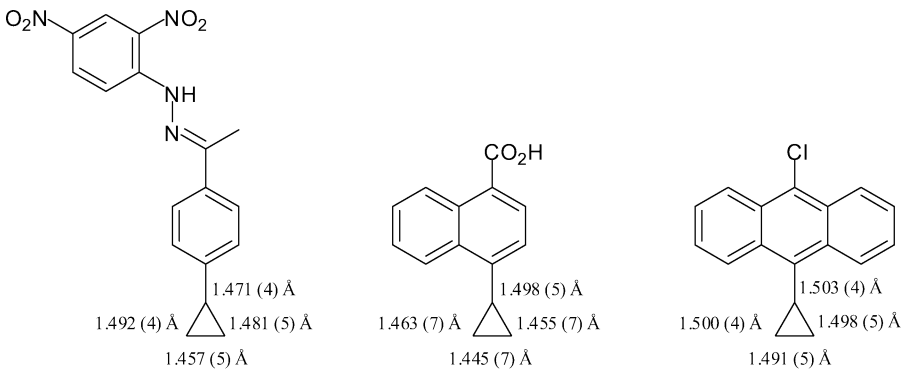
9
bisected conformation

10
"locked" perpendicular conformation

Figure 5

exists predominently in the bisected conformation. However, in the *endo* analogue **10**, a shielding effect for the C8 protons of the norbonene skeleton was observed, indicating a preference for the perpendicular conformation. This observation was rationalized by a high energy bisected conformation resulting from major steric interactions between the *ortho* protons of the aryl ring in **10** and the norbornene C8 hydrogens, leading to a "locked" perpendicular conformation. These experiments suggest that arylcyclopropanes preferentially adopt the bisected conformation, unless steric repulsions prevent the compound from reaching this state.

X-Ray crystallographic experiments on different arylcyclopropanes have allowed the investigation on the conformation of the cyclopropyl group relative to the aryl moiety. The X-ray structure determination of phenylcyclopropane itself revealed that the molecule adopts the bisected conformation exclusively.[24] The structure also featured a shortened distal C—C bond of the cyclopropane ring relative to the average ring bond-length, consistent with conjugation with the π-system of the phenyl ring. X-ray structures of a number of analogs of phenylcyclopropane have also highlighted the unique conformational properties of this substructure class. For example, the X-ray crystal structure of the (2,4-dinitrophenyl)hydrazine derivative of *p*-cyclopropylacetophenone **11**, 4-cyclopropyl-1-naphthalenecarboxylic acid **12**, and 9-chloro-10-cyclopropylanthracene **13** (*Figure 6*) revealed that the minimum energy conformation was reached in each case through minimization of repulsive interactions and optimization of conjugative effects.[25] As predicted by molecular mechanics calculations, the X-ray structure of compound **11** revealed that the arylcyclopropane perfectly adopts the bisected conformation. However, due to steric interactions between the cyclopropyl ring and the naphthyl 8-hydrogen, compound **12** adopted an intermediate conformation with an angle $\theta = 54^\circ$, thus minimizing repulsive interactions while maintaining some degree of overlap between the orbitals of the cyclopropane and the aromatic ring. Finally, the anthracene compound **13** crystallized in the perpendicular conformation ($\theta = 88^\circ$) due to strong repulsive interactions that prevented the molecule from reaching the bisected conformation. Important lengthening of the vicinal C—C bonds and shortening of the distal C—C bond was observed for compounds that were approaching the bisected conformation, suggesting a more optimal conjugation between the cyclopropyl group and the aromatic



11 **12** **13**

Figure 6

system. This distortion of the C—C bond lengths was however negligible in the case of the anthracene compound **13**, as a consequence of the adopted perpendicular conformation.

In another study, the X-ray crystal structure of 4-cyclopropylacetanilide clearly showed that at −100°C, the compound adopts the bisected conformation.[26] Moreover, as predicted from molecular orbital theory, a lengthening of the vicinal C—C bonds and shortening of the distal C—C bond was observed, as a result of the conjugative effects between the cyclopropyl group and the phenyl ring.

2. Microsomal Metabolism

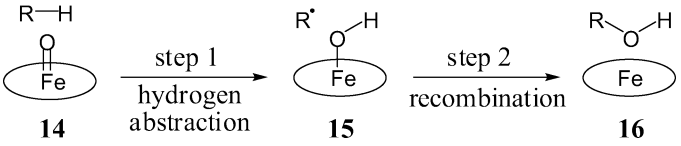
Cytochrome P450 (CYP450) monooxygenase isozymes are membrane-bound enzymes that are found in the smooth endoplasmic reticulum of the liver and other tissues. These iron-containing enzymes are responsible for the phase 1 metabolism of endogenous and exogenous (xenobiotics) compounds. This process results in the incorporation of oxygen into the chemical structure of exogenous molecules through an oxidative mechanism. The introduction of a hydroxyl group in hydrophobic substances allows further conjugation with hydrophilic compounds through phase 2 metabolism, thus facilitating the elimination of the metabolite *via* conventional excretion pathways.

Drugs are exogenous substances and are therefore susceptible to degradation by cytochromes P450 during the phase 1 metabolism. Seven human isoforms of CYP450 are responsible for the metabolism of more than 90% of all pharmaceuticals in clinical use.[27] The microsomal half life $t_{\frac{1}{2}}$ of a biologically active compound is used as an *in vitro* model intended to predict the susceptibility of a compound toward *in vivo* phase 1 metabolism. Consequently, during the early phase of drug discovery, optimization of the potency of a lead compound is often performed in parallel with the optimization of the microsomal stability in order to obtain a desirable pharmacokinetic profile.[28]

Oxidation of exogenous compounds by CYP450 usually involves one of three mechanisms:[29]

1. abstraction of one hydrogen atom from the substrate followed by recombination of the transient radical with the oxoferryl intermediate leading to the hydroxylated product;
2. electron transfer from the substrate to the ferryl species followed by rearrangement and hydroxylation (for substrates with heteroatoms or compounds with low oxidation potential);
3. direct addition of the ferryl oxygen to a π-bond (for compounds with double bonds).

The commonly accepted mechanism for the hydroxylation of hydrocarbons by CYP450 isozymes involves a two-step process that results in the insertion of an oxygen atom into a C—H bond of the molecule (*Scheme 1*). The first step consists of a transfer of a hydrogen

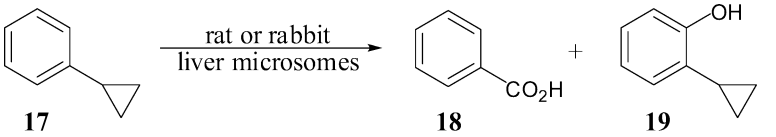


Scheme 1

atom from the carbon of **14** to the ferryl oxygen center, leading to the formation of the radical species **15**. In the second step, this radical reacts with the iron complex to generate the hydroxylated product **16**. In the case of substrates with low oxidation potential, an alternative mechanism that implies electron transfer has also been proposed.[30]

One widely used method for detecting radical intermediates and thus differentiating between hydrogen abstraction and electron transfer mechanisms involves introducing a cyclopropyl group into a substrate and searching for rearranged products.[31] Since the introduction of a cyclopropyl group in an aromatic compound results in a lower oxidation potential, the metabolism by cytochromes then favors the electron transfer mechanism over the hydrogen atom abstraction. For these reasons, arylcyclopropanes have been frequently utilized as probes to study the mechanism of CYP450 enzymes.

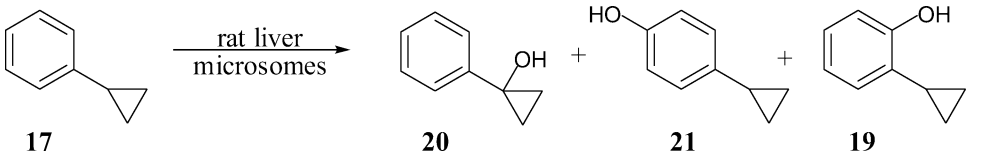
The oxidation of cyclopropylbenzene by rat liver microsomal (RLM) cytochrome P450 was first studied by Suckling *et al.* in 1982.[32] The oxidation of phenylcyclopropane **17** by RLM P450s (obtained from the livers of rats treated with phenobarbitone) gave benzoic acid **18** as the major metabolite with a small amount of 2-cyclopropylphenol **19** (*Scheme 2*). To explain the formation of benzoic acid, the authors proposed a mechanism



Scheme 2

involving a triple oxidation of **17**. The same metabolites were also observed following the oxidation of cyclopropylbenzene by partially purified rat liver or rabbit liver microsomes in the presence of NADPH-generating system. However, performing the oxidation with purified rabbit cytochromes led exclusively to the production of benzoic acid, suggesting that the nature of the microsomal CYP450 has a considerable impact on the metabolism of phenylcyclopropane.[33]

Contrary to earlier reports, Hanzlik *et al.* could not generate benzoic acid during metabolism studies on cyclopropylbenzene **17** using phenobarbitone (PB) or β-naphthylflavone (BNF) induced rat liver microsomes (RLM) (*Scheme 3*).[34] Instead,

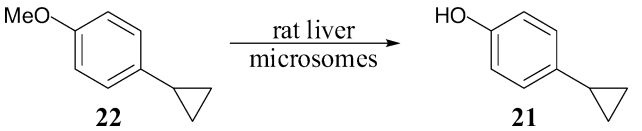


Scheme 3

treatment of **17** with RLM or PB-RLM led to 1-phenylcyclopropanol **20** and 4-cyclopropylphenol **21**, whereas treatment with BNF-RLM gave 2-cyclopropylphenol **19** as an additional metabolite. In addition, the kinetics of the oxidation of cumene (isopropyl benzene) by PB-RLM was found to be altered when performed in the presence of cyclopropylbenzene, suggesting that **17** is a suicide substrate for one or more isozymes of

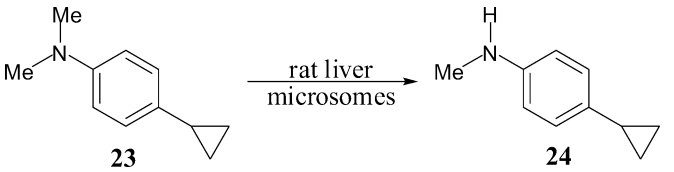
P450. Since no ring opening products were detected, a hydrogen abstraction mechanism was proposed for the metabolism of cyclopropylbenzene by rat liver microsomes.

In another study, the incorporation of a methoxy group *para* to the cyclopropane (compound **22**) redirected the metabolism towards the ether and led predominantly to *O*-demethylation (product **21**, *Scheme 4*).



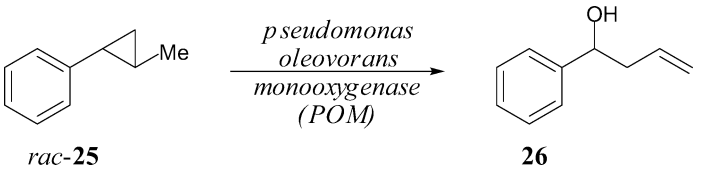
Scheme 4

Similarly, the metabolism of *para*-cyclopropyl *N*,*N*-dimethylaniline **23** by horseradish peroxidase, liver microsomes (from phenobarbital-induced rats) or purified reconstituted CYP450–2B1 also led to metabolism at the heteroatom position, giving the demethylation product **24** as the major metabolite (*Scheme 5*).[35] These two examples show that, in the presence of CYP450 isozymes, the arylcyclopropane moiety is metabolically more stable than a methylether or a dimethylamine.



Scheme 5

Pseudomonas oleovorans monooxygenase (POM) is a non-heme NAD(P)H/O_2-dependent metalloenzyme that catalyzes the incorporation of molecular oxygen into unactivated organic molecules. Upon treatment of racemic *trans*-2-phenyl-1-methylcyclopropane **25** with this enzyme, the ring opening product **26** was obtained (*Scheme 6*). Since the

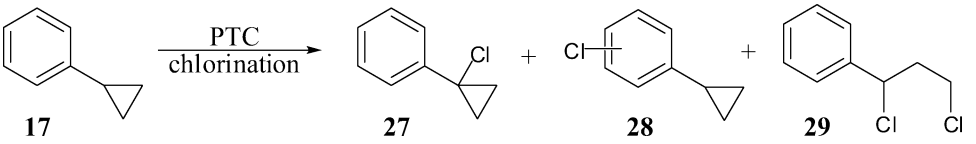


Scheme 6

product was obtained in 23% *ee*, the authors hypothesized that the overall sequence proceeded through a non concerted radical mechanism.[36]

Chemical models have been designed in order to investigate the mechanism of the CYP450 induced metabolism of cyclopropylarenes and to shed light over the controversy between hydrogen abstraction and electron transfer mechanisms. Towards this goal, Riley and Hanzlik studied the free radical chlorination of arylcyclopropanes using hypochlorite-based phase transfer catalysis (PTC) and observed that chlorination of

phenylcyclopropane **17** leads to a mixture of 1-chloro-1-phenylcyclopropane **27**, 2-, 3-, and 4-chloro-cyclopropylbenzene **28** and 1,3-dichloro-1-phenylpropane **29** (*Scheme 7*). The authors concluded that the formation of the ring opening product supports the electron transfer mechanism for the metabolism of arylcyclopropanes by CYP450 enzymes.[37]



Scheme 7

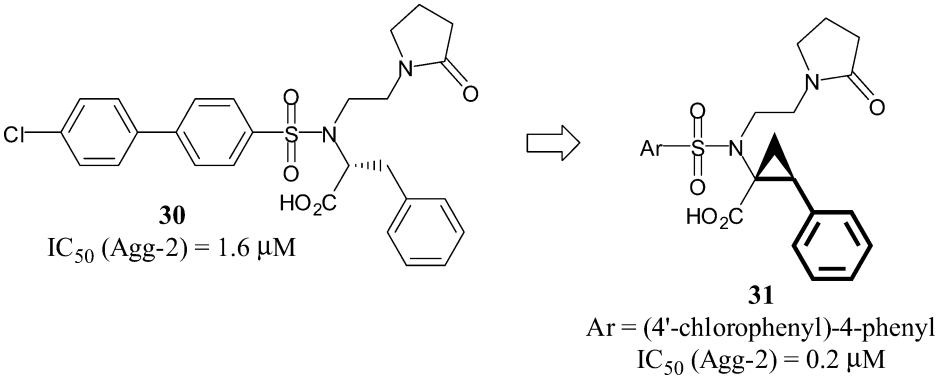
The prediction of metabolism sites of exogenous compounds through computational methods is finding increasing use in the pharmaceutical industry. For example, metabolite predictions on different *para*-substituted anisoles was recently performed through *ab initio* calculations.[38] Using the concept of hydrogen atom abstraction, spin delocalization, and hydroxyl radical recombination, de Groot *et al.* were able to rationalize the oxidative metabolites observed experimentally by Hanzlik for those specific substrates. They established that hydrogen atom abstraction from the benzylic carbon atom was primarily determined by the stability of the radical formed. In the case of anisole, the study predicted hydrogen atom abstraction from the methyl ether, leading to demethylated product. However, in the case of *para*-cyclopropyl anisole, hydrogen atom abstraction from the benzylic cyclopropyl carbon was predicted, which would lead to the corresponding benzylic alcohol with no demethylation of the ether group. According to their calculations, the abstraction of a hydrogen from a benzylic position would be favored over hydrogen abstraction from other positions. However, this was not in agreement with the study of Hanzlik where the demethylated product was observed as the major metabolite.

The generally accepted mechanism for hydroxylation of hydrocarbons by CYP450 has recently been questioned by some research groups. Recent studies have demonstrated that the lifetime of a radical during P450 hydroxylation would be too short for the formation of a transient radical intermediate. Mechanistic alternatives that involve five-coordinate carbon species or agostic interactions to the oxygen atom of the ferryl center have therefore been proposed. The use of "hypersensitive mechanistic probes"[39] as well as density functional theoretical (DFT) calculations recently supported such mechanisms.[40] However, the debate regarding the exact mechanism of metabolism by CYP450 isozymes is still ongoing.[41]

3. Arylcyclopropanes in Medicinal Chemistry

The cyclopropyl group is ubiquitous in medicinal chemistry, mainly because of its steric, electronic and conformational properties and also because of its microsomal metabolic stability. Cyclopropanes have also been used to lock biologically relevant compounds into their bioactive conformations, thus providing enhancement in potency. For these reasons, it is not surprising to find this smallest cycloalkyl group in many structure activity relationship (SAR) studies from different therapeutic fields of medicinal chemistry. Selected examples on the use of arylcyclopropanes in medicinal chemistry are illustrated in this section.

In one example, researchers at Japan Tobacco reported the preparation of compound **30** as potent ADAMTS-5 (A Disintegrin and Metalloprotease with Thrombospondin Motifs) inhibitor[42] and observed an important increase in potency following the introduction of a cyclopropyl linker in the structure (compound **31**, *Scheme 8*, Agg-2 = aggrecanase-2). This improvement in activity was attributed to the rigidifying effect provided by the cyclopropyl group which positioned the pharmacophores in the optimal binding conformation.



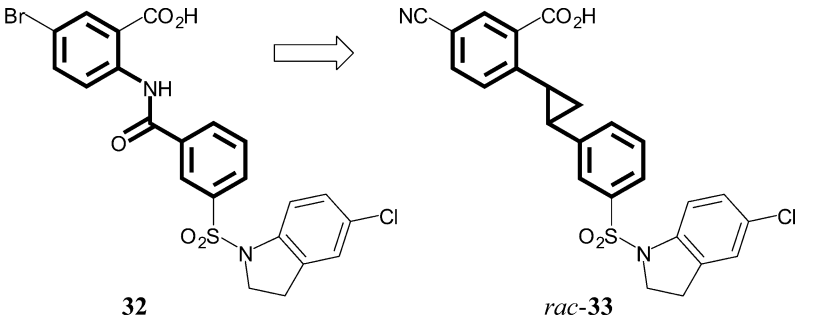
30
IC_{50} (Agg-2) = 1.6 μM

31
Ar = (4'-chlorophenyl)-4-phenyl
IC_{50} (Agg-2) = 0.2 μM

Scheme 8

In another example from Pharmacia, the arylcyclopropane played a prominent role in the optimization of the antimicrobial lead compound **32**.[43] During the course of their discovery of a broad spectrum antibiotic, a *trans*-cyclopropyl linker was utilized as a bioisostere of the secondary amide of compound **32** (*Scheme 9*, MIC-SAUR = Minimal Inhibitory Concentration *Staphylococcus aureus*). In concert with other amide replacements, it was shown that compound **33** displayed antimicrobial potency against *Staphylococcus aureus* within a few fold of the control amide **32**, indicating that the amide functionality was most likely not involved in specific interactions with its biological target and that the cyclopropyl linker was merely projecting key pharmacophores into optimal three-dimensional positions.

The cyclopropyl group can also be used to improve the *in vivo* properties of pharmaceutical agents. For example, during a program aimed at the discovery of sphingosine-1-phosphate receptor-1 selective agonists for use as immunosuppressive agents, researchers



32
MIC-SAUR = 0.5 μg/mL

rac-**33**
MIC-SAUR = 4.0 μg/mL

Scheme 9

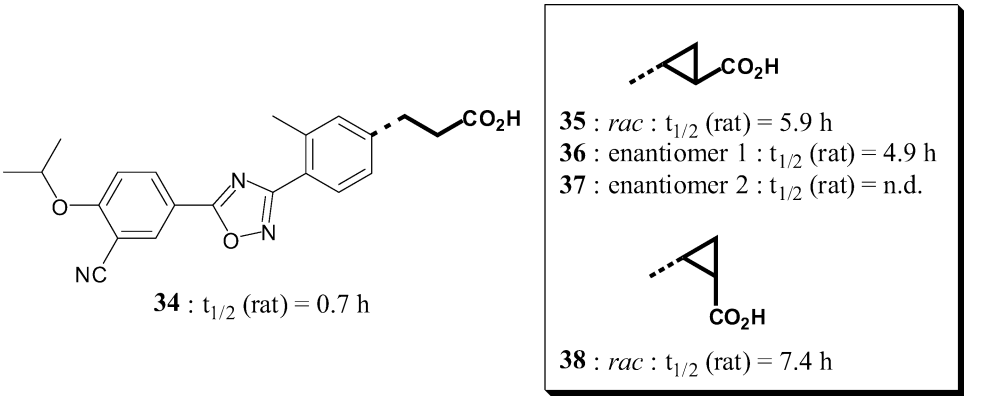


Figure 7

at Merck Research Laboratories disclosed compound **34** as a potential lead compound with excellent potency (*Figure 7*).[44] However, a poor pharmacokinetic profile was obtained for compound **34** with a very short half-life in the rat. Since phase 1 metabolism on the ethylene linker was suspected to be responsible for the poor rat *in vivo* half-life, this fragment was replaced by a cyclopropyl linker (compounds **35** to **38**), thus leading to dramatic improvement in overall pharmacokinetic profile of this series of inhibitors.

Another example of using the arylcyclopropane motif to improve metabolic stability was described during the discovery of inhibitors of the human immunodeficiency virus' reverse transcriptase by researchers at Boehringer Ingelheim (*Figure 8*). It was found that the bulky lipophilic *tert*-butyl group at the *para*- position of compound **39** was beneficial for potency, although detrimental to metabolic stability. A solution to this problem was to replace this alkyl group with a cyclopropyl group, leading to compound **40** which showed a longer half-life in the presence of human liver microsomes (HLM), with only a minor loss in potency.[45]

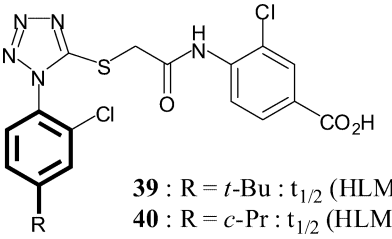
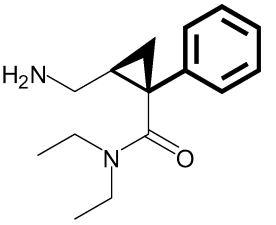
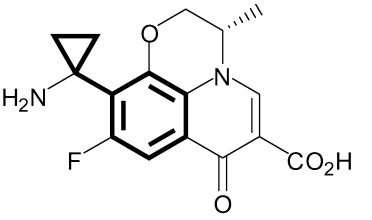


Figure 8

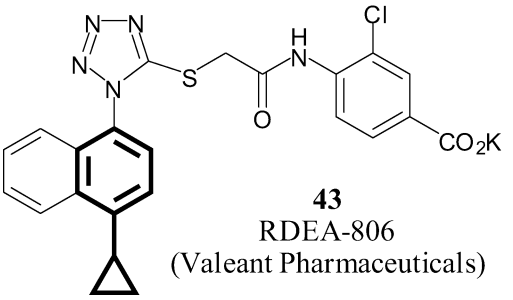
The combination of aryl and cyclopropyl moieties results in an attractive motif for medicinal chemists. Two compounds possessing this scaffold are currently on the market (*Figure 9*). Milnacipran **41** is an antidepressant that acts as a norepinephrine serotonine reuptake inhibitor (NSRIs).[46] It has equal potency for inhibiting the reuptake of serotonin and noradrenaline. Milnacipran has also demonstrated clinical efficacy in patients suffering from fibromyalgia or systemic lupus erythematosus. Pazufloxacin **42** is an antibiotic that



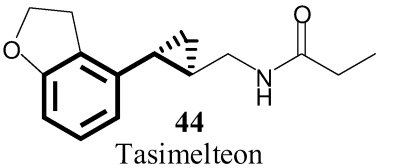
41
Milnacipran
(Pierre Farbre SA)



42
Pazufloxacin
(Toyama Chemical Co. Ltd)



43
RDEA-806
(Valeant Pharmaceuticals)



44
Tasimelteon
(BMS)

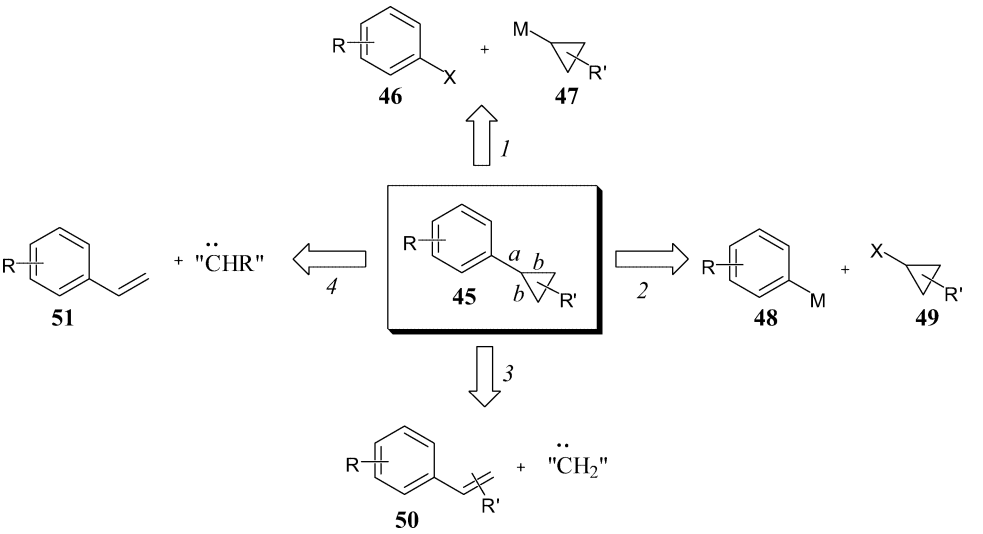
Figure 9

incorporates an aminocyclopropylphenyl moiety in its structure.[47] Compounds to treat AIDS (RDEA-806, **43**)[48] and insomnia (tasimelteon **44**)[49] that have an arylcyclopropane are currently in clinical studies.

Numerous examples of pharmaceutically relevant compounds that include an arylcyclopropane motif in their structure and that are in the development phase are found in patents and in the literature. In fact, arylcyclopropanes can be found in most therapeutic fields of the pharmaceutical industry and include inhibitors of HIV reverse transcriptase[50,51] and hepatitis C NS5B polymerase,[52] PDE 4 inhibitors,[53] alpha-1 adrenoceptor and factor-IIa antagonists, dopamine receptor antagonists,[54,55] TNF alpha-1 inhibitor agonists,[56] γ-secretase subunit inhibitor, and others.[57–60] These examples of pharmaceutically relevant compounds clearly demonstrate the value of the arylcyclopropane motif in medicinal chemistry.

I. Synthesis

From a retrosynthetic perspective, arylcyclopropanes can be prepared by following one of four distinct retrosynthetic disconnections (*Scheme 10*): 1) formation of the arylcyclopropane $C_{sp}2-C_{sp}3$ bond *a* from aryl halide **46** and cyclopropyl metal **47** or 2) aryl metal **48** and cyclopropyl halide **49**; 3) formal cyclopropanation (bond *b*) of styrene **50** or 4) **51** with a carbene or carbenoid. Full coverage of the cyclopropanation reaction has recently appeared and is beyond the scope of this review. Instead, we focus herein on alternative approaches for the introduction of a cyclopropyl group using coupling methodologies. In the

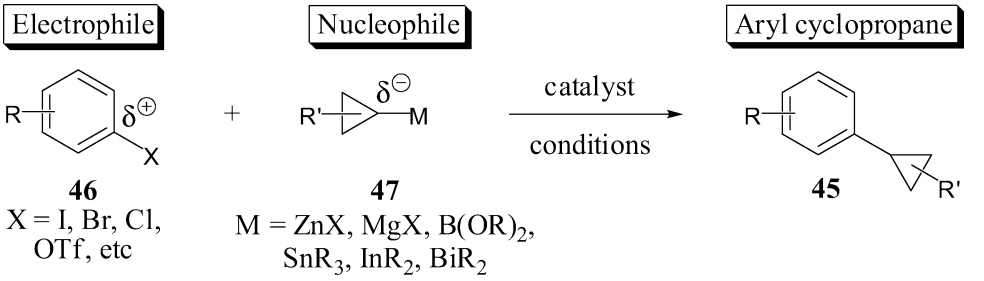


Scheme 10

last section of the review, methods involving addition to cyclopropenes, C—H activation, formal S_NAr reactions of cyclopropyl anions and migration-type reactions are discussed.

1. Cross-Coupling Reactions Between Cyclopropylmetals and Aryl Halides and Pseudohalides

The direct cross-coupling reaction between aryl halides **46** or pseudohalides and cyclopropyl metal reagents **47** is one of the most straightforward approach for the preparation of arylcyclopropanes (*Scheme 11*). Different metals such as zinc, magnesium, boron, tin,

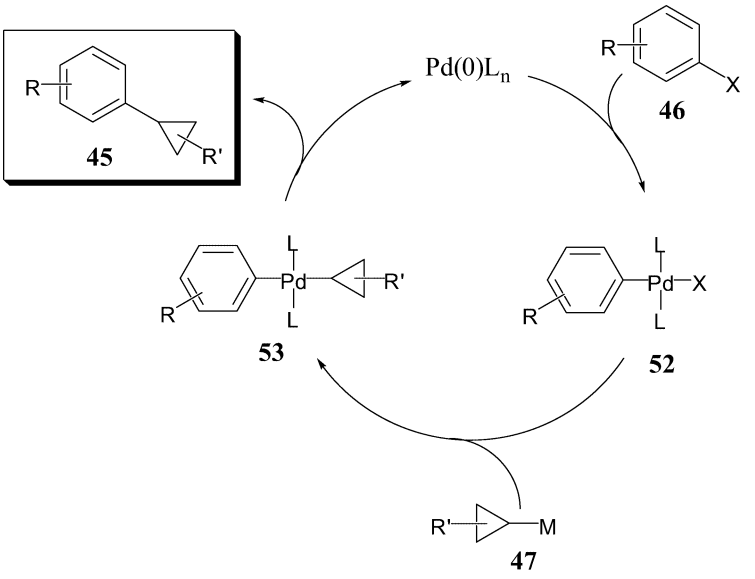


Scheme 11

indium and bismuth have been successfully used to access these compounds through this disconnection. Most of the reported methodologies employ palladium or nickel catalysts to promote this transformation. The efficiency of these protocols depends on the capacity of the cyclopropyl metal to react with different aryl electrophiles such as iodides, bromides, chlorides, triflates and other pseudohalides in high conversion, high chemoselectivity and minimal generation of side products. Conversely, limitations are sometimes found in the number of cyclopropyl groups that are transferred from the reagent, the low functional

group tolerance, the toxicity of the inorganic waste or the requirement for complex ligands or catalysts.[61]

In the case of palladium-catalyzed cross-coupling reactions, the mechanism begins with an oxidative addition of the palladium (0) complex into the carbon-halogen bond of **46** (*Scheme 12*). Transmetallation of the cyclopropyl metal reagent **47** to the aryl-palladium

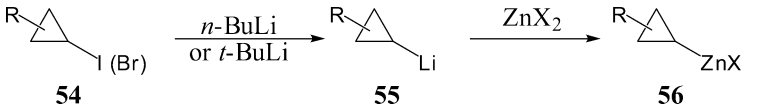


Scheme 12

intermediate **52** then leads to the formation of the aryl-alkyl organometallic complex **53**. This intermediate then undergoes reductive elimination to provide the desired arylcyclopropane **45** with concomitant regeneration of the catalyst. The rate-limiting step of the catalytic cycle depends on the reactivity of the C—X bond of the aryl halide **46** and on the reactivity of the cyclopropyl metal reagent **47**, which is in turn affected by the nature of the metal. Highly reactive cyclopropyl metal reagents result in a faster transmetallation and therefore, in a more efficient process. Additives have been used in some cases to facilitate the overall process through acceleration of the rate-limiting step. Contrary to the coupling of other alkyl groups possessing hydrogens in β-position, the β-hydride elimination is generally not a predominant side reaction in the coupling of cyclopropyl groups.

a) Negishi Reaction of Cyclopropylzinc Halides

The Negishi-type catalyzed cross-coupling reaction between cyclopropyl zinc reagents and aryl electrophiles is a well established method for the preparation of arylcyclopropanes. This approach has been used for the introduction of substituted and unsubstituted cyclopropyl units on aryl scaffolds. The required cyclopropyl zinc reagents **56** are usually prepared from the corresponding cyclopropyl bromide or iodide **54** through a lithium-halogen exchange reaction with *n*-butyllithium or *t*-butyllithium followed by transmetallation of the generated cyclopropyllithium species **55** with a zinc salt (*Scheme 13*). Cyclopropylzinc reagents have

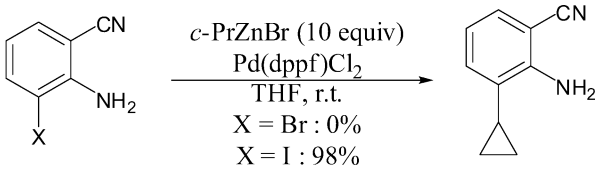


54 **55** **56**

Scheme 13

also been prepared from the corresponding Grignard reagents (*vide infra*). Strict exclusion of water is mandatory in this sequence since moisture sensitive species are generated.[62,63]

While the high reactivity of the organometallic reagent implies the need for anhydrous conditions, it also results in a more efficient transmetallation to the arylpalladium intermediate, thus giving good yields of the desired products. Good functional group tolerance is often observed in the coupling of organozinc reagents. For example, in a study on cross-coupling reaction of cyclopropyl zinc bromide with 3-halo-anthranilonitrile, starting material was recovered when the reaction was performed on the bromo derivative **57** (*Scheme 14*).[64] However, the reaction proceeded smoothly in the case of the iodo anthranilonitrile **58**,



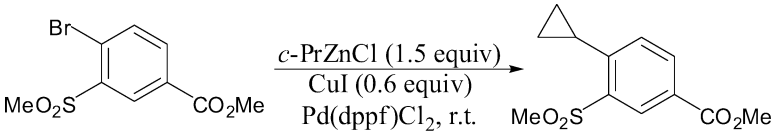
57: X = Br
58: X = I

59

Scheme 14

giving the desired product **59** in 98% yield. In this example, 10 equivalents of the organozinc reagent were used, presumably due to the presence of the unprotected amino group and also to ensure maximum conversion of the desired arylcyclopropane.

In 1996, Weichert reported the use of copper salts as cocatalysts in the palladium-catalyzed cross-coupling reaction of cyclopropylzinc chloride with electron deficient aryl bromides (*Scheme 15*).[65] Similarly to the coupling reaction involving tin reagents, the use

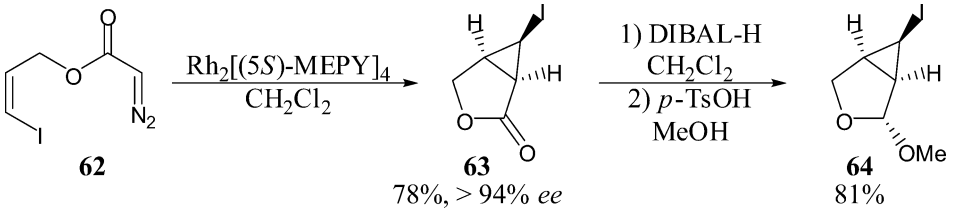


60 **61** 70%

Scheme 15

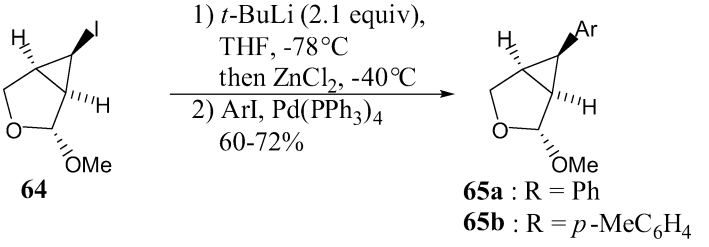
of copper salts exerted a beneficial effect on the reaction rates, favoring the formation of the desired cross-coupling products. For example, aryl bromide **60** reacted smoothly with cyclopropylzinc chloride in the presence of 1,1′-bis(diphenylphosphino)ferrocenedichloro palladium (II) and copper iodide to afford the desired cross-coupling product **61** in 70% yield (*Scheme 15*). The methyl sulfone and the methyl ester were unaffected during this transformation, showing the mildness of the reaction conditions.

The preparation of highly functionalized cyclopropylzinc reagents and their use in cross-coupling reactions was illustrated by Martin in 1998.[66] In this report, the iodocyclopropane **64**, prepared *via* asymmetric cyclization of the allylic diazoacetate **62** followed by reduction of the lactone, was used as a precursor in the formation of the cyclopropylzinc species (*Scheme 16*).



Scheme 16

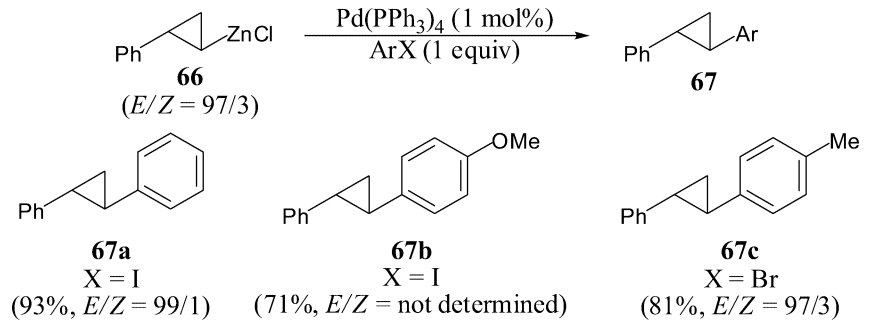
Lithium-halogen exchange reaction on iodocyclopropane **64**, followed by trapping with zinc chloride and subsequent palladium-catalyzed cross-coupling reaction of the *in situ* generated cyclopropylzinc reagent then led to the corresponding arylcyclopropanes **65a** and **65b** with complete retention of configuration (*Scheme 17*). Yields above 60% were obtained when iodobenzene and *para*-iodotoluene were used as the electrophilic partners. In a complementary approach, these arylcyclopropanes were also prepared *via* a direct cross-coupling reaction of the cyclopropyl iodide with aryl boronic acids (see *Scheme 85*).



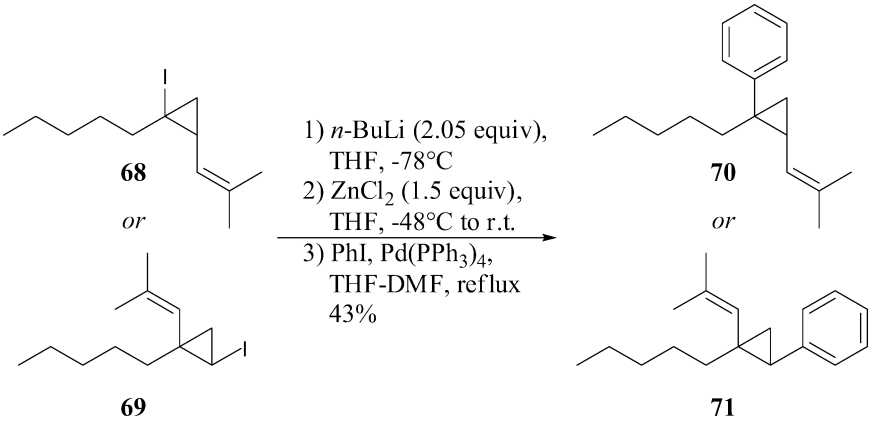
Scheme 17

In another example by Brandsma, 2-phenylcyclopropylzinc chloride **66**, prepared from the corresponding cyclopropyl bromides through a *n*-butyllithium-bromide exchange reaction at low temperature, were efficiently coupled with different aryl halides under the influence of tetrakis(triphenylphosphine) palladium to give the corresponding unsymmetrical 1,2-diarylcyclopropanes **67** (*Scheme 18*).[67] In all cases, the cross-coupling reaction proceeded in good yield with retention of the *E:Z* ratio. The yield and selectivity was not affected by the electronic nature of the aryl halide.

In 2001, Piers reported a Negishi-type cross-coupling reaction involving alkenyl cyclopropyl zinc species, obtained from alkenyl iodocyclopropanes (*Scheme 19*).[68] The first step consisted in a lithium-halogen exchange reaction on the iodo cyclopropanes **68** or **69** with *n*-butyllithium, providing the corresponding configurationally stable cyclopropyllithium species. Transmetallation with zinc chloride and coupling with iodobenzene under the influence of tetrakis(triphenylphosphine) palladium then afforded **70** and **71** with complete retention of configuration. In these examples, the zinc-bearing cyclopropyl carbon



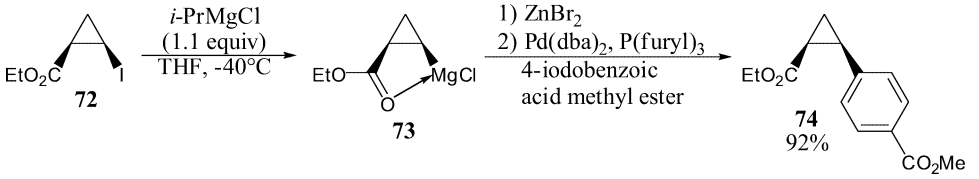
Scheme 18



Scheme 19

center that had to participate in the coupling operation was sterically very hindered, thus accounting for the moderate yield.

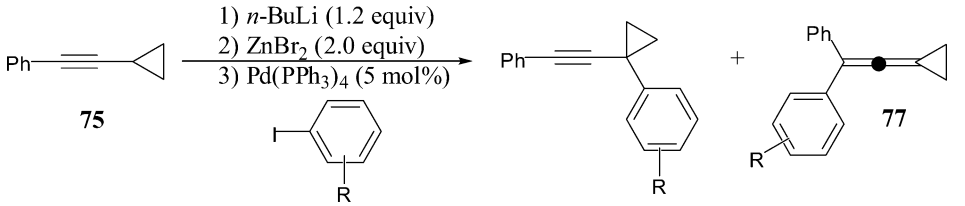
Functionalized cyclopropyl metal reagents are important species for the preparation of substituted arylcyclopropanes. In 2002, Knochel reported the synthesis of the functionalized cyclopropylmagnesium species **73**, which was obtained *via* the iodine-magnesium exchange reaction between the *cis*-1,2-iodocyclopropane carboxylate ester **72** and isopropylmagnesium chloride (*Scheme 20*).[69] The stabilizing chelating and inductive effect of the



Scheme 20

ester group provided excellent stability for this cyclopropylmagnesium reagent. After transmetallation from **73** to the corresponding zinc species and subsequent palladium-catalyzed cross-coupling with 4-iodobenzoic acid methyl ester, a fast Negishi cross-coupling reaction took place, affording **74** in excellent yield.

It is possible, in certain cases, to prepare cyclopropylzinc reagents by deprotonation of a cyclopropyl derivative with a strong base followed by transmetallation using zinc salts. This strategy was utilized by Ma in 2006 in the preparation of alkynyl arylcyclopropanes (*Scheme 21*).[70] Deprotonation of cyclopropyl-arylacetylene **75** was performed using

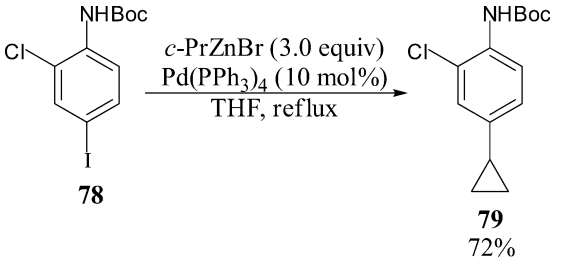


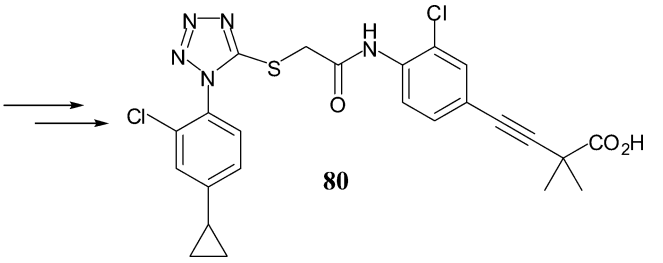
76a : R = H (72%)
76b : R = *o*-Me (25%)
76c : R = *p*-CO_2Me (98%)
76d : R = *p*-CN (88%)
76e : R = *p*-OMe (33%)

Scheme 21

n-butyllithium as the base, affording the corresponding aryl lithium reagent which then underwent transmetallation with zinc bromide to provide the cyclopropylzinc species. Subsequent regioselective palladium-catalyzed cross-coupling reaction with different aryl iodides then gave the desired arylcyclopropanes **76** in modest to excellent yields, with no formation of the allenic product **77**.

A cross-coupling reaction between an unsubstituted cyclopropylzinc reagent and a functionalized aryl iodide was recently utilized by Gagnon and coworkers in the preparation of a potent HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) (*Scheme 22*).[45] The cross-coupling reaction between the Boc-protected 2-chloro-4-iodoaniline **78**



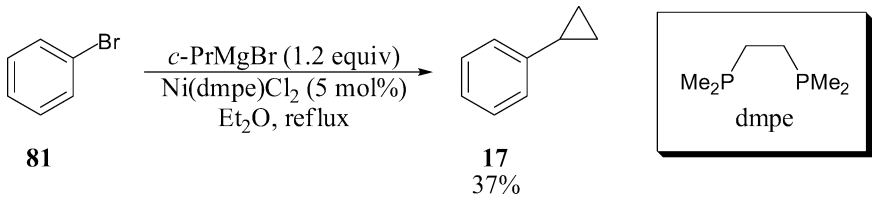


Scheme 22

and cyclopropylzinc bromide efficiently provided the corresponding arylcyclopropane **79** in good yield. This intermediate was then transformed into the desired inhibitor **80** in a few simple steps. Good potency combined with excellent metabolic stability was obtained for this compound in conjunction with a good overall rat pharmacokinetic profile.

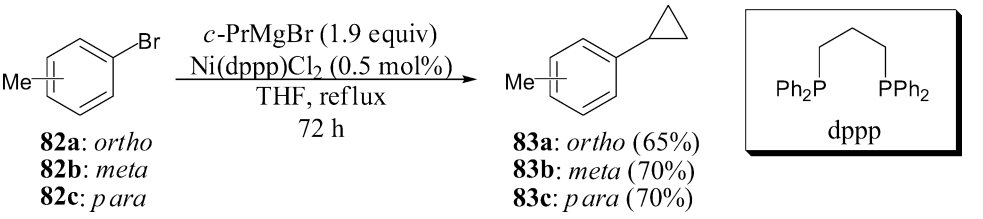
b) Kumada-Corriu Reaction of Cyclopropylmagnesium Halides

The direct cross-coupling reaction between a cyclopropylmagnesium reagent and an aryl halide or pseudohalide offers an expedient approach to the preparation of arylcyclopropanes. Contrary to the coupling reaction involving cyclopropylzinc reagents, functional group tolerance is expected to be lower in the case of cyclopropylmagnesium reagents due to the increased reactivity and basicity of the organometallic species. This approach is nevertheless highly attractive, particularly in cases where the transfer of an unsubstituted cyclopropyl group is required since cyclopropylmagnesium bromide is commercially available. In 1976, Kumada reported the first nickel-catalyzed cross-coupling reaction between a cyclopropylmagnesium reagent and an aryl halide. In this report, bromobenzene **81** was coupled with cyclopropylmagnesium bromide in the presence of $Ni(dmpe)Cl_2$ to afford the corresponding phenyl cyclopropane **17** in modest yield (*Scheme 23*).[71]



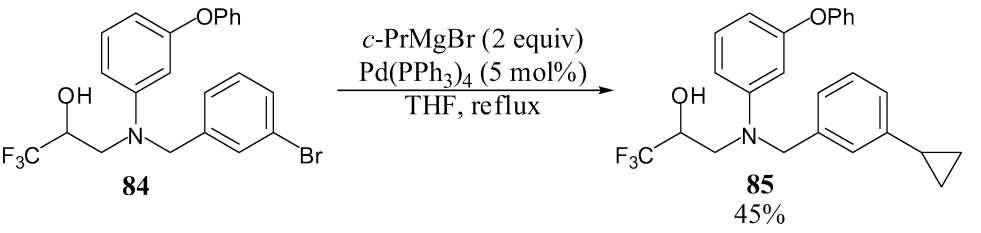
Scheme 23

Using similar conditions, Ogle reported in 1992 the preparation of *ortho*, *meta*, and *para*-tolylcyclopropanes **83** from the corresponding bromides **82** in much higher yields (*Scheme 24*).[72] All three isomeric tolylcyclopropanes were obtained in similar yields, showing that the substitution pattern had little impact on the efficiency of the reaction.



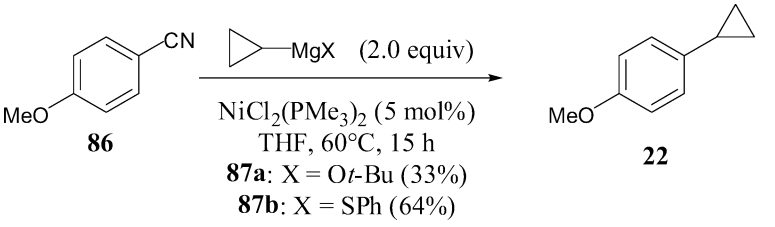
Scheme 24

The cross-coupling between a cyclopropyl Grignard reagent and an aryl halide was recently used in the synthesis of the aminoalcohol **85** (*Scheme 25*), a potent inhibitor of the cholesteryl ester transfer protein (CETP).[73] In this case, two equivalents of the cyclopropylmagnesium bromide were utilized due to the presence of the unprotected alcohol in **84** which consumed one equivalent of the organometallic reagent.



Scheme 25

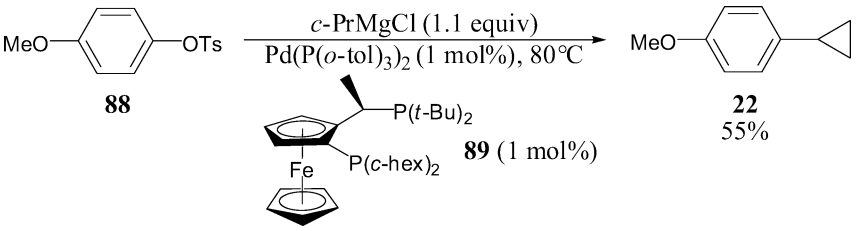
In most cross-coupling reactions involving cyclopropyl metal reagents, arylhalides or triflates are utilized as the electrophilic partners. In 2003, Dankwardt reported that benzonitriles such as **86** can be used as coupling partners in the cross-coupling reaction with cyclopropylmagnesium salts. Using a nickel catalyst, the corresponding arylcyclopropane **22** was obtained in modest yield (*Scheme 26*).[74,75] In order to minimize the amount of



Scheme 26

nucleophilic addition to the nitrile group during the cross-coupling event, the Grignard reagent was modified by the addition of *t*-BuOLi (reagent **87a**) or PhSLi (reagent **87b**). A survey of the catalyst indicated that $NiCl_2(PMe_3)_2$ was generally superior to other nickel or palladium catalysts.

Aryl tosylates are useful electrophiles for cross-coupling reactions since they can be easily prepared from phenols and because they are more stable to water than triflates. However, this greater stability also results in reduced reactivity during the cross-coupling reaction. In 2005, Hartwig reported conditions that allow the direct cross-coupling of cyclopropyl Grignard reagents with aryl tosylates, providing a convenient access to arylcyclopropanes (*Scheme 27*).[76] For instance, the coupling of tosylate **88** with cyclopropylmagnesium chloride in the presence of bis(tritolylphosphine)palladium and phosphine **89** in toluene at 80°C afforded the desired cyclopropylanisole **22** in 55% yield. In this example,



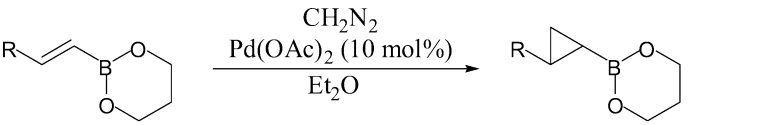
Scheme 27

a moderate yield was obtained even in the presence of the electron donating *para*-methoxy group. Also noteworthy was the very low catalyst loading required for this transformation to proceed.

c) Suzuki Reaction of Cyclopropylboronic Acids and Cyclopropylboronic Esters

The advancement seen in the past decades in the field of Suzuki-Miyaura cross-coupling reactions has greatly contributed to the use of cyclopropylboron species in the synthesis of arylcyclopropanes. The stereospecific nature of the Suzuki reaction can be advantageously exploited to make highly substituted and stereodefined arylcyclopropanes. The cyclopropylboron species are easily accessed *via* cyclopropanation of the corresponding vinylboron reagents, which can in turn be synthesized through hydroboration of alkynes. Enantioenriched substituted arylcyclopropanes have also been prepared through Suzuki cross-coupling of chiral cyclopropylboronic acids. The commercially available cyclopropylboronic acid is a very attractive reagent for the preparation of unsubstituted arylcyclopropanes. A recent review by Doucet and co-workers comprehensively covered the Suzuki-Miyaura cross-coupling of secondary alkylboronic acid derivatives, including cyclopropylboronic acids and esters, with aryl halides and triflates.[77] Therefore, emphasis will be placed on more recent examples of cross-coupling reactions of cyclopropylboron reagents in the synthesis of cyclopropylarenes.

It has been reported that cyclopropylboronic esters which show considerable steric hindrance on the boronic ester component are sluggish partners in the cross-coupling reaction with aryl halides. The cyclopropylboronate esters are thus commonly hydrolyzed to the corresponding boronic acids, which can then react smoothly with aryl halides and triflates under standard palladium-catalyzed cross-coupling conditions. Although Carboni and co-workers reported the synthesis of cyclopropylboronates in 1989,[78,79] the first examples of Suzuki cross-coupling reactions between cyclopropylboronates and aryl halides were only reported in 1996 (*Scheme 28*).[80] The substituted cyclopropylboronic esters used



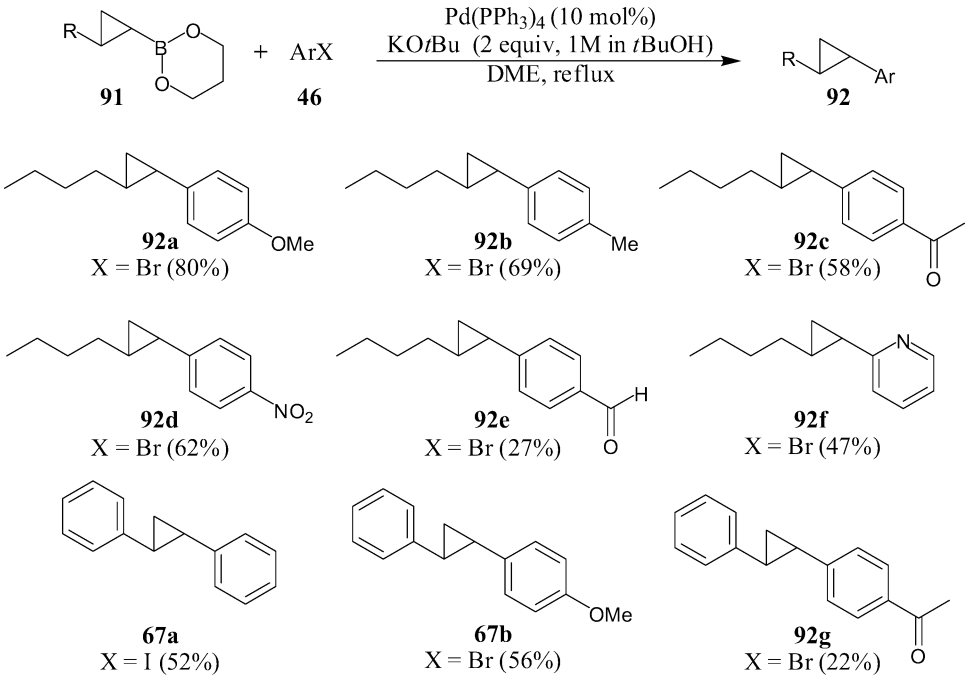
90

91a : R = C_4H_9 (75%)
91b : R = C_6H_{13} (79%)
91c : R = Ph (70%)

Scheme 28

in that study (compound **91**) were prepared from the corresponding vinylboronates **90** through palladium-catalyzed cyclopropanation using diazomethane. The cyclopropanation was stereospecific, such that the *trans* geometry of the vinylboronates **90** was transferred to the cyclopropylboronates **91**.

The Suzuki cross-coupling reaction of cyclopropylboronic esters **91** proceeded smoothly with different aryl halides **46** in the presence of tetrakis(triphenylphosphine) palladium to afford the corresponding *trans*-1,2-disubstituted cyclopropanes **92** in modest



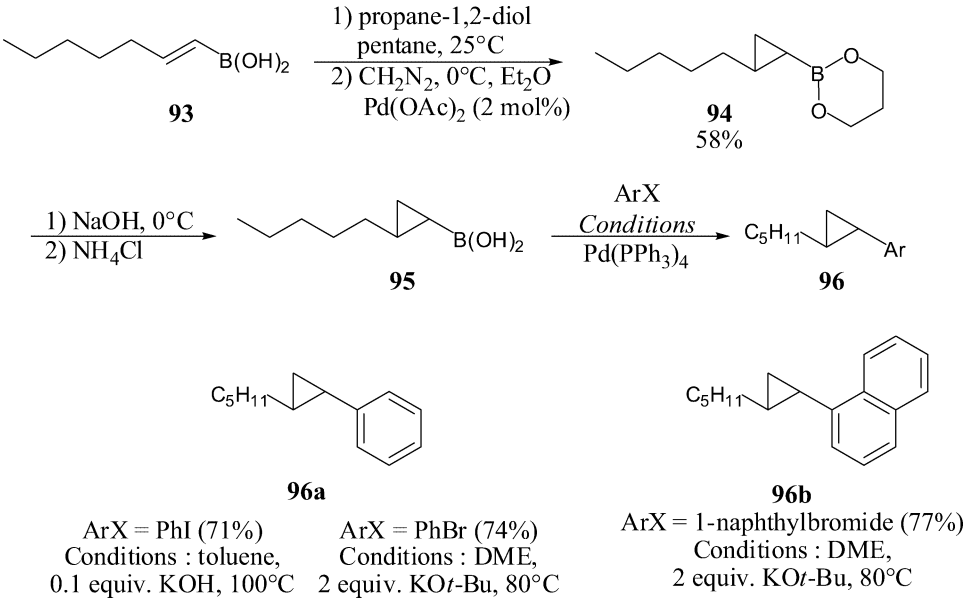
Scheme 29

to good yields (*Scheme 29*). In this protocol, potassium *tert*-butoxide was used as the base. Aryl bromides and iodides possessing electron attracting or donating groups were efficiently coupled with the boronic esters **91**.

Another example of palladium-catalyzed cross-coupling reaction involving racemic *trans*-cyclopropylboronic esters was reported by Pietruszka in 1999.[81] The cyclopropylboron reagent **94** required for this study was prepared from vinylboronic acid **93** through formation of the boronic ester and subsequent cyclopropanation using diazomethane in the presence of palladium acetate. Hydrolysis of the boronic ester **94** then afforded the boronic acid **95**, which was finally cross-coupled with different aryl bromides and iodides, affording the desired arylcyclopropanes **96** in good yields (*Scheme 30*).

Aryl trifluoromethanesulfonates are valuable partners in cross-coupling reactions since they are easily accessed from the corresponding phenols. In 2000, Deng and coworkers reported the preparation of *trans*-1,2-disubstituted arylcyclopropanes **92** *via* the cross-coupling of cyclopropylboronic acids **97** with aryl trifluoromethanesulfonates (*Scheme 31*).[82] A survey of different conditions led to the identification of potassium fluoride dihydrate or potassium phosphate as the optimal base. The addition of one equivalent of sodium bromide prevented the decomposition of the catalyst to palladium black, presumably by replacing the triflate on the palladium intermediate, thus forming a more reactive palladium bromide species. Broad substrate scope and functional group tolerance were observed for this transformation, providing a very attractive method for the preparation of this class of compounds.

These palladium-catalyzed cross-coupling conditions were then utilized in the coupling of heteroaryl trifluoromethanesulfonates (*Scheme 32*).[83] In the event, an efficient



Scheme 30

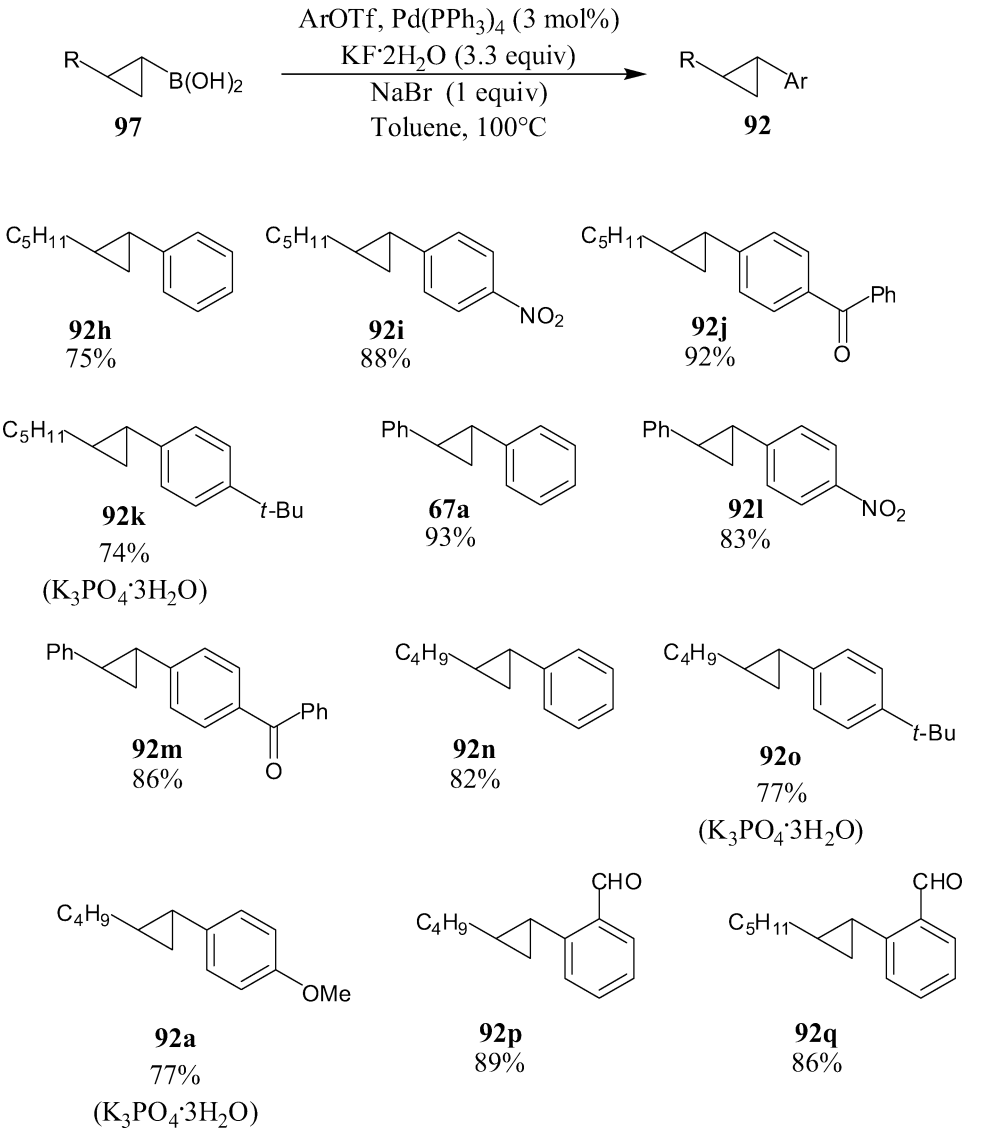
cross-coupling of cyclopropylboronic acid **97** with 2-pyridinetrifluorosulfonate **98** was achieved, affording the racemic or enantioenriched pyridylcyclopropanes **99** in good yields.

Using the same conditions, the reaction between cyclopropylboronic acids **97** and 2-trifluoromethanesulfonylquinoline **100** also proceeded uneventfully, affording the desired arylcyclopropylquinolines **101** in good yields (*Scheme 33*).

Finally, 8-trifluoromethanesulfonylquinoline **102** was utilized as the electrophilic coupling partner in the cross-coupling reaction with the substituted cyclopropylboron reagents **97** (*Scheme 34*).

Aryl perfluorosulfonates offer a cost-effective alternative to the more usual trifluorosulfonate cross-coupling partners. With this in mind, Deng and coworkers developed a methodology for the palladium-catalyzed cross-coupling of racemic *trans*-1,2-disubstituted cyclopropylboronic acids **97** with aryl perfluorosulfonates **104** (*Scheme 35*).[84] Using similar conditions as previously reported for the coupling of aryl triflates, racemic *trans*-1,2-disubstituted arylcyclopropanes **92** were obtained from a wide scope of substrates having electon withdrawing and donating groups. The cyclopropyl configuration of the boronic acids was retained during this transformation. For the coupling of these triflate derivatives, the reaction did not require sodium bromide to proceed.

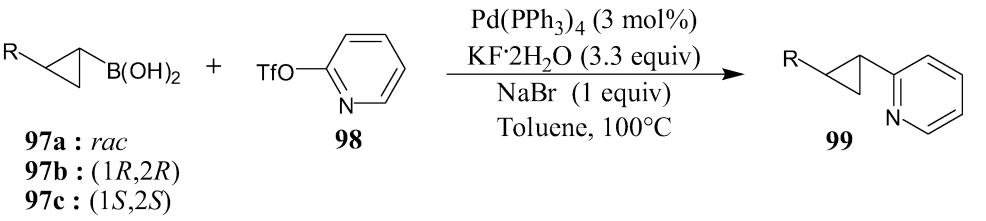
Potassium cyclopropyltrifluoroborates have been used in cross-coupling reactions as an alternative to cyclopropylboronic acids and esters because they show increased reactivity and good functional group tolerance. For example, Deng reported in 2004 the synthesis of racemic substituted arylcyclopropanes *via* the Suzuki coupling of potassium cyclopropyl trifluoroborates.[85] The cyclopropylboron reagents **106** utilized in this study were prepared in two steps from the corresponding alkenylboronic acids **105** through formation of the pinacolboronic ester followed by cyclopropanation with diazomethane in the presence of palladium acetate (*Scheme 36*). The reaction proceeded stereospecifically, allowing the



Scheme 31

transposition of the geometry of the alkene to the cyclopropane. Subsequent treatment of the cyclopropylboronic ester **106** with KHF_2 following the protocol of Vedejs[86] afforded the potassium cyclopropyl trifluoroborates **107**, bearing either alkyl or aryl substituents.

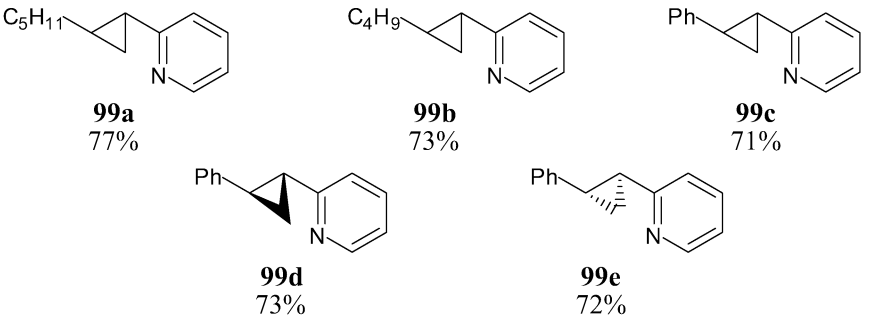
The potassium cyclopropyltrifluoroborates **107** were then efficiently cross-coupled with different arylbromides under mild conditions, affording the desired arylcyclopropanes **108** in good to excellent yields and with retention of configuration (*Scheme 37*). In addition, the reaction tolerated electron-donating and electron-withdrawing groups on the aryl bromide coupling partner. Contrary to the methodologies presented above, *anti* as well as *syn* 1,2-disubstituted arylcyclopropanes were accessed using this sequence, clearly adding value to this methodology.



97a : *rac*
97b : (1*R*,2*R*)
97c : (1*S*,2*S*)

98

99



99a 77%

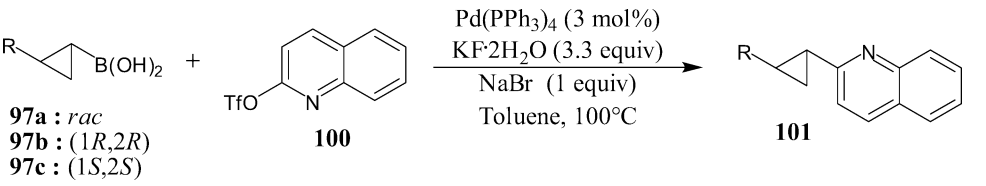
99b 73%

99c 71%

99d 73%

99e 72%

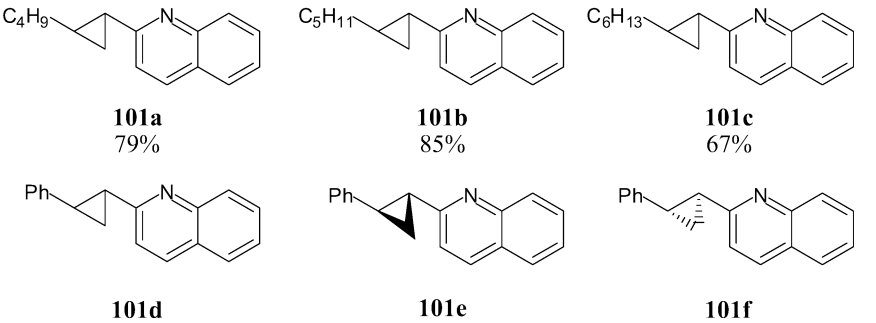
Scheme 32



97a : *rac*
97b : (1*R*,2*R*)
97c : (1*S*,2*S*)

100

101



101a 79%

101b 85%

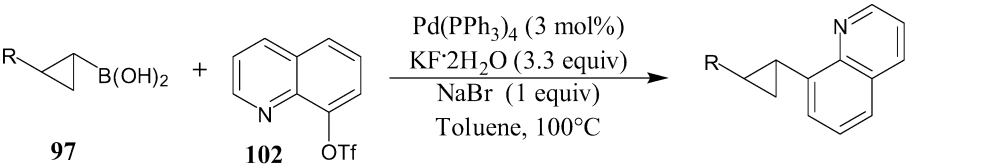
101c 67%

101d 75%

101e 67%

101f 71%

Scheme 33

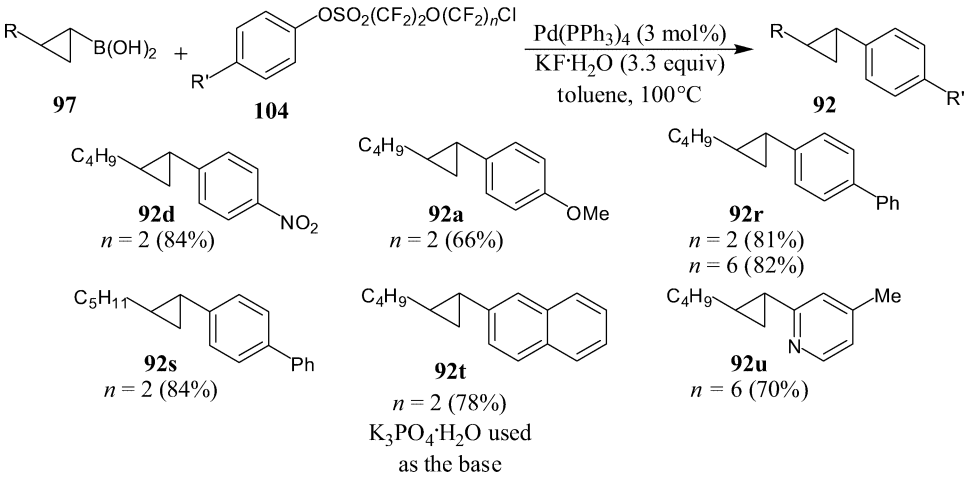


97

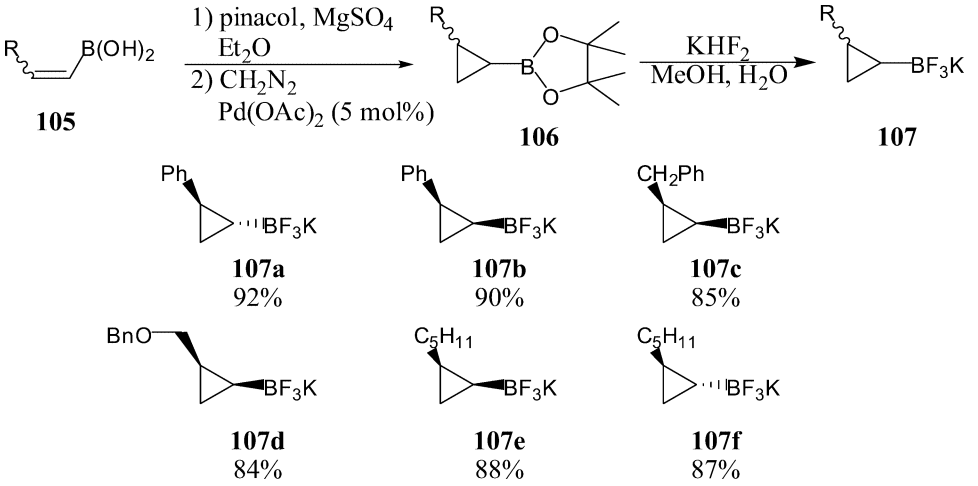
102

103a : R = C_4H_9 (73%)
103b : R = C_6H_{13} (73%)

Scheme 34

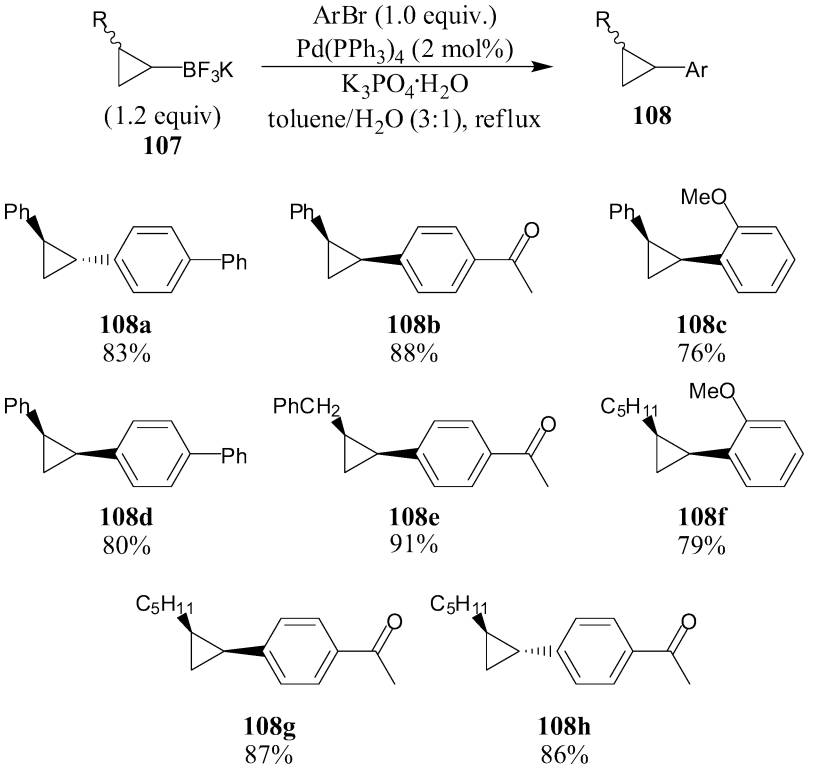


Scheme 35



Scheme 36

The transfer of enantiomerically pure substituted cyclopropyl groups through cross-coupling reactions is of great utility in the preparation of bioactive arycyclopropanes. For this purpose, different approaches that give access to enantiopure cyclopropylboron reagents and allow their subsequent use in cross-coupling reactions have been developed. A common strategy consists in introducing the chirality on the vinyl boronic ester through the use of a chiral diol which subsequently serves as a chiral auxiliary that directs the cyclopropanation diastereoselectively to one face of the alkene, providing enantioenriched cyclopropylboronic esters. Using this strategy, Deng and co-workers reported an elegant example of synthesis of enantiomerically enriched cyclopopylboronic acids and their subsequent use in cross-coupling reactions with arylbromides (*Scheme 38*).[87] The strategy envisioned the enantioselective cyclopropanation of vinylboronic ester **109**, where (−)-tetramethyltartramide (TMTA) serves as the chiral auxiliary. A direct palladium-catalyzed cross-coupling reaction of cyclopropylboronic ester **110** with different arylbromides to



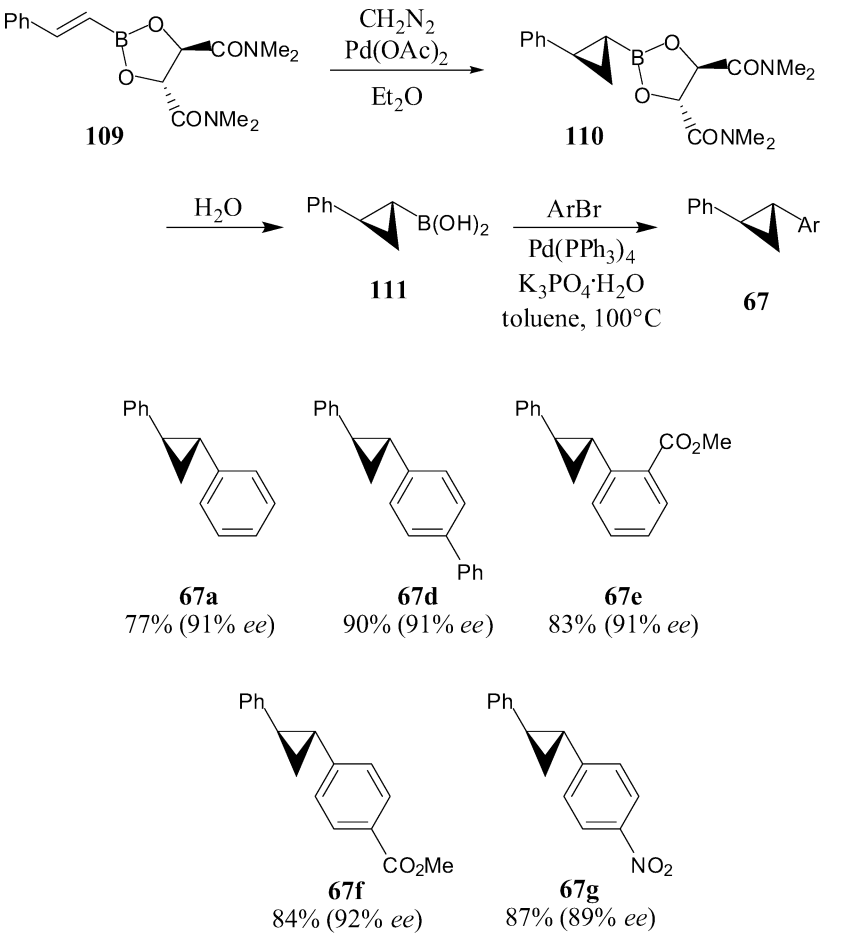
Scheme 37

generate the corresponding arylcyclopropanes **67** was originally envisaged. However, since cyclopropylboronic ester **110** was a very poor cross-coupling partner, the corresponding cyclopropylboronic acid **111** had to be generated prior to the cross-coupling step. In the event, the boronic acid **111** reacted smoothly with different arylbromides under mild conditions to afford the desired enantiomerically enriched *trans*-diarylcyclopropanes **67**.

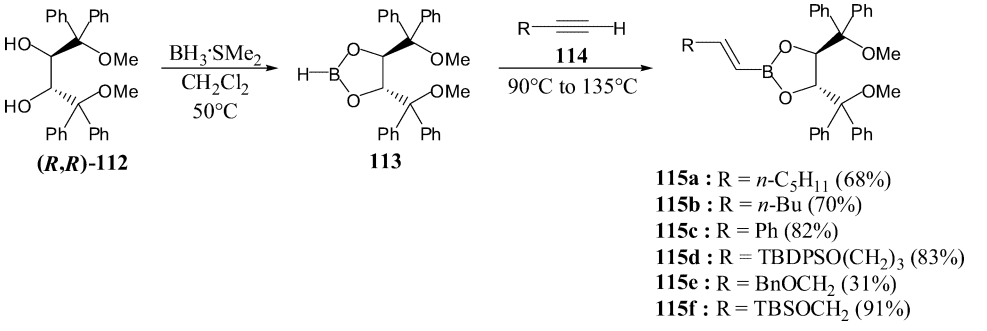
Pietruszka and co-workers utilized a different diol derived from tartaric acid as the source of chiral induction in the synthesis of enantiomerically pure cyclopropylboronic acids. The chiral vinylboronic esters **115** used in this methodology were prepared by the reaction between borane-dimethyl sulfide with diol **112** and subsequent hydroboration of the generated intermediate **113** with different terminal alkynes **114** (*Scheme 39*).

Diastereoselective cyclopropanation of vinylboronic ester **115a** was then performed using diazomethane catalyzed by palladium acetate, affording the corresponding cyclopropylboronic esters **116a** and **116b** in excellent yield and diastereoselectivity (*Scheme 40*). In addition to providing good stereocontrol during the cyclopropanation step, the robust chiral diol auxiliary utilized in this sequence allowed for the silica gel purification of the cyclopropylboronate esters **116a** and **b**.[88]

Pietruszka observed that boronate ester **116a** was a poor coupling reagent in the Suzuki cross-coupling reaction. In order to effectively perform the cross-coupling transformation, conversion to the boronic acid **118** was required (*Scheme 41*). This was accomplished by reduction of the boronic ester **116a** to the intermediate **117** which was then hydrolyzed,

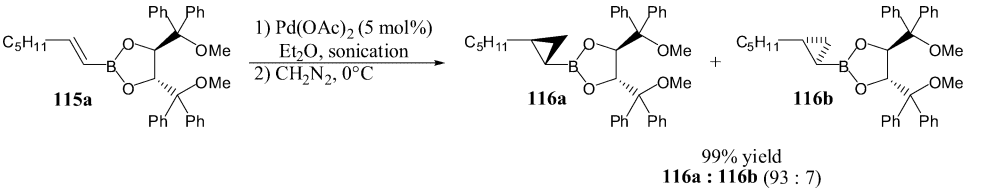


Scheme 38

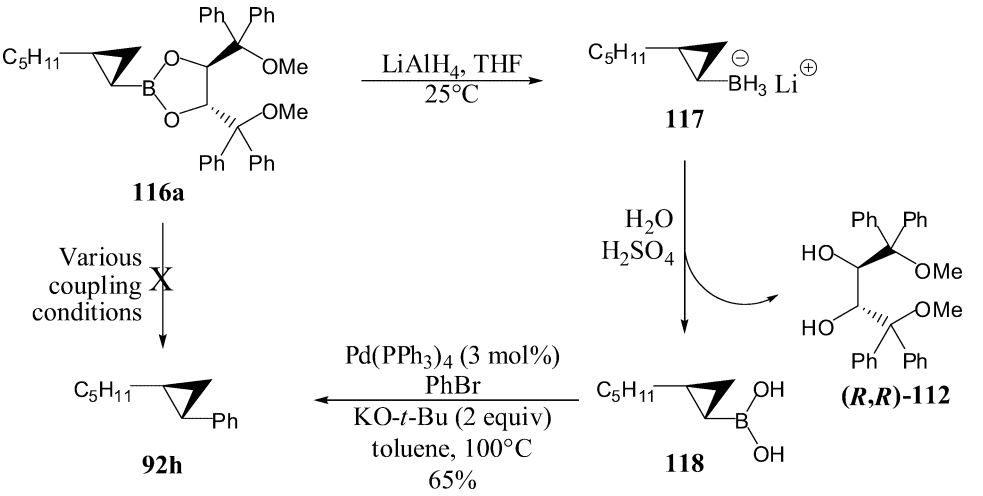


Scheme 39

giving the desired cyclopropylboronic acid **118** with concomitant liberation of the diol **112**. The optically enriched cyclopropylboronic acid **118** was finally coupled under standard palladium-catalyzed cross-coupling conditions, giving the desired arylcyclopropane **92h** in modest yield.

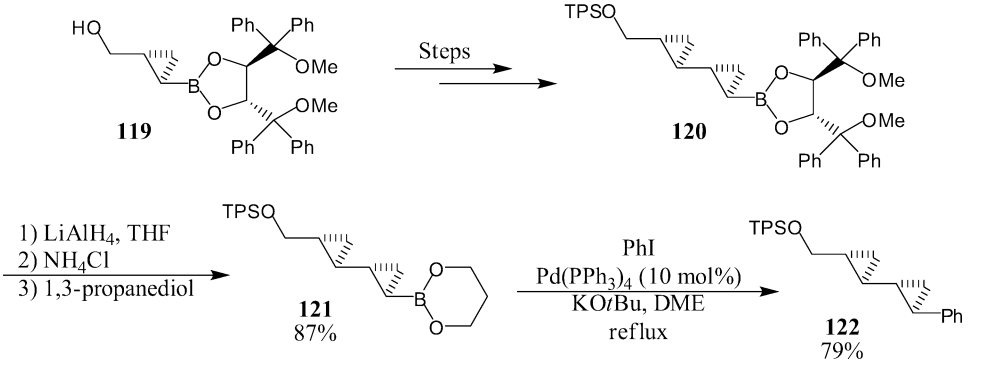


Scheme 40



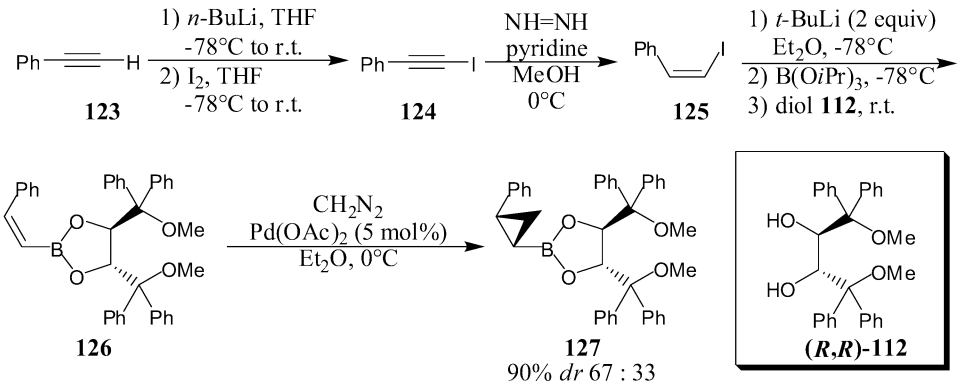
Scheme 41

Using the same chiral auxiliary, Pietruszka reported an elegant strategy giving access to enantiopure biscyclopropylarenes such as **122** (*Scheme 42*).[89] In this sequence, the biscyclopropylboronic ester **120**, obtained from the cyclopropylmethanol **119**, was reduced with lithium aluminum hydride and then treated with ammonium chloride followed by 1,3-propanediol, giving the boronic ester **121** required for the cross-coupling step. 1,3-Propanediolboronic ester **121** was directly used in the cross-coupling step, affording the desired arylcyclopropane **122** in good yield.



Scheme 42

Chiral *trans*-1,2-disubstituted cyclopropylboron species are easily accessible *via* cyclopropanation of the corresponding (*E*)-alkenylboronic acids and esters using previously shown methods. However, an alternative and general approach was required for the preparation of the *cis*-cyclopropylboronic acid reagents. To fulfill that need, Pietruszka reported the synthesis of chiral *cis*-vinyl boronic esters such as **126** from phenylacetylene **123** (*Scheme 43*).[90] The synthesis commenced with the stepwise lithiation and iodination of



Scheme 43

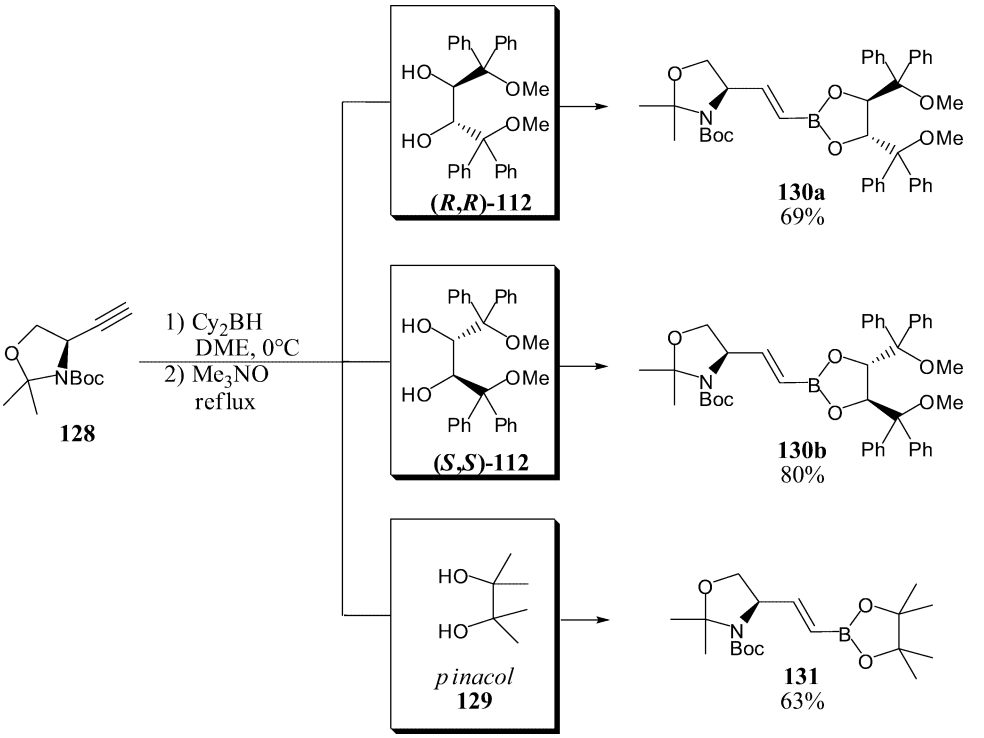
the terminal alkyne **123** to afford the iodoalkyne **124**, which was then submitted to diimide reduction, providing the (*Z*)-iodoalkene **125.** Lithium-halogen exchange followed by formation of an ate complex and transesterification afforded the *cis*-vinylboronic ester **126** which was then treated with diazomethane in the presence of palladium acetate, providing **127** in modest diastereoselectivity. Unfortunately, the authors did not report any cross-coupling reaction with this species.

Pietruszka also reported the synthesis of vinylboronic esters **130a**, **130b**, and **131**, derived from the Garner aldehyde (*Scheme 44*).[91] The synthesis was achieved commencing with the hydroboration of **128**, followed by formation of the boronic ester with either tartrate-derived diols **(*R,R*)-112** or **(*S,S*)-112**, affording **130a** and **130b**. Alternatively, vinylboronic ester **131** was prepared using pinacol **129**.

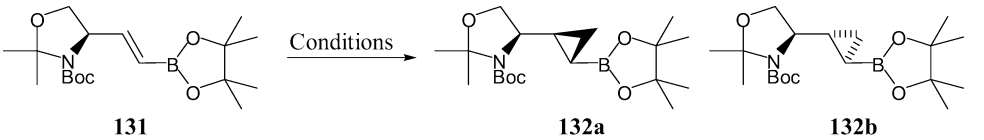
Palladium-catalyzed cyclopropanation of vinylboronic ester **131** using diazomethane then afforded cyclopropylboronic esters **132a** and **132b** in a 70:30 diastereomeric ratio (*Scheme 45*). Alternatively, the ratio could be inverted through a Simmons-Smith cyclopropanation reaction of **131**, leading to **132b** as the major product.

The pinacolboronic ester **132a** and **132b** then proved amenable to Suzuki cross-coupling under standard conditions, giving access to the diastereomeric pair of arylcyclopropanes **133a** and **133b** (*Scheme 46*).

Following Deng's report on the coupling of potassium cyclopropyltrifluoroborates, Pietruszka reported in 2006 the synthesis of enantiomerically pure arylcyclopropanes from potassium cyclopropyltrifluoroborates derived from cyclopropylboronic esters **136a** and **136b**.[92] Using a tartrate derived diol, the chiral vinylboronic ester **134** was prepared and submitted to the Denmark modification of the Simmons-Smith reaction (*Scheme 47*).[93] In the *matched* case, cyclopropanation of the vinylboronic acid **134** in the presence of (*R*,*R*)-*bis*-sulfonamide **135** afforded the cyclopropylboronic ester **136a** in a 95:5

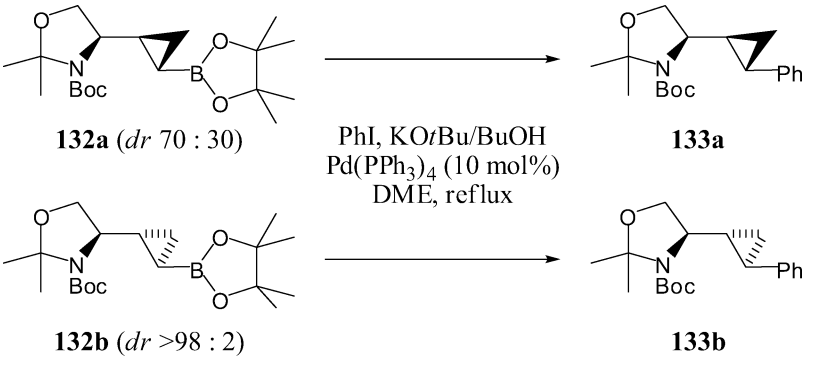


Scheme 44

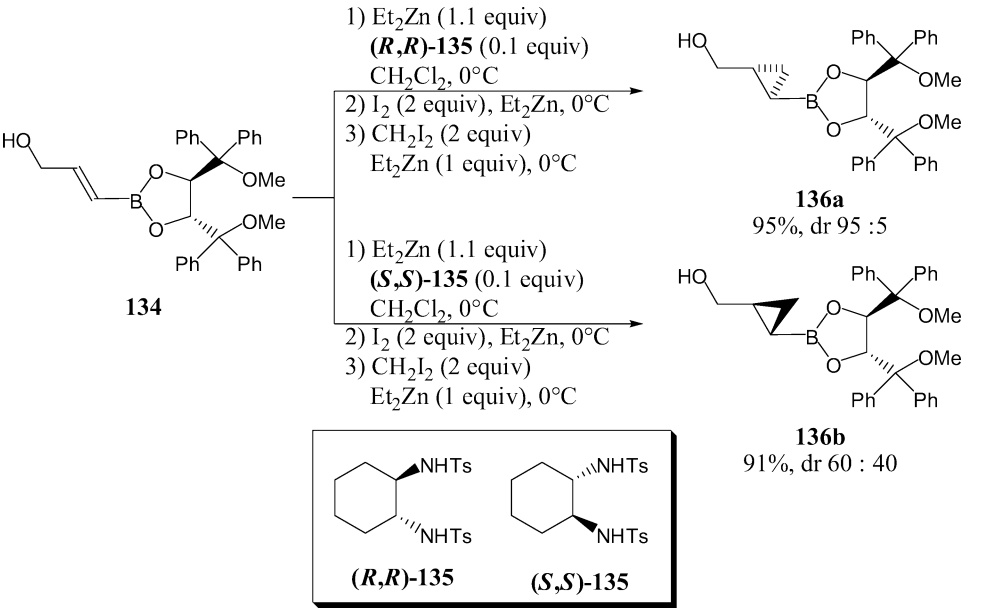


CH_2N_2, $Pd(OAc)_2$, Et_2O, 0°C : 69%; *dr* (**132a** : **132b**) = 70 : 30
Et_2Zn, CH_2I_2, CH_2Cl_2, -78°C : 48%; *dr* (**132a** : **132b**) = 22 : 78

Scheme 45



Scheme 46



Scheme 47

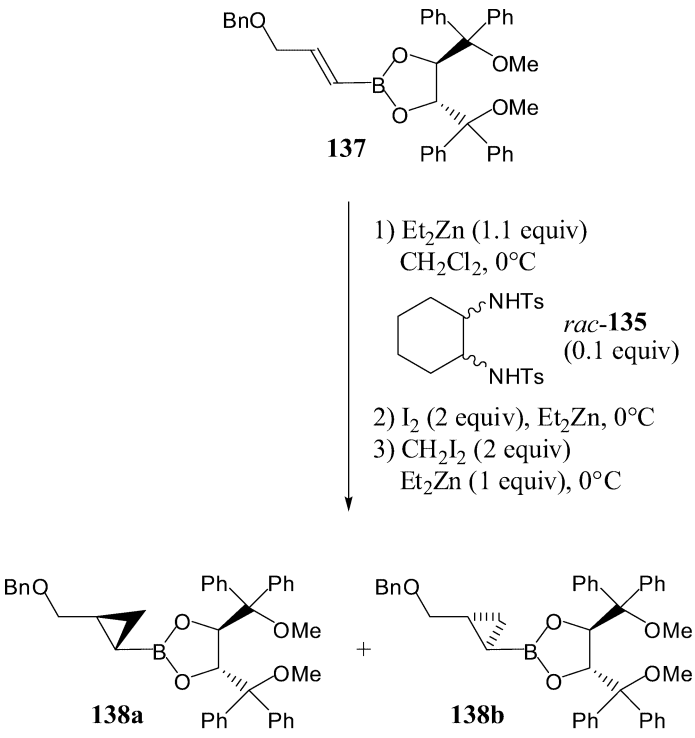
diastereomeric ratio. In the *mismatched* case, the use of the (*S*,*S*)-*bis*-sulfonamide **135** provided the diastereomer **136b** in a 60:40 ratio.

The use of racemic *bis*-sulfonamide **135** as the ligand in the cyclopropanation of the benzylether **137** provided diastereoisomers **138a** and **138b** in a 1:1 ratio (*Scheme 48*). These products could then be separated through silica gel column chromatography.

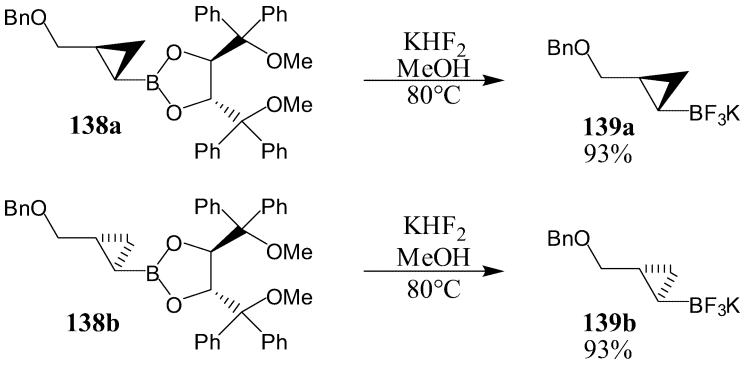
In preparation for the cross-coupling step, the cyclopropylboronic esters **138a** and **138b** were converted to the potassium cyclopropyltrifluoroborates **139a** and **b** using a modification of the Vedejs protocol (*Scheme 49*).[94]

Finally, the Suzuki cross-coupling reaction between the potassium cyclopropyltrifluoroborates **139a** and **139b** and aryl bromides was accomplished using Deng's conditions, affording the desired arylcyclopropanes **140** and **141** in modest to good yields (*Scheme 50*).

The direct enantioselective synthesis of a pinacolato boronic ester of a cyclopropane having a *trans*-2-silyl group has also been reported (*Scheme 51*).[95] In this approach, γ-silylated *cis*-allylic carbonate **142** undergoes regioselective *syn*-addition of the copper-boron species generated from Cu(O*t*—Bu) and *bis*[pinacolato]diborane, resulting in an intermediate having the copper and silicon atoms on the same carbon atom. This is then followed by ring closing attack of the C—Cu bond on the pendant alkyl carbonate to give the *trans*-cyclopropylboronic ester in excellent yield. A number of chiral phosphines were screened in this reaction with (*R*)-segphos **143** emerging as the ligand capable of delivering the desired cyclopropane with the highest enantioselectivity. A limitation is that the *cis*-derivative of **145** cannot be prepared through this approach since the use of the *trans*-allylic carbonate also gives the *trans*-cyclopropane derivative.

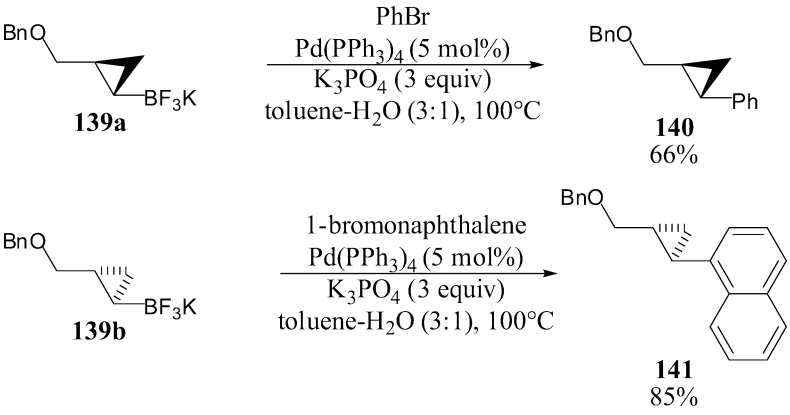


Scheme 48

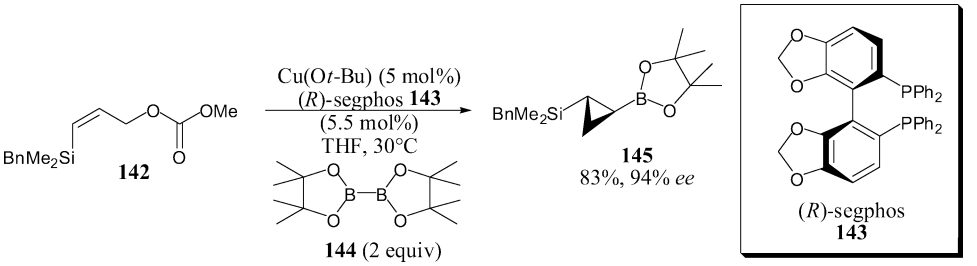


Scheme 49

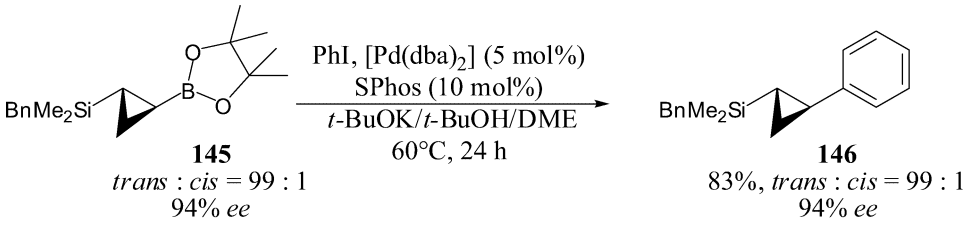
Boronic esters such as **145** are competent coupling partners in Suzuki-type coupling reactions with aryl iodides, giving access to enantiomerically pure arylcyclopropanes. For example, boronate **145** was coupled with phenyl iodide to give the arylcyclopropane derivative **146** in excellent yield and with complete retention of configuration on the cyclopropane ring (*Scheme 52*). The silicon based substituent may subsequently serve as a functional group for the introduction of other functionalities. For example, the authors



Scheme 50



Scheme 51

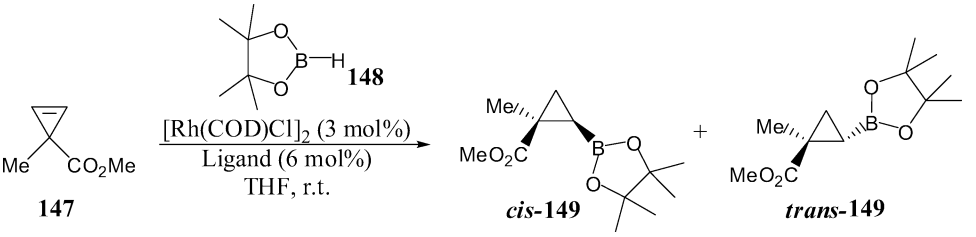


(SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl)

Scheme 52

performed an efficient Tamao-Flemming oxidation of **146** to deliver the corresponding *trans*-hydroxyphenylcyclopropane.

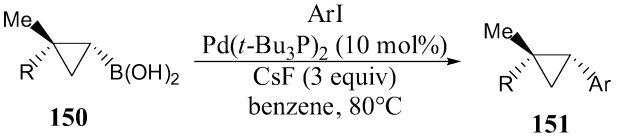
In 2003, Gevorgyan disclosed a powerful protocol for the synthesis of optically active 1,1,2-trisubstituted cyclopropylarenes.[96] In this methodology, the disubstituted cyclopropene **147** undergoes enantio- and diastereoselective hydroboration with pinacolborane **148** in the presence of Wilkinson's catalyst and a chiral phosphine to afford *cis* and *trans* cyclopropylboronic esters **149** in up to >99:1 ratio (*Scheme 53*). The *cis* selectivity was driven by the presence of the ester which acted as a directing group. Excellent enantioselectivities were obtained with chiral phosphines such as (*R*)-BINAP, (*R*)-PHANEPHOS or (*S*)-tol-BINAP.



(*R*)-BINAP : 96%; >99:1 *cis*/trans; 94% *ee* (*1S,2R*)
(*R*)-PHANEPHOS : 89%; >99:1 *cis*/*trans*; 97% *ee* (*1R,2S*)
(*S*)-Tol-BINAP : 94%; >99:1 *cis*/*trans*; 96% *ee* (*1R,2S*)

Scheme 53

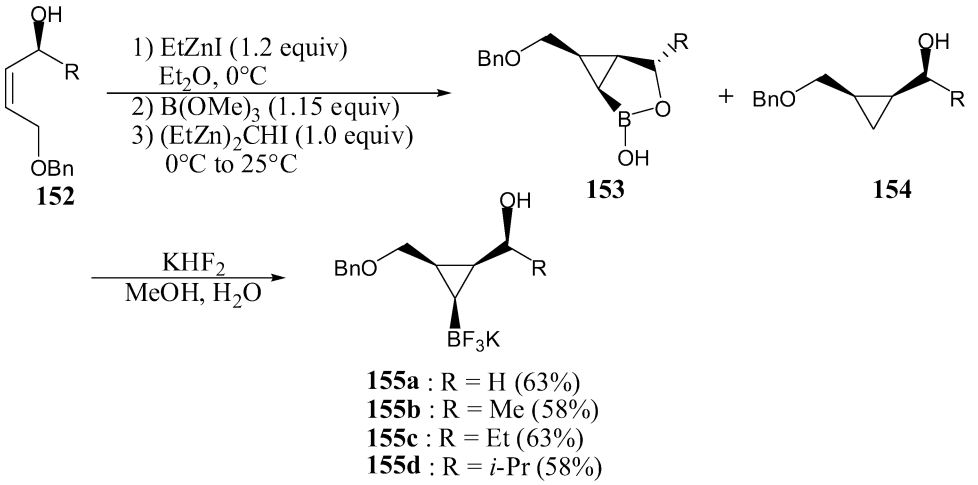
As the cyclopropylboronic ester *cis*-**149** did not undergo cross-coupling (a case analogous to those of Deng and Pietruszka), hydrolysis to afford the corresponding boronic acid such as **150** was required.[97] Optically pure cyclopropylboronic acids were thus prepared prior to the cross-coupling reaction, without erosion of diastereomeric excess. Finally, the Suzuki reaction proceeded smoothly employing Fu's conditions[98] (Pd(*t*-$Bu_3P)_2$, CsF or NaOH) (*Scheme 54*). Electron-donating and electron-withdrawing groups were equally tolerated.



151a: R = CO_2Me; Ar = Ph (76%)
151b: R = CO_2Me; Ar = *p*-(MeO)C_6H_4 (77%)
151c: R = CO_2Me; Ar = *p*-(MeO_2C)C_6H_4 (64%)
151d: R = CO_2Me; Ar = 1-Naphthyl (65%)
151e: R = CH_2OMe; Ar = Ph; NaOH (85%)

Scheme 54

Charette and co-workers reported in 2005 the synthesis of all *cis*-1,2,3-substituted cyclopropanes bearing aryl substituents.[99] This type of trisubstituted cyclopropyl motif is extremely difficult to generate through conventional methods. This was accomplished through a cross-coupling reaction involving potassium cyclopropyltrifluoroborate reagents **155** which were prepared *via* cyclopropanation of the chiral allylic alcohol **152** using a *gem*-dizinc carbenoid, followed by an immediate *in situ* transmetallation from zinc to boron using boron trimethoxide (*Scheme 55*). The cyclopropanation reaction was highly diasteroselective, the alcohol acting as the control element to afford the all-*cis* geometry (>95:5 ratio). However, concomitant formation of the reduction product of cyclopropylzinc species (product **154**) could not be completely avoided. Treatment of the crude mixture with KHF_2 followed by a simple washing procedure then afforded the desired pure potassium cyclopropyltrifluoroborates **155**.



Scheme 55

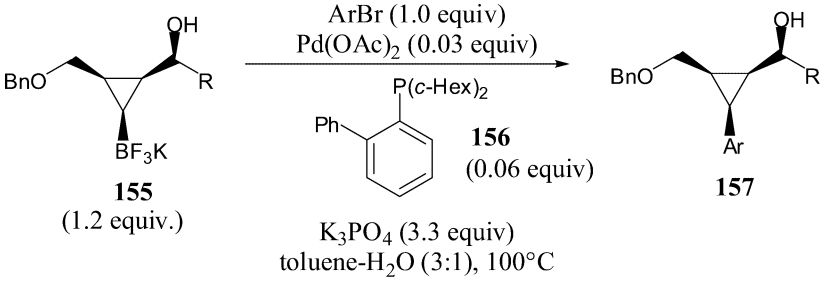
The Suzuki cross-coupling of species **155** was accomplished using a minor modification of Deng's protocol (*Scheme 56*). In the event, the all-*cis*-1,2,3-substituted arylcyclopropanes **157** were obtained in modest to good yields. Electron-donating as well as electron-withdrawing substituents on the aryl halide coupling partner were tolerated.

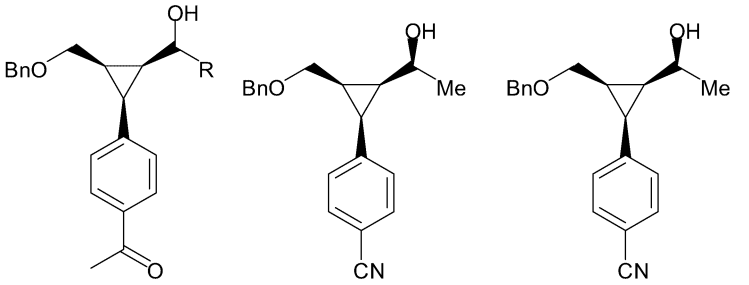
De Meijeire developed an elegant approach for the synthesis of *trans*-arylcyclopropylcyclopropanes from bicyclopropylidenes (*Scheme 57*).[100] The bicyclopropylideneborolane **160**, prepared from **158**, was found to be unreactive under palladium-catalyzed coupling conditions (possibly due to the olefin binding to the palladium) and was consequently transformed into its reduced *trans*-2-cyclopropylcyclopropylborolane **161** counterpart in preparation for the cross-coupling step.

In the event, the bis-cyclopropylboronic ester **161** proved to be a competent cross-coupling partner. While high reactivity was observed in the Suzuki reaction with numerous electron-neutral and electron-rich aryl halides, compounds **162j** and **k** derived from electron-deficient aryl halides could not be obtained (*Scheme 58*).

The preparation of unsubstituted cyclopropylarenes is of crucial importance in medicinal chemistry. The introduction of an unsubstituted cyclopropyl group onto biologically active compounds allows for the exploration of lipophilic binding pockets and can thus be of considerable use in the context of SAR studies. As a consequence, many methods allowing the coupling of unsubstituted cyclopropyl groups through Suzuki-type cross-coupling reactions have appeared over the past years. For instance, Soderquist and co-workers reported in 2000 a general method for the transfer of an unsubstituted cyclopropyl moiety through the coupling of boron reagent **165** (*Scheme 59*). This reagent was prepared *via* hydroboration of propargyl bromide **163** and subsequent sodium hydroxide-promoted rearrangement.[101] Suzuki-type cross-coupling reaction with different aryl halides was then performed *in situ*, affording the corresponding arylcyclopropanes **166** in modest to good yields.

Because aryl chlorides are less expensive than the corresponding bromides or iodides, many methods have focused on their use in cross-coupling reactions. For example, Fürstner reported a protocol for the Suzuki cross-coupling reaction between the cyclopropylboronate **169** and 4-chloromethylbenzoate **167** (*Scheme 60*).[102] The use of the imidazolium salt **168**

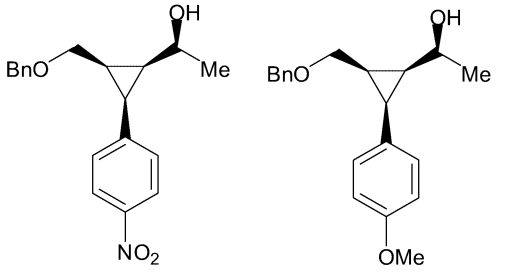




157a: R = H (88%)
157b: R = Me (89%)

157c
62%

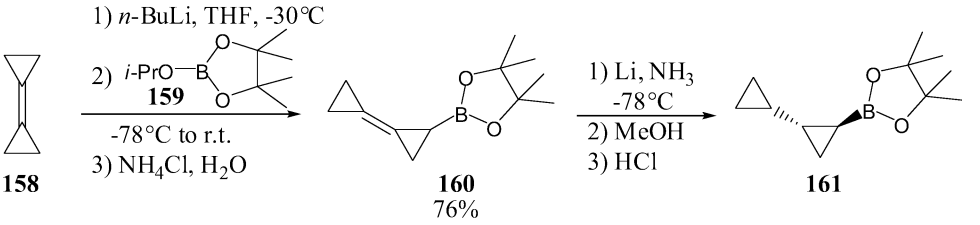
157d
47%



157e
84%

157f
69%

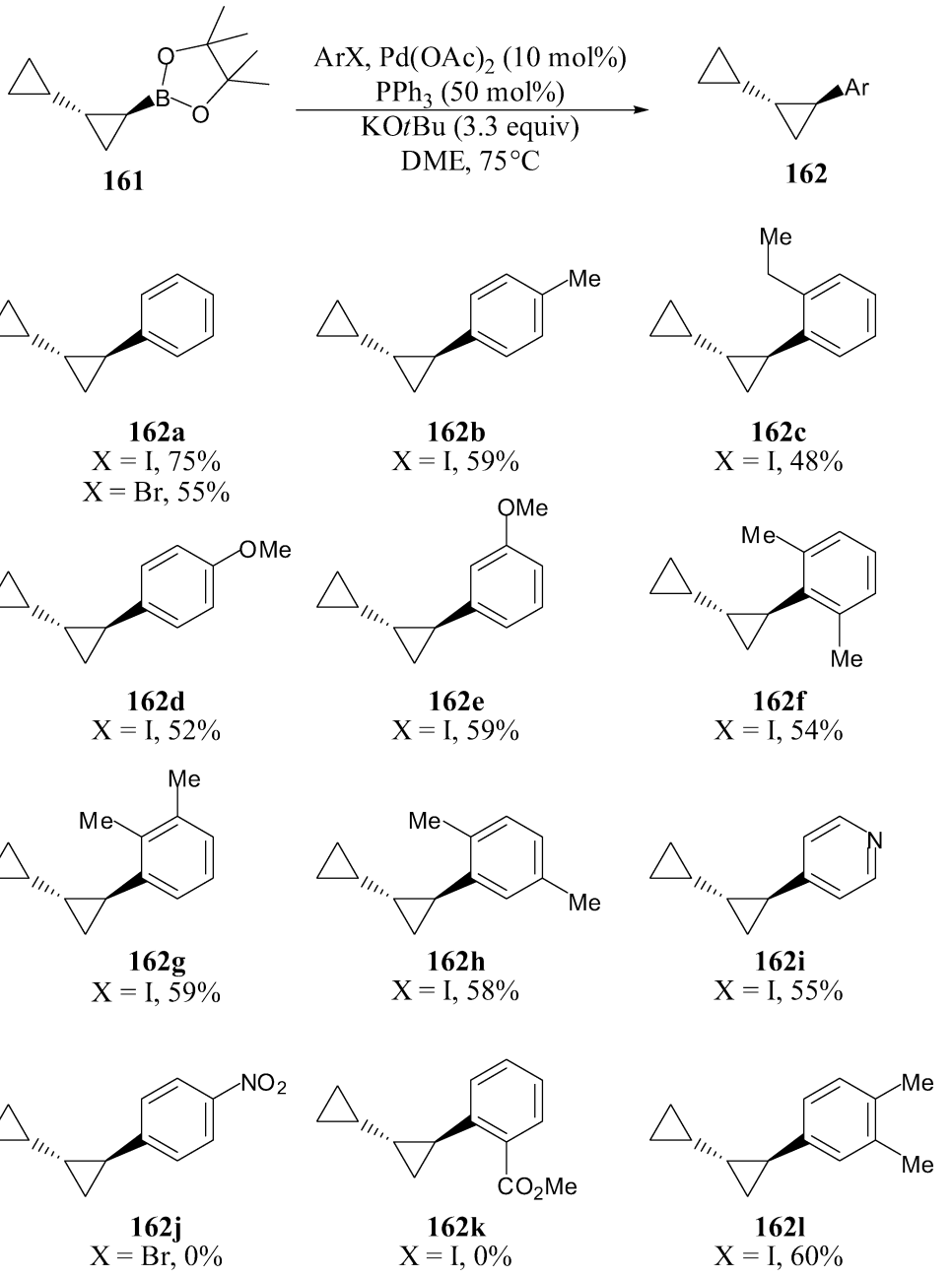
Scheme 56



Scheme 57

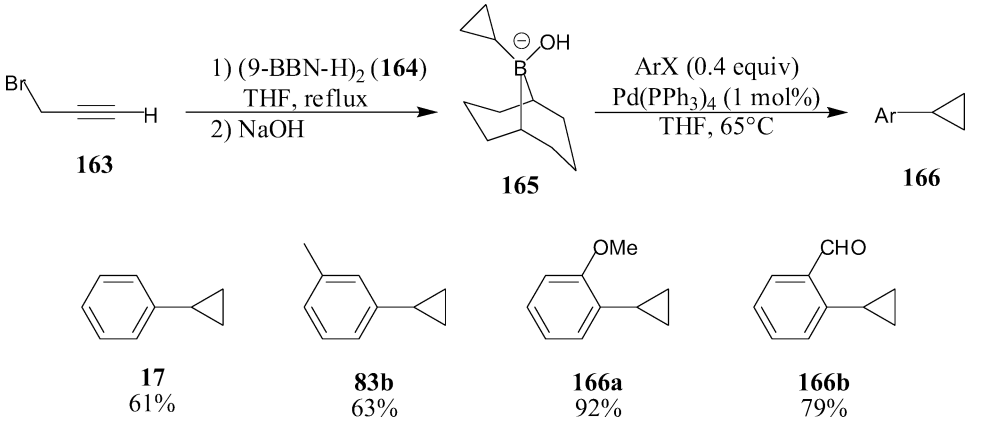
as a ligand was key to the success of this transformation, affording the desired coupling product **170** in excellent yield.

In 2002, Wallace published a simple and general protocol for the introduction of an unsubstituted cyclopropyl moiety onto aryl scaffolds using the commercially available cyclopropylboronic acid **172** (*Scheme 61*).[103] In this procedure, the coupling of

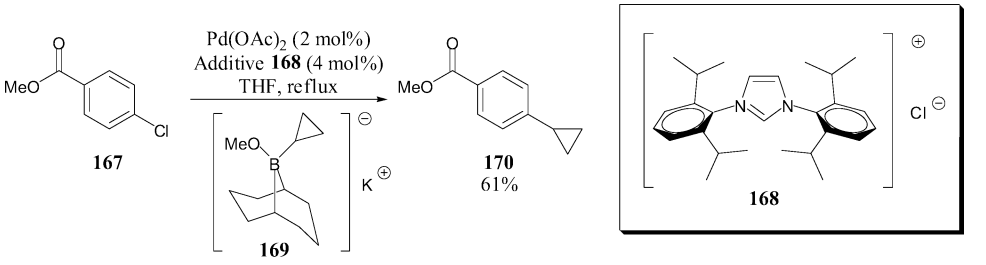


Scheme 58

cyclopropylboronic acid was performed through the action of palladium acetate combined with the bulky tricyclohexylphosphine in presence of potassium phosphate tribasic as the base. Although the conditions were not applicable to the coupling of arylchlorides, this limitation was greatly compensated by a broad substrate scope and an excellent functional group tolerance. This work clearly provides a method of choice for the synthesis of unsubstituted arylcyclopropanes.



Scheme 59



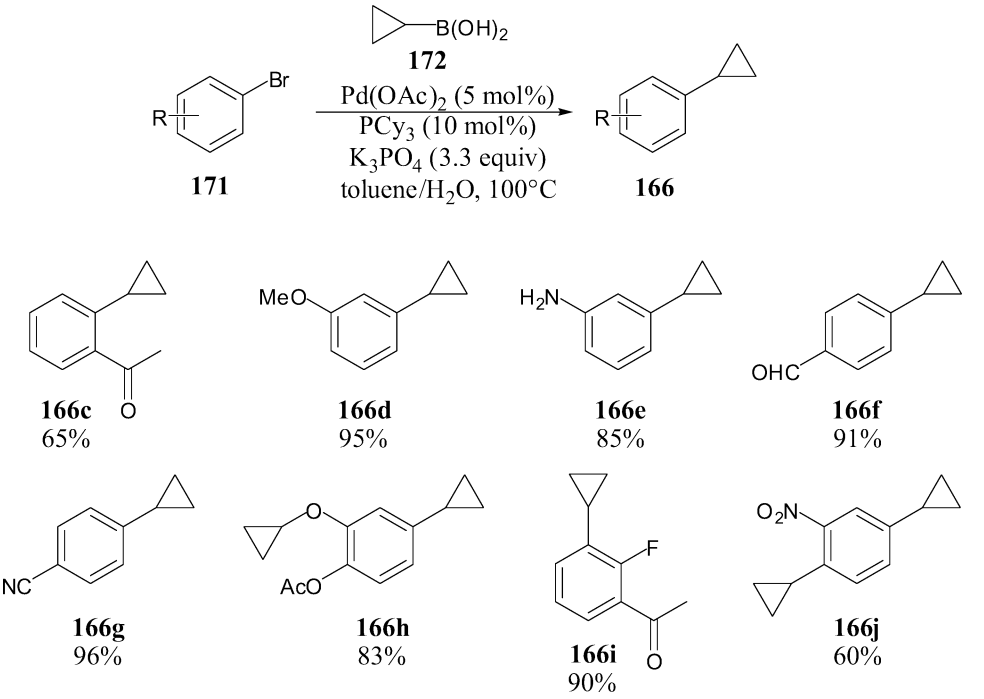
Scheme 60

Cross-coupling of cyclopropylboronic acid **172** with heteroaryl halides **173** was also accomplished using these reaction conditions (*Scheme 62*). Arylchlorides and triflates failed to undergo cross-coupling reaction under the optimized reaction conditions.

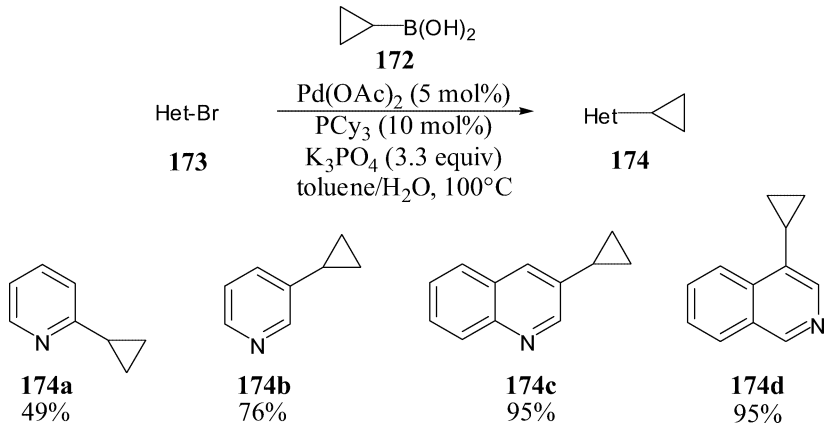
In 2006, Doucet reported the preparation of the novel tetradentate phosphine ligand Tedicyp **175** which was designed to facilitate the cross-coupling of cyclopropylboronic acid with aryl bromides and chlorides.[104] Tedicyp is synthesized in seven steps from commercially available starting materials.[105] An important improvement provided by the introduction of this ligand lies in low catalyst loadings (0.1 to 1% loading) required for the preparation of the desired arylcyclopropanes. Moreover, significant functional group tolerance and high yields were obtained for most aryl bromides (*Scheme 63*). In addition, using only 1% catalyst loading, sterically congested arylcyclopropanes such as **166o** were efficiently prepared.

Due to the availability and lower cost associated with aryl chlorides, this method was also extended to the cross-coupling reaction of these electrophilic coupling partners. Although lower turnovers were observed with aryl chlorides compared to aryl bromides, good yields were nonetheless obtained in most cases (*Scheme 64*).

Although the methodology developed by Doucet represents a nice achievement for the synthesis of unsubstituted cyclopropylarenes from aryl chlorides, alternative procedures were highly desirable due to the complex synthesis inherent to the preparation of the tetradentate ligand. In 2008, Molander reported the cross-coupling reaction of aryl



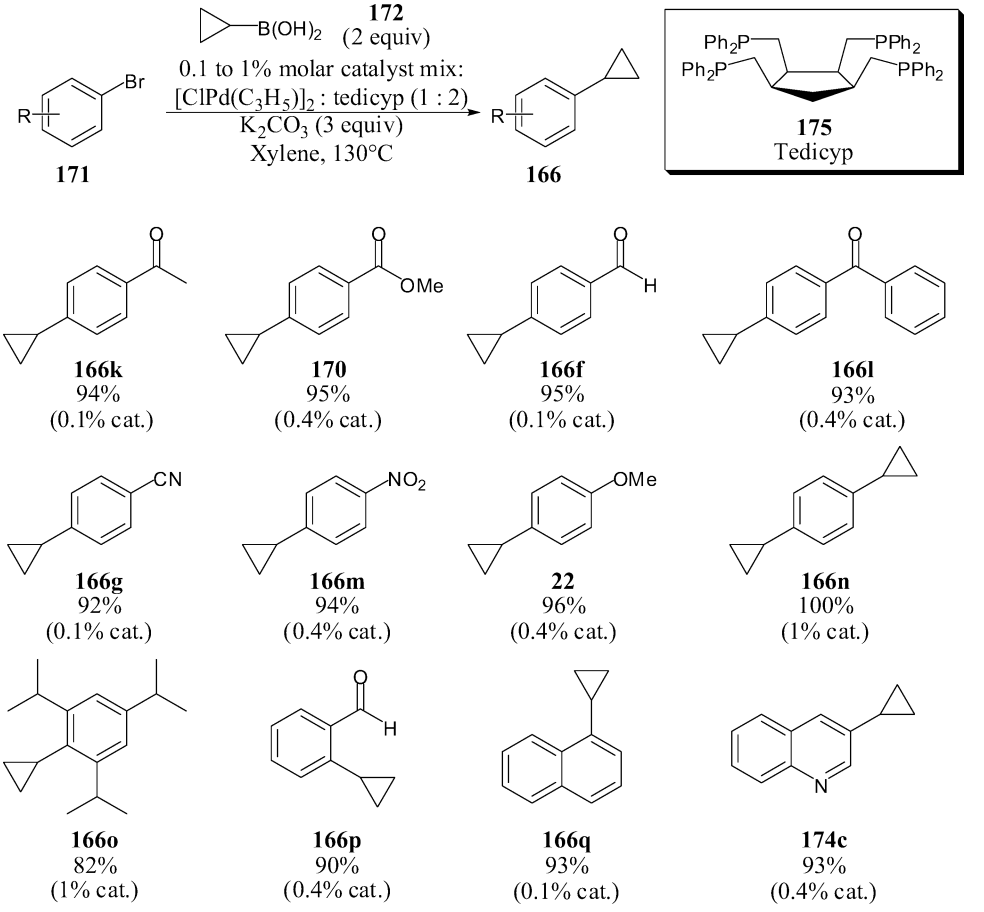
Scheme 61



Scheme 62

chlorides with potassium cyclopropyltrifluoroborate using simple conditions.[106] The optimal conditions, which require palladium acetate in combination with XPhos as a ligand and cyclopentyl methyl ether (CPME) as the solvent, afforded arylcyclopropanes **166** in good to excellent yields (*Scheme 65*).

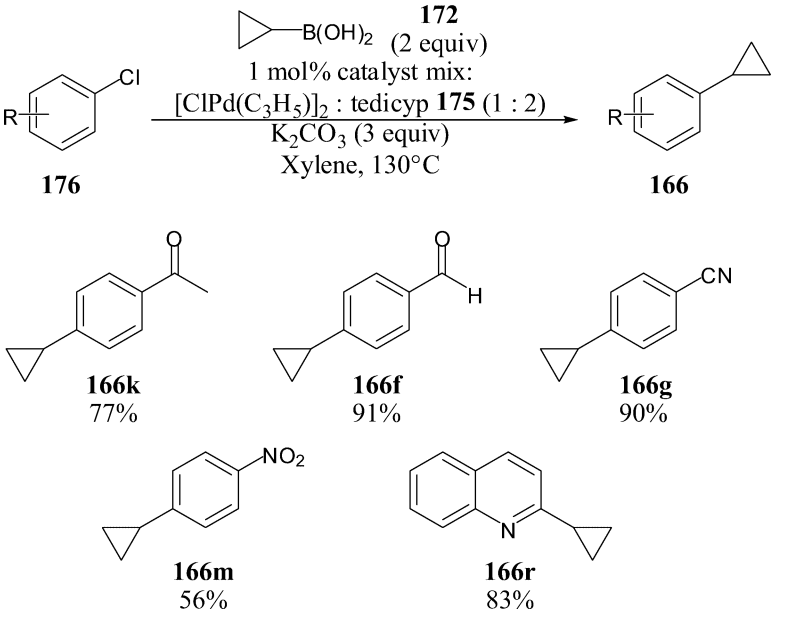
Using slightly modified conditions, this methodology was then successfully applied to the coupling of heteroaryl chlorides **178** (*Scheme 66*). For this purpose, a highly sterically hindered phosphine ligand was required, in combination with cesium carbonate as the base.



Scheme 63

In 2007, Kakiuchi and co-workers reported the ruthenium-catalyzed cross-coupling reaction of a variety of boronate esters with dimethylanilines such as **179**, *via* C—N bond cleavage and concomitant C—C bond formation (*Scheme 67*).[107] The *ortho*-pivaloyl substituent was found to be essential for reactivity, allegedly providing chelation assistance. This report included the synthesis of the arylcyclopropane **181**, which was obtained in 82% yield. Although this novel method was also applied to the coupling of a wide variety of aryl and alkylboronate esters, it is not clear how general the method would be for the synthesis of diversely functionalized cyclopropylarenes.

The importance of arylcyclopropanes in medicinal chemistry has been illustrated previously in this review. Not surprisingly, the Suzuki cross-coupling reaction involving cyclopropylboronic acid reagents has been utilized for the preparation of biologically relevant compounds. In one example, research groups at Viropharma/Wyeth have reported the preparation of the hepatitis C virus polymerase NS5B inhibitor **184** through a sequence that implies a Suzuki cross-coupling between an aryl triflate and cyclopropylboronic acid (*Scheme 68*).[108] Using palladium tetrakis(triphenylphosphine) as the catalyst, product **183**



Scheme 64

was obtained in 86% yield from the corresponding triflate **182**. This advanced intermediate was then transformed into the final inhibitor **184** in a few steps.

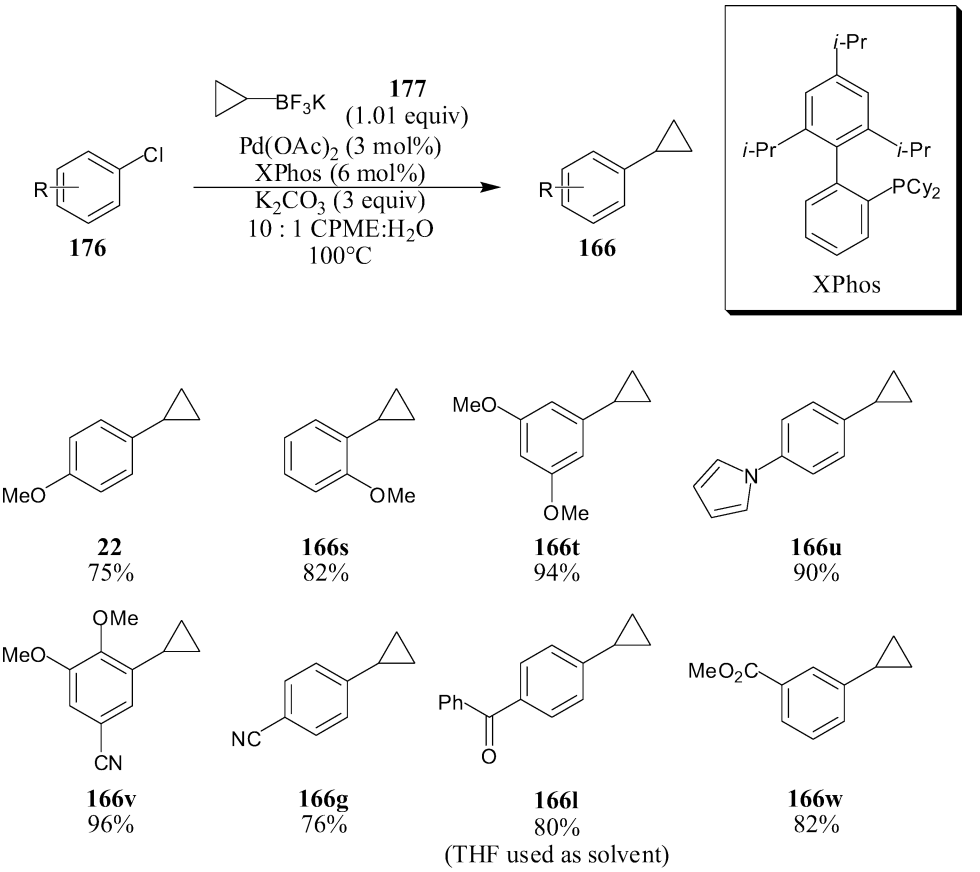
In a recent publication, chemists at Abbott employed the cyclopropylboronic acid **172** in a Suzuki coupling reaction with aryl bromide **185** as part of a program aimed at the discovery of potent TRPV1 antagonists, exemplified by compound **188**, for pain management (*Scheme 69*).[109]

Similarly, pinacolato cyclopropylboronate **190** was used in Suzuki coupling reactions within medicinal chemistry applications by groups at UCB Cambridge and Amgen for discovery of inhibitors of PI3K (*Scheme 70*)[110] and Tie-2 Kinase (*Scheme 71*),[111] respectively.

d) Stille Reaction of Cyclopropyltin Reagents

The introduction of a cyclopropyl group onto an aryl scaffold through a cross-coupling reaction between a tin reagent and an aryl halide appears as a possible approach for the preparation of arylcyclopropanes.[112] However, contrary to the cross-coupling reaction involving cyclopropylboron, magnesium and zinc reagents, the analogous reaction involving a tin derivative usually gives low yields of the desired arylcyclopropanes. Generally, it is believed that the poor yields are mainly due to the low reactivity of the organostannane species, which results in a sluggish transmetallation step. As a consequence, very few Stille reactions between aryl electrophiles and cyclopropyltin reagents have been reported. In one example, Gronowitz reported that the cross-coupling between tributylcyclopropyltin **197** and heteroaryl halides **196a** and **196b** gives poor yield of the corresponding heteroarylcyclopropanes **198a** and **198b** (*Scheme 72*).[113]

In another example, the coupling of aryl triflate **199** with tributylcyclopropyltin **197** in the presence of Pd_2dba_3 and triphenylarsine led to the desired product **200** in a very low



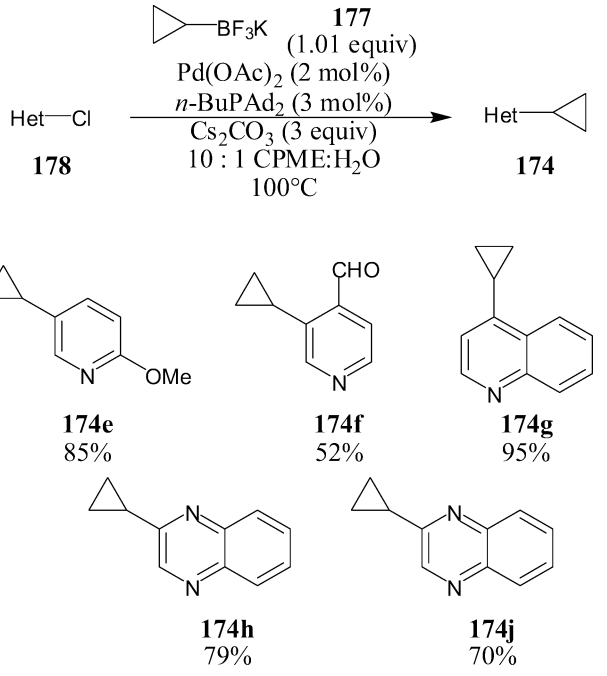
Scheme 65

yield (*Scheme 73*).[114] In this particular case, the weak reactivity of the tin reagent combined with a highly congested reactive center were most likely responsible for the poor efficacy of the transformation.

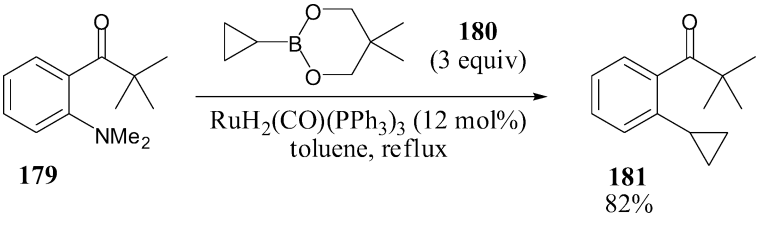
The palladium-catalyzed cross-coupling reaction between triflate **201** and tributylcyclopropyltin **197** also proved ineffective, giving the desired arylcyclopropane **202** in only 4% yield (*Scheme 74*).[115]

In light of these precedent examples, the synthesis of arylcyclopropanes through cross-coupling reactions involving cyclopropyltin reagents appears to be impractical. However, the following case illustrates that, under certain conditions, highly electron deficient aryl electrophiles can be competent partners in this coupling reaction. In this example, the highly functionalized aryl bromide **203** underwent cross-coupling reaction with cyclopropylstannyl derivative **204** in the presence of a mixture of two different palladium catalysts, giving the desired product **205** in modest yield (*Scheme 75*).[116]

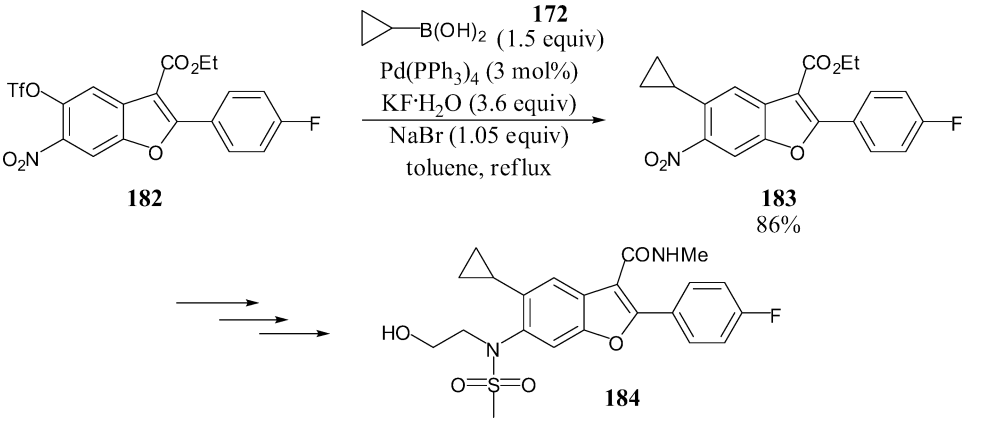
In order to overcome the low reactivity of cyclopropylstannyl reagents in the context of cross-coupling reactions, de Meijere utilized conditions that were based on a report by Farina, where a copper co-catalyst was used in conjunction with triphenylarsine and lithium chloride.[117] The amino-cyclopropyl stannyl **208** used in this study was obtained



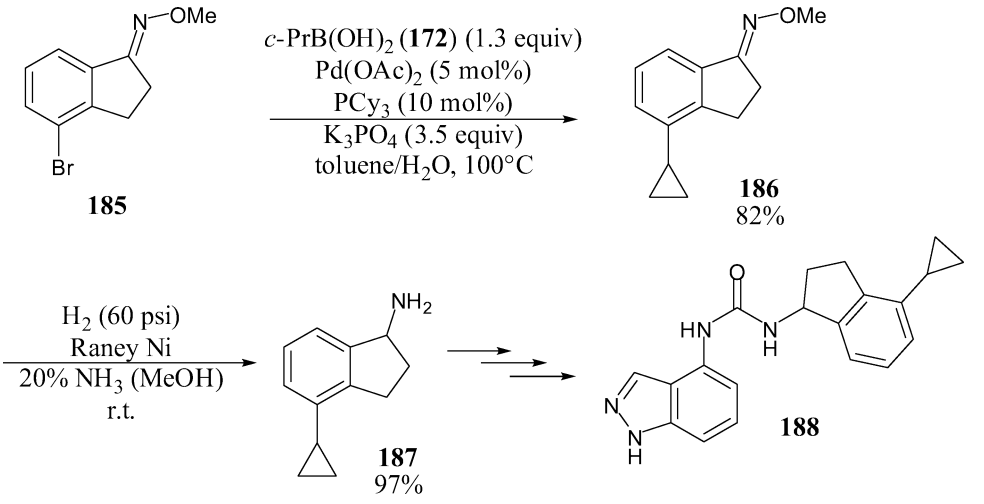
Scheme 66



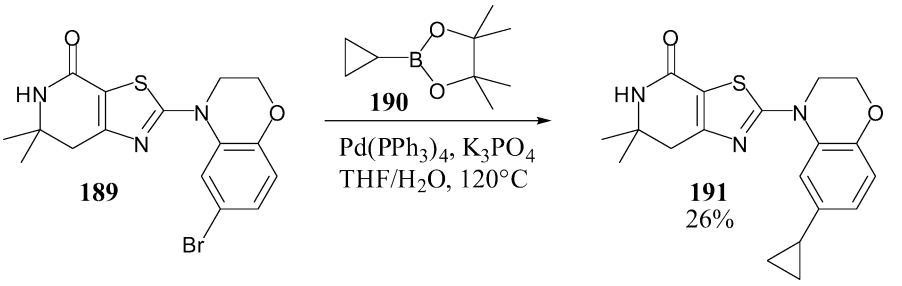
Scheme 67



Scheme 68



Scheme 69



Scheme 70

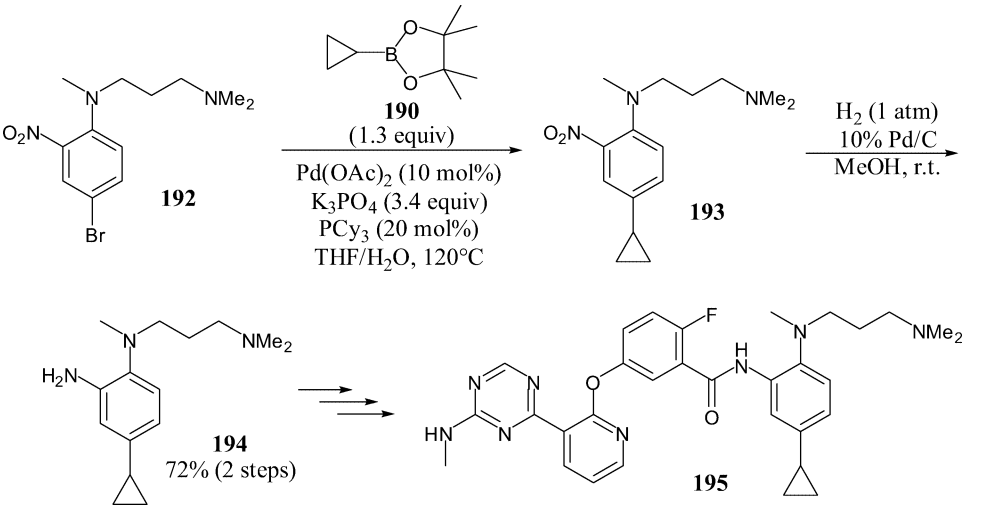
via a titanium-mediated aminocyclopropanation between tributylvinylstannane **206** and *N*,*N*-dialkylformamide **207** (*Scheme 76*).

This substrate was then efficiently cross-coupled with different aryl iodides under Farina's conditions, giving the desired arylcyclopropanes **209** in yields ranging from 43% to 67% (*Scheme 77*). The *ortho* substituted iodo-toluene was however found to be unreactive under those conditions.

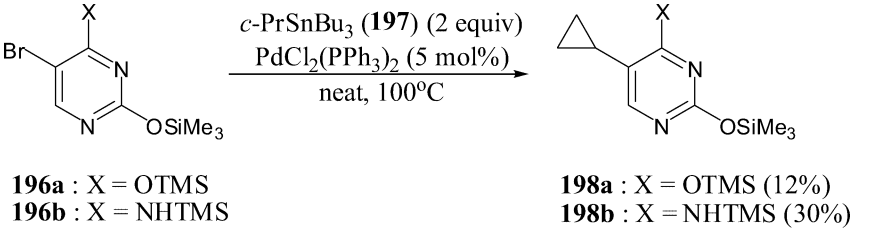
Using the same conditions, Markó reported the coupling of *trans-bis*-tributylstannyl cyclopropane **210** with iodobenzene, affording an inseparable mixture of mono phenyl product **211** and bis phenyl product **67a** in 60% yield (*Scheme 78*).[118] While the use of equimolar amount of iodobenzene did not solve this issue, the *bis*-phenylcyclopropane **67a** could be obtained as the sole product by using an excess of the aryl iodide.

e) Other Metals

The chemistry of indium has attracted considerable interest in the past years due in part to the reactivity and selectivity of alkylindium reagents as well as the low toxicity of indium salts. The palladium-catalyzed cross-coupling reaction of tricyclopropylindium with aryl



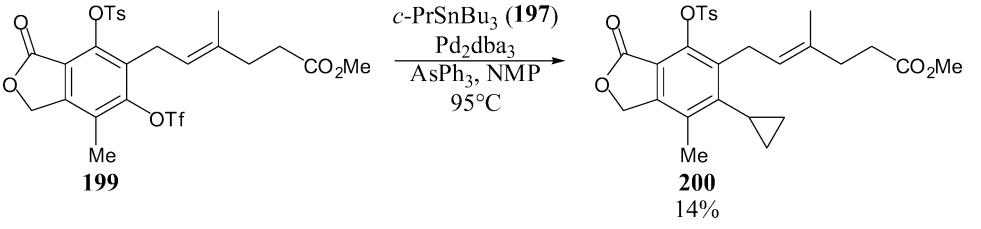
Scheme 71



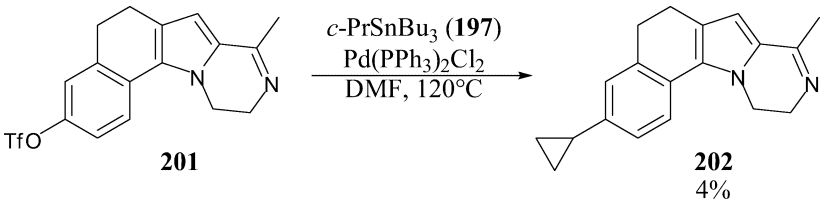
196a : X = OTMS
196b : X = NHTMS

198a : X = OTMS (12%)
198b : X = NHTMS (30%)

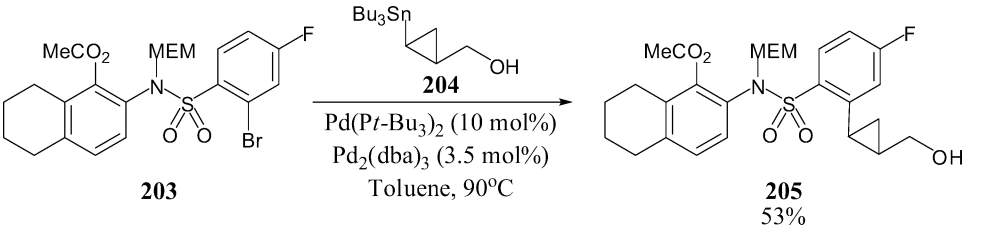
Scheme 72



Scheme 73

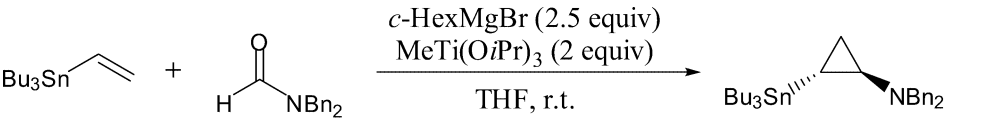


Scheme 74



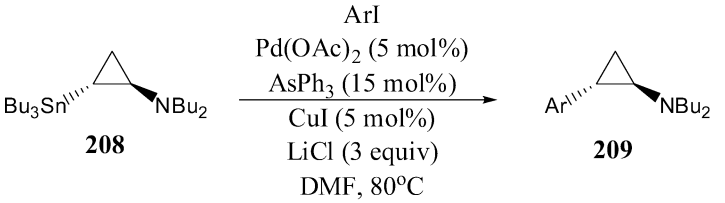
203 **205**
53%

Scheme 75



206 **207** **208**
92%, *cis:trans* = 1:45

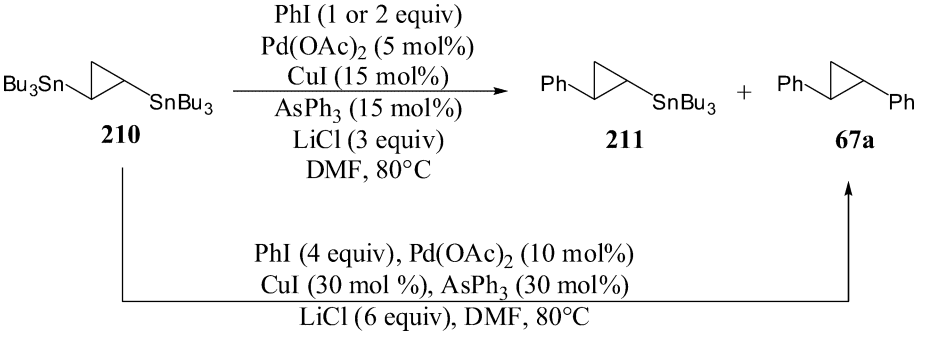
Scheme 76



208 **209**

209a : Ar = Ph (67%)
209b : Ar = 2-MePh (0%)
209c : Ar = 4-MePh (65%)
209d : Ar = 3,5-(*t*-Bu)$_2$Ph (63%)
209e : Ar = 4-MeO$_2$CPh (45%)
209f : Ar = 4-MeOPh (43%)

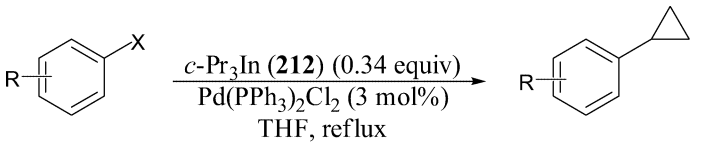
Scheme 77



210 **211** **67a**

Scheme 78

idodides has allowed the synthesis of functionalized arylcyclopropanes in excellent yields. In a recent report by Sarandeses, tricyclopropylindium **212** was used as a cyclopropyl transfer agent in the cross-coupling reaction with aryl halides **46**, giving the corresponding coupling products **83c** and **166k** in excellent yield (*Scheme 79*).[119] All three cyclopropyl groups were efficiently transferred from the indium reagent, allowing the use of only one third of an equivalent of the cyclopropylindium reagent **212**.[120]



46

83c: X = I; R = *p*-Me (92%)
166k : X = OTf; R = *p*-COMe (89%)

Scheme 79

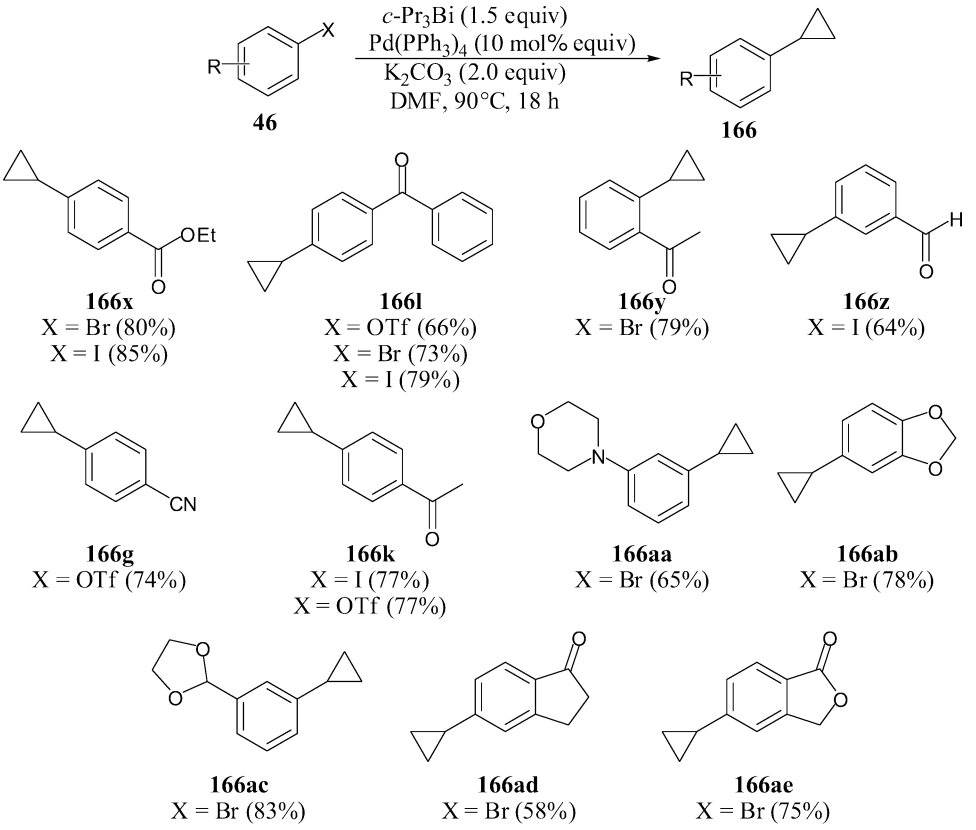
The chemistry of organobismuth reagents has also found wide application in numerous C—C, C—O and C—N bond forming reactions, in part due to the low toxicity of bismuth salts. Gagnon and coworkers reported in 2008 the palladium-catalyzed cross-coupling reaction between a cyclopropylbismuth reagent and aryl halides and triflates (*Scheme 80*).[121] This reaction was shown to tolerate many functional groups and to proceed efficiently under standard conditions for cross-coupling reactions, without requiring anhydrous conditions. The transformation was performed on iodides, bromides and triflates having diverse functional groups such as esters, benzophenones, acetophenones, aldehydes, benzonitriles, indanones and phtalates, giving the corresponding arylcyclopropanes in modest to good yields. Contrary to the cross-coupling involving tricyclopropyl indium, only two cyclopropyl groups could be transferred from the tricyclopropylbismuth reagent.

2. Cross-Coupling Reactions Between Arylmetals and Halocyclopropanes

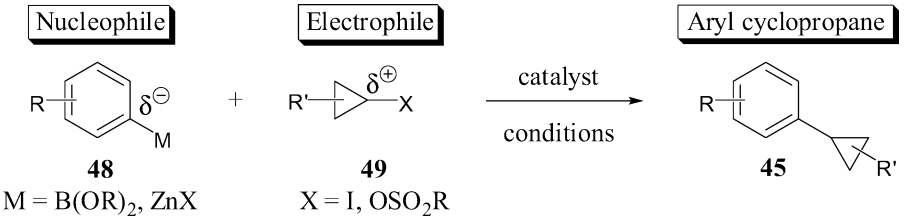
In the previous section, arylcyclopropanes were accessed *via* the cross-coupling reaction between a cyclopropyl metal and an aryl electrophile. The reversal of the roles of the cross-coupling partners, that is the reaction between an aryl metal **48** and a cyclopropyl electrophile **49**, provides a complementary approach to the synthesis of arylcyclopropanes **45** (*Scheme 81*). Since many arylboronic acids are commercially available and since many methods are available for the preparation of halocyclopropanes, this strategy represents an attractive route for the synthesis of highly functionalized cyclopropylarenes.

The mechanism for this transformation is very similar to the catalyzed cross-coupling reaction described in the previous section, except that the oxidative addition now occurs in the C—X bond of the halocyclopropane **49,** leading to the cyclopropyl palladium species **213** (*Scheme 82*). Transmetallation from the arylmetal **46** to **213** then affords the same palladium intermediate **53** that is generated during the coupling between an arylhalide and a cyclopropyl metal reagent (see *Scheme 12*). Reductive elimination finally leads to the desired arylcyclopropane **45** and to the regeneration of the palladium (0) catalyst.

Although this approach has been somewhat less explored than the complementary cross-coupling reaction involving cyclopropyl metal reagents, the reported examples



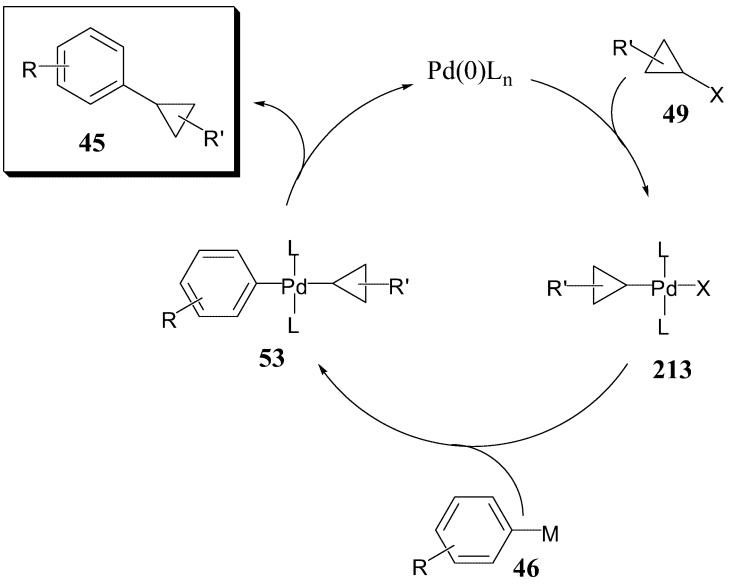
Scheme 80



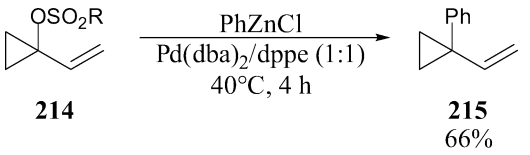
Scheme 81

involving this strategy clearly demonstrate the potential of this route. The first example of cross-coupling reaction between an arylmetal and a cyclopropyl electrophile was disclosed by de Meijere in 1991.[122] In this report, palladium-catalyzed allylic substitution was performed on the vinyl cyclopropyl tosylate **214,** yielding the geminal aryl-vinyl cyclopropane **215** (*Scheme 83*). The attack of the phenylzinc chloride occurred exclusively at the more hindered carbon, affording the desired product in 66% yield.[123,124]

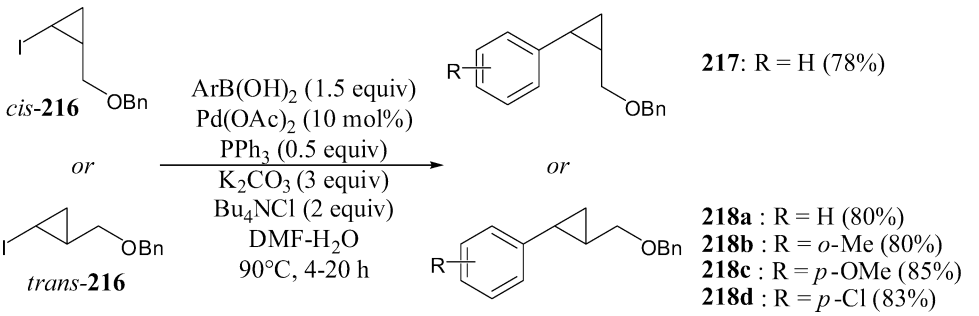
In 1996, Charette and Giroux reported the first general palladium-catalyzed cross-coupling reaction of iodocyclopropanes with arylboronic acids, giving expedient access to functionalized arylcyclopropanes (*Scheme 84*).[125] While the coupling of cyclopropylboronic acids with aryl halides was a well established strategy for the preparation of



Scheme 82



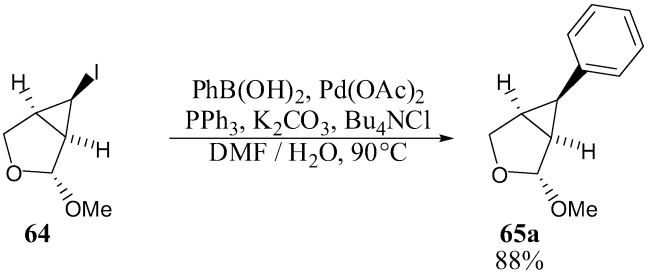
Scheme 83



Scheme 84

arylcyclopropanes, the reverse approach involving the coupling of an electrophilic iodocyclopropane with an arylboronic acid was until then unexplored. This study demonstrated that the oxidative addition into the cyclopropyl iodide bond occurs smoothly under mild conditions, giving after cross-coupling with the arylboronic acid, the corresponding cross-coupled product. The *cis*- and the *trans*-iodocyclopropanes **216** led to products **217** and **218** respectively, indicating a complete retention of stereochemistry during the course of the transformation.

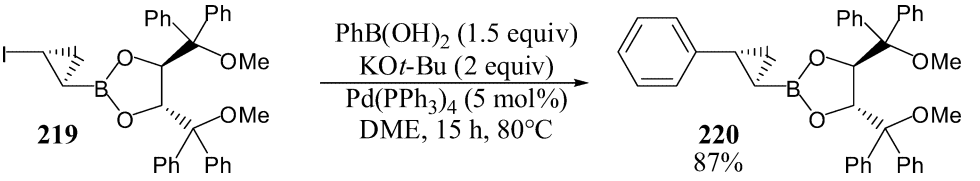
Using the methodology developed by Charette and Giroux, Martin prepared the highly functionalized arylcyclopropane **65a** *via* a Suzuki cross-coupling reaction between the iodocyclopropane **64** and phenylboronic acid (*Scheme 85*). The reaction occurred with



Scheme 85

complete retention of configuration, affording **65a** in good yield as the sole product. This methodology constitutes a complementary approach to the coupling of the cyclopropylzinc species derived from **64** previously described (see *Scheme 17*).

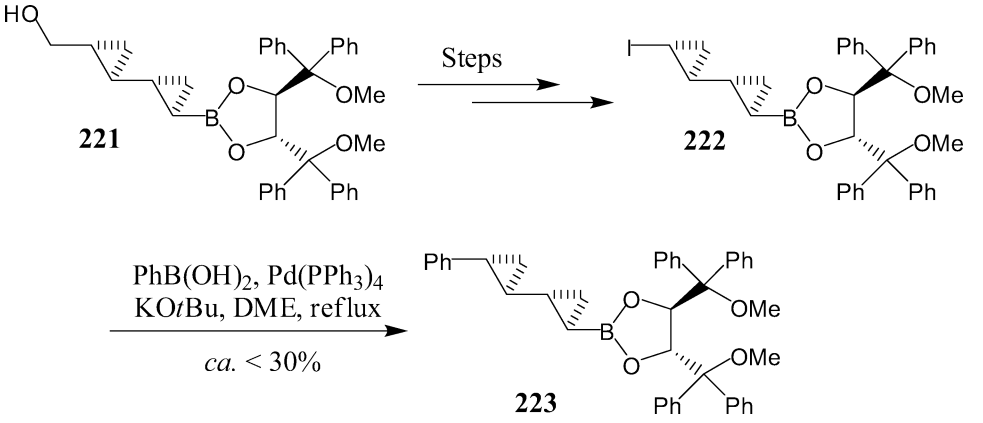
Pietruszka demonstrated that under standard conditions, 2-iodocyclopropylboronic esters undergo palladium-catalyzed cross-coupling selectively at the carbon bearing the iodide, leaving the boronic ester intact (*Scheme 86*).[126] Thus, when the *trans*-iodocyclopropylboronic ester **219** was treated with phenylboronic acid in the presence of potassium *tert*-butoxide and tetrakis(triphenylphosphine)palladium, the corresponding product **220** was obtained with complete retention of configuration as the sole product.



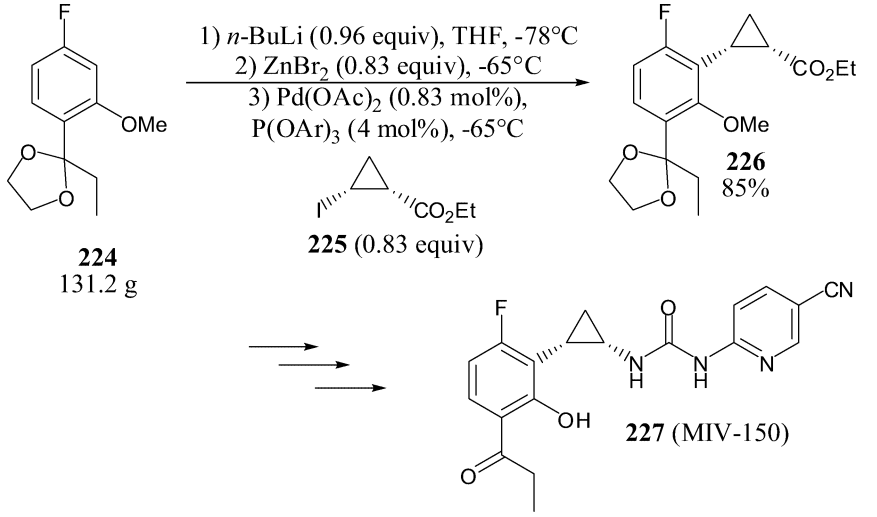
Scheme 86

In another example, the iodobiscyclopropylboronic ester **222** prepared from the alcohol **221** was submitted to Suzuki-type cross-coupling conditions with phenylboronic acid (*Scheme 87*). Similarly to the previous example, the coupling occurred exclusively at the carbon bearing the iodide, leaving the boronic ester in place. Although product **223** could not be isolated in pure form, its formation was confirmed through mass spectroscopy, supporting the fact that hindered cyclopropylboronic esters are poorer nucleophilic partners than arylboronic acids in cross coupling reactions.[127]

The cross-coupling reaction between a cyclopropyl iodide and an arylzinc species has been utilized as the key step in the synthesis of MIV-150 (**227**), a potent HIV non-nucleoside reverse transcriptase inhibitor (NNRTI).[128] The synthesis of MIV-150, which was accomplished on a multi-gram scale, started with the *ortho* lithiation of the fluoroketal **224** followed by trapping of the generated aryllithium species with zinc bromide (*Scheme 88*). The arylzinc species thus generated was then coupled with the iodocyclopropane **225** to afford the corresponding arylcyclopropane **226** which was further transformed



Scheme 87



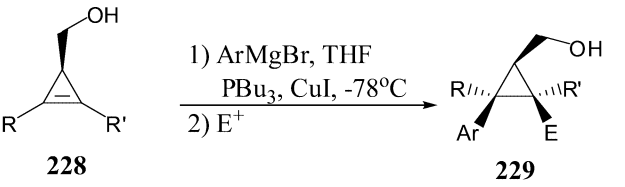
Scheme 88

into the final product **227**. The low catalyst loading utilized for this transformation is remarkable and indicates a high catalyst turnover for this cross-coupling reaction.

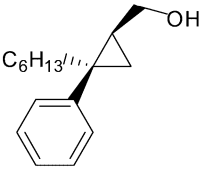
3. Other Coupling Methods

a) Addition to Cyclopropenes

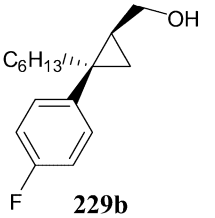
Arylcyclopropanes can be accessed by carbometalation of a suitably functionalized cyclopropene with an aryl Grignard reagent, as reported by Fox and coworkers.[129] In this approach, a hydroxymethyl-directed copper (I) mediated arylmagnesiation is performed on cyclopropene **228**, followed by a reaction of the formed cyclopropyl Grignard reagent with an electrophile, affording compound **229** (*Scheme 89*). This process delivers a highly substituted arylcyclopropane with high diastereoselectivity. In the simplest case, where the cyclopropene is unsubstituted at positions 1 and 2, the hydroxymethyl substituent directs



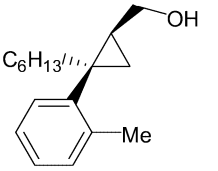
228 **229**



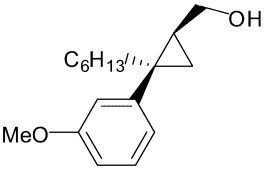
229a
R = C_6H_{13}; R'= H; E = H^+
83%, 96% *syn*



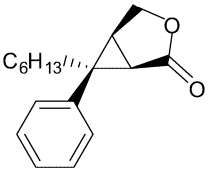
229b
R = C_6H_{13}; R'= H; E = H^+
84%, 97% *syn*



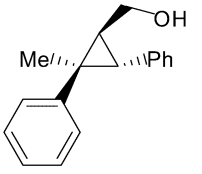
229c
R = C_6H_{13}; R'= H; E = H^+
82%, 3:2 *syn:anti*



229d
R = C_6H_{13}; R'= H; E = H^+
85%, 96% *syn*



229e
R = C_6H_{13}; R'= H; E = CO_2
70%



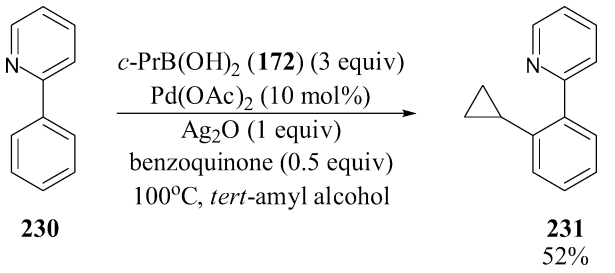
229f
R = C_6H_{13}; R'= Ph; E = H^+
83%, 96% *syn*

Scheme 89

the carbometalation on the *syn*-face of the alkene, even in the absence of a catalyst. However, when the alkene is tri- or tetrasubstituted, essentially no product is formed under these conditions, or in the presence of catalytic amounts of cuprous iodide. As a general solution to this problem, a catalyst screen was performed and revealed that cuprous iodide in the presence of the ligand tri-*n*-butylphosphine efficiently catalyzed the *syn*-selective aryl magnesiation of 1-substituted-3-hydroxymethylcyclopropenes. The electrophilic quench was performed with aqueous acid, iodine, allyl bromide, CO_2 (to give the lactone) or DMF (to give the lactol). Although the substrate scope is limited in terms of the diversity of the cyclopropene building block, a good range of Grignard reagents was employed, indicating that a broad range of complex arylcyclopropanes can be accessed by this method.

b) C—H Activation

The impressive progress seen in the field of C—H activation over the past years greatly contributed to the development of methodologies allowing the preparation of arylcyclopropanes using this type of transformation. For example, Yu and coworkers reported in 2006 the Pd(II) catalyzed alkylation of sp^2 and sp^3 centers with methyl boroxine and alkylboronic acids *via* a C—H activation mechanism (*Scheme 90*).[130,131] Using cyclopropylboronic acid, this method was nicely extended to the introduction of a cyclopropyl group on aryl rings. This reaction relies on neighboring group participation of a pyridine ring which coordinates

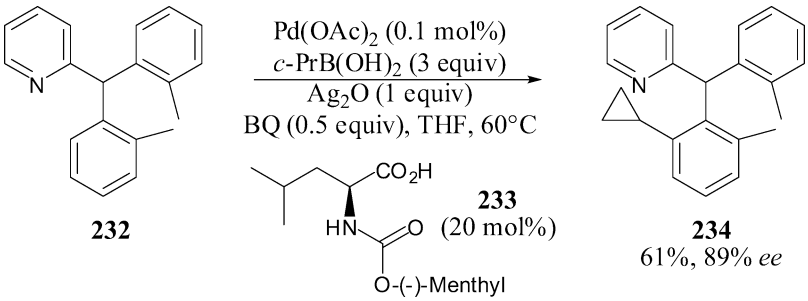


230 **231** 52%

Scheme 90

to the Pd(II) center and facilitates cyclopalladation and is consequently mainly applicable to substrates of this type. However, a variety of substituents, from electron donating to electron withdrawing, were tolerated on the arene. Since the cyclopropyl building block used was cyclopropylboronic acid **172**, substituted cyclopropylboron species described in the Suzuki section (*vide supra*) could presumably be utilized in this methodology for the preparation of functionalized arylcyclopropanes.

A fascinating application of this type of reactivity was later reported by the Yu group where a chiral ligand allowed the selective differentiation of enantiotopic C—H bonds of substrates such as **232** (*Scheme 91*)[132] In this approach, it was possible to introduce a



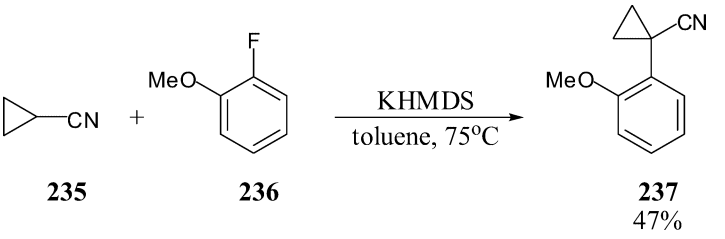
232 **234** 61%, 89% *ee*

Scheme 91

cyclopropane group into this very challenging structural class of compounds with good yield and enantioselectivity.

c) Formal S_NAr Reaction Involving Cyclopropyl Anions

Arylcyclopropanes have been prepared in rare occasions through reactions involving cyclopropyl anion species. In these transformations, the cyclopropyl anion is formed by deprotonation and is used as the nucleophilic coupling partner. A recent example of this strategy was reported by Caron and coworkers wherein a range of secondary aliphatic nitrile derivatives were deprotonated with potassium hexamethyldisilazide and added onto diverse fluoroarenes, giving the formal nucleophilic aromatic substitution products.[133] For example, arylcyclopropane **237** was obtained in modest yield following the addition of the anion of cyanocyclopropane **235** onto 2-fluoroanisole **236** (*Scheme 92*). The procedure prescribes the use of 1.5 equivalents of KHMDS, THF or toluene as the solvent and elevated temperatures (60–100°C). While the protocol appears general for a range of simple aryl

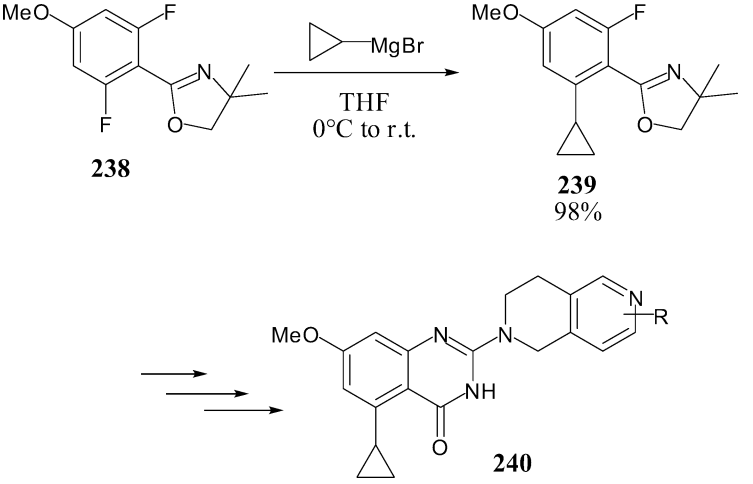


235 **236** **237**
47%

Scheme 92

fluorides and a short list of aliphatic nitriles, it is not clear how general it would be for the preparation of substituted-arylcyclopropanes, as only one example was reported in this communication.

This type of disconnection which involves a formal S_NAr reaction has been used in the context of a medicinal chemistry program reported by a group at Pfizer, where cyclopropylmagnesium bromide displaced one of the fluorine atoms flanking the oxazoline ring of compound **238** (*Scheme 93*).[134] Contrary to the Kumuda-type cross-coupling reaction,



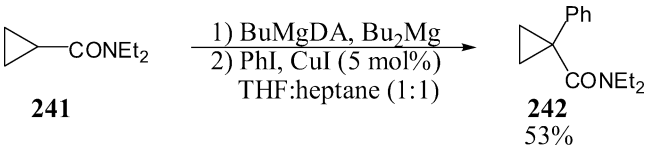
238 **239**
98%

240

Scheme 93

this transformation did not require any catalyst. The arylcyclopropane **239** was then transformed into the biologically relevant compound **240** which can be used in the treatment of hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia.

In a second example of this type, the base prepared by mixing dibutylmagnesium and diisopropylamine ($BuMgNiPr_2$ denoted as BuMgDA) effected stoichiometric deprotonation of a number of activated C—H acids, including the alpha proton of cyclopropane *N*,*N*-diethylcarboxamide **241** (*Scheme 94*).[135] In this example, following deprotonation, α-arylation by iodobenzene catalyzed by cuprous iodide then led to the arylcyclopropane derivative **242**. Again in this case, it is not clear how applicable this method would be for the preparation of a range of arylcyclopropanes.

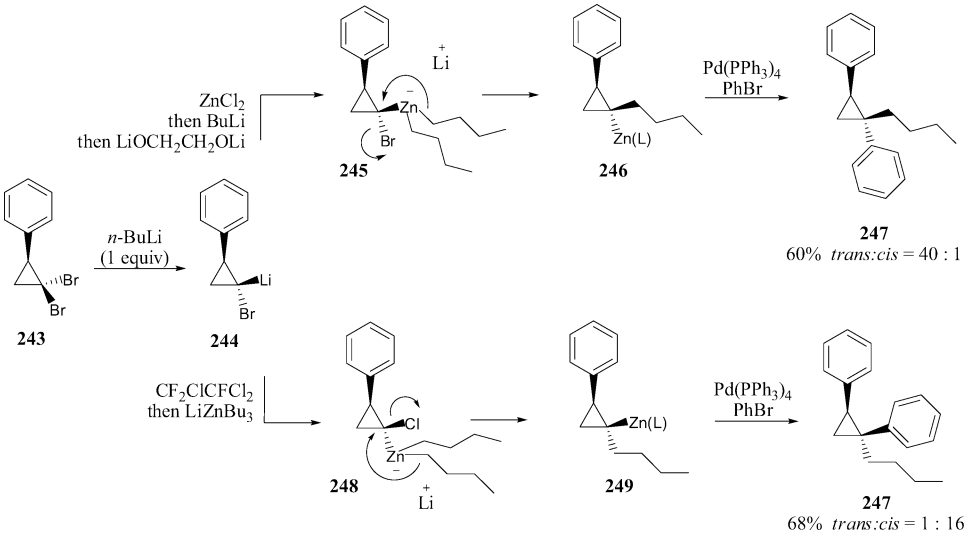


241 **242** 53%

Scheme 94

d) Migration Reactions

gem-Dihalocyclopropanes, which are obtained by the addition of dihalocarbenes onto olefins, have been used in the preparation of arylcyclopropanes. Harada and Oku reported in 1989 a two-step procedure for the stereoselective synthesis of *gem*-disubstituted cyclopropanes, starting from *gem*-dibromocyclopropanes.[136,137] The first step of the sequence consists in a stereoselective lithium-halogen exchange reaction on **243** to give lithium carbenoid **244** (*Scheme 95*). Then either the *trans*- or *cis*- mixed dialkylzinc reagent is



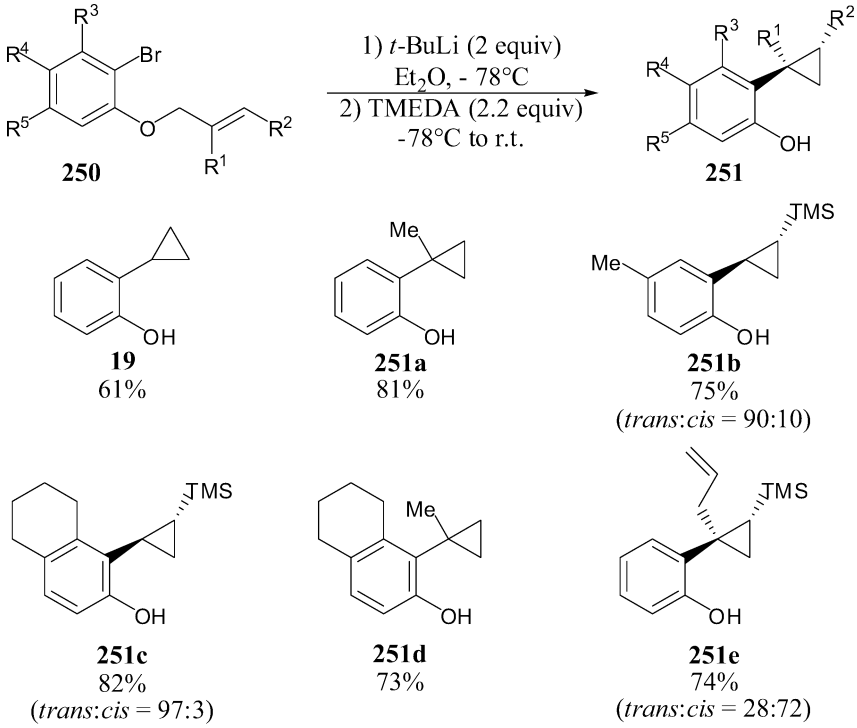
Scheme 95

formed depending on which reaction conditions are employed. The mechanism in both cases involves the formation of a cyclopropylzinc carbenoid which is then transformed into a mixed zincate complex. In the first case, treatment of the lithium carbenoid with zinc dichloride followed by sequential treatment with butyllithium and the dianion of ethylene glycol leads to the *cis*-zincate **245**. In the second case, the lithium carbenoid is quenched with an electrophilic chlorine source and the 1-chloro-1-bromocyclopropane obtained is then converted to the *trans*-zincate complex **248** by treatment with lithiumtributylzincate. In both cases, 1,2-alkyl migratory displacement of the halide by the zinc-bound butyl group then affords stereoselectively either mixed dialkylzinc intermediate **246** or **249**. It is noteworthy that in each case, the migration occurs with inversion without significant erosion of stereochemical integrity of the zincate complex. The dialkylzinc complexes then serve

as competent substrates for Negishi cross-coupling reactions with arylhalides to give either *trans*- or *cis*- arylcyclopropane **247**.

e) Other Methods

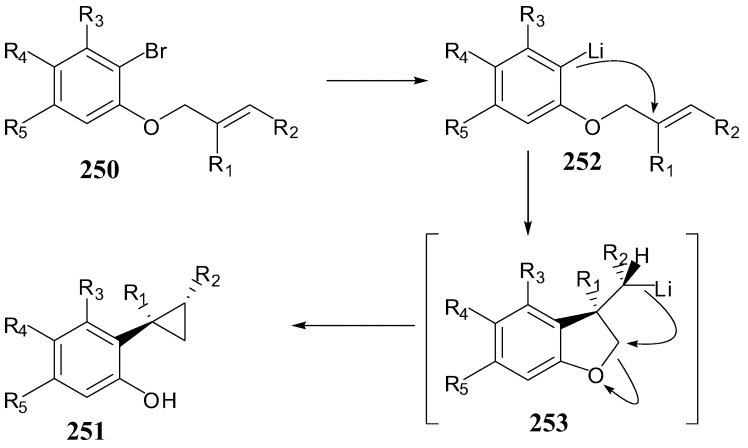
A number of other methods for arylcyclopropane synthesis have been described that do not fall under the umbrella of those outlined above. One example is that detailed by the Barluenga group which involves the intramolecular carbolithiation of alkenes tethered to aryllithiums (*Scheme 96*).[138,139] To date the substrate scope includes a range of substitutions on the arene scaffold and that are attached to terminal, di- and trisubstituted allylic alcohols.



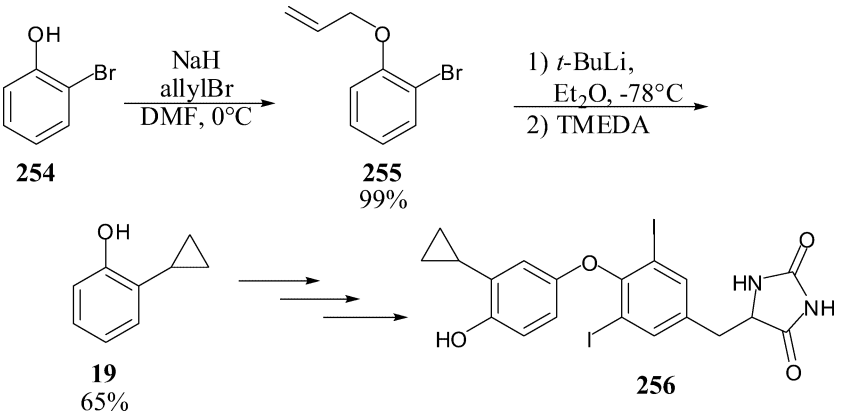
Scheme 96

The first step in the mechanism involves halogen metal exchange of an aryl bromide **250** with butyllithium, followed by 5-*exo-trig* cyclization and *syn*-addition across the double bond to give the bicyclic alkyllithium intermediate **253** (*Scheme 97*). The stereochemical outcome of the reaction is rationalized by minimization of steric interactions between the newly formed adjacent chiral centers which can lead to epimerization of the anionic carbon atom. Follows a 1,3-elimination with retention of configuration at the anionic center. It is noteworthy that the reaction is facilitated by alkene substituents that stabilize the developing negative charge of the alkyllithium intermediate.

This lithiation-cyclization reaction developed by Barluenga has recently been utilized by Scanlan and corworkers in the synthesis of compound **256**, a thyroid hormone receptor α-specific analog.[140] The adopted route involved the preparation of the key compound **19** from the allylic alcohol **255** using the previously described methodology (*Scheme 98*).



Scheme 97

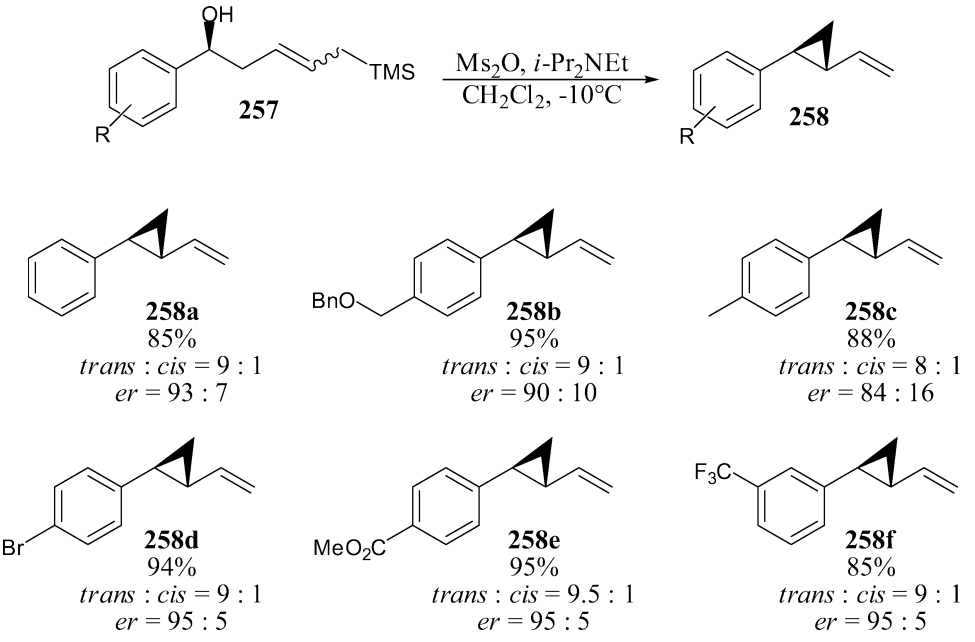


Scheme 98

Another stepwise approach to arylcyclopropanes involves the activation of homoallylic benzylic alcohols such as **257** as the corresponding mesylate, followed by nucleophilc ring closure by a pendant allyl silane to give *trans*-susbstituted vinylcyclopropanes **258** (*Scheme 99*).[141]

The enantiomeric purity of the final product is determined by that of the starting material, implying that the ring-closing step of the mechanism proceeds through an S_N2-type displacement. Furthermore, the reaction proceeds with good levels of diastereoselection as well, which the authors propose is derived from minimization of developing steric interactions in the transition state (*Figure 10*).

Aromatic ketones and aldehydes may also be converted to arylcyclopropanes using the method of Szymoniak (*Scheme 100*).[142] In this Kulinkovich-type cyclopropanation, an ethylene bound zirconocene reacts with the carbonyl of compound **261** to give an oxazirconacycle intermediate, which upon acidic work-up liberates the arylcyclopropane **262**. This method appears to be a very general approach to 1,1-disubstituted cyclopropanes since the carbonyl compound may also be aliphatic.



Scheme 99

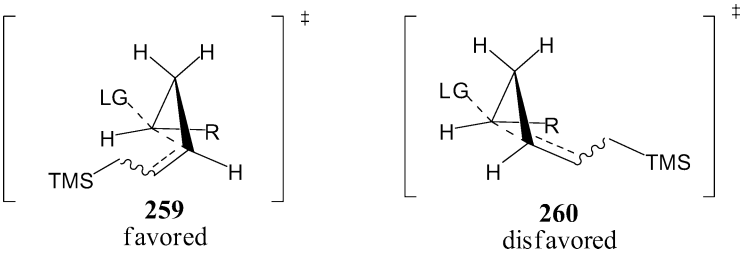
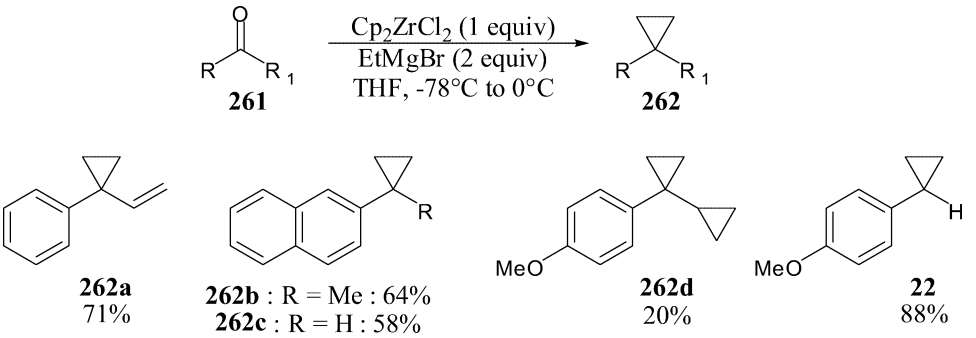
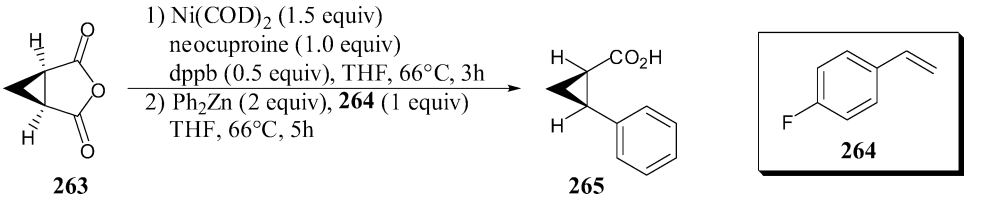


Figure 10

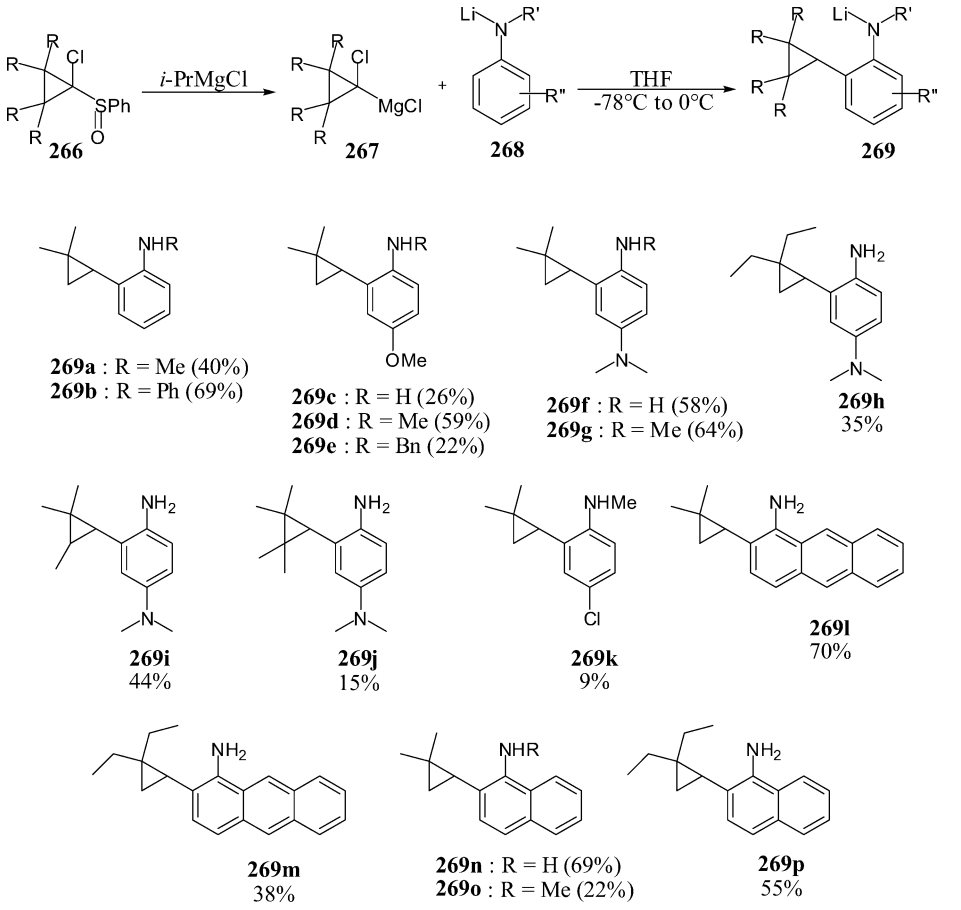


Scheme 100

A very elegant decarboxylative cross-coupling method for the conversion of cyclic anhydrides to arylcyclopropanes and other derivatives has been disclosed by Rovis and coworkers.[143] For this approach to be applied to arylcyclopropane synthesis, cyclic anhydride **263** was employed and coupled to diphenylzinc using a stoichiometric amount of a chiral nickel complex to provide the corresponding arylcyclopropane **265** (*Scheme 101*). Although the method may be limited in applicability at the current level of development, it represents an innovative approach to the introduction of chirality on the cyclopropane ring using achiral building blocks.



Scheme 101



Scheme 102

A recent report by Satoh and coworkers described an approach that is suitable for the synthesis of *o*-aminoarylcyclopropanes.[144] In this methodology, a substituted 1-chlorocyclopropyl phenyl sulfoxide **266** is transformed to the magnesium cyclopropylidene **267**, which in turn reacts with *N*-lithioanilides such as **268** to install a cyclopropyl unit on the arene *ortho* to the amino group in modest to good yields (*Scheme 102*). A salient feature of this method is that the magnesium cyclopropylidene can be formed in the presence the *N*-lithioanilide with the consequence that the entire process can be performed in a single reaction vessel. A range of alkyl-substituted cyclopropyl groups were introduced using this method, but a minor drawback was that 1-chlorocyclopropyl phenyl sulfoxide itself did not work in this reaction. However, since there are many other methods for the installation of an unsubstituted cyclopropyl group, this method remains a very versatile approach for the introduction of highly substituted cyclopropyl fragments on the aryl ring.

II. Conclusions

The arylcyclopropane is a privileged substructure owing to its unique physical properties. The cyclopropane ring preferentially adopts one of two extreme conformations. In the bisected conformation, the distal C—C bond of the cyclopropane ring is orthogonal to the plane of the phenyl ring, allowing for conjugation of the π-system with the molecular orbitals of the cyclopropyl group. Mounting evidence indicates that this allows for conjugative transmission of electronic effects to or from the phenyl ring through the cyclopropane ring. This in turn can have an impact on the physical and chemical properties of molecules having the phenylcyclopropane substructure. In the perpendicular conformation, the C—H bond of the cyclopropane ring that is in a geminal relationship with the phenyl ring is orthogonal to the plane of the phenyl ring, precluding the possibility of conjugation of the π-system with the cyclopropane. In this situation, it can be expected that conjugative effects would not be transmitted through the cyclopropane ring.

In addition to the conformational relationship between the phenyl and cyclopropyl rings and the related effects on a molecule's properties, arylcyclopropanes have a unique chemical behavior that can be exploited.[145–151] It is the combination of these features and the conjugative effects described above that have attracted medicinal chemists to this class of molecules. On one hand, the arylcyclopropane moiety can make van der Waal's contacts just as alkyl arenes similar in size and with similar electrostatic surface potentials do.[3] On the other had, the cyclopropyl moiety may also impart unique metabolic properties and provide a distinctive three-dimensional arrangement of substituents unattainable by other alkyl linkers.

Numerous approaches that allow the preparation of arylcyclopropanes have been described in the literature. The direct cross-coupling reaction between a cyclopropyl metal species and an aryl halide or pseudohalide constitutes one of the most efficient strategy for the preparation of cyclopropylarene. In this approach, metals such as zinc, boron, tin, indium and bismuth have been exploited to couple unsubstituted as well as highly functionalized cyclopropyl groups. Although the complementary approach involving the cross-coupling between an arylmetal and a cyclopropyl halide or pseudohalide has been less studied, this strategy is nevertheless very powerful in cases where highly functionalized

arylcyclopropanes are required. Alternative and creative routes which involve addition to cyclopropenes, C—H activation, S_NAr reaction of cyclopropyl anion, and migration reactions have also been explored and have recently come to maturity, adding to the toolbox of methodologies for the preparation of arylcyclopropanes.

As highlighted in the special context of medicinal chemistry in this review, the preparation of even structurally complex arylcyclopropanes is well developed and permits access to a wide range of drug-like molecules possessing this motif. Given the unique properties of arylcyclopropanes and the advanced state of the methods available for their preparation, the future of medicinal chemistry and drug-discovery will likely continue to feature molecules of this type.

Acknowledgements

The authors would like to thank Dr. Benoît Moreau and Dr. Claudio Sturino from Boehringer Ingelheim Canada Ltd. for their valuable help during the preparation of this manuscript.

References

1. For a review on the biological activities of cyclopropane derivatives, see J. Salaün, *Topics Curr. Chem.*, **207**, 1 (2000).
2. For a recent review on the synthesis of cyclopropanes, see H. Pellissier, *Tetrahedron*, **64**, 7041 (2008) and references cited therein.
3. For a study on CH/π interactions involving cyclopropanes, see J. Ran and M. W. Wong, *J. Phys. Chem. A*, **110**, 9702 (2006).
4. For a review on the introduction of cyclopropanes into peptides to achieve a bioactive conformation, see A. Reichelt and S. F. Martin, *Acc. Chem. Res.*, **39**, 433 (2006).
5. R. C. Hahn, T. F. Corbin and H. Shechter, *J. Am. Chem. Soc.*, **90**, 3404 (1968).
6. E. P. Carr and C. P. Burt, *J. Am. Chem. Soc.*, **40**, 1590 (1918).
7. M. T. Rogers, *J. Am. Chem. Soc.*, **69**, 2544 (1947).
8. R. J. Mohrbacher and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 401 (1957).
9. R. P. Mariella, L. F. A. Peterson and R. C. Ferris, *J. Am. Chem. Soc.*, **70**, 1494 (1948).
10. M. F. Hawthorne, *J. Org. Chem.*, **21**, 1523 (1956).
11. E. N. Trachtenberg and G. Odian, *J. Am. Chem. Soc.*, **80**, 4018 (1958).
12. R. Fuchs and J. J. Bloomfield, *J. Am. Chem. Soc.*, **81**, 3158 (1959).
13. R. Fuchs, C. A. Kaplan, J. J. Bloomfield and L. F. Hatch, *J. Org. Chem.*, **27**, 733 (1962).
14. See also R. C. Hahn, T. F. Corbin and H. Shechter, *J. Am. Chem. Soc.*, **90**, 3404 (1968).
15. R. G. Pews and N. D. Ojiha, *J. Am. Chem. Soc.*, **91**, 5769 (1969).
16. R. Fuchs, J. H. Hallman and M. O. Perlman, *Can. J. Chem.*, **60**, 1832 (1982).
17. R. E. Drumright, R. H. Mas, J. S. Merola and J. M. Tanko, *J. Org. Chem.*, **55**, 4098 (1990).
18. G. L. Closs and H. B. Klinger, *J. Am. Chem. Soc.*, **87**, 3265 (1965).

19. For photoelectron studies on arylcyclopropanes, see I. Prins, J. W. Verhoeven and TH. J. DeBoer, *Tetrahedron*, **33**, 127 (1977).

20. K. Shudo, T. Kobayashi and C. Utsunomiya, *Tetrahedron*, **33**, 1721 (1977).

21. The ability of the cyclopropyl group to enter conjugation with aryl groups was also quantified using ^{19}F: R. G. Pews and N. D. Ojha, *J. Am. Chem. Soc.*, **91**, 5769 (1969).

22. For ^{13}C and ^{15}N NMR experiments, see D. R. Crist, G. J. Jordan, D. W. Moore, J. A. Hashmall, A. P. Borsetti and S. A. Turujman, *J. Am. Chem. Soc.*, **105**, 4136 (1983).

23. X. Creary, *J. Org. Chem.*, **45**, 4653 (1980).

24. J. S. A. M. de Boer, B. O. Loopstra and C. H. Stam, *Recl. Trav. Chim. Pays-Bas*, **106**, 537 (1987).

25. R. E. Drumright, R. H. Mas, J. S. Merola and J. M. Tanko, *J. Org. Chem.*, **55**, 4098 (1990).

26. I. Bernal, D. C. Levendis, R. Fuchs, G. M. Reisner and J. M. Cassidy, *Structural Chem.*, **8**, 275 (1997).

27. M. J. De Groot, *Drug Discovery Today*, **11**, 601 (2006).

28. G. Zlokarnik, P. D. J. Grootenhuis and J. B. Watson, *Drug Discovery Today*, **10**, 1443 (2005).

29. For a review on the mechanism of cytochromes P-450, see F. P. Guengerich and T. L. Macdonald, *Acc. Chem. Res.*, **17**, 9 (1984).

30. P. R. Ortiz de Montellano and R. A. Stearns, *Drug Metabolism Rev.*, **20**, 183 (1989).

31. C. J. Suckling, *Angew. Chem. Int. Ed.*, **27**, 537 (1988).

32. K. E. Suckling, C. G. Smellie, I. E. S. Ibrahim, D. C. Nonhebel and C. J. Suckling, *FEBS Letters*, **145**, 179 (1982).

33. C. J. Suckling, D. C. Nonhebel, L. Brown, K. E. Suckling, S. Seilman and C. R. Wolf, *Biochem. J.*, **232**, 199 (1985).

34. P. Riley and R. P. Hanzlik, *Xenobiotica*, **24**, 1 (1994).

35. H. Chen, M. J. de Groot, N. P. E. Vermeulen and R. P. Hanzlik, *J. Org. Chem.*, **62**, 8227 (1997).

36. H. Fu, M. Newcomb and C.-H. Wong, *J. Am. Chem. Soc.*, **113**, 5878 (1991).

37. P. Riley and R. P. Hanzlik, *Tetrahedron Lett.*, **30**, 3015 (1989).

38. M. J. de Groot, G. M. Donné-Op den Kelder, J. N. M. Commandeur, J. H. van Lenthe and N. P. E. Vermeulen, *Chem. Res. Toxicol.*, **8**, 437 (1995).

39. P. H. Toy, M. Newcomb and P. F. Hollenberg, *J. Am. Chem. Soc.*, **120**, 7719 (1998).

40. D. Kumar, S. P. de Visser and S. Shaik, *J. Am. Chem. Soc.*, **125**, 13024 (2003).

41. For a general review on the metabolism of cyclopropyl rings in natural products, see L. A. Wessjohann and W. B. T. Thieman, *Chem. Rev.*, **103**, 1625 (2003).

42. M. Shiozaki, K. Maeda, T. Miura, Y. Ogoshi, J. Haas, A. M. Fryer, E. R. Laird, N. M. Littmann, S. W. Andrews, J. A. Josey, T. Mimura, Y. Shinozaki, H. Yoshiuchi and T. Inaba, *Bioorg. Med. Chem. Lett.*, **19**, 1575 (2009).

43. A. Thorarensen, B. D. Wakefield, D. L. Romero, K. R. Marotti, M. T. Sweeney, G. E. Zurenko, D. C. Rohrer, F. Han and G. L. Bryant Jr., *Bioorg. Med. Chem. Lett.*, **17**, 2823 (2007).

44. L. Yan, P. Huo, J. J. Hale, S. G. Mills, R. Hajdu, C. A. Keohane, M. J. Rosenbach, J. A. Milligan, G.-J. Shei, G. Chrebet, J. Bergstrom, D. Card and S. M. Mandala, *Bioorg. Med. Chem. Lett.*, **17**, 828 (2007).

45. A. Gagnon, M. H. Amad, P. R. Bonneau, R. Coulombe, P. L. DeRoy, L. Doyon, J. Duan, M. Garneau, I. Guse, A. Jakalian, E. Jolicoeur, S. Landry, E. Malenfant, B. Simoneau and C. Yoakim, *Bioorg. Med. Chem. Lett.*, **17**, 4437 (2007).

46. C. Puozzo, *et al. Int. Clin. Psychopharmacology*, **17**, *suppl. 1*, 525 (2002).

47. H. Milamo, K. Karazoe, Y. Sato and J. Tamaya, *Chemotherapy*, **44**, 99 (1998).

48. Z. K. Sweeney and K. Klumpp, *Curr. Opin. Drug Disc. Dev.*, **11**, 458 (2008).

49. S. M. V. Rajaranum, M. M. Polymeropoulos, D. M. Fischer, J. Roth, C. Scott, G. Birzaieks and E. B. Klerman, *Lancet*, **373**, 482 (2009).

50. J.-L. Girardet, Y.-H. Koh, M. De La Rosa, Z. Hong, S. Lang, US Patent US 2006/270725 A1; *Chem. Abstr.,* **146**, 27840 (2007).

51. P. Bonneau, P. DeRoy, A. M. Faucher, A. Gagnon, S. Landry, S. Morin, J. O'Meara, B. Simoneau, B. Thavonekham and C. Yoakim, *International Patent WO 2005/118575 A1*; *Chem. Abstr.,* **144**, 51586 (2006).

52. M. J. Flint and A. Y. M. Howe, *International Patent WO 2009/021121 A2*; *Chem. Abstr.,* **150**, 206303 (2009).

53. D. Dubé, M. Gallant and P. Lacombe, *International Patent WO 2007/048225 A1*; *Chem. Abstr.,* **146**, 482047 (2007).

54. X. Zhang, J. Tran, H. Zhao and A. Thurkauf, *US Patent US 6284761*; *Chem. Abstr.,* **135**, 211058 (2001).

55. V. L. Coffin, *International Patent WO 9944615 A1*; *Chem. Abstr.,* **131**, 194299 (1999).

56. R. Li and X. Li, *International Patent WO 2009/045397 A1*; *Chem. Abstr.,* **150**, 414307 (2009).

57. R. J. Thurlow and C. P. Wayman, *International Patent WO 2004/041259 A1*; *Chem. Abstr.,* **140**, 400111 (2004).

58. J. M. Fevig, J. Buriak Jr., J. Cacciola, R. S. Alexander, C. A. Kettner, R. M. Knabb, J. R. Pruitt, P. C. Weber and R. R. Wexler, *Bioorg. Med. Chem. Lett.*, **8**, 301 (1998).

59. C. Klein, A. D. Gassman, L. Bhoite and J. Manfredi, International Patent WO 2008/036733 A2; *Chem. Abstr.,* **148**, 394443 (2008).

60. X. Zhao, K. Hodgetts, S. Rachwal, H. Zhao, J. W. F. Wasley, K. Craven, R. Brodbeck, A. Kieltyka, D. Hoffman, M. D. Bacolod, B. Girard and J. Tran, *J. Med. Chem.*, **43**, 3923 (2000).

61. A review on the transition metal chemistry of cyclopropanes that partially covers this subject has appeared recently: M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, **107**, 3117 (2007).

62. For the preparation of cyclopropylzinc reagents *via* cyclopropanation of alkenylzinc derivatives, see: K. Yachi, H. Shinokubo and K. Oshima, *Angew. Chem. Int. Ed.*, **37**, 2515 (1998).

63. For the preparation of cyclopropylzinc reagents through cyclopropanation of alkenes using a geminal dizinc reagent, see: A. B. Charette, A. Gagnon and J.-F. Fournier, *J. Am. Chem. Soc.*, **124**, 386 (2002).

64. J. B. Campbell Jr., J. W. Firor and T. W. Davenport, *Syn. Commun.*, **19**, 2265 (1989).

65. A. Weichert, M. Bauer and P. Wirsig, *Synlett*, 473 (**1996**).

66. S. F. Martin and M. P. Dwyer, *Tetrahedron Lett.*, **39**, 1521 (1998).

67. R.-J. de Lang and L. Brandsma, *Syn. Commun.*, **28**, 225 (1998).

68. E. Piers and P. D. G. Coish, *Synthesis*, 251 (**2001**).

69. V. A. Vu, I. Marek, K. Polborn and P. Knochel, *Angew. Chem. Int. Ed.*, **41**, 351 (2002).

70. S. Ma and Q. He, *Tetrahedron*, **62**, 2769 (2006).

71. K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S.-i. Kodama, I. Nakajima, A. Minato and M. Kumada, *Bull. Chem. Soc. Jpn*, **49**, 1958 (1976).

72. C. A. Ogle, K. C. Black and P. F. Sims, *J. Org. Chem.*, **57**, 3499 (1992).

73. R. C. Durley, M. L. Grapperhaus, B. S. Hickory, M. A. Massa, J. L. Wang, D. P. Spangler, D. A. Mischke, B. L. Parnas, Y. M. Fobian, N. P. Rath, D. D. Honda, M. Zeng, D. T. Connolly, D. M. Heuvelman, B. J. Witherbee, M. A. Melton, K. C. Glenn, E. S. Krul, M. E. Smith and J. A. Sikorski, *J. Med. Chem.*, **45**, 3891 (2002).

74. J. A. Miller and J. W. Dankwardt, *Tetrahedron Lett.*, **44**, 1907 (2003).

75. J. A. Miller, J. W. Dankwardt and J. M. Penney, *Synthesis*, 1643 (**2003**).

76. M. E. Limmert, A. H. Roy and J. F. Hartwig, *J. Org. Chem.*, **70**, 9364 (2005).

77. H. Doucet, *Eur. J. Org. Chem.*, **12**, 2013 (2008).

78. P. Fontani, B. Carboni, M. Vaultier and R. Carrié, *Tetrahedron Lett.*, **30**, 4815 (1989).

79. P. Fontani, B. Carboni, M. Vaultier and G. Maas, *Synthesis*, 605 (**1991**).

80. J. P. Hildebrand and S. P. Marsden, *Synlett*, 893 (**1996**).

81. J. E. A. Luithle and J. Pietruszka, *J. Org. Chem.*, **64**, 8287 (1999).

82. M.-L. Yao and M.-Z. Deng, *Synthesis*, 1095 (**2000**).

83. M.-L. Yao and M.-Z. Deng, *New J. Chem.*, **24**, 425 (2000).

84. M. Yao, J. Wang and M. Deng, *Chinese Sci. Bull.*, **46**, 1277 (2001); *Chem. Abstr.,* **136**, 216465 (2004).

85. G.-H. Fang, Z.-J. Yan and M.-Z. Deng, *Org. Lett.*, **6**, 357 (2004).

86. E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin and M. R. Schrimpf, *J. Org. Chem.*, **60**, 3020 (1995).

87. S.-M. Zhou, M.-Z. Deng, L.-J. Xia and M.-H. Tang, *Angew. Chem. Int. Ed.*, **37**, 2845 (1998).

88. J. E. A. Luithle and J. Pietruszka, *J. Org. Chem.*, **64**, 8287 (1999).

89. J. E. A. Luithle and J. Pietruszka, *J. Org .Chem.*, **65**, 9194 (2000).

90. J. E. A. Luithle and J. Pietruszka, *Eur. J. Org. Chem.*, 2557 (2000).

91. J. Pietruszka, A. Witt and W. Frey, *Eur. J. Org. Chem.*, 3219 (2003).

92. E. Hohn, J. Pietruszka and G. Solduga, *Synlett*, 1531 (**2006**).

93. S. E. Denmark, S. P. O'Connor *J. Org. Chem.*, **62**, 584 (1997).

94. E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin and M. R. Schrimpf, *J. Org. Chem.*, **60**, 3020 (1995).

95. H. Ito, Y. Kosaka, K. Nonoyama, Y. Sasaki and M. Sawamura, *Angew. Chem. Int. Ed.*, **47**, 7424 (2008).

96. M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, **125**, 7198 (2003).

97. J. R. Falck, M. Bondlela, S. K. Venkataraman and D. Srinivas, *J. Org. Chem.*, **66**, 7148 (2001).

98. A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, **122**, 4020 (2000).

99. A. B. Charette, S. Mathieu and J.-F. Fournier, *Synlett*, 1779 (**2005**).

100. S. Löhr and A. de Meijere, *Synlett*, 489 (**2001**).

101. J. A. Soderquist, R. Huertas and G. Leon-Colon, *Tetrahedron Lett.*, **41**, 4251 (2000).

102. A. Fürstner and C. Leitner, *Synlett*, 290 (**2001**).

103. D. J. Wallace and C.-y. Chen., *Tetrahedron Lett.*, **43**, 6987 (2002).

104. M. Lemhadri, H. Doucet and M. Santelli, *Synth. Commun.*, **36**, 121 (2006).

105. D. Laurenti, M. Feuerstein, G. Pèpe, H. Doucet and M. Santelli, *J. Org. Chem.*, **66**, 1633 (2001).

106. G. A. Molander and P. E. Gormisky, *J. Org. Chem.*, **73**, 7481 (2008).

107. S. Ueno, N. Chatani and F. Kakiuchi, *J. Am. Chem. Soc.*, **129**, 6098 (2007).

108. C. Burns, A. M. Del Vecchio, T. R. Bailey, B. A. Kulkarni, T. H. Faitg, S. R. Sherk, C. W. Black-Ledge, D. J. Rys, T. A. Lessen, J. Swestock, Y. Deng, T. J. Nitz, J. A. Reinhardt, H. Feng and A. K. Saha, *International Patent WO 2004/041201 A2, 21 May 2004*; *Chem. Abstr.,* **140**, 423576 (2004).

109. A. Gomtsyan, E. K. Bayburt, R. G. Schmidt, C. S. Surowy, P. Honore, K. C. Marsh, S. M. Hannick, H. A. McDonald, J. M. Wetter, J. P. Sullivan, M. F. Jarvis, C. R. Faltynek and C.-H. Lee, *J. Med. Chem.*, **51**, 392 (2008).

110. B. Perry, R. Alexander, G. Bennett, G. Buckley, T. Ceska, T. Crabbe, V. Dale, L. Gowers, H. Horsley, L. James, K. Jenkins, K. Crépy, C. Kulisa, H. Lightfoot, C. Lock, S. Mack, T. Morgan, A.-L. Nicolas, W. Pitt, V. Sabin and S. Wright,. *Bioorg. Med. Chem. Lett.*, **18**, 4700 (2008).

111. B. L. Hodous, S. D. Geuns-Meyer, P. E. Hughes, B. K. Albrecht, S. Bellon, J. Bready, S. Caenepeel, V. J. Cee, S. C. Chaffee, A. Coxon, M. Emery, J. Fretland, P. Gallant, Y. Gu, D. Hoffman, R. E. Johnson, R. Kendall, J. L. Kim, A. M. Long, M. Morrison, P. R. Olivieri, V. F. Patel, A. Polverino, P. Rose, P. Tempest, L. Wang, D. A. Whittington and H. Zhao, *J. Med. Chem.*, **50**, 611 (2007).

112. For a review on cyclopropylstannanes, see: M. Rubina and V. Gevorgyan, *Tetrahedron*, **60**, 3129 (2004).

113. D. Peters, A.-B. Hörnfeldt and S. Gronowitz, *J. Heterocycl. Chem.*, **28**, 1629 (1991).

114. P. H. Nelson, S. F. Carr, B. H. Devens, E. M. Eugui, F. Franco, C. Gonzalez, R. C. Hawley, D. G. Loughhead, D. J. Milan, E. Papp, J. W. Patterson, S. Rouhafza, E. B. Sjogren, D. B. Smith, R. A. Stephenson, F. X. Talamas, A.-M. Waltos, R. J. Weikert and J. C. Wu, *J. Med Chem.*, **39**, 4181 (1996).

115. Q. Branca, R. Jakob-Røtne, R. Kettler, S. Röver and M. Scalone, *Chimia*, 381 (**1995**).

116. G. S. Sheppard, J. Wang, M. Kawai, S. D. Fidanze, N. Y. BaMaung, S. A. Erickson, D. M. Barnes, J. S. Tedrow, L. Kolaczkowski, A. Vasudevan, D. C. Park, G. T. Wang, W. J. Sanders, R. A. Mantei, F. Palazzo, L. Tucker-Garcia, P. Lou, Q. Zhang, C. H. Park, K. H. Kim, A. Petros,

E. Olejniczak, D. Nettesheim, P. Hajduk, J. Henkin, R. Lesniewski, S. K. Davidsen and R. L. Bell, *J. Med. Chem.*, **49**, 3832 (2006).

117. S. Wiedemann, K. Rauch, A. Savchenko, I. Marek and A. de Meijere, *Eur. J. Org. Chem.*, 631 (**2004**).

118. N. Heureux, M. Marchant, N. Maulide, G. Berthon-Gelloz, C. Hermans, S. Hermant, E. Kiss, B. Leroy, P. Wasnaire and I. E. Markó, *Tetrahedron Lett.*, **46**, 79 (2005).

119. I. Pérez, J. P. Sestelo and L. A. Sarandeses, *Org. Lett.*, **1**, 1267 (1999).

120. I. Pérez, J. P. Sestelo and L. A. Sarandeses, *J. Am. Chem. Soc.*, **123**, 4155 (2001).

121. A. Gagnon, M. Duplessis, P. Alsabeh and F. Barabé, *J. Org. Chem.*, **73**, 3604 (2008).

122. A. Stolle, J. Salaün and A. de Meijere, *Synlett*, 327 (**1991**).

123. A. Stolle, J. Ollivier, P. P. Piras, J. Salaün and A. de Meijere, *J. Am. Chem. Soc.*, **114**, 4051 (1992).

124. J. Ollivier, N. Girard and J. Salaün, *Synlett*, 1539 (**1999**).

125. A. B. Charette and A. Giroux, *J. Org. Chem.*, **61**, 8718 (1996).

126. E. Hohn and J. Pietruszka, *Adv. Synth. Catal.*, **346**, 863 (2004).

127. J. E. A. Luithle and J. Pietruszka, *J. Org. Chem.*, **65**, 9194 (2000).

128. S. Cai, M. Dimitroff, T. McKennon, M. Reider, L. Robarge, D. Ryckman, X. Shang and J. Therrien, *Org. Proc. Res. Dev.*, **8**, 353 (2004).

129. N. Yan, X. Liu and J. M. Fox, *J. Org. Chem.*, **73**, 563 (2008).

130. X. Chen, C. E. Goodhue and J.-Q., *J. Am. Chem. Soc.*, **128**, 12634 (2006).

131. J.-Q. Yu, *International Patent WO2008/024953*, 28 February 2008; *Chem. Abstr.,* **148**, 308183 (2008).

132. B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, **47**, 4882 (2008).

133. S. Caron, E. Vazquez and J. M. Wojcik, *J. Am. Chem. Soc.*, **122**, 712 (2000).

134. J. Blagg, M. J. Fray, M. L. Lewis, J. P. Mathias, M. H. Stefaniak and A. Stobie, *International Patent; WO2003/076427 A1, 18 September 2003*; *Chem. Abstr.,* **139**, 261314 (2003).

135. M.-X. Zhang and P. E. Eaton, *Angew. Chem. Int. Ed.*, **41**, 2169 (2002).

136. T. Harada, T. Katsuhira, K. Hattori and A. Oku, *J. Org. Chem.*, **58**, 2958 (1993).

137. T. Harada, T. Katsuhira, K. Hattori and A. Oku, *Tetrahedron Lett.*, **30**, 6039 (1989).

138. J. Barluenga, F. J. Fañanás, R. Sanz and C. Marcos, *Org. Lett.*, **4**, 2225 (2002).

139. J. Barluenga, F. J. Fañanás, R. Sanz and C. Marcos, *Chem. Eur. J.*, **11**, 5397 (2005).

140. C. A. Ocasio and T. S. Scanlan, *Bioorg. Med. Chem.*, **16**, 762 (2008).

141. B. C. Melancon, N. R. Perl and R. E. Taylor, *Org. Lett.*, **9**, 1425 (2007).

142. V. Gandon, P. Bertus and J. Szymoniak, *Eur. J. Org. Chem.*, 3713 (**2000**).

143. E. M. O'Brien, E. A. Bercot and T. Rovis, *J. Am. Chem. Soc.*, **125**, 10498 (2003).

144. Y. Yamada, M. Miura and T. Satoh, *Tetrahedron Lett.*, **49**, 169 (2008).

145. J. P. Dinnocenzo, T. R. Simpson, H. Zuilhof, W. P. Todd and T. Heinrich, *J. Am. Chem. Soc.*, **119**, 987 (1997).

146. J. P. Dinnocenzo, H. Zuilhof, D. R. Lieberman, T. R. Simpson and M. W. McKechney, *J. Am. Chem. Soc.*, **119**, 994 (1997).

147. Y. Wang and J. M. Tanko, *J. Am. Chem. Soc.*, **119**, 8201 (1997).

148. Y. Wang, K. H. McLean and J. M. Tanko, *J. Org. Chem*, **63**, 628 (1998).

149. Y. Wang and J. M. Tanko, *J. Chem. Soc., Perkin Trans.* 2, 2705 (**1998**).

150. S. S. Mochalov and R. A. Gazzaeva, *Chem. Het. Comp.*, **39**, 975 (2003).

151. Z. He and A. K. Yudin, *Org. Lett.*, **8**, 5829 (2006).