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Very Important Publication

Recent Advances in Pd-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions with Triflates or Nonaflates

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1. Introduction

The Pd-catalyzed cross-coupling between aryl- and alkenyl halides and nucleophilic organometallic substrates, such as organoboronic acids (Suzuki-coupling), organostannanes (Stille coupling), or zinc organyls (Negishi coupling) has become one of the most widely used C–C coupling reactions, which has found many applications in medicinal chemistry and material sciences.

Already in the 1980s it was recognized that pseudohalogenides such as aryl triflates or alkenyl triflates can also be used instead of the corresponding organohalide compounds for this transformation.[1] The reactivity of these substrates in the oxidative addition reaction is considered similar to the corresponding bromides and is stated in the following order –I > –Br ~ –OTf > Cl.[2] Importantly, organotriflates have the advantage of convenient and simple accessibility.

Aryl triflates can be easily prepared by reaction of the corresponding phenols with Tf_2O/pyridine, which is very often easier to accomplish than the direct halogenation of arenes. Alkenyl triflates are typically synthesized by trapping of enolates with Tf_2O, $PhNTf_2$, or Comins' reagent (*N*-(5-chloro-2-pyridyl)triflimide) for which the extensive repertoire of stereoselective enolization of carbonyl compounds can be used, allowing full control over regioselectivity and *E/Z*-configuration (Figure 1).

In addition to the most commonly employed triflates, aryl or alkenyl nonaflates (perfluorobutanesulfonates) have emerged as a suitable alternative. Similar in reactivity, nonaflates can be more efficiently prepared from inexpensive nonaflate fluoride and have the advantage of higher hydrolytic stability compared to triflates.[7]

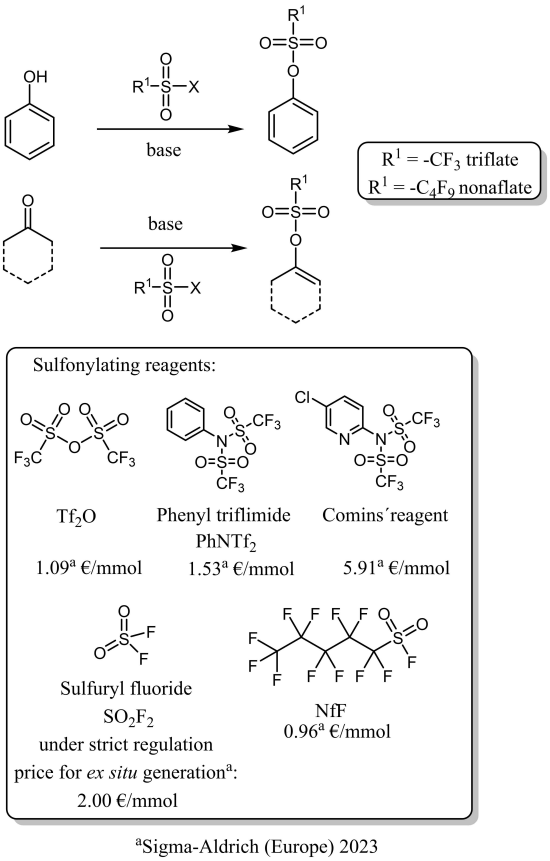

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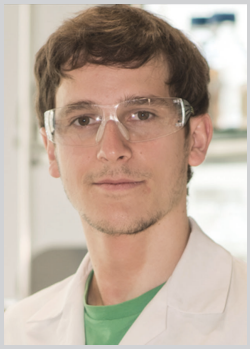
Figure 1. Sulfonylation reactions and commonly used sulfonylating reagents.

Maria Degli Innocenti was born in 1996 in Ruit/Ostfildern (Germany). She completed her undergraduate studies in Chemistry at the University of Stuttgart in 2017. After a 6-month stay each at the Università degli Studi di Padova (Italy) and the Technical University Dresden (Germany) she received her M.Sc. in 2021 from the University of Stuttgart (Germany). She then joined the group of Prof. Rolf Breinbauer at the Graz University of Technology for her PhD studies, where she focuses on the development of tool compounds for the investigation and inhibition of biosynthetic pathways.



Till Schreiner was born 1995 in Lüneburg (Germany). He studied chemistry at the universities of Göttingen and Graz before receiving his M.Sc. from Graz University of Technology in 2019. He is currently a PhD student in the group of Prof. Rolf Breinbauer at Graz University of Technology, where his main research interest lies in developing inhibitors for protein-protein interactions.

Rolf Breinbauer was born in 1970 in Schärding (Austria). He studied Chemistry in Vienna and Heidelberg and received his PhD at the MPI für Kohlenforschung in Mühlheim/Ruhr (Germany) with Prof. M. T. Reetz. After post-doctoral studies at Harvard University with Prof. E. N. Jacobsen, he started his independent career at the MPI of Molecular Physiology in Dortmund (Germany). Since 2007 he is full professor of Organic Chemistry at the University of Technology (Graz/Austria).

In the last decade, work by Sharpless has raised interest in fluorosulfonates as coupling partners, which are typically prepared using sulfuryl fluoride (SO_2F_2) as fluorosulfonyl source.[3] While cheap, SO_2F_2 is a highly toxic gas and under strict regulation in many regions outside the US. An alternative, but more expensive approach is the *ex situ* generation of SO_2F_2 in a 2-chamber reactor from 1,1′-sulfonyldiimidazole (SDI), KF and TFA.[4]

Pd-catalyzed cross-coupling of aryl- and alkenyl triflates with arylboronic acids or other nucleophiles has become a widely used transformation, which benefits from the convenient access of substrates from readily available phenols and carbonyl compounds. Notably, this transformation has found industrial application in the synthesis of active pharmaceutical ingredients (APIs).[5]

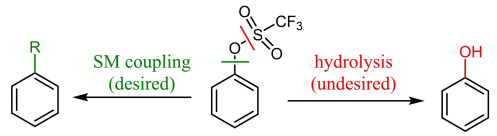
However, despite this advantage the cross-coupling of triflates has not become as popular as the corresponding reactions with aryl halides for which robust coupling protocols exist which work for many substrates in a predictable way. In our own work we experienced that Suzuki-Miyaura (SM) couplings of aryltriflates require careful optimization of reaction conditions.[6–10] In addition, the undesired hydrolysis of the triflate moiety to the corresponding phenol is often observed as a side reaction.

In this review, we aim to systematically review the developments in the Suzuki coupling of organotriflates and nonaflates over the last decade, with a focus on new catalysts and strategies to overcome the described side reactions. Special emphasis is also put on the question of regio- and chemoselective reactions, which can be exploited for sequential Pd-catalyzed cross coupling reactions.[11] We provide a matrix table of substrate combinations with reaction conditions. This should enable the practitioners to efficiently find conditions, which could be applied for their planned syntheses.

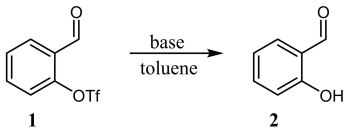
This review is meant to complement earlier comprehensive reviews by Doucet[12] about the coupling of alkylboron reagents with triflates and by Reissig[13] about cross coupling reactions with nonaflates. A recent review published by Vessally[14] in 2023 summarizes the use of fluorosulfonates.

2. General Considerations

Organotriflates exhibit several advantages as electrophilic substrates for Pd-catalyzed SM cross-coupling,



Scheme 1. Pd-cross-coupling of aryl triflates vs. undesired hydrolysis reaction.



Scheme 2. Cleavage of salicylaldehyde triflate **1.**

Table 1. Investigation of cleavage reaction of salicylaldehyde triflate **1**.

Entry	Conditions	Time (h)/temperature (°C)	Conversion
1	No base	15/80	0%
2	Cs_2CO_3 (3.0 eq)	4/80	100%
3	Cs_2CO_3 (1.0 eq)	15/80	33%
4	Na_2CO_3 (3.0 eq)	15/80	0%
5	K_2CO_3 (3.0 eq)	15/80	0%
6	K_3PO_4 (3.0 eq)	15/80	37%
7	CsF (3.0 eq)	15/80	22%

but can suffer from undesired hydrolysis under basic conditions (Scheme 1).

Green et al. reported that aryl triflates rapidly hydrolyze in presence of Cs_2CO_3 at elevated temperatures.[15] This effect was observed in various organic solvents. CsF and K_3PO_4 promoted hydrolysis to a lesser extent, while other bases such as Na_2CO_3 and K_2CO_3 did not lead to hydrolysis under the chosen conditions (Scheme 2 and Table 1).

This work highlights the importance of choosing the right base for cross-coupling reactions with aryl triflates.[16] Otherwise, this issue has not been systematically investigated in the literature.

The combination of base/solvent with the Pd/ligand catalytic system with respect to the electronic and steric nature of the organotriflate, influences the rate of oxidative addition towards the Pd complex.[17] Addition of salts can also tune the reaction, due to an increase in polarity of the solvent. In particular, LiCl has been used often when THF was employed as a solvent.[18] Therefore, careful reaction design is very important to lead to a successful outcome.

3. Triflate as Leaving Group

Organotriflates are the most commonly used pseudohalogenides in Pd-catalyzed cross coupling reactions. In this section, the current literature of different triflates as electrophilic coupling partners is summarized.

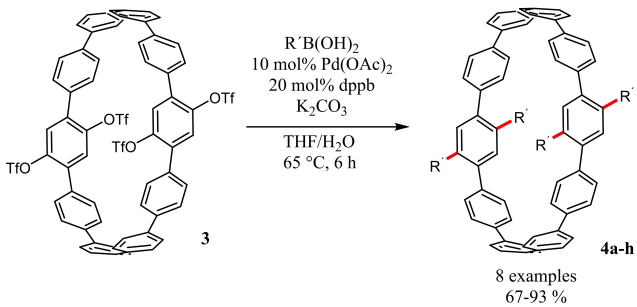
3.1. Aryl Triflates

Many examples of SM cross-coupling reactions between aryl triflates and different arylboronic acids with $Pd(PPh_3)_4$ have been reported. As it would be impossible to provide a comprehensive coverage of all SM cross-couplings with aryltriflates catalyzed by $Pd(PPh_3)_4$, we have focused on those which are synthetically most challenging.

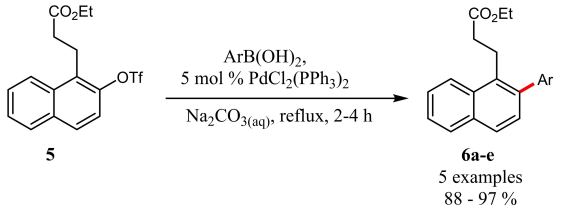
In 2020 Kayahara et al. constructed tetrasubstituted [10]cycloparaphenylenes in the presence of K_2CO_3 in THF/H_2O. They reported that the reaction was highly sensitive to the Pd source. $Pd(PPh_3)_4$ converted **3** in 72% yield. Surprisingly, catalysts with more electron-donating phosphine ligands like $(t\text{-}Bu)_3P$ or SPhos led to a decrease in yield. Bidentate ligands like dppb delivered the best results, allowing the synthesis of **4 a–h** in up to 93% yield. The larger bite angle facilitated the reductive elimination. Reducing the catalyst loading led to a loss in yield. Ultimately, both electron-rich and -deficient aryl and heteroaryl, alkenyl and alkyl boronic acids could be converted (Scheme 3).[19]

Otálvaro and coworkers improved the synthesis of 4-phenylphenalenones by introducing diversification via a SM cross-coupling with $PdCl_2(PPh_3)_2$. Independent from the electronic nature of the arylboronic acid, the authors were able to convert electron-rich, -deficient and heteroaryl boronic acids in the key coupling step towards the desired products in 88–97% yield (Scheme 4).[20]

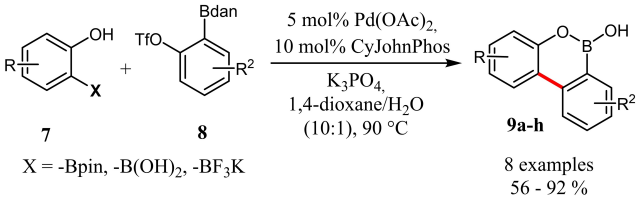
Hosoya and coworkers introduced a boron-selective efficient SM cross-coupling towards dibenzoxaborines. Different starting materials with electron-rich and -deficient substituents or heteroatoms were converted in good to excellent yields. $Pd(OAc)_2$, CyJohnPhos as a ligand and K_3PO_4 as a base in a 1,4-dioxane/H_2O solvent mixture were utilized as a catalytic reaction system. Different boron sources like boronic acids,



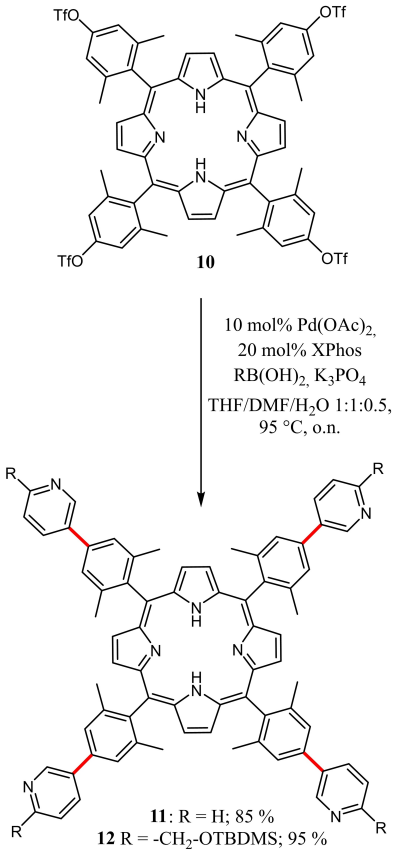
Scheme 3. Synthesis of tetrasubstituted [10]cycloparaphenylenes.



Scheme 4. SM cross-coupling of 3-(naphthalene-1-yl)propanoic acid analogue **5**.



Scheme 5. Boron-selective SM cross-coupling towards dibenzoxaborines. dan: 1,8-diaminonaphthalene.



Scheme 6. SM cross-coupling reaction towards 3-pyridyl porphyrin derivatives.

pinacol esters or trifluoroborate salts were applicable. A slight increase in yield was observed when $Pd(PPh_3)_4$ was used with several pinacol esters (Scheme 5).[21]

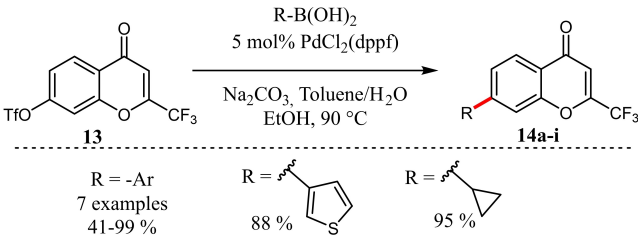
Taesch et al. investigated the derivatization of bulky *ortho*-dimethyl substituted *meso*-tetrakis-arylporphyrins. The coupling of 3-pyridyl boronic esters with tetrakis-triflate **10** was performed with $Pd(OAc)_2$, XPhos and K_3PO_4 in a THF/DMF/H_2O mixture and yielded the desired products in 85–95% (Scheme 6).[22]

The derivatization of the biologically relevant chromenone scaffold was investigated by Izquierdo et al. utilizing a SM cross-coupling with $PdCl_2$(dppf) as the most reactive Pd species, which led to complete conversion within 30 min. In contrast, $Pd(PPh_3)_4$ required longer reaction times and was not able to convert alkyl boronic acids. Both electron-deficient as well as electron-rich aryl and heteroaryl boronic acids were converted with the optimized conditions to the desired products in good to excellent yields (Scheme 7). The strong electron-withdrawing effect of the CF_3 group exerts a positive influence on the reactivity compared with the unsubstituted parent scaffold.[23]

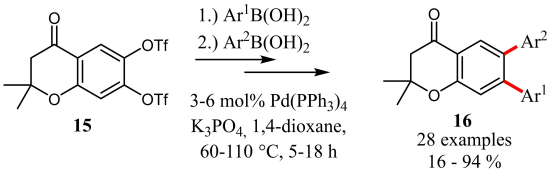
3.1.1. Regioselective Cross-Coupling

Langer and coworkers explored the regioselective SM cross-coupling of aromatic bis(triflates) and its steric and electronic effects.[24] In 2016 they reported about a site-selective SM cross-coupling of 6,7-ditriflyloxy-2,2-dimethylchroman-4-one (**15**) with different arylboronic acids with $Pd(PPh_3)_4$ and K_3PO_4 in 1,4-dioxane at 90 °C. First, coupling at the electron-deficient C-7 position occurs with both electron-poor as well as electron-rich arylboronic acids in moderate to good yields. As the electron-rich C-6 position was further influenced by the steric bulk of the previously installed aryl group the second coupling of the remaining triflate group required increased temperatures to proceed in good yields (Scheme 8).[25]

Another site-selective SM cross-coupling depending on the electronic and steric effects of the substrate was investigated by the same group. Treatment of **17** with arylboronic acid, $Pd(PPh_3)_4$ and K_3PO_4 in 1,4-dioxane furnished the desired products **18a–l** in good to excellent yields. Both electron-deficient and -rich



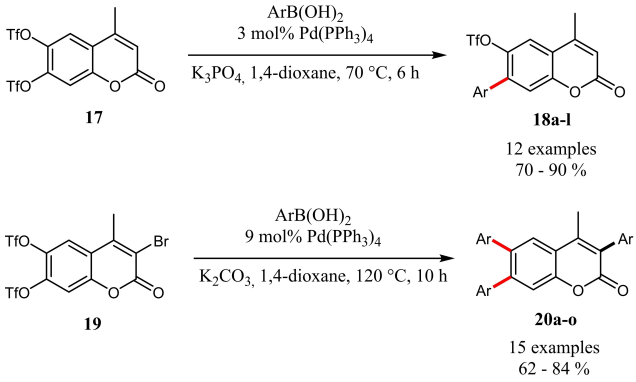
Scheme 7. SM cross-coupling towards 7-trifluoromethane-chromenone derivatives.



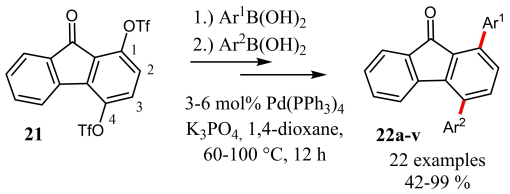
Scheme 8. Regioselective SM cross-coupling of bis(triflate) **15**.

arylboronic acids were successfully applied in the synthesis. When a bromide was additionally employed in C-3 position (substrate **19**), the reaction with 2 equivalents of boronic acid resulted in the formation of mixtures. It is not possible to selectively address C-3 or C-7 positions under the given conditions (Scheme 9). Increasing the temperature to 120 °C and further addition of aryl boronic acids resulted in substitution of all leaving groups. A one-pot reaction with sequential addition of aryl boronic acids could be successfully applied.[26]

In the following example, the Langer group was able to invert the reactivity of the triflate. The first attack of Pd(0) occurs generally at sterically less hindered and electronically more deficient positions. Here, position C-1 reacts first and could be fruitfully converted to the desired product under mild reactions conditions. The authors argue that due to electronic reasons and chelation of the Pd catalyst with the carbonyl group, reaction at C-1 is more favored, even though position C-4 is considered to be sterically easier to reach. Increasing the temperature to 100 °C led to additional reaction of the second triflate at C-4 (Scheme 10).[27]



Scheme 9. Site-selective SM cross-coupling of bis(triflate) **17** and bromo derivative **19**.

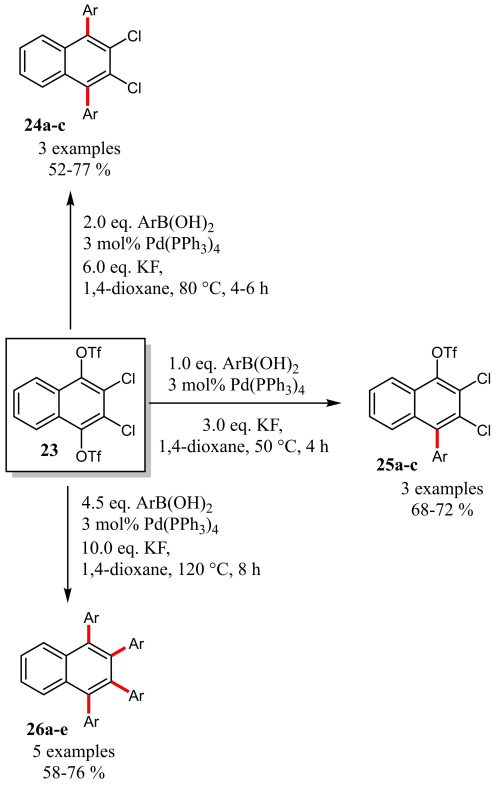


Scheme 10. Regioselective SM cross-coupling of bis(triflate) **21**.

3.1.2. Chemoselective Cross Coupling

Csuk and coworkers presented in 2015 the regio- and chemoselective SM cross-coupling of 2,3-dichloro-1,4-(trifluoromethanesulfonyloxy)naphthalene (**23**) using $Pd(PPh_3)_4$ and KF in 1,4-dioxane for the synthesis of diverse substituted naphthalene derivatives. By varying the temperature, the equivalents of the base and aryl boronic acid, the outcome of the derivatization was influenced. Both electron-deficient and -rich arylboronic acids were successfully converted (Scheme 11).[28]

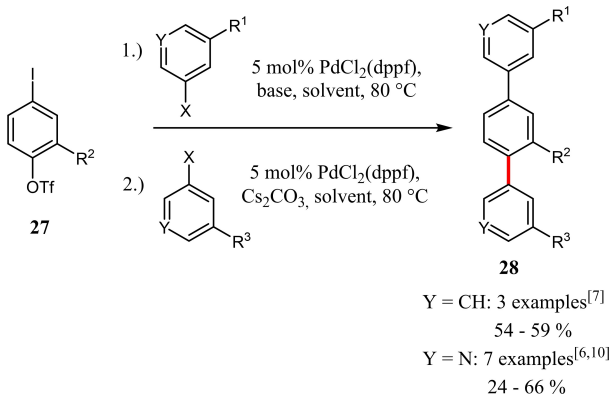
The Breinbauer group introduced in 2013 a protocol for the modular synthesis of teraryl-based α-helix mimetics. The strategy consisted of a 4-iodophenyl triflate core unit featuring two leaving groups of attenuated reactivity, which were further decorated in sequential SM cross-coupling reactions. Various arylboronic acids with the side chains of proteinogenic amino acids were coupled with $PdCl_2$(dppf) as catalyst. The more reactive iodo group reacted first by using CsF as a base in 1,2-DME at 80 °C. The less reactive



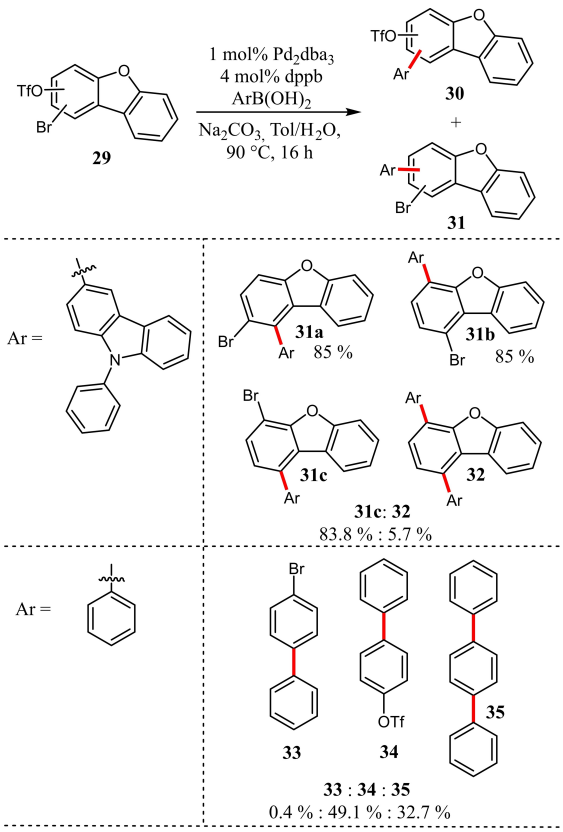
Scheme 11. Regio- and chemoselective SM cross-coupling of bis(chloro)bis(triflate)arenes.

triflate leaving group reacted by switching to the stronger base Cs_2CO_3 producing two terphenyl derivatives with 54–59% yield (Scheme 12).[7] In the following years, Breinbauer and coworkers reported pyridine based boronic acid fragments for the modular synthesis with an almost complete set of proteinogenic amino acids (Scheme 12).[6,8–10] The iodo triflate approach showed to be well applicable for apolar, hydrophobic building blocks, like Leu or Phe. In these cases, the desired cross-coupling was faster than triflate hydrolysis, even though Cs_2CO_3 is known to promote this undesired side reaction (see Scheme 2). On the other hand, polar side chains like His were limited by the increased hydrolysis of the triflate leaving group, which outcompeted cross-coupling already in the presence of the weaker base K_2CO_3. Such side chains were more compatible with a 4-bromoaryliodide core fragment approach.[8]

A possibility to directly address bifunctional substrates bearing a halide and a triflate leaving group was demonstrated by a ligand-dependent SM cross-coupling with Pd_2dba_3. By changing the phosphine ligand from P(*o*-Tol)$_3$ to the more bulky ligand dppb König and coworkers were able to convert the triflate **29** with electron-deficient aryl boronic acids, while the bromide remained intact (**31 a–c**). Electroneutral or electron-rich aryl boronic acids led to mixtures. The authors argued that the bulkiness of dppb accelerates the rate of oxidative addition regarding the triflates, because of its formation of a coordinatively unsaturated and electron-rich Pd(0) species. Consequently, the oxidative addition is faster and can be further improved by adding electron-withdrawing groups on the arylboronic acid. Unfortunately, this protocol cannot be applied for electron-neutral and -rich arylboronic acids (Scheme 13).[29]



Scheme 12. Sequential SM cross-couplings towards teraryls **28**. Yields of isolated products over two steps. If Y=CH: CsF used as base, X = –B(OH)$_2$ and 1,2-DME as solvent. If Y=N, K_2CO_3 or Ag_2CO_3 were used as base, X = –BPin and MeCN, DMF or toluene as solvent.

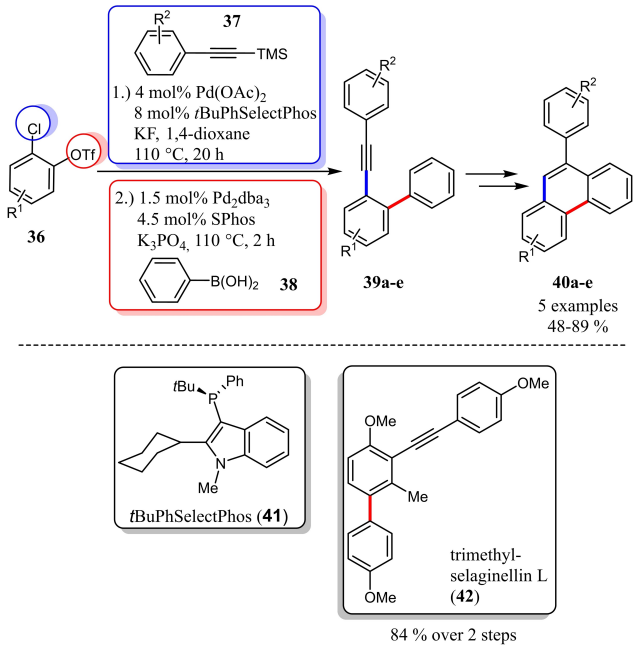


Scheme 13. Selected examples for the site selective SM cross-coupling with electron-deficient and neutral aryl boronic acids.

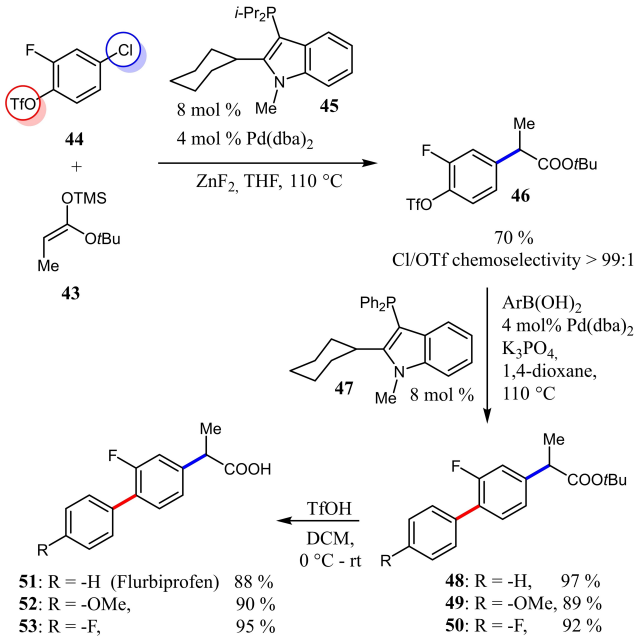
In 2022 So and coworkers demonstrated a sequential chemoselective Sonogashira cross-coupling, where the conventional chemoselectivity order of Ar–OTf > Ar–Cl was inverted through control by the *t*BuPhSelectPhos ligand. TMS-arylalkynes reacted first with the chloride leaving group of *o*-chloroaryl triflates. Followed by a SM cross-coupling in a one-pot reaction the remaining triflate was converted with arylboronic acids. This allowed, after cyclization, the synthesis of polycyclic aromatic hydrocarbons (PAH). The authors tested electron-rich aryl triflates and different sizes of aryl/heteroaryl boronic acids and were able to synthesize five different PAHs (Scheme 14). They also showed the synthesis of the natural product analogue trimethyl-selaginellin L (**42**) in 84% overall yield.[30]

Following these results they developed an α-arylation of carbonyl compounds using a similar SelectPhos/Pd catalyst system. This combination resulted in excellent Ar–Cl over Ar–OTf chemoselectivity. After α-arylation the authors were able to fruitfully employ the synthesis of Flurbiprofen (**51**) and its derivatives **52**–**53** using Pd(dba)$_2$, ligand **45** and K_3PO_4 in 1,4-dioxane at 110 °C, yielding in 89–97% yield (Scheme 15).[31]

The Schoenebeck group reported in 2014 about the steric effects of phosphine ligands in the site-selective



Scheme 14. One-pot Sonogashira/SM cross-coupling towards PAH derivatives.



Scheme 15. Chemoselective synthesis of Flurbiprofen **51** and its derivatives **52** and **53** using SM cross-coupling.

SM cross-coupling. They introduced a hybrid ligand P(*i*Pr)(*t*Bu)$_2$, characterized by a cone angle which lies between PCy$_3$ and P*t*Bu$_3$ and comes with all their mechanistic reactivity properties. The ligand P-(*i*Pr)(*t*Bu)$_2$ can be used as a very bulky ligand (mono-phosphine Pd species) or as a less bulky ligand (higher Pd coordination sphere) due to its ability to vary between the mono- and dinuclear Pd complex. By varying the equivalents of phosphine ligand (Scheme 16 and Table 2, entries 2 and 3) the dissociation of the ligand and therefore change from mono- to bidentate Pd(0) complex could be controlled, which led to the functionalization of the triflate. Unfortunately, the yield was very low with 10%, because of unreacted starting material (entry 3), while Cl functionalization yielded 86% of the desired product (entry 2) (Scheme 16). Overall this study provides interesting insight into the mechanistic pathway of P(*i*Pr)(*t*Bu)$_2$ as a new hybrid phosphine ligand.[32] Subsequently, Schoenebeck and coworkers introduced a Pd(I) bidentate catalyst for the chemoselective Negishi coupling with which 57 different chlorophenyltriflates were converted in good to excellent yields.[33]

Based on the previous results from Fu, Houk and Schoenebeck, Neufeldt and coworkers introduced in 2023 a triflate-selective SM cross-coupling reaction under ligand-free conditions. In the absence of strong ancillary ligands, the use of simple Pd-salts, like PdCl$_2$, with KF, H$_2$O and arylbroronic acids led for chloro aryl triflates in MeCN and for bromo aryl triflates in DMSO to the desired cross-coupled products (Scheme 17). Interestingly, the authors were able to inverse the natural chemoreactivity, according to which the bromide would react before the triflate. This strategy provides an elegant access to bromo-substituted biaryls, without the need of introduction of an iodine to overcome the bromide reactivity. The authors also state, that this methodology is cleaner due to side product minimization. The choice of the highly coordinating solvent is of immense importance. Furthermore, conversion of 2- and 4-pyridinetriflates does not work under the reaction conditions, due to competing triflate hydrolysis. Sterically hindered triflates were not converted.[34]

Pd catalysts with *N*-heterocyclic carbene (NHC) ligands have also shown their potential in chemodivergent SM cross-couplings. In 2019, Neufeldt and coworkers introduced SIPr and SIMes as NHC-ligands, which enable selective coupling of various chloroaryl triflates with aryl boronic acids. The triflate group reacted selectively with both electron-rich and -deficient aryl boronic acids in presence of Pd/SIMes, KF and H$_2$O in THF in good to excellent yields. Unprotected phenolic and heteroarylboronic acids also reacted to the desired products (Scheme 18). Notably, this method improved the previously reported ineffective protocol with Pd[P(*i*Pr)(*t*Bu)$_2$] for electron-rich and -deficient aryl boronic acids.[32,33,35] The authors outline that the triflate functionalization of chloroaryl-triflates with SIMes results from the oxidative addition at the bisligated [Pd(SIMes)$_2$] or [Pd(SIMes)L], while the chloride is activated via a monoligated [Pd(SIPr)] species.[36]

3.1.3. Cross-Coupling with Chiral Substrates

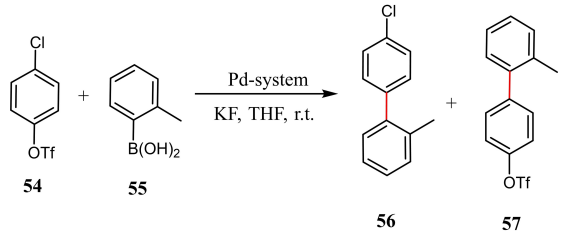
In 2015 Wang et al. modified chiral substrate **62** using a SM cross-coupling with $Pd(OAc)_2$ to install allyl or phenyl groups with excellent efficiency and retaining the integrity of the diarylmethane stereocenter (Scheme 19).[37]

For the late-stage introduction of side chains on a tetrahydrocannabinoid scaffold Studer and coworkers used the (−)-Δ^8 –THC–OTf building block **65** in a SM cross-coupling reaction, without protection of the phenolic hydroxy group. Bulky side chains, aromatic moieties with electron-withdrawing and -donating substituents or side chains containing double bonds could be introduced via this transformation in good to excellent yields. The methodology could not be used in accessing an sp^2–sp^3-coupling product (Scheme 20).[38]

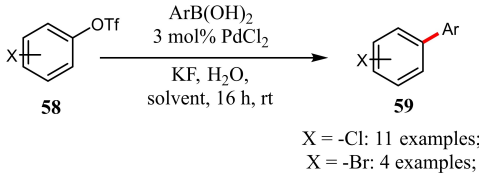
In the enantioselective synthesis of the dimeric pyranonaphthoquinone core of Cardinalins, SM homo-coupling was introduced by Sperry and coworkers at a late stage to form the key biaryl bond.

After optimization, the authors found that triflate **68** reacted with bis(pinacolato)diboron, which formed the arylboronate in situ. The arylboronate was homo-coupled with the remaining aryltriflate, with $PdCl_2$(dppf) and freshly ground, dried K_2CO_3 under microwave irradiation in a dioxane solution to the desired product **69** in 51% yield (Scheme 21).[39]

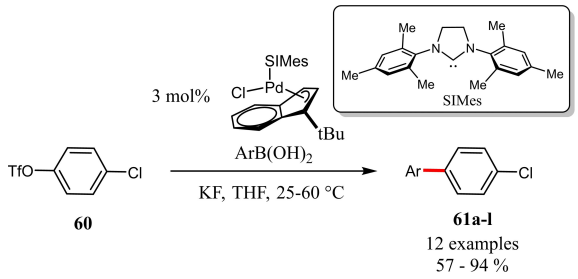
Di Shen et al. reported in 2019 about the use of bulky chiral NHC carbene ligands, which enable a highly enantioselective SM cross-coupling towards biaryl atropisomers. The protocol was primarily



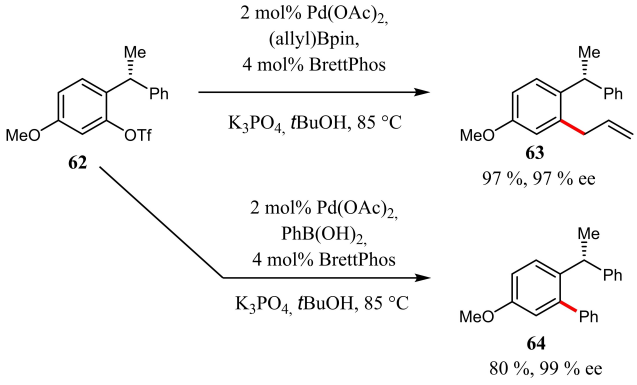
Scheme 16. SM cross-coupling of chloroaryl triflates with selectivity switch depending on excess ligand.



Scheme 17. Ligand-free SM cross-coupling of haloaryltriflates **58**. When X = –Cl, MeCN as solvent, when X = –Br, DMSO as solvent.



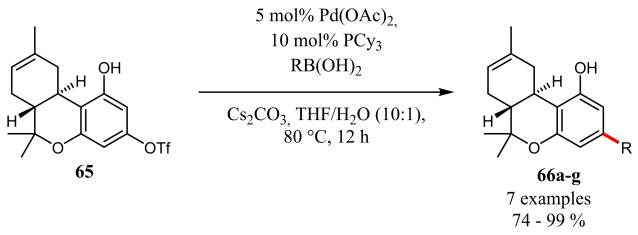
Scheme 18. NHC ligand-controlled chemodivergent SM cross-coupling.



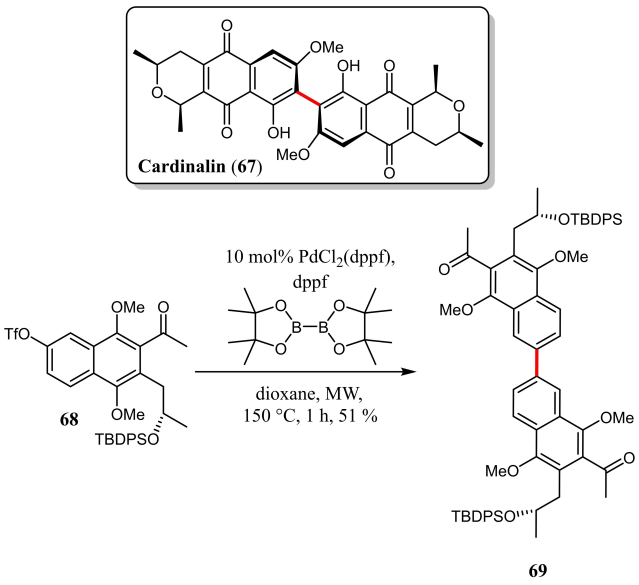
Scheme 19. Derivatization of substrate **62** with SM cross-coupling reactions.

Table 2. Results of the chemoselective cross-coupling.

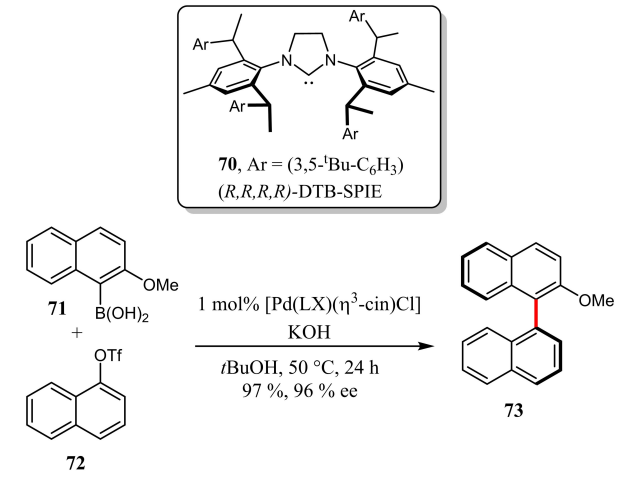
Entry	Catalyst (mol%)	Time (h)	Yield	
			56	**57**
1	$Pd[P(iPr)(tBu)_2]_2$ (3)	125	0%	15%
2	$Pd_2(dba)_3$ (1.5) $P(iPr)(tBu)_2$ (3)	24	0%	86%
3	$Pd[P(iPr)(tBu)_2]_2$ (3) $P(iPr)(tBu)_2$ (3)	125	10%	0%
4	Pd_2dba_3 (1.5) $PtBu_3$ (30)	169	0%	5%



Scheme 20. SM cross-coupling products of THC triflate.



Scheme 21. SM homocoupling towards the key biaryl compound **69** in the synthesis of Cardinalins.



Scheme 22. NHC ligand controlled enantioselective SM cross-coupling towards the biaryl atropisomer **73**.

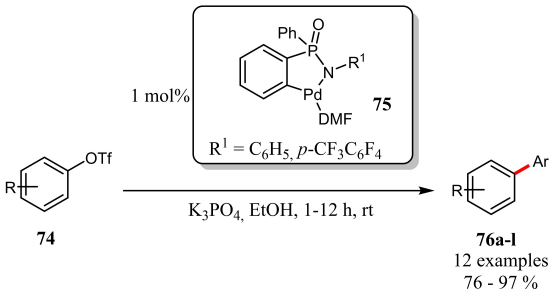
applied to halides as leaving groups, but the authors could show that triflate **72** is also a competent coupling partner (Scheme 22).[40]

3.1.4. Other SM cross-couplings

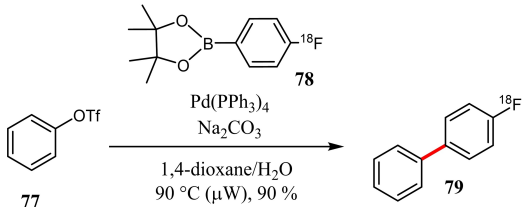
Wu et al. utilized new palladacycles for a mild SM cross-coupling of aryl halides, but also of less stable aryl triflates. A wide array of electron-donating and electron-withdrawing aryl and heteroaryl boronic acids were converted with electron-deficient aryl triflates in good to excellent yields using palladacycle **75** and K_3PO_4 in EtOH at rt (Scheme 23).[41]

In 2022 Higuchi and coworkers described a novel synthesis of [^{18}F]aryl boronic acid esters, which are used in a ^{18}F-labeling SM cross-coupling. Phenyl triflate **77** was coupled with [^{18}F]aryl boronic ester using $Pd(PPh_3)_4$ and Na_2CO_3 in a 1,4-dioxane/H_2O solvent mixture at 90 °C in a microwave (μW) reactor in 90% yield (Scheme 24). This result shows the potential of [^{18}F]aryl boronic acid esters for the incorporation of [^{18}F] in drug-like molecules. However, triflates of higher structural complexity have not been tested yet.[42]

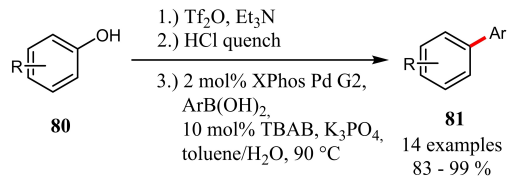
Buchwald and coworkers introduced a SM cross-coupling in a continuous-flow microfluidic system. Commercially available phenols were converted into aryl triflates followed by a SM cross-coupling to the desired biaryl coupled products. Both electron-deficient and -rich as well as bulky aryl boronic acids showed to be good substrates and delivered the products in 83–95% yield (Scheme 25).[43]



Scheme 23. Mild SM cross-coupling with palladacycle **75**.



Scheme 24. SM cross-coupling with [^{18}F]aryl boronic ester.



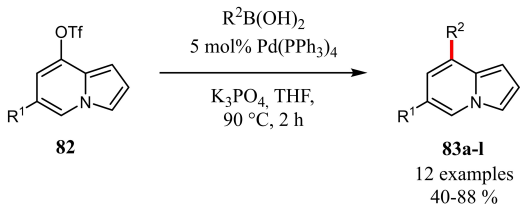
Scheme 25. SM cross-coupling in a microfluidic reaction setup.

3.2. Heteroaryl Triflates

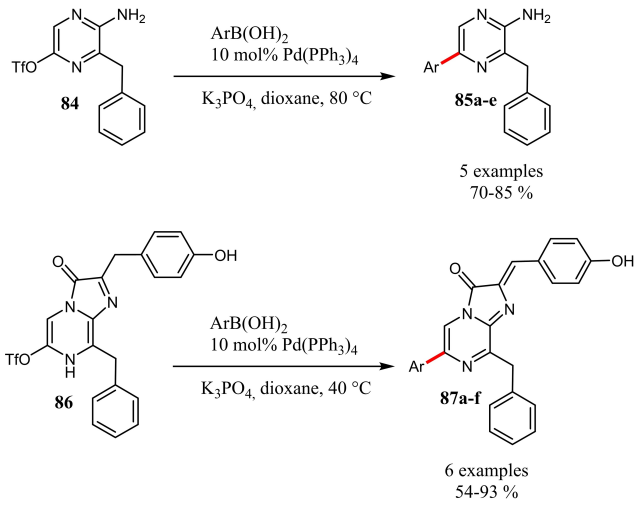
Due to their electron-deficient character heteroaryl triflates are very good substrates for SM cross-coupling reactions with $Pd(PPh_3)_4$.

Kim and coworkers introduced a new synthetic pathway to indolizines with various substituents. SM cross-coupling of *O*-triflates **82** with aryl and heteroaryl boronic acids, $Pd(PPh_3)_4$ and K_3PO_4 in THF afforded the desired products **83 a–l** in 40–88% yield (Scheme 26).[44]

Isobe and coworkers reported a new access to dehydrocoelentrazine and diversification of the 6-position. Coupling of the free aminopyrazin-*O*-triflate **84** and dihydroimidazopyrazinone 6-triflate **86** with various arylboronic acids, $Pd(PPh_3)_4$ and K_3PO_4 in



Scheme 26. SM cross-coupling towards various indolizine derivatives.



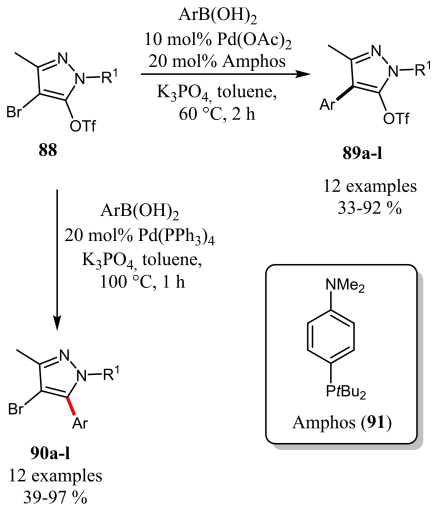
Scheme 27. SM cross-coupling of 2-aminopyrazin-5-triflate **84** and dihydroimidazopyrazinone-6-triflate **86**.

dioxane led to the desired derivatives in good to excellent yields. Electron-withdrawing and -donating groups were tolerated by this reaction (Scheme 27). Notably, for starting material **86** the temperature had to be decreased to 40 °C due to the instability of the triflate. The authors also described the importance of fast conversion of the triflate **86**, because of partial decomposition after storage. When changing the triflate to tosylate in starting material **86** to enhance the stability, reduced reactivity was observed which made the optimization of the reaction conditions necessary. The details of the oxidation to the dehydrocoelenterazine form **87** during the SM cross-coupling are not described.[45]

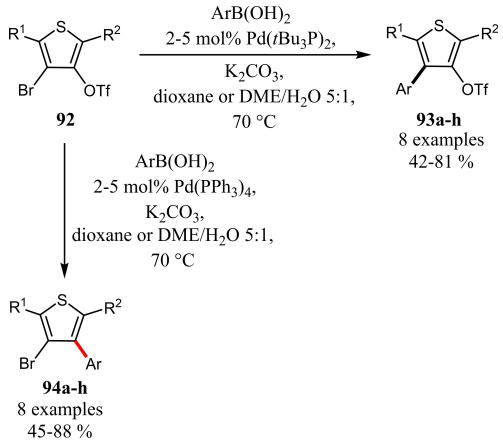
In 2019 Fujii and coworkers developed a ligand-dependent site-selective SM cross-coupling. By switching between PPh_3 and Amphos as phosphine ligands the bromine or triflate group can selectively be brought to reaction. A wide range of electron-deficient and -rich arylboronic acids and heteroaryl boronic acids were tolerated in this transformation, even though a high amount of 20 mol% of $Pd(PPh_3)_4$ as the catalyst were required (Scheme 28).[46]

Another example for a ligand-dependent site-selective SM cross-coupling was introduced by Wang et al.. 3-Bromo-4-triflyloxy-thiophenes **92** were converted by a Pd(0) catalyst and K_2CO_3 with different electron-deficient and -rich aryl and heteroaryl boronic acids. Here, just 2–5 mol% of the Pd(0) catalyst were required. Change of the ligand from PPh_3 to the more electron-rich and hindered tBu_3P led to a reversal of the selectivity and to different coupling products (Scheme 29).[47]

SM cross-coupling was also used by Sackus and coworkers to introduce various heterocycles into complex molecules. The synthesis of versatile 1-phenyl-1*H*-pyrazole derivatives was successfully ac-



Scheme 28. Ligand-dependent SM cross-coupling.

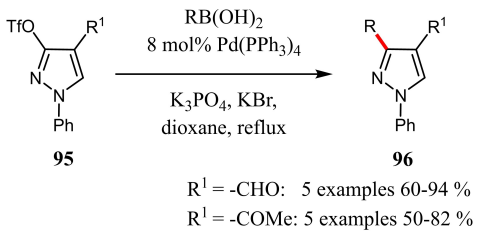


Scheme 29. Ligand-dependent SM cross-coupling of 3-bromo-4-trifloxy-thiophenes.

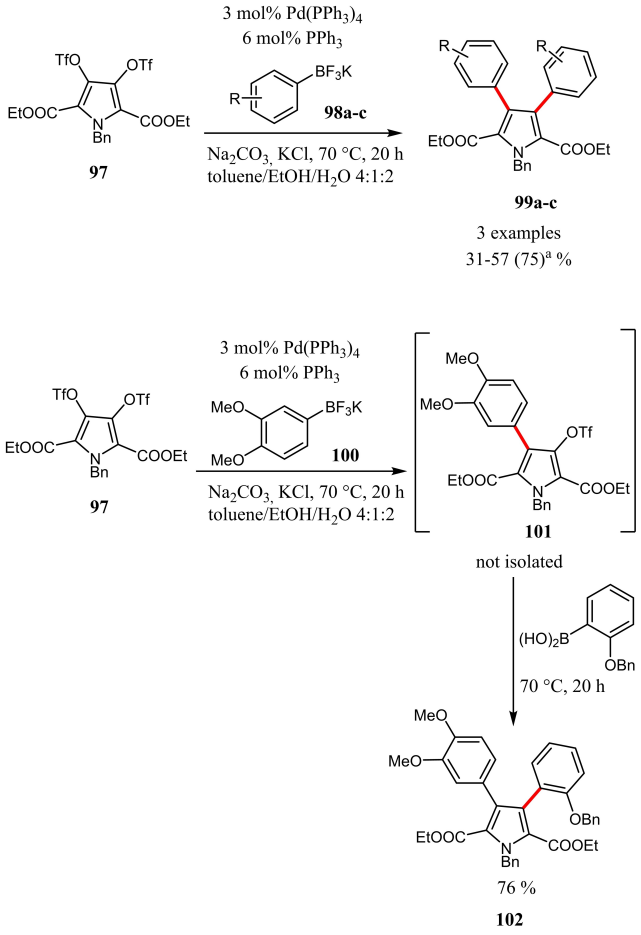
complished by the use of $Pd(PPh_3)_4$ and K_3PO_4, heating under reflux in dioxane for 6–17 h. KBr was added as an additive to prevent triflate reduction by stabilizing the cationic (σ-aryl)-Pd transition state (Scheme 30).[48]

SM monocoupling is an interesting methodology to introduce unsymmetric triaryls. Dodd and coworkers investigated a selective SM monocoupling with symmetrical aryl di(pseudo)halides. The authors showed a broad applicability using dibromobenzene. To further broaden the scope, they investigated the use of various arene ditriflates. With the optimized reaction conditions of 3 mol% $Pd(PPh_3)_4$, PPh_3, KCl and Na_2CO_3 in a toluene/EtOH/H_2O (4:1:2) solvent mixture, the desired products were synthesized (Scheme 31). During the studies the authors showed that electron-withdrawing moieties are limiting the reaction, because of the increased reactivity of the monocoupled product, which led to further coupling and unreacted starting materials. Their robust monocoupling strategy was expanded by the one-pot desymmetrizing double SM coupling, to show the possibility to synthesize unsymmetrical triaryl **102** (Scheme 31).[49]

Kuo and coworkers constructed highly bright-luminescent fluorophore derivatives **104** using SM cross coupling with bulky triflates. Changing the phosphine ligands to PCy_3 or SPhos and varying the



Scheme 30. SM cross-coupling towards 1-phenyl-1*H*-pyrazole derivatives.

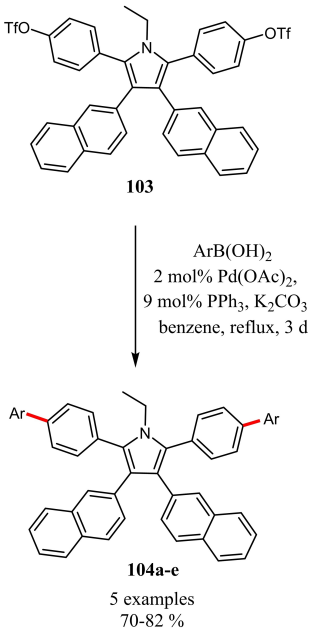


Scheme 31. Example for a monocoupling reaction of **97** and a one-pot synthesis of unsymmetrical triaryls. [a] ^{1}H-NMR yield in brackets.

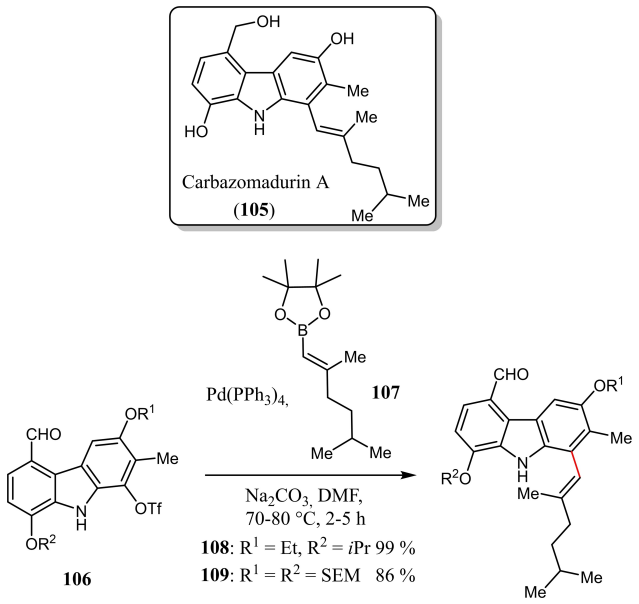
bases did not lead to a higher yield. Although harsh conditions were applied for this reaction, different bulky arylboronic acids were successfully reacted (Scheme 32). The replacement of benzene as a solvent should be taken into consideration.[50]

A SM cross-coupling with alkenyl pinacol boronate **107** was successfully implemented by Hibino and coworkers in the synthesis of Carbazomadurin A (**105**) (Scheme 33). In the presence of Na_2CO_3 and $Pd(PPh_3)_4$ in DMF at 80 °C the desired 1-alkenylcarbazoles **108** and **109** were furnished in good to excellent yield.[51]

In 2021 Domínguez and coworkers tested the reactivity of 4-pyrimidyl triflate **110** with different arylboronic acids under microwave irradiation in a water solution. They showed that electron-donating groups at the boronic acid were favourable for the reaction, while electron-withdrawing boronic acids were converted in moderate yields (Scheme 34). Changing the triflate to a nonaflate group improved the yield of electron-withdrawing aryl boronic acids by 20% (more information in Chapter 4.2).[52]

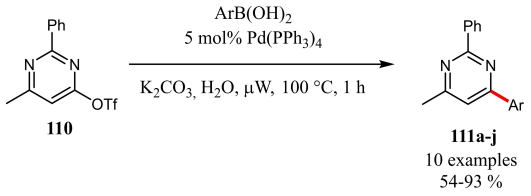


Scheme 32. SM cross-coupling of pyrrole/polycyclic aromatic units towards hybrid fluorophores.



Scheme 33. SM cross-coupling with alkenyl pinacol boronate **107**.

Marchand and coworkers developed an efficient method towards 2-arylimidazol[1,2-α]pyridines. Triflates as leaving groups instead of halides proved to be more reactive and improved the reaction time from previously 6 h to 45 min. Electron-donating arylboronic acids furnished the products **113 i** and **113 j** in good to excellent yields. In contrast, electron-deficient or halide-bearing arylboronic acids were converted in

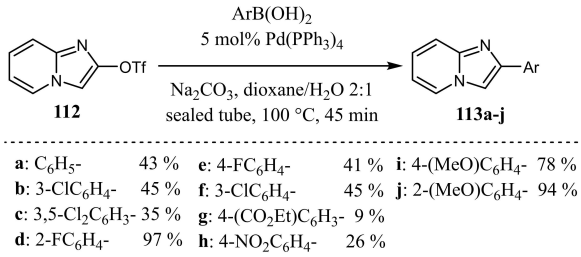


Scheme 34. SM cross-coupling reactions in water under microwave irradiation.

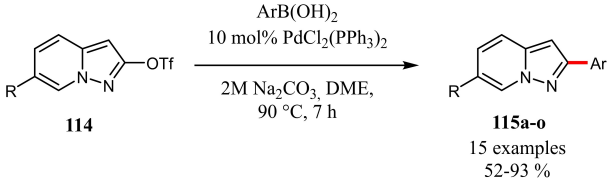
low to moderate yields. Interestingly, 2-fluorophenyl boronic acid unexpectedly afforded the desired product **113 d** in excellent yield, while the 4-fluorophenyl product was produced in only 41% yield (Scheme 35).[53]

Umei et al. introduced in 2015 a concise and versatile approach towards 2-arylpyrazolo[1,5-α]pyridines. Changing the position of nitrogen in the heterocycle required the use of $PdCl_2(PPh_3)_2$ and Na_2CO_3 in DME and afforded the desired product **115**. Both electron-donating as well as -withdrawing groups, even sterically hindered and heteroaryl boronic acids were tolerated in the reaction (Scheme 36).[54]

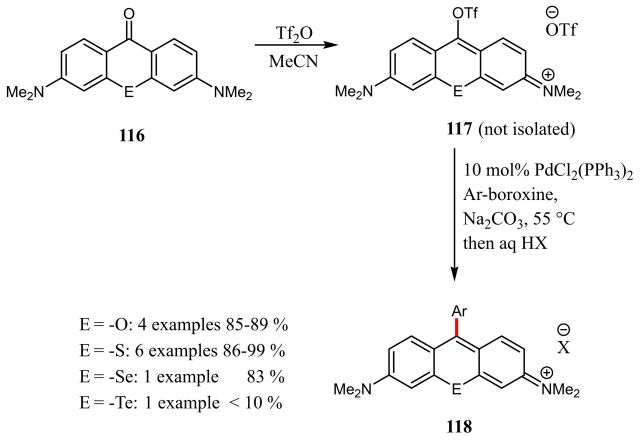
In the synthesis of novel rhodamine dyes Detty and coworkers introduced a one-pot procedure to install the triflate leaving group, followed by a Pd-mediated SM cross-coupling between the xanthone triflate and arylboroxine. The authors showed that the use of $Pd(PPh_3)_4$ was not effective enough. Changing the catalyst to $PdCl_2(PPh_3)_2$ led to an improvement in yield. Successful coupling was achieved with electron-donating or -withdrawing arylboroxines (Scheme 37).[55]



Scheme 35. SM cross-coupling towards 2-arylimidazol[1,2-α]pyridines.

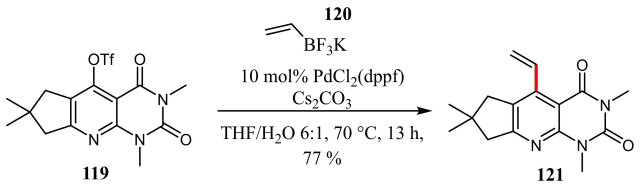


Scheme 36. SM cross-coupling towards 2-arylpyrazolo[1,5-α]pyridines.

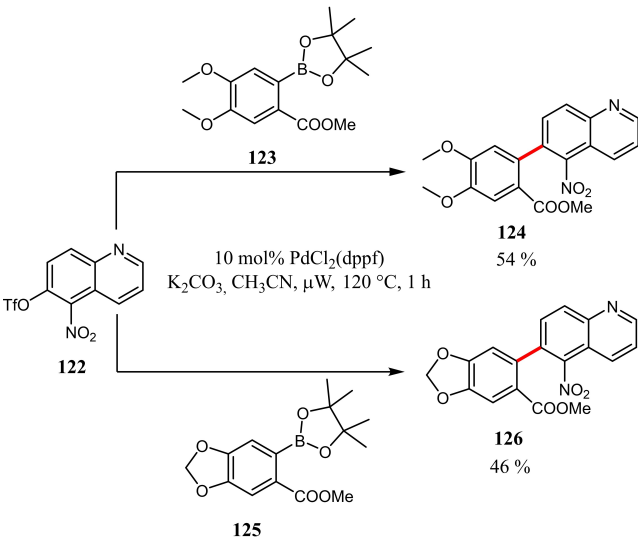


Scheme 37. One-pot procedure for the synthesis of rhodamine dyes.

A SM cross-coupling with alkenyl trifluoroborate for the functionalization of pyrido[2,3-*d*]pyrimidinones was developed by Coquerel and coworkers. With $PdCl_2$(dppf) as a catalyst and Cs_2CO_3 as a base in a THF/H_2O (6:1) mixture at 70 °C the authors were able to synthesize the desired cross-coupled product **121** in 77% yield (Scheme 38).[56]



Scheme 38. SM cross-coupling with alkenyl trifluoroborate for the functionalization of pyrido[2,3-*d*]pyrimidinones.



Scheme 39. SM cross-coupling towards arylquinolines.

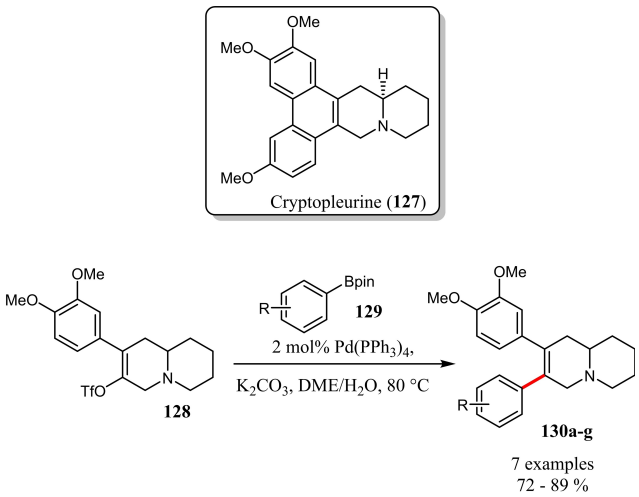
Genès et al. investigated an intermolecular SM cross-coupling reaction towards arylquinolines. They tested different Pd/base combinations and found that KOAc, mild organic bases and stronger bases like NaOH gave only inferior results. $PdCl_2$(dppf)/K_2CO_3 in MeCN for 18 h proved to be the best system. The yields of the products were in a range of 50% and could not be further optimized. Microwave irradiation decreased the reaction time, but led to no additional improvement in yield (Scheme 39).[57]

3.3. Vinyl Triflates

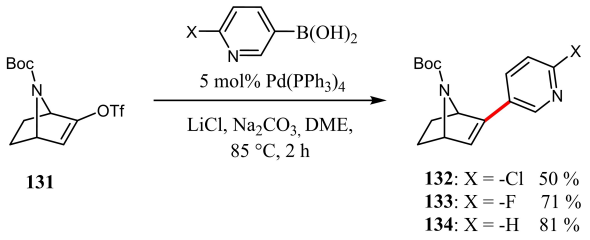
In 2022 Takasu and coworkers were able to achieve the total synthesis of Cryptopleurine (**127**) in 8 steps, using vinyl triflates as key intermediates. With this, a late-stage installation of various electron-donating and -withdrawing aryl substituents was possible via SM cross-coupling using standard reaction conditions with $Pd(PPh_3)_4$ as a catalyst and K_2CO_3 as a base in a DME/H_2O solvent mixture at 80 °C (Scheme 40).[58]

A group of novel racemic nicotinic ligands, where SM cross-coupling with vinyl triflates was also utilized as a key step, was introduced by De Micheli and coworkers. They were able to synthesize three different derivatives using diverse arylboronic acids, in a Pd-$(PPh_3)_4$, anhydrous LiCl, Na_2CO_3 and DME reaction system (Scheme 41).[59]

In 2018 Mourino and coworkers described the first example of an efficient convergent synthesis of Vitamin D_3 without an A-ring hydroxyl protection. They relied on different strategies, especially on a domino carbocyclization-SM cross-coupling with vinyl triflates. Here, a Pd(II) catalyst, like $PdCl_2(PPh_3)_2$ or $Pd(dppf)Cl_2$, was tested in different reaction systems, revealing that $PdCl_2(PPh_3)_2$ suited the best in a K_2CO_3 and THF/H_2O base/solvent system stirred at RT



Scheme 40. SM cross-coupling of Cryptopleurine derivatives.

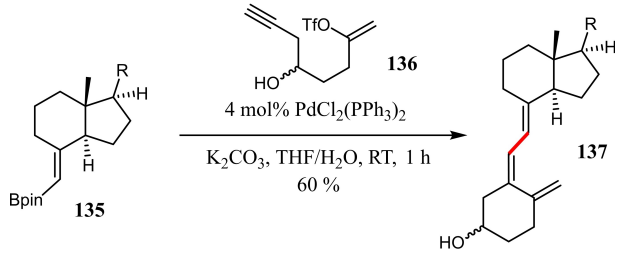


Scheme 41. Synthesis towards nicotine intermediates using SM cross-coupling.

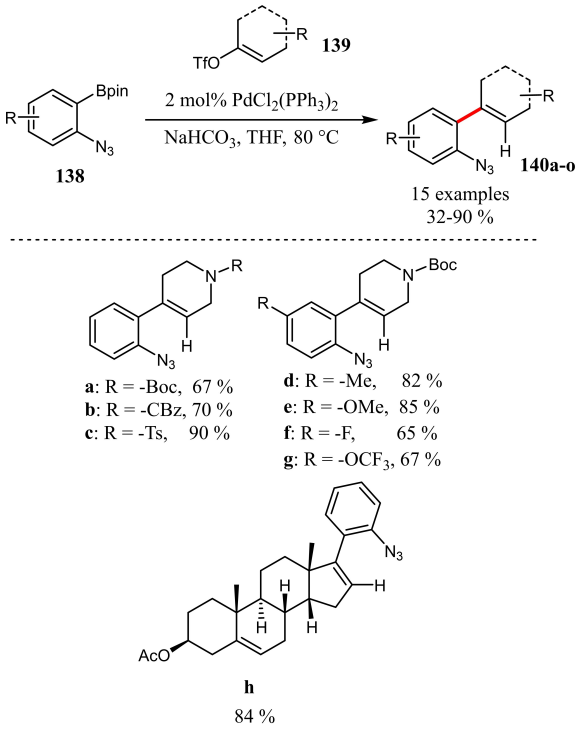
(Scheme 42), while the bidentate ligand Pd(dppf)Cl_2 led to a complex mixture.[60]

Jana et al. developed in 2014 a mild SM cross-coupling reaction involving *o*-azidoarylboronic acid pinacolate esters and vinyl triflates towards a step-economic synthesis of 2-alkenylaryl azides, which were further converted to different *N*-heterocycles. They proved that a smaller number of phosphine ligands coordinating to the Pd center could improve the yield. Employing $Pd(OAc)_2/PCy_3$ as a catalyst/ligand system gave at 25 °C a yield of 83% compared to 72% using $Pd(PPh_3)_4$. Due to no further optimization possibilities and economic concerns regarding the phosphine ligands, they implemented the less expensive $PdCl_2(PPh_3)_2$ in a $NaHCO_3$/THF reaction system at 80 °C, which led to 99% yield. Further reduction of the temperature diminished the yield. Different cyclic *N*-protected vinyltriflates were successfully transformed, although changing the position of the nitrogen from the 4-piperidone derived vinyltriflate to the 3-piperidone derived one diminished the yield to 32%. Electron-donating and -withdrawing substituents were tolerated. Furthermore, the authors were able to demonstrate the generality of their concept through the successful synthesis of the steroid hormone 5,6-dehydroandrosterone **140 h** in 84% yield (Scheme 43).[61]

In 2020 Lou et al. were able to simplify and derivatize Paclitaxel-dehydroepiandrosterone (DHEA) (**141**) utilizing the Pd-catalyzed SM cross-coupling as a key step. Using a $PdCl_2(PPh_3)_2$, Na_2CO_3 and toluene/EtOH/H_2O reaction system at 75 °C, the authors were



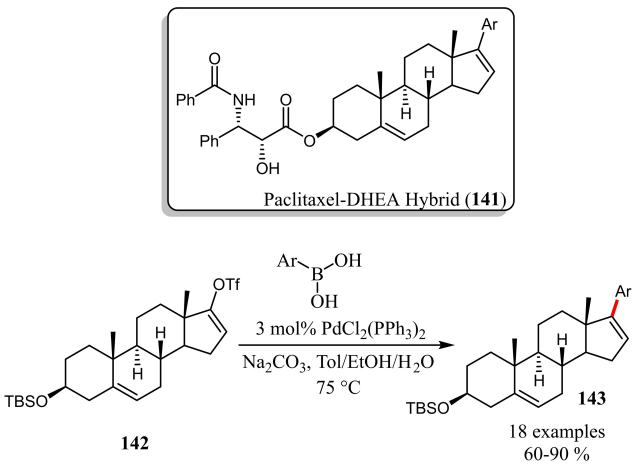
Scheme 42. Synthesis of 3-*epi*-Vitamin D_3 with a domino carbocylization-SM cross-coupling.



Scheme 43. SM Cross-coupling of *o*-azidoarylboronic acid pinacolate esters and vinyl triflates.

able to introduce different electron-rich or -poor aromatic and heteroaromatic chains in the D-ring of the DHEA, in 60–90% yield (Scheme 44).[62]

Several examples of SM using $Pd(OAc)_2$ as a catalyst were successfully performed. Elitzin et al. developed a practical large-scale synthesis of the antidepressant GSK1360707 (**147**), where in the final route 10 kg of the antidepressant were synthesized in a 200-gal pilot plant. The synthesis faced problems



Scheme 44. SM cross coupling towards different Paclitaxel-DHEA derivatives.

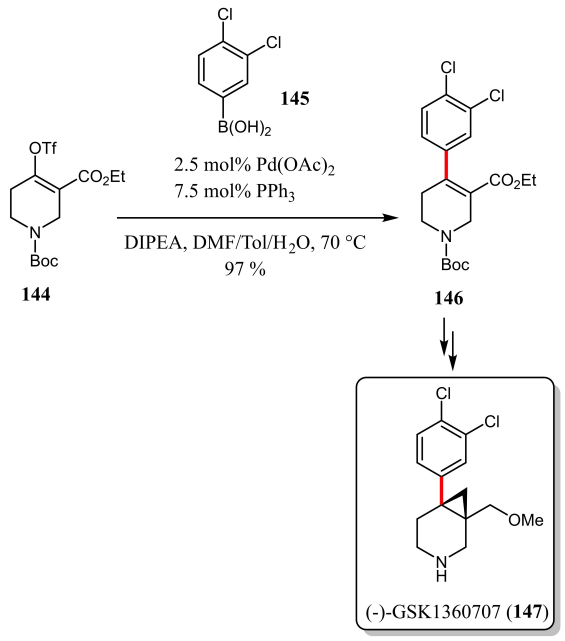
through formation of 1–5% 3,3',4,4'-tetrachloro-1,1'-biphenyl (PCB) dimer when using 1:1 vinyl triflate/boronic acid, 2.5 mol% $Pd(OAc)_2$, 7.5 mol% PPh_3, Hünig's base and water in toluene at 70 °C as initial conditions. By avoiding of combining all reagents at once the PCB formation was decreased to < 30 ppm. Here, the active Pd(0) complex was formed by combining the vinyl triflate with 2.5 mol% $Pd(OAc)_2$, 7.5 mol% PPh_3, Hünig's base and water in toluene at RT, followed by heating the mixture to 70 °C. After preforming the active Pd(0) catalyst 0.95 equivalents of boronic acid as a DMF/toluene solution were added over 1 h and resulted in the desired product **146** in 97% yield (Scheme 45).[63]

A base-free version of a SM cross-coupling with $Pd(OAc)_2$ was implemented in 2020 by Zhou and coworkers. Standard SM conditions led to several unknown byproducts, when α-(trifluoromethyl)alkenyltriflate **148** was reacted with phenylboronic acids. Interestingly, when leaving out the base, product formation in 75% yield was observed, which could be improved to 84% yield by increasing the amount of PPh_3 ligand. Several precoordinated Pd-catalysts failed to give higher yields. With 10 mol% $Pd(OAc)_2$ and 40 mol% PPh_3 in DMSO at 120 °C the optimal conditions for the base-free SM cross-coupling were found. Phenyl boronic acids with electron-withdrawing and -donating groups, and heteroarylboronic acids were successfully converted. The authors state that the trifluoromethyl group is mandatory for performing under base-free conditions, because it promotes the transmetallation (Scheme 46).[64]

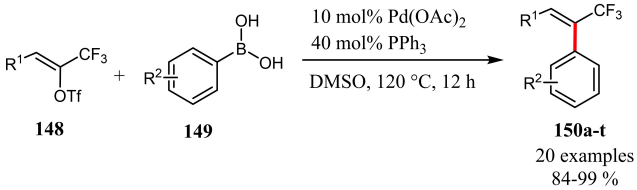
Mahecha-Mahecha et al. focused on the synthesis of functionalized angular cycloalkane-fused naphthalenes, where they investigated a sequential SM cross-coupling of ketal-containing pinacol boronic esters with cyclic vinyl triflates, followed by an acid-catalyzed cyclization. Under optimized conditions the authors were able to convert electron-donating and -withdrawing arylboronic acids in the presence of $PdCl_2$(dppf) as a catalyst, a substochiometric amount of CuCl as an additive and NaOH as a base. Diminished yields were observed for reactions with phenyl boronic acids carrying electron-withdrawing groups or with heteroaromatic boronic acids (Scheme 47).[65]

A mild SM cross-coupling with $PdCl_2$(dppf) in the synthesis of Zealexin B1 was thoroughly investigated by Matsushima and coworkers in 2022. Using K_2CO_3 as a base in MeCN at 40 °C for 5 h gave the desired Zealexin B1 methyl ester (**156**) in 77% yield. The 4-step synthesis proved to be short, simple and scalable (Scheme 48).[66]

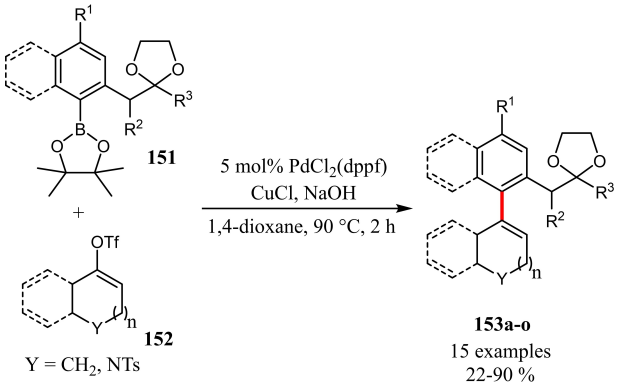
Another example for a mild SM cross-coupling was disclosed by Lindbäck and Sydnes, where the key step towards the hexahydropyrrolo[3,2-*c*]quinolone core structure, found in *Martinella* alkaloids, consists of an sp^2–sp^3 coupling between a vinyl triflate and an *N*-protected ß-aminoethyl boron species. The authors performed a one-pot hydroboration/SM cross-coupling with 9-BBN, $PdCl_2$(dppf), $AsPh_3$ and $CsCO_3$ in a H_2O/



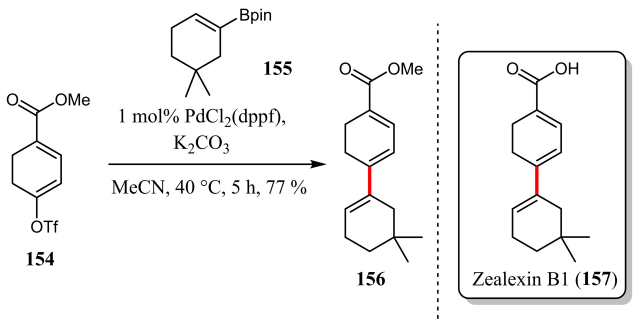
Scheme 45. Key step of large-scale preparation of the antidepressant GSK1360707, without PCB dimer formation.



Scheme 46. Base-free SM cross-coupling towards trifluoromethylarylenes.



Scheme 47. Sequential SM cross-coupling towards functionalized cycloalkane-fused naphthalenes.

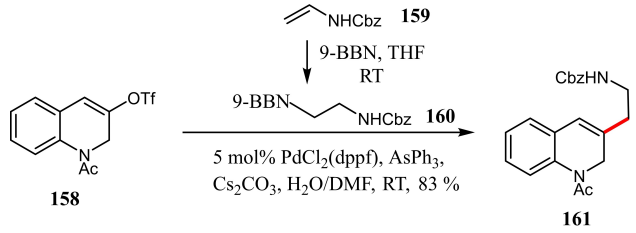


Scheme 48. Mild SM cross-coupling towards Zealexin B1 methyl ester.

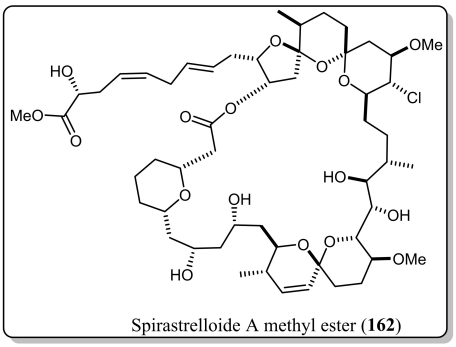
DMF solvent system at RT, yielding 83% of the desired product (Scheme 49).[67]

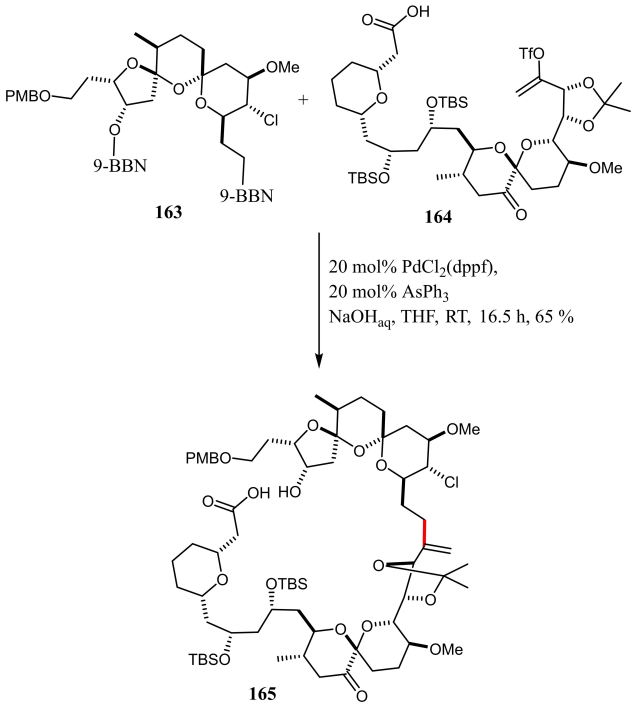
In 2013 Fürstner and coworkers accomplished the total synthesis of Spirastrelloide A methyl ester (**162**) using a particularly challenging alkyl-SM sp^3–sp^2 cross-coupling as a key step, which connected two advanced fragments forming the macrocyclic perimeter. After hydroboration of the terminal alkene with 9-BBN, the alkylborane **163** was reacted with polyfunctionalized vinyl triflate **164** in the presence of $PdCl_2$(dppf), $AsPh_3$ and aqueous NaOH in THF at RT. The structural and functional complexity of the substrates made the use of 20 mol% of the catalyst and ligand each necessary, but was rewarded with 65% of product **165**, which allowed the completion of the total synthesis within 5 steps (Scheme 50).[68]

In most cases, commercially available Pd-catalysts were employed for vinyl triflates. Cao et al. examined the catalytic efficiency of palladacycle **170** for the total synthesis of (−)-Hamigeran B (**166**) and (−)-4-Bromohamigeran B (**167**), where the key step was also a mild SM cross-coupling. The authors were able to improve the previously reported synthesis by Trost et al.[69] by using pinacol boronate **169** instead of the free boronic acid and changing $Pd(PPh_3)_4$ to palladacycle **170**, in combination with dppf as a ligand and K_3PO_4 as a base in a DMF/EtOH solvent mixture at RT. The formed double bond migrated side product **172** could be easily separated (Scheme 51).[70]



Scheme 49. Mild one-pot hydroboration SM cross coupling reaction sequence towards **161**.



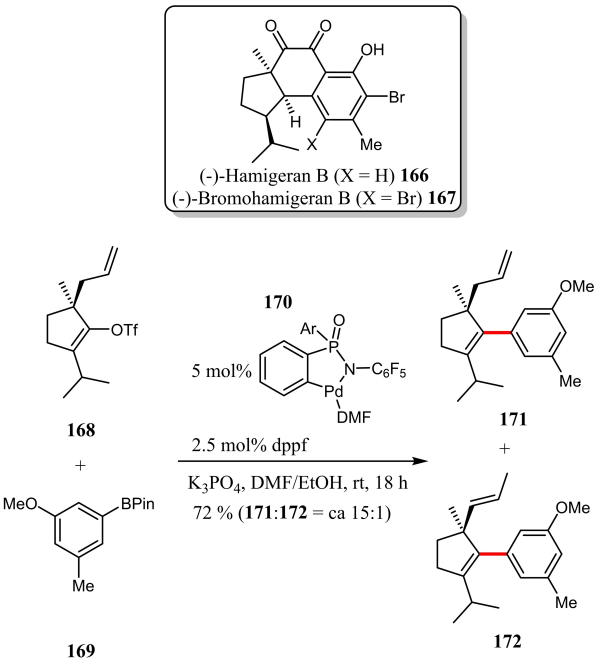


Scheme 50. Mild alkyl-SM cross-coupling towards the formation of a macrocyclic perimeter.

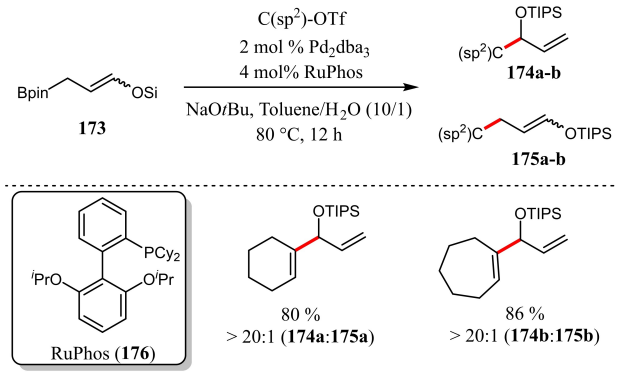
In 2022 Li et al. developed an efficient SM cross-coupling of oxygen-substituted allylboronates with vinyltriflates, towards allylic siloxanes. Pd_2dba_3 and RuPhos as a catalytic system ensured high regioselectivity. $Pd(PPh_3)_4$ gave good yields but poor regioselectivity, which was not improved by diversifying the ligand. The authors also proved that the protocol worked with a wide range of arylhalides, but vinylic building blocks could only be introduced by triflates as a leaving group (Scheme 52).[71]

3.4. Ketovinyl Triflates

Ketovinyl triflates are useful and versatile building blocks for SM cross-couplings, which in comparison to vinyl halides have the advantage of increased stability towards chromatography and against light without



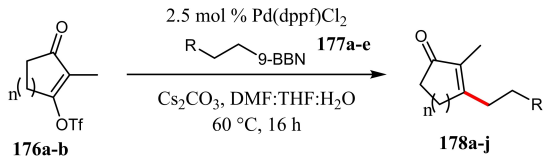
Scheme 51. Mild SM cross-coupling with palladacycle **170**.



Scheme 52. SM cross-coupling of oxygen-substituted allylboronates with vinyltriflates, towards allylic silylethers.

affecting their reactivity. Furthermore, they provide access towards products with interesting complexity. In 2019 Newhouse and coworkers[72] presented an alternative, mild SM cross-coupling protocol to produce cyclic α,ß-disubstituted enones. $Pd(dppf)Cl_2$ in a DMF/THF/H_2O solvent system with Cs_2CO_3 emerged as the best catalyst system producing **178 a** in 99% yield after 16 h. The use of K_3PO_4 diminished the yields relative to Cs_2CO_3, while NaOH led to complete cleavage of the triflate. The authors were able to use five- and six membered cyclic ß-triflyl enones and different protected hexanol boranes for the SM cross-coupling, demonstrating that sensitive functional groups could be transformed (Scheme 53).

Langer and co-workers reported the site selective SM cross-coupling of cyclic bis(triflates) of the 4,7-

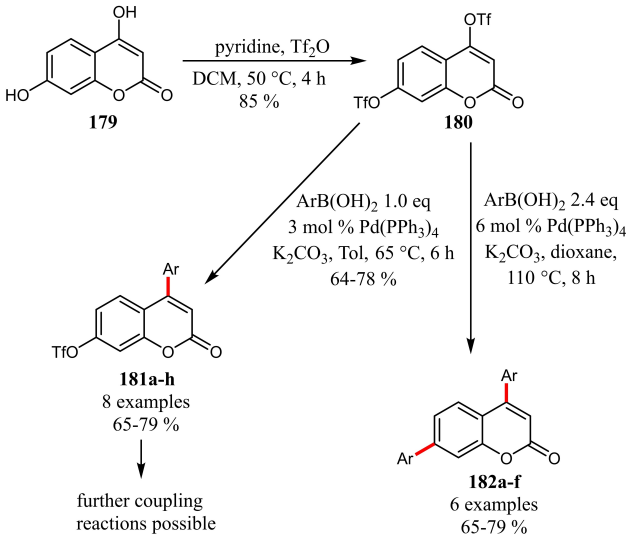


a,b: R = -$(CH_2)_4$-OBn — n = 1, 99 % / n = 2, 94 %
c,d: R = -$(CH_2)_4$-OTBS — n = 1, 79 % / n = 2, 74 %
e,f: R = -$(CH_2)_4$-OAc — n = 1, 32 % / n = 2, 73 %
g,h: R = -Ph-OMe — n = 1, 69 % / n = 2, 76 %
i,j: R = -$(CH_2)_4$-NPhth — n = 1, 56 % / n = 2, 67 %

Scheme 53. Synthesis of α,ß-disubstituted cyclic enones from cyclic ß-triflyl enones.

dihydroxycoumarin **179**.[73] With standard SM cross-coupling reaction conditions, the synthesis with electron-rich and poor arylboronic acids was achieved. Aryl substituents were introduced at both triflate groups successfully. 3 mol% Pd catalyst and 1.0 eq aryl boronic acid led to a subsequent conversion of triflate in C-4 position for electron-rich and -poor aryl boronic acids. In addition to this, it seemed to be of great importance to decrease the temperature of the reaction from 110 to 65 °C. Interestingly, in the bistriflate substrate **180** the sterically more hindered, but electronically activated 4-triflate reacts first, while for the corresponding bis(halogenated) coumarins the sterically less hindered C-7 position reacts first. This approach can be used to access various arylated coumarin derivatives, which are difficult to access by other methods (Scheme 54).

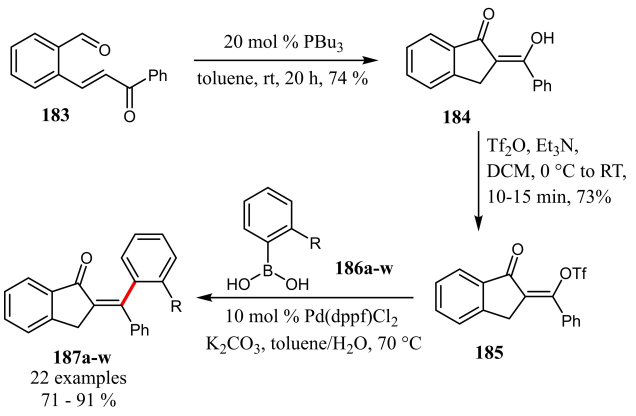
In 2021 Ramasastry and coworkers reported the atropselective SM cross-coupling of ß-keto enol triflate **185** with aryl boronic acids delivering the axially chiral diarylmethylidene indanones (DAIs).[74] An unusual



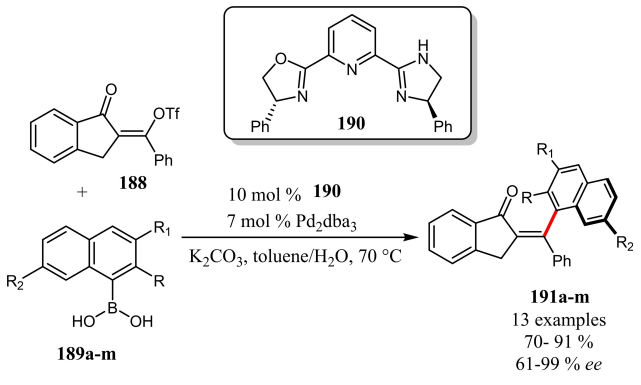
Scheme 54. Synthesis towards arylated coumarin derivatives, starting from 4,7-dihydroxycoumarin.

intramolecular Morita-Baylis-Hillman reaction was used to transform enone-aldehyde **183** to the desired substrate **185** for the planned SM cross-coupling, via a [1,3]-H shift and tautomerization. After optimization $Pd(dppf)Cl_2$ and K_2CO_3 as a base in a toluene-water mixture at 70 °C showed a broad scope for the racemic reaction, where electron-deficient and -donating, as well as sterically hindered boronic acids, proved to be efficient. The presence of water seemed to be of highest importance, because it improved the yield from 71% to 90% (Scheme 55).

With Pd_2dba_3 and the chiral PyBOX ligand **190** the reaction could be performed in an enantioselective manner, producing products **191 a–m** in 66–99% *ee.* (Scheme 56). The authors tested various electronically and sterically different *ortho*-substituted naphthalene boronic acids, resulting in the synthesis of different axially chiral DAIs with moderate *ee.* Introducing an additional substituent in position 3 or 7 of the substrate **189** dramatically increased the enantioselectivity (Scheme 56). An additional substituent in position 6 proved to be counterproductive for the *ee.* Furthermore, the reaction did not tolerate other substituents than alkoxy groups, due to the oxygen of the alkoxy substituent, which additionally stabilizes the conformation of the transition state of the reductive elimination step. This is discussed as the key contributor towards enantioinduction.



Scheme 55. Reaction towards keto-enol **185**, followed by racemic SM cross-coupling towards different DAIs.

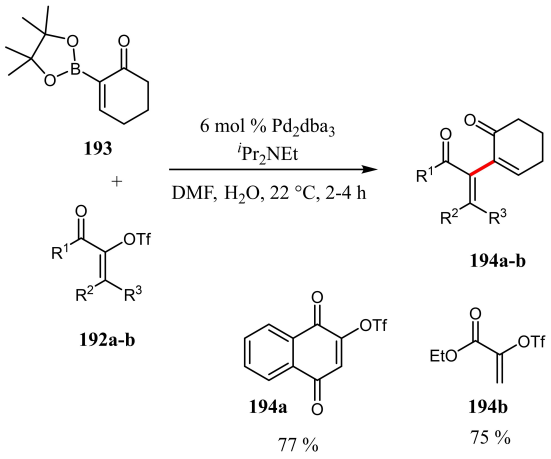


a: R = -OMe, R^1 = -H, R^2 = H 73 %, 66 % *ee*
b: R = -OMe, R^1 = -OMe, R^2 = H 84 %, 85 % *ee*
c: R = -O^{i}Pr, R^1 = -O^{i}Pr, R^2 = H 87 %, 99 % *ee*
d: R = -O^{i}Pr, R^1 = -H, R^2 = -O^{i}Pr 84 %, 97 % *ee*
e: R = -Me, R^1 = -H, R^2 = H 91 %, 0 % *ee*

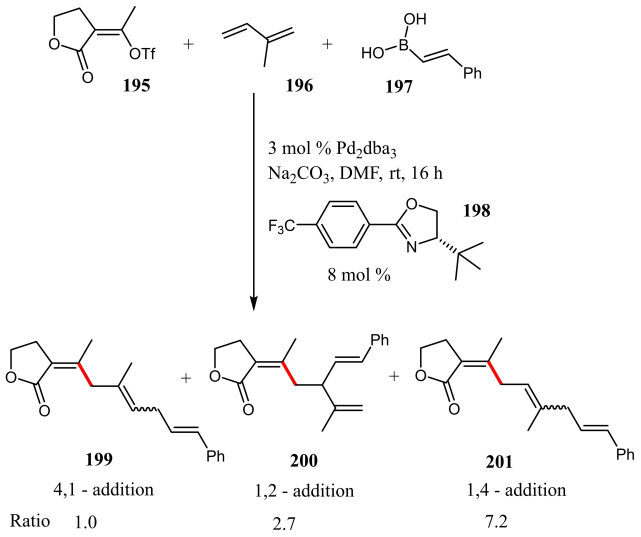
Scheme 56. Atroposelective SM cross-coupling towards different chiral DAIs.

Bawel and coworkers discovered in 2017 a Pd cross-coupling with Pd_2dba_3 to synthesize unsymmetrical α-linked bisenone systems.[75] Interestingly, they found that no additional ligand was needed. They focused on Stille coupling but showed some examples of SM cross-coupling to extend their methodology (Scheme 57). The application of this reaction is quite limited because of boronate availability, but shows novel opportunities to access reactive, highly unsaturated systems, which could be used for new ring-formations.

The difunctionalization of alkenes from simple chemical feedstocks represents an attractive access to structurally diverse functionalized chemicals. Wiest and coworkers reported the three-component coupling of isoprene with cyclic ketovinyl triflates and styrenyl boronic acids catalyzed by a Pd-pyrox complex (Scheme 58).[76] The authors provide deep insights into the mechanism with regard to the formation of 16 possible stereoisomers through a wide range of computational experiments, which resulted in determining the transmetalation as the regioselectivity determining step of the 1,2 vs 1,4-addition products. The distortion of the Pd coordination sphere in the transition structure of the migratory insertion step controls the 4,1- vs 1,2 or 1,4-selectivity. A drawback of this transformation is that it proceeds with only moderate yields and selectivity.



Scheme 57. Ligandless SM cross-coupling for preparation of unsymmetrical α-linked bisenones.



Scheme 58. Difunctionalization of isoprene with Pd-catalyzed SM cross-coupling.

3.5. Imino Triflates

SM cross-couplings play an important role as key steps for synthesis of natural products and alkaloids.

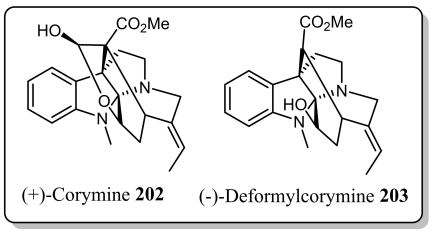
Li and coworkers[77] reported in 2020 the first enantioselective total synthesis of Akuammiline alkaloids (Scheme 59) in 11 steps. In the course of the synthesis they planned to introduce an alkyl substituent at the 2-position of the indole scaffold. However, neither a direct alkylation with Grignard reagents, nucleophilic dialkylzinc or organocuprates nor a Sonogashira coupling led to the desired intermediates. They could solve the problem via an sp^2–sp^3 SM cross-coupling of iminotriflate **204** with 9-(3,3-diethoxypropyl)-9-BBN, a catalyst system consisting of 6 mol% $Pd(PPh_3)_4$ and (*o*-tolyl)$_3$P and K_2CO_3 as a base in aqueous THF. The synthesis of the C-2 alkylated product **206** (formed C–C bond highlighted in red, Scheme 59) was successfully accomplished in 54% yield.

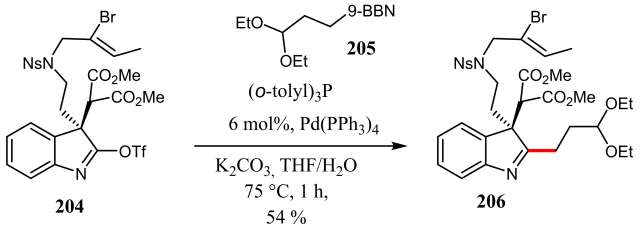
Thopate and coworkers synthesized different phthalazin derivatives using iminotriflates in the SM cross-coupling. Screening of different Pd catalysts, bases and solvent systems revealed that $Pd(dppf)Cl_2$ and K_3PO_4 in 1,4-dioxane were most suitable for this transformation. The change from K_2CO_3 to K_3PO_4 was of special importance, because K_2CO_3 as a stronger base led to cleavage of triflate **207**, which was also influenced by higher temperature (reflux). With optimised conditions in hand, the group was able to explore the scope, which encompassed electron-donating and -withdrawing groups in *ortho, meta* and *para* position. Boronic acids with halogen substituents were also compatible with this transformation, like sterically demanding substituents, even though the yield decreased slightly (Scheme 60).[78]

3.6. ß-Enamido Triflates

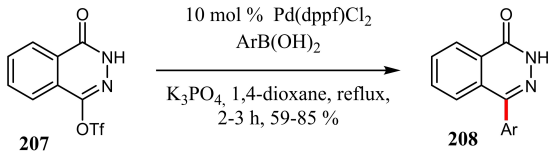
Beier and coworkers reported the stereoselective SM cross coupling of enamido triflates with aryl boronic acids (Scheme 61).[79] While $Pd(PPh_3)_4$ provided the selective formation of enamide **210** with retention of the double bond, $Pd(dppf)Cl_2$ led to the formation of enamide **211** under inversion of the double bond.

The authors argued that the very bulky ligand of $Pd(dppf)Cl_2$ caused a tautomerization of the Pd-complex after transmetallation towards a zwitterionic carbene, which isomerized towards the thermodynamically more stable Pd-complex (Scheme 62). This concept allowed the broad application of electron-rich and -poor aryl boronic acids with good to excellent NMR yields. However, the isolation of the different products proved to be problematic, because of decomposition on silica gel. Therefore, the yield dropped when comparing the ^{1}H-NMR yield to the isolated yields (Scheme 61). Furthermore, despite considerable optimization the use of alkylboronic acids did not lead to any reaction, indicating the limitation of this transformation.[79]

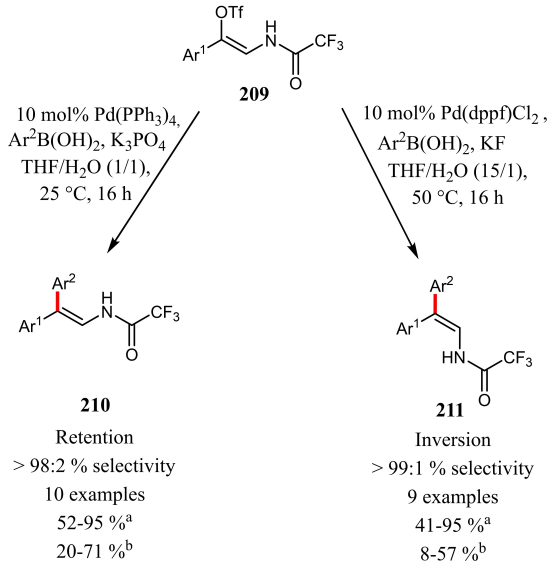




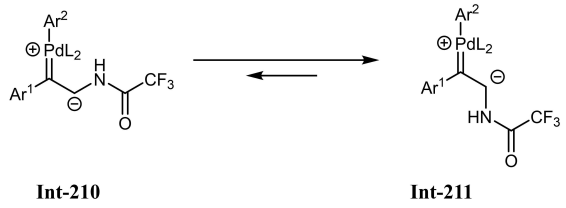
Scheme 59. SM cross-coupling of key intermediate **204** in the synthesis of Akuammiline alkaloids.



Scheme 60. SM cross-coupling towards different phthalazinone derivatives.



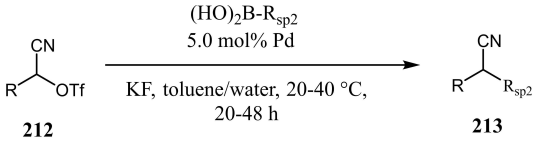
Scheme 61. Ligand-controlled SM cross-coupling of (*Z*)-ß-enamido triflates with aryl boronic acids. [a]Ratio determined by ^{19}F-NMR. [b]isolated yield.



Scheme 62. Mechanistic explanation of inversion reaction using Pd(dppf)Cl_2.

3.7. Alkyl Triflates

Falck and coworkers succeeded in the reaction of functionalized sp^3-hybridized stereogenic alkyl triflates with aryl, heteroaryl and vinyl boronic acids under mild conditions using the commercially available Pd catalysts Pd(amphos)Cl_2 (**A**) and Pd(dtbpf)Cl_2 (**B**).[80] The electron-withdrawing cyano group in α-position facilitates the oxidative addition towards the Pd catalyst even at room temperature. Furthermore, small amounts of water led to improved yield during optimization screening. The yields of sterically hindered substrates were enhanced changing catalyst **A** towards the bidentate catalyst **B**. The couplings were tolerant towards electron-donating and electron-withdrawing substituents. The stereospecificity was also investigated and resulted in complete inversion of the configuration during coupling (Scheme 63 and Table 3).[80]



Scheme 63. Cross-coupling of alkyl α-cyanohydrin triflates.

Table 3. SM cross-coupling of alkyl α-cyanohydrin triflate with different Pd catalysts (A: Pd(amphos)Cl_2 or B: Pd-(dtbpf)Cl_2).

Entry	R	R_{sp}^2	Cat	Yield
1	–$(CH_2)_2$Ph	–Ph–4-Me	**A**	91%
2		–Ph–2-Me	**B**	74%
3		–Ph–4-Ac	**A**	51%
4		–$(CH)_2$Ph	**A**	94%
5	-Cy	–Ph–4-Me	**B**	31%
6	-*t*Bu	–Ph–4-Me	**B**	78%
7	–$(CH_2)_2$Ph	-3-thiophenyl	**A**	56%
8	-(*S*)–$(CH_2)_2$Ph	–Ph–4-Me	**A**	91% (98% ee)

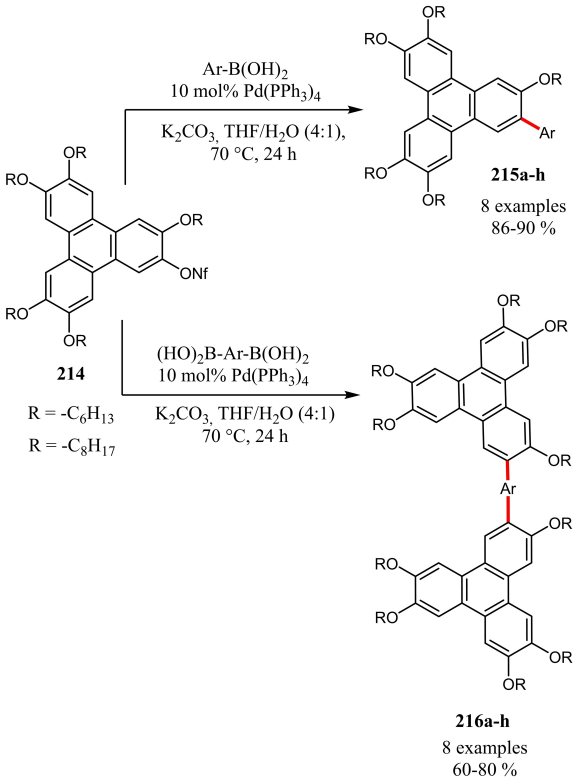
4. Nonaflates as Attractive Alternatives to Triflates

As has been reported in the previous chapters, in certain applications the hydrolysis of the triflate substrate is an undesired side reaction. In such cases, nonaflates should be considered as a possible replacement for triflates due to their known higher stability towards O–S hydrolysis.[13] Furthermore, nonaflyl fluoride (NfF) is cheaper than the commonly used triflating reagents (Figure 1).

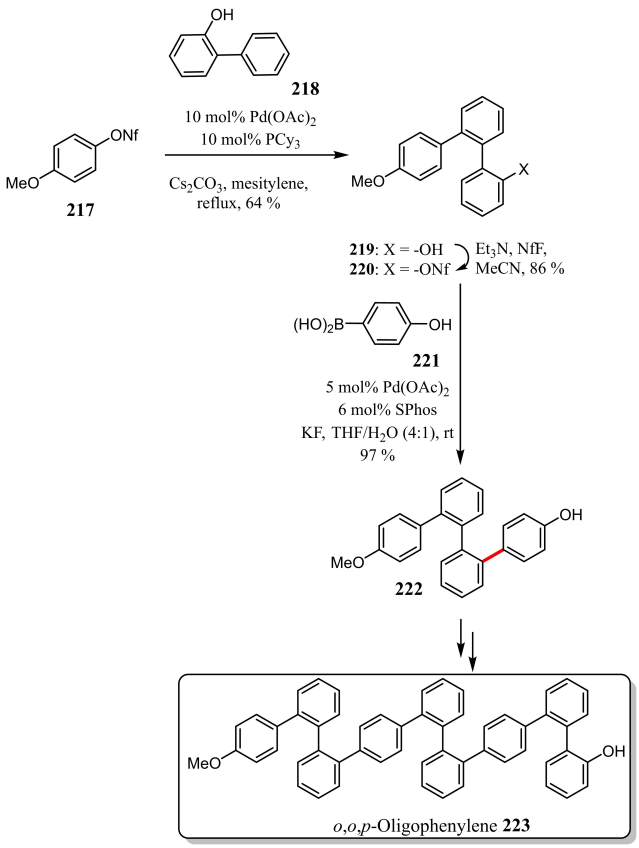
4.1. Arylnonaflates

In the large-scale synthesis of aryl-triphenylene and triphenylene discotic dimers SM cross-coupling with aryl nonaflates was successfully implemented. Triphenylene triflates were replaced by nonaflates due to availability and for economic reasons regarding the reagents. Heteroaryl boronic acids were fruitfully converted in excellent yields (> 80%) with $Pd(PPh_3)_4$ and K_2CO_3 in a THF/H_2O solvent system at 70 °C for 24 h (Scheme 64).[81]

Aryl nonaflates were used by Manabe and Kimura in an iterative SM synthetic method for *o,o,p*-oligophenylenes. Instability of aryl triflates under harsh reaction conditions (basic and high temperature) led to low yields and many byproducts, while aryl nonaflates showed to be less prone to O–SO_2 cleavage. After the C–H-functionalization reaction the C–H arylated product was converted to the corresponding nonaflate **220**, which was reacted with *p*-hydroxyphenylboronic acid, $Pd(OAc)_2$, SPhos as the ligand and KF in a THF/H_2O mixture to **222** in good to excellent yields. The *o,o,p*-



Scheme 64. SM cross-coupling of triphenyl nonaflates towards different monomeric and dimeric products.



Scheme 65. SM cross-coupling towards the desired product **223**.

oligophenylene **223** was synthesized via subsequent repetition of nonaflation, SM coupling, nonaflation and C–H arylation in good yield (Scheme 65).[82]

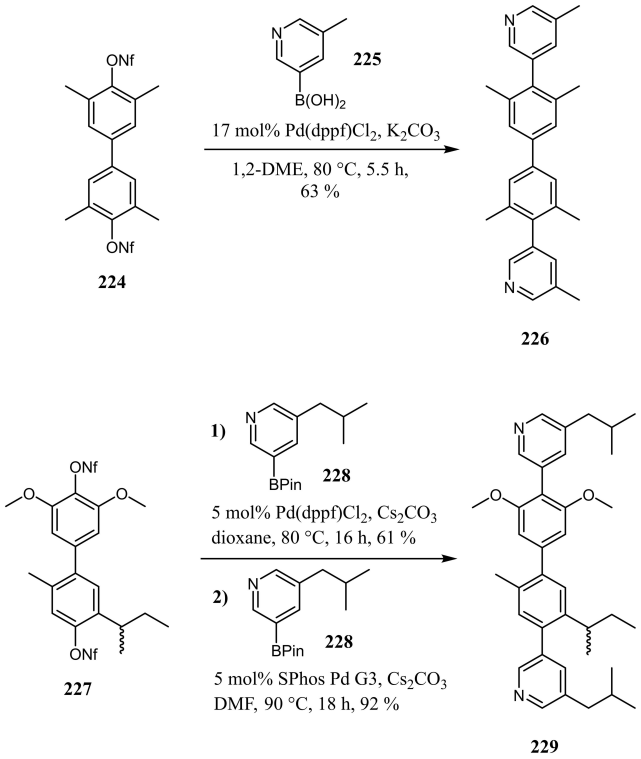
In 2020 Breinbauer and coworkers were able to synthesize Bcl9 quarteraryl mimetics by changing the triflate to a nonaflate leaving group in the Pd-catalyzed cross-coupling reaction. Also in this case the authors described that the hydrolytic lability of the triflate against various bases caused problems. Depending on the desired assembly the use of different Pd catalysts and bases in different solvents led to the desired products **226** and **229** (Scheme 66).

4.2. Heteroaryl Nonaflates

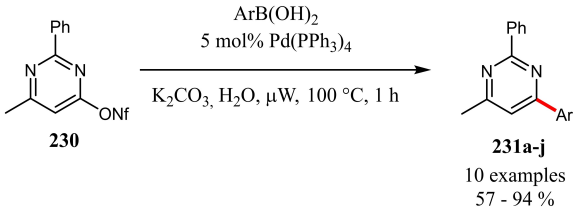
In 2021 Domínguez et al. tested the reactivity of 4-pyrimidyl nonaflate **230** with different arylboronic acids under microwave irradiation in water. Electron-poor boronic acids led to a higher yield when nonaflates as coupling partners were employed. Also, here the slower O–S bond cleavage proved advantageous for nonaflates over the corresponding triflates (Scheme 67). The yield of electron-withdrawing aryl boronic acids was improved by 20%.[52]

The Reissig group developed a flexible procedure for the preparation of highly functionalized pyridine nonaflates by an intramolecular condensation of ß-ketoenamides, followed by *O*-nonaflation. Subsequent functionalization was carried out by Pd-catalyzed cross-coupling reactions. With this they were able to systematically prepare a series of oligo(2-thienyl)-substituted pyridine derivatives. The 3-component reaction towards the key intermediate **234** with Pd-$(PPh_3)_4$, thiophenyl boronic acid and K_2CO_3 in DMF at 70 °C furnished the desired product in good yields. The different di-, tri- or tetrasubstituted pyridine derivatives **235** were synthesized via subsequent repetition of nonaflation, reductive removal of the nonafloxy group, deprotection, triflation and SM coupling in good yields (Scheme 68). For the tetrasubstituted pyridine the change from nonaflate to triflate was important due to improved yields. Unfortunately, it was not possible to prepare 2,3,4,5,6-penta(2-thienyl)-pyridine because of steric reasons.[83] Highly substituted pyridine derivatives could also be accessed through the 3-component reaction (Scheme 69), followed by SM cross-coupling reactions.[74]

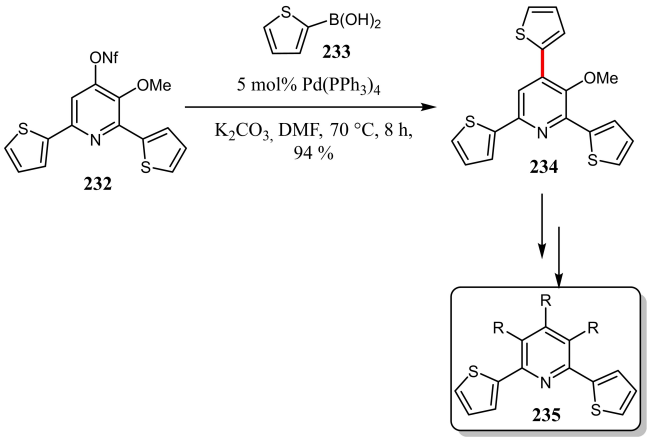
Coupling of different electron-rich and -deficient aryl boronic acids in a $Pd(OAc)_2/PPh_3$ and K_2CO_3 catalytic system in DMF at 70 °C provided a diverse set of heterobiarylic products in good to excellent yields (Scheme 70). Furthermore, the pyridyl nonaflate



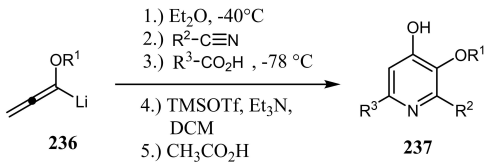
Scheme 66. Synthesis of quarteraryls.



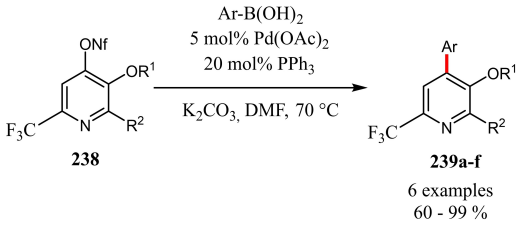
Scheme 67. SM cross-coupling reactions in water under microwave irradiation with pyrimidyl nonaflates.



Scheme 68. SM cross-coupling towards a series of di-, tri-, or tetrasubstituted pyridine derivatives.



Scheme 69. 3-component synthesis of hydroxypyridine derivatives.



Scheme 70. SM cross-coupling towards 4-arylpyridine derivatives.

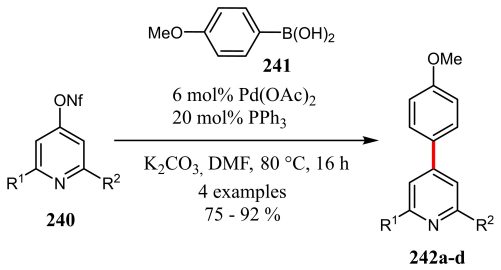
reacted under Stille- and Buchwald-Hartwig reaction conditions.[84]

Next, Reissig and coworkers demonstrated a flexible preparation of pyridine-based solvatochromic push-pull dyes. Pyridine nonaflate derivatives were coupled with anisole boronic acid, $Pd(OAc)_2$, PPh_3 and K_2CO_3 in DMF at 80 °C for 16 h and yielded the desired products in good to excellent yields (75–92%) (Scheme 71). Besides SM cross-coupling reactions, they also demonstrated the possibility of applying Heck-Mizoroki and Sonogashira reaction conditions.[85]

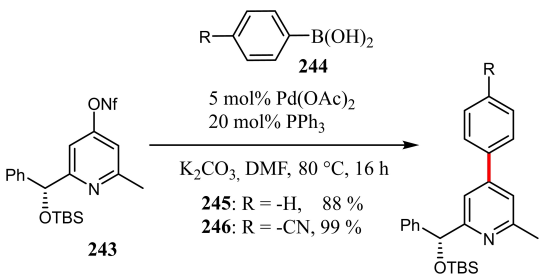
The use of chiral 4-pyridyl nonaflates in different Pd-cross coupling reactions was also demonstrated. C-4 aryl substituents were easily introduced by the corresponding aryl boronic acid, $Pd(OAc)_2$, PPh_3 and K_2CO_3 in DMF at 80 °C for 16 h (Scheme 72).[86]

The pyridinyl nonaflate **247** was used as a starting material for a fast access to the Glenvastatin building block **249**, with common SM reaction conditions in an excellent yield (Scheme 73).[87]

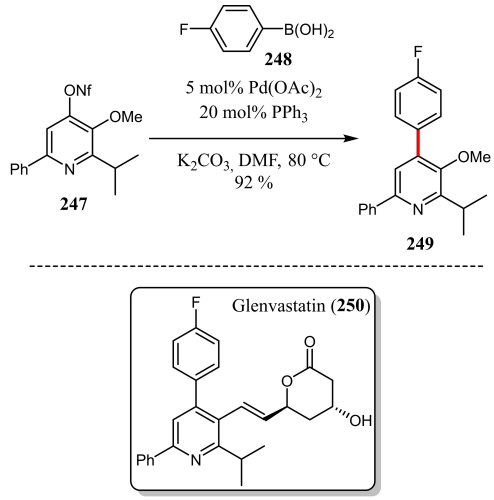
In the same report, the Reissig group showed the possibility to prepare other complex heterocycles.



Scheme 71. SM cross-coupling of 4-pyridyl nonaflates derivatives.



Scheme 72. SM cross-coupling of chiral 4-pyridyl nonaflates.



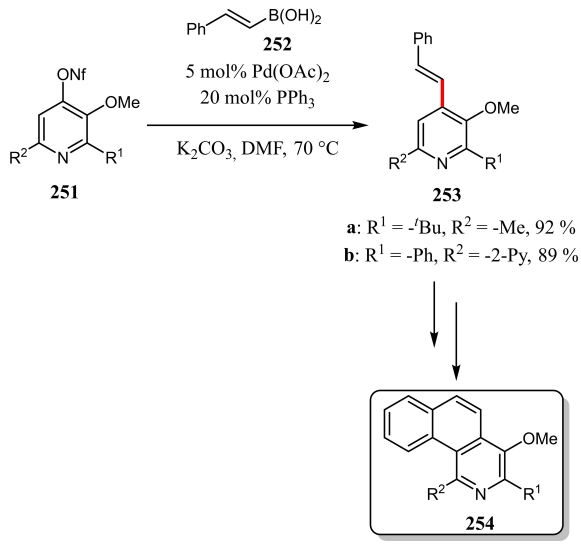
Scheme 73. SM cross coupling of pyridinyl nonaflate **247** towards key intermediate **249** for further reaction towards Glenvastatin.

Starting from pyridinyl nonaflate derivative **251** SM cross-coupling revealed the desired product **253** with *trans*-2-styryl boronic acid, $Pd(OAc)_2$, PPh_3 and K_2CO_3 in DMF at 70 °C. Compound **253** was further converted towards benzoisoquinoline **254** (Scheme 74).[87]

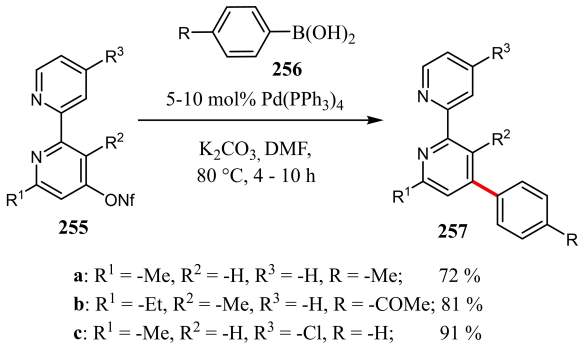
In 2016 the same group published a new flexible route to unsymmetrically functionalized bipyridines. Starting from 2,2'-bipyridyl nonaflates consecutive cross-coupling reactions were carried out. Introducing a chloride leaving group (**257c**) enabled a sequential cross-coupling, where the more reactive nonaflate moiety reacted under standard SM reaction conditions first. Further reaction of the chloro leaving group was tested by applying SM or Sonogashira cross-coupling reactions towards unsymmetrically substituted bipyridine derivatives (Scheme 75).[88]

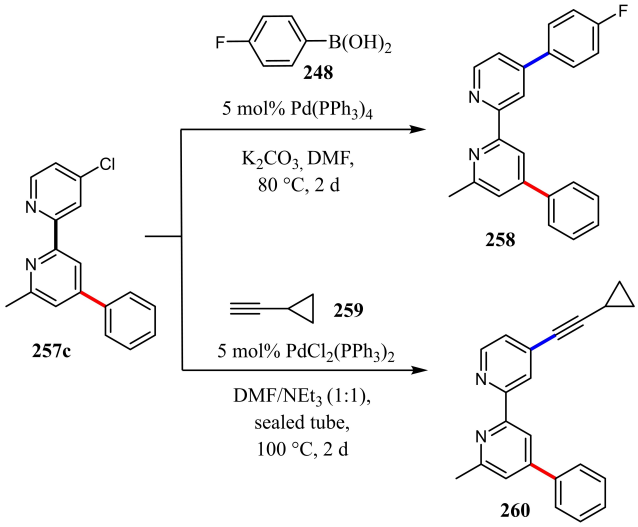
4.3. Vinyl Nonaflates

Vinyl nonaflates can be utilized for vinylation via SM cross-coupling reactions. Gu and coworkers developed a new mild method towards α-aryl vinylphosphonates



Scheme 74. SM cross-coupling towards 4-pyridyl stilbene **253** and benzoisoquinoline derivatives **254**.





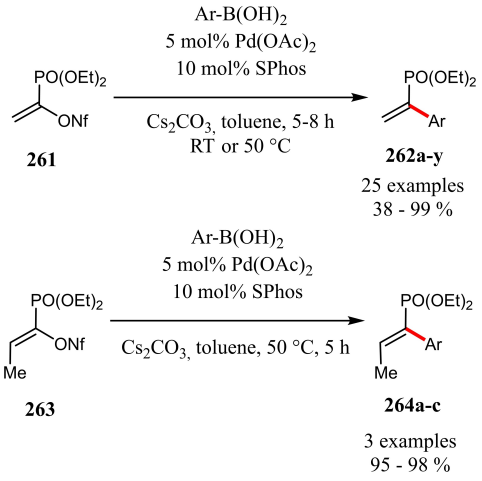
Scheme 75. SM cross-coupling of 2,2'-bipyridyl nonaflates derivatives.

using $Pd(OAc)_2$, SPhos and Cs_2CO_3 in toluene at RT. During optimization reactions, the authors found that

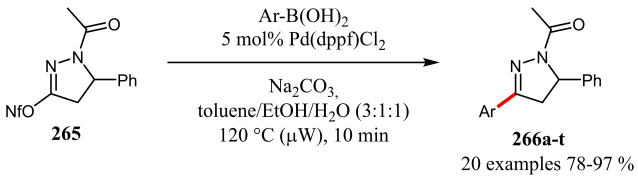
34% isolated yield was achieved, also in the absence of an external supporting ligand. Addition of SPhos as a ligand improved the yield to 98%. Electron-neutral, -rich and -deficient aryl boronic acids could be converted in excellent yields. Sterically demanding and sulfur-containing heteroaryl boronic acids reacted also in good to excellent yields, albeit the temperature needed to be increased from RT to 50 °C. The introduction of pyridine containing boronic acids seemed to be limited, even after optimization. Introducing substrates with defined stereochemistry were converted under retention of the original stereochemistry (Scheme 76).[89]

4.4. Imino Nonaflates

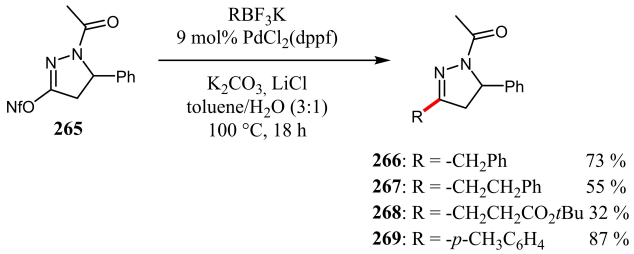
Grimm et al. developed an efficient synthesis protocol towards diverse 3-substituted-2-pyrazolines. Imidoyl triflates were successfully converted in Sonogashira, Stille and Negishi cross-couplings, while they failed in the application of SM cross-coupling reaction conditions, due to triflate hydrolysis. Replacement of triflate with nonaflate showed to prevent the O–S hydrolysis and displayed an enhanced reactivity. The use of $PdCl_2$(dppf) as a catalyst and Na_2CO_3 as a base in a toluene/EtOH/H_2O solvent mixture at 120 °C (μW) for 10 min revealed an extensive and diverse reaction



Scheme 76. SM cross-coupling of various α-aryl vinylphosphonates.



Scheme 77. SM cross-coupling of imidoyl nonaflates with aryl boronic acids.



Scheme 78. SM cross-coupling of imidoyl nonaflates with organotrifluoroborates.

scope. Different electron-deficient, -rich and sterically hindered aryl, alkenyl and heteroaryl boronic acids were fruitfully converted in good to excellent yields (78–97%). 2-Pyridine boronic acids could not be transformed to the desired cross-coupling product (Scheme 77).[90]

The authors were also able to further expand the applicability of their concept with organotrifluoroborates as coupling partners. With this, functional moieties, like alkyl groups, could be introduced (Scheme 78).[90]

5. Synopsis of Reaction Conditions

Over the last decade the use of aryl- and alkenylsulfonates as reagents in SM couplings has seen widespread application and methodological progress. While no universally applicable catalyst system suitable for all substrate combinations has been developed yet, certain patterns of reactivity have emerged. In order to help the practitioners to find a suitable starting point for their own synthetic problem, we provide Figure 2 as a matrix table, in which for any type of substrate and arylboronic acid reagent a successful catalyst/base/solvent/temperature combination based on the literature analysis in this review article is recommended.

6. Conversion of Triflates into Halides

Despite the advances in cross-coupling reactions with sulfonate esters, efficient and versatile methods for the conversion to halide leaving groups (Cl, Br or I) are highly desirable. This way, the convenient synthetic accessibility of aryl and vinyl sulfonate esters can be combined with the enhanced reactivity and versatility of the corresponding aryl and vinyl halides.[91,91] For very electron-deficient aromatic systems, direct S_NAr substitution of triflates with halide ions may be possible.[92] A more broadly applicable functional group interconversion is traditionally achieved via a two-step process through an activated intermediate. For instance, Huffman and coworkers reported a Pd-catalyzed borylation of aryl triflates followed by Cu-mediated substitution to give aryl chlorides, bromides

KEY	
	independent from electronic nature of aryl boronic acid
	electron-rich and electron-neutral BA
	electron-neutral BA
	electron-poor BA
	heteroaryl BA
	other (total synthesis, sp^2-BA, sp^3-BA, ...)

	electron-	$Pd(PPh_3)_4$	$PdCl_2$-$(PPh_3)_2$	$Pd(OAc)_2$	$PdCl_2$-(dppf)	Pd_2dba_3	Pd (NHC)	Palladacycle	$PdCl_2$	$PdCl_2$ (amphos)
Aryltriflates	rich		Na_2CO_3, H_2O, reflux	CyJohn Phos, K_3PO_4, dioxane/ H_2O, 90 °C	Cs_2CO_3, DME, 80 °C	dppb, Na_2CO_3, toluene/ H_2O, 90 °C	SIMes, KF, THF, 25-60 °C	XPhos Pd G2, K_3PO_4, toluene/ H_2O, 90 °C		
				BrettPhos, K_3PO_4, *t*BuOH, 85 °C		SPhos, K_3PO_4, dioxane, 110 °C			KF, H_2O/ MeCN or DMSO, rt	
	neutral	K_3PO_4, dioxane, 60-110 °C					**70**, KOH, *t*BuOH, 50 °C			
		Na_2CO_3, dioxane. 90 °C								
		KF, dioxane, 50-120 °C								
	poor				Na_2CO_3, toluene/ H_2O/ EtOH, 90 °C			**75**, K_3PO_4, EtOH, rt		
	sterically hindered			dppb, K_2CO_3 THF/H_2O, 65 °C						
				XPhos, K_3PO_4, THF/ DMF/ H_2O, 95 °C						
				PCy_3, Cs_2CO_3, THF/H_2O, 80 °C						

	electron-	$Pd(PPh_3)_4$	$PdCl_2$-$(PPh_3)_2$	$Pd(OAc)_2$	$PdCl_2$-(dppf)	Pd_2dba_3	Pd-(NHC)	Palladacycle	$PdCl_2$	$PdCl_2$-(amphos)
Heteroaryltriflates	rich	K_3PO_4, THF, 90 °C	Na_2CO_3, MeCN, 55 °C							
		K_3PO_4, dioxane, 80 °C								
		K_2CO_3, dioxane, 70 °C								
		K_2CO_3, DME/H_2O, 70 °C								
	poor	K_3PO_4, dioxane, 40 °C	Na_2CO_3, DME, 90 °C		Alkenyl trifluoroborate, Cs_2CO_3, THF/H_2O, 70 °C					
		K_3PO_4, toluene, 100 °C			K_2CO_3, MeCN, µW, 120 °C					
		K_3PO_4, KBr, dioxane, reflux								
		K_2CO_3, H_2O, µW, 100 °C								
		Na_2CO_3, dioxane/H_2O, 100 °C								
	sterically hindered	KCl, Na_2CO_3, toluene/EtOH/H_2O, 70 °C								
		K_2CO_3, benzene, reflux								
		Na_2CO_3, DMF, 70-80 °C								

	electron-	$Pd(PPh_3)_4$	$PdCl_2$-$(PPh_3)_2$	$Pd(OAc)_2$	$PdCl_2$-(dppf)	Pd_2dba_3	Pd (NHC)	Pallada cycle	$PdCl_2$	$PdCl_2$ (amphos)
Vinyltriflates	rich	K_2CO_3, DME/H_2O, 80 °C	$NaHCO_3$, THF, 80 °C		NaOH, CuCl, dioxane, 90 °C	RuPhos, NaO*t*Bu toluene/H_2O, 80 °C		**170**, K_3PO_4, DMF/EtOH, rt		
		Na_2CO_3, LiCl, DME, 85 °C			K_2CO_3, MeCN, 40 °C					
					$AsPh_3$, Cs_2CO_3, H_2O/DMF rt					
	neutral		K_2CO_3, THF/H_2O, rt							
	poor			PPh_3, DIPEA, DMF/toluene/H_2O, 70 °C						
				PPh_3, DMSO, 120 °C						
	sterically hindered		Na_2CO_3, toluene/EtOH/H_2O, 75 °C		$AsPh_3$, NaOH, THF, rt					
ß-Keto-Vinyltriflates	poor	K_2CO_3, toluene, 65 °C			Cs_2CO_3, DMF/THF/H_2O, 60 °C	**190**, K_2CO_3, toluene/H_2O, 70 °C				
		K_2CO_3, dioxane, 110 °C			K_2CO_3, toluene/H_2O, 70 °C	*i*Pr_2NEt, H_2O/DMF, rt				
						Na_2CO_3, DMF, rt				
Imino-triflates	rich				K_3PO_4 dioxane, reflux					
	sterically hindered	P(*o*-tolyl)$_3$, K_2CO_3, THF/H_2O, 75 °C								

	electron-	$Pd(PPh_3)_4$	$PdCl_2$-$(PPh_3)_2$	$Pd(OAc)_2$	$PdCl_2$-(dppf)	Pd_2dba_3	Pd (NHC)	Palladacycle	$PdCl_2$	$PdCl_2$ (amphos)
ß-Enamido-triflates	poor	K_3PO_4, THF/H_2O, rt			KF, THF/H_2O, 50 °C					
Alkyl-triflates	rich									KF, toluene/H_2O, 20-40 °C
Arylnonaflates	rich	K_2CO_3, THF/H_2O, 70 °C		SPhos, KF, THF/H_2O, rt						
Heteroaryl-nonaflates	rich	K_2CO_3, DMF, 70 °C		PPh_3, K_2CO_3, DMF, 70-80 °C						
	poor	K_2CO_3, H_2O, µW, 100 °C								
Vinyl-nonaflates	poor			SPhos, Cs_2CO_3, toluene, 25-50 °C						
Imino-nonaflates	rich				Na_2CO_3, toluene/EtOH/H_2O, µW, 120 °C					

Figure 2. Matrix guide for suitable reaction conditions for substrate combination between various triflates and boronic acids.

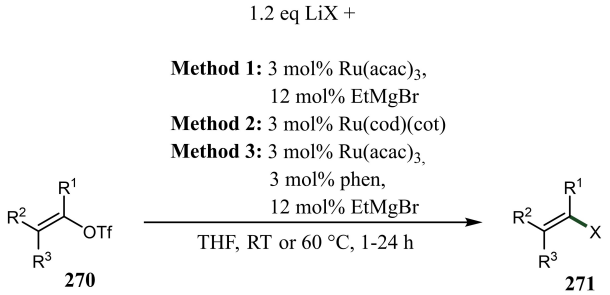
and iodides.[93] Similarly, conversion of vinyl triflates to vinyl chlorides or bromides can proceed through preparation of the corresponding vinyl stannanes[94] and subsequent substitution with NBS or $CuCl_2$.[95] However, these methods require expensive reagents and time-consuming multi-step synthesis. Therefore, researchers have sought reactions that enable the transformation in a single step under mild conditions, ideally utilizing cheap alkali metal salts as the halide source. We wish to give an overview of the most relevant developments in this area. All reactions utilize either transition metal (Ru, Pd or Ni) catalysis, or photochemistry. Some of the work presented here has already been highlighted in other reviews up to 2016,[96] but not in the context of strategic use as in this review. We have included also the most recent developments.

6.1. Ru-catalyzed Transformations

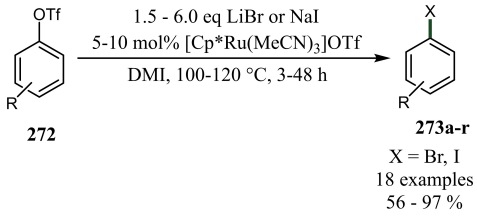
In 2009 the Hayashi group demonstrated the first transition metal-catalyzed halogenation of vinyl triflates. When investigating the Ru-catalyzed cross-couplings of vinyl triflates with Grignard reagents, they found that considerable amounts of vinyl bromide were formed in presence of LiBr. After optimizing the reaction towards this outcome, a versatile and high-yielding method was presented. 12 (hetero)cyclic and

acyclic enol triflates were converted to the corresponding bromides in excellent yields. Additionally, two examples each for chlorination and iodination were provided (Scheme 79).[97] The methodology also proved successful for the conversion of 2-naphthyl triflate to 2-naphthyl bromide. However, *p*-tolyl triflate was not converted and other aromatic triflates were not investigated.[97]

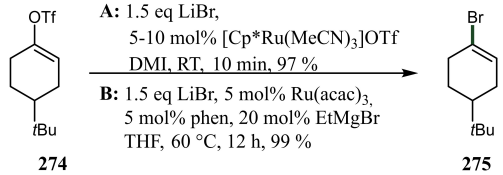
Three years later, the same group reported that Cp*Ru complexes enable transformation of aryl triflates. Using 5 mol% [Cp*Ru(MeCN)$_3$]OTf and either LiBr or NaI as halide source in 1,3-dimethyl-2-imidazolidinone (DMI), a diverse set of electron-poor aryl triflates was efficiently converted to the corresponding aryl bromides or iodides. It is worth mentioning that aryl chloride substrates were tolerated, offering potential for synthesis of dihalogenides with leaving groups of orthogonal reactivity. Electron-rich substrates were also converted but often required higher catalyst loadings (Scheme 80).[98]



Scheme 79. Hayashi's Ru-catalyzed halogenation of enol triflates.



Scheme 80. Ru-catalyzed bromination and iodination of aryl triflates.



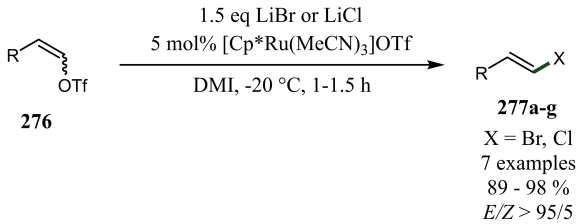
Scheme 81. Comparison of different Ru catalysts in the transformation of vinyl triflate **274** to vinyl bromide **275**.

Compared to their low-valent counterparts, the Cp*Ru complexes proved much more active in the transformation of vinyl triflates as well. Synthesis of 4-*tert*-butylcyclohexen-1-yl bromide (**275**) from triflate **274** required 12 h reaction time and elevated temperatures when the reaction conditions from the previous report were applied. Under the new reaction conditions, **275** was obtained after 10 min at room temperature (Scheme 81).[98]

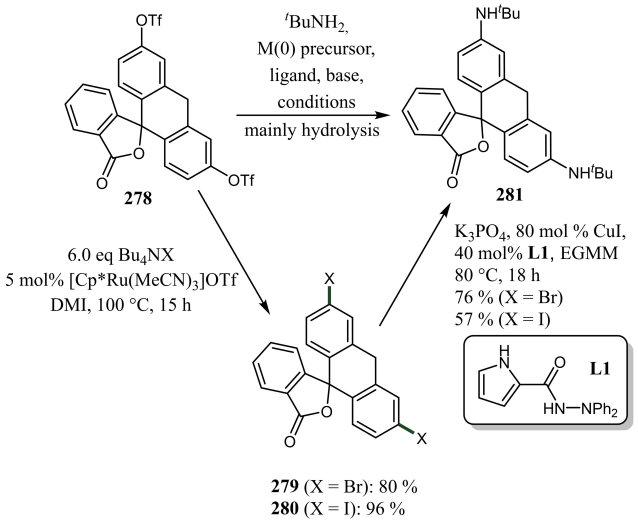
Interestingly, *E/Z* mixtures of acyclic vinyl triflates – which are much more convenient to obtain compared to pure (*E*)-vinyl triflates – converged to pure (*E*)-haloalkanes when subjected to [Cp*Ru(MeCN)$_3$]OTf and LiBr or LiCl at low temperature (Scheme 82). These (*E*)-haloalkanes isomerized back to a constant *E/Z* ratio after longer reaction times at room temperature. The authors conclude that the (*E*)-isomer is kinetically favoured in this reaction and only at higher temperature re-enters the Ru cycle to get isomerized.[98]

Hell and coworkers used this methodology with slight modifications in the synthesis of *N,N'*-di-*tert*-alkylrhodamines, which are promising fluorophores that show resistance to oxidative photobluing. In order to convert fluorescein ditriflate **278** to the desired compound **281**, the authors first attempted a Buchwald-Hartwig amination. However, hydrolysis of the triflate was the dominant pathway and **281** could only be isolated in very low yields. They therefore converted **278** to the corresponding bromide or iodide, which was then subjected to an Ullmann reaction, furnishing **281** in good overall yields (Scheme 83). In a similar manner, several other fluorescein ditriflate derivatives were converted. In one case the same procedure was applied for a fluorescein nonaflate.[99]

Very recently, the Leroux group published a Ru-catalyzed transformation of aryl and vinyl halides from fluorosulfonates. The authors argue that fluorosulfonates can be prepared in a more atom-economic manner compared to triflates since the use of triflic anhydride is circumvented. The reaction conditions are similar to Hayashi's procedure, using either Cp*RuCl(cod) or [Cp*Ru(MeCN)$_3$]PF$_6$ as catalyst. Overall, a broad scope of (hetero)aryl and vinyl fluorosulfonates was investigated. As with Hayashi's procedure, *E/Z* mixtures of vinyl fluorosulfonates

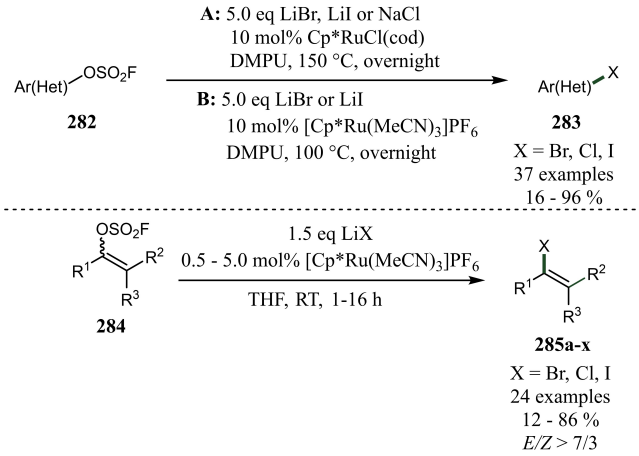


Scheme 82. Conversion of acyclic (*E/Z*)-vinyl triflates to (*E*)-vinyl halides.

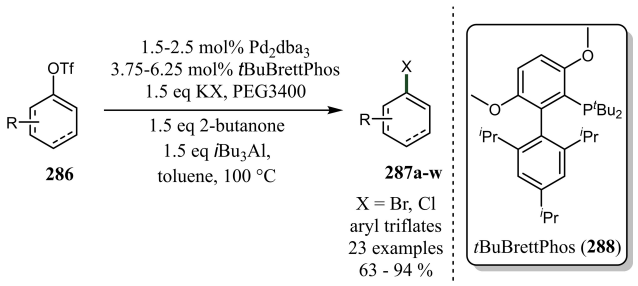


Scheme 83. Hell's synthesis of *N,N'*-di-*tert*-alkylrhodamines.

converged to *E*-vinyl halides during the reaction (Scheme 84).[100]



Scheme 84. Leroux' conversion of aryl and vinyl fluorosulfonates into halides.



Scheme 85. Buchwald's original procedure for Pd-catalyzed halogenation.

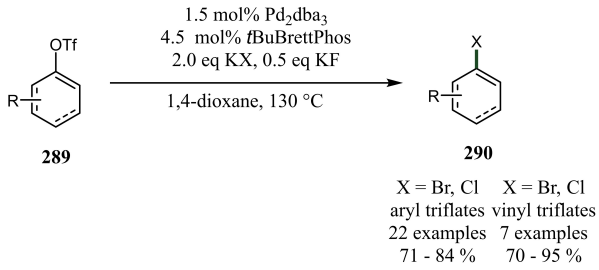
6.2. Pd-catalyzed Transformations

In 2010, the Buchwald group disclosed the synthesis of aryl chlorides and bromides under Pd-catalysis. Utilizing the bulky ligand *t*BuBrettPhos (**288**) and KCl or KBr as halide source, a wide array of aryl triflates containing electron-rich, electron-deficient as well as heteroaromatic compounds could be converted. Additionally, four vinyl triflates were successfully subjected to the same reaction conditions (Scheme 85).[91]

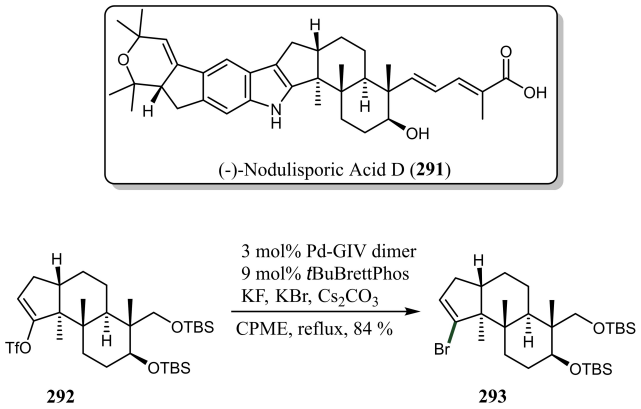
This procedure, however, was hampered by its complexity, since addition of phase transfer catalyst, 2-butanone and *i*Bu$_3$Al was necessary. It was therefore improved upon by the same group one year later. The authors found that use of KF as an additive significantly improved reaction efficiency (Scheme 86). Furthermore, ketones and esters, which had caused problems in the original procedure, were now well tolerated.[101]

This methodology was later exploited by Zou et al. in their total synthesis of Nodulisporic acid D (**291**). Triflate **292** was converted to the corresponding bromide **293** in excellent yield, using slightly modified reaction conditions (Scheme 87).[102]]

Here, the transformation of triflate to bromide was not strictly necessary, since the authors found that the



Scheme 86. Buchwald's improved procedure for Pd-catalyzed halogenation.



Scheme 87. Conversion of vinyl triflate to vinyl bromide during the total synthesis of Nodulisporic acid D.

subsequent cross-coupling/indole construction cascade worked similarly well with **292** and **293**.[102] However, it demonstrated the applicability of Buchwald's methodology to a complex intermediate in natural product synthesis.

An example where the transformation of triflate to halide was necessary was provided by Ji et al. in their total synthesis of Aristolactam BII. In the final steps of the synthesis, aryl triflate **294** was subjected to Buchwald's procedure. The resulting bromide could then be cyclized and to furnish the desired natural product (Scheme 88).[103]

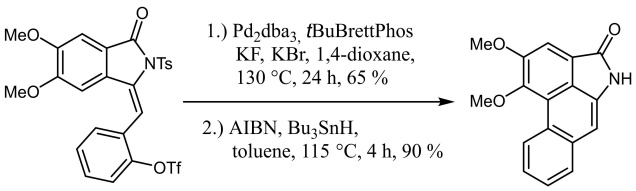
In contrast to Ru-catalysis, the preparation of aryl iodides from aryl triflates has not been reported for Pd-catalyzed reactions.

6.3. Ni-catalyzed Transformations

In 2019, the Reisman group reported a vinyl triflate-halide exchange reaction which uses a cheap and readily available Ni catalyst system. A wide array of cyclic and acyclic vinyl triflates could be converted into the corresponding chlorides, bromides and iodides (Scheme 89). While all three species were generally obtained in good to excellent yields, iodination was more challenging than bromination or chlorination. The authors observed that addition of catalytic amounts of DMAP and, in some cases, higher excess of NaI, was beneficial for the iodination reaction. They speculate that the role of DMAP is to coordinate ZnI_2 salts generated by the initial Ni^{II} reduction.[104] The reaction exhibited broad functional group compatibility, with amines, pyridines, esters, aryl chlorides and aryl boronates tolerated. Switching the catalyst to $Ni(cod)_2$ improved the yields for 1-arylvinyl triflates and resulted in selectivity for the vinyl triflate in presence of an aryl triflate group (Scheme 90). However, aryl bromides and iodides underwent competitive halide exchange reactions. Whether this procedure would also produce (*E*)-vinyl halides from (*E/Z*)-vinyl triflates was not investigated.[104]

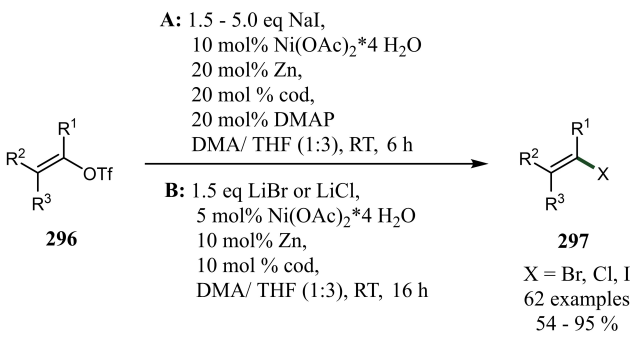
Nicolaou et al. employed Reisman's protocol during their total synthesis of Monolomaiviticin A (**301**). Cyclohexenyl triflate **302** was converted to iodide **303** in good yield (Scheme 91). This leaving group exchange was necessary to pave the way for a metal-halide exchange reaction with the vinyl iodide.[105]

An alternative approach was presented in 2020 by Hintermann and coworkers. They found that a Ni complex of diazine ligand **305** catalyzed the insertion of activated Zn powder into aryl tosylates. The organozincate so formed was quenched with I_2 in a one-pot reaction, delivering a set of aryl iodides (Scheme 92).[106] Electron-rich as well as electron-poor substituents, among them esters, nitriles and aryl chlorides, were tolerated in this reaction. While the authors laid their focus on aryl tosylates as substrate,



294 Aristolactam BII **295**

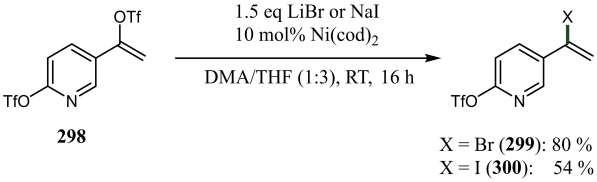
Scheme 88. Conversion of aryl triflate to aryl bromide during the total synthesis of Aristolactam BII.



296 **297**

X = Br, Cl, I
62 examples
54 - 95 %

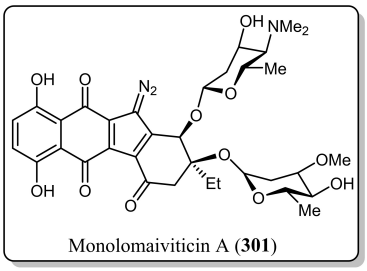
Scheme 89. Reisman's Ni-catalyzed halogenation of vinyl triflates.



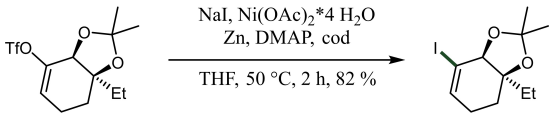
298

X = Br (**299**): 80 %
X = I (**300**): 54 %

Scheme 90. Selectivity of the reaction for vinyl triflate in presence of aryl triflate.

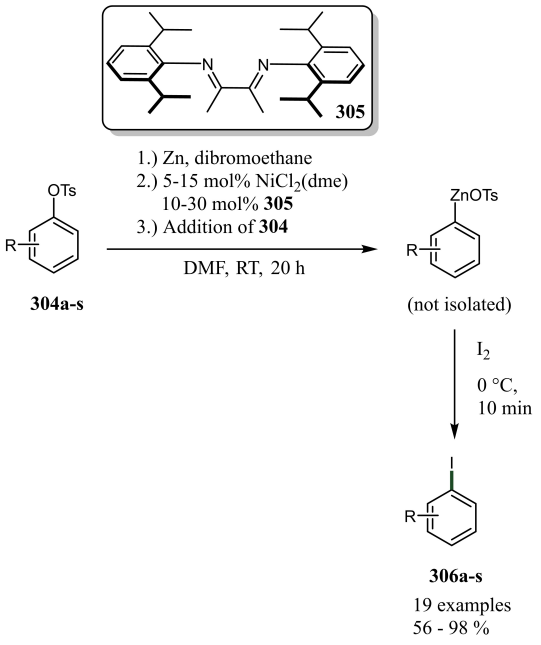


Monolomaiviticin A (**301**)



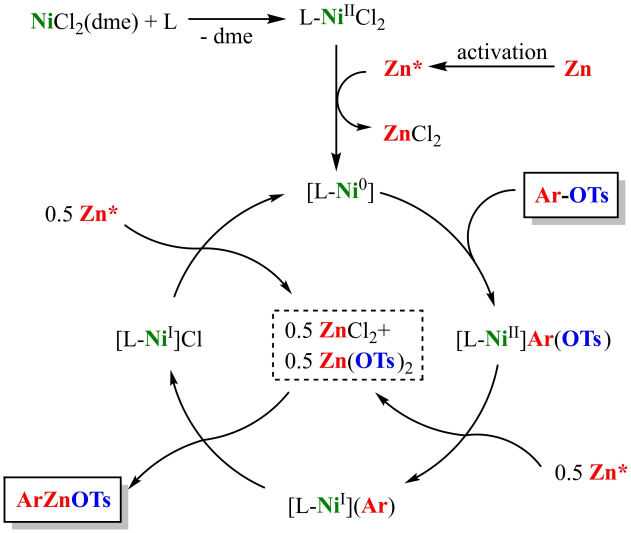
302 **303**

Scheme 91. Application of Reisman's procedure in the total synthesis of Monolomaiviticin A (**301**).



Scheme 92. Hintermann's Ni-catalyzed Zn insertion into aryl tosylates followed by iodolysis.

they demonstrated that insertion into naphthyl triflate is also possible. Furthermore, one aryl bromide was prepared by quenching the organozincate with NBS. The mechanism was proposed as shown in Scheme 93. The initial Ni^{II} catalyst is reduced to Ni^0 by activated Zn. After oxidative addition of the substrate to the Ni center, SET-reduction forms a Ni^I species. This then undergoes transmetallation with $Zn(OTs)_2$, releasing the organozincate intermediate. From the remaining $(L)Ni^ICl$, the Ni^0 species is regenerated via a second SET from Zn metal.[106]



Scheme 93. Proposed mechanism.

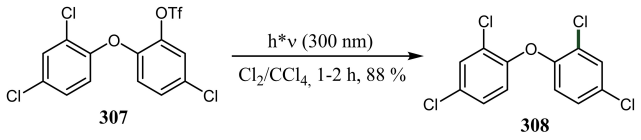
6.4. Photochemical Transformations

An early report on the photochemical conversion of aryl triflates to chlorides was put forth in 1990 by Chang et al. Four polychlorinated diphenylethers (PCDPEs) and one polychlorinated dibenzofuran (PCDBF) were synthesized from polychlorinated phenoxy phenol (PCPP) triflates. The reaction proceeded by irradition at 300 nm in a chlorine-saturated CCl_4 solution (see Scheme 94) and was limited to this particular substrate class.[107]

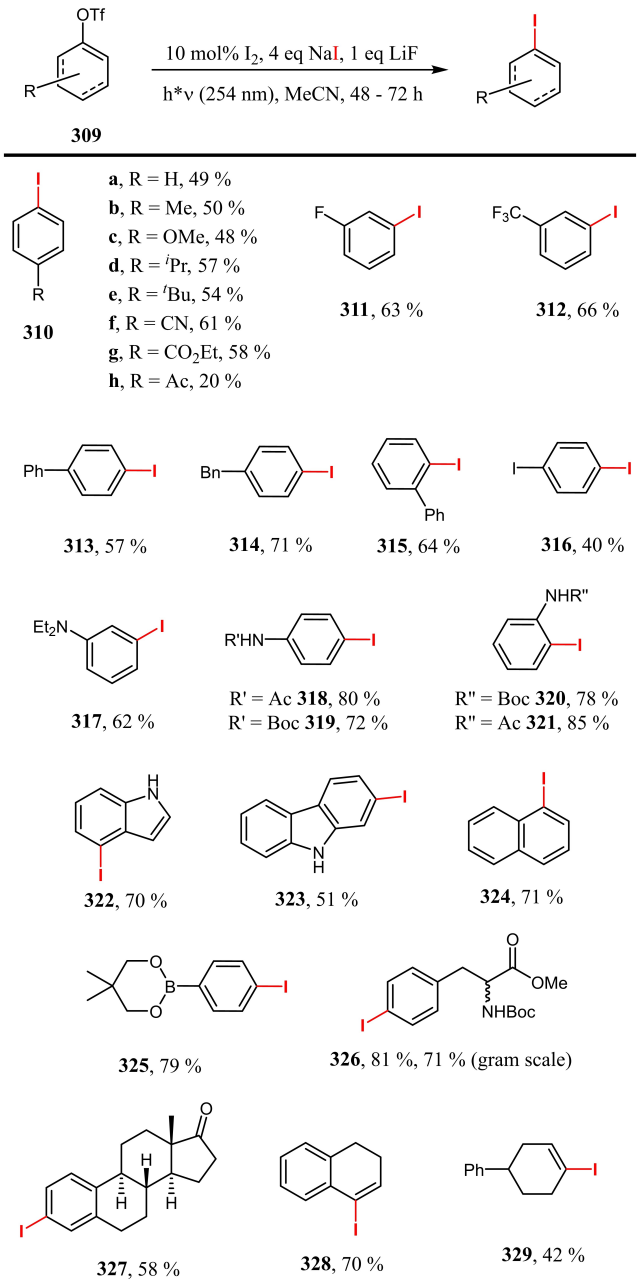
Seminal work on the generation of aryl or vinyl radicals from triflates was disclosed in 2017 by Li and coworkers. They found that simple NaI is uniquely suited in this regard as a soft electron donor that promotes homolytic cleavage of the C–O rather than the S–O bond. Irradiation (254 nm) of an MeCN solution of aryl or vinyl triflates in presence of NaI, LiF and catalytic I_2 resulted in formation of the corresponding iodides in decent to good yields. The transformation showed wide functional group tolerance and only in one case (**310 h**) a low yield was observed (Scheme 95).[108] In a similar manner, the authors were also able to convert aryl triflates into pinacol boronates when B_2Pin_2 and *N,N,N',N'*-tetramethyldiaminomethane (TMDAM) were used instead of I_2 and LiF. To date, Li's protocol is the only transition-metal-free option to convert triflates into boronates or iodides in a single step and under mild conditions. However, it requires some special equipment since ultra-pure argon and a photoreactor were used.[108] Surprisingly, the method has – to the best of our knowledge – not yet found its way into the synthesis of complex organic molecules.

7. Conclusion and Perspectives

Suzuki-Miyaura cross-coupling of aryl and alkenyl triflates is a widely utilized method for C–C bond formation. Compared to the corresponding halides, triflates offer the advantage of convenient accessibility from readily available phenols or ketones. However, identifying suitable coupling conditions can be more challenging for triflate substrates. Currently, the coupling of *ortho*-substituted or *ortho,ortho*-disubstituted aryl triflates as well as electron-poor heteroaryl triflates remains challenging in certain cases.



Scheme 94. Photochemical conversion of PCCP triflates to chlorides.



Scheme 95. Li's photochemical conversion of aryl and vinyl triflates into iodides.

Despite the widespread use of aryl and alkenyl triflates in cross-coupling reactions, there are few reports in the literature in which general coupling conditions applicable to a wider range of substrates were systematically explored. It is surprising that the common side reaction of triflate hydrolysis has not been investigated in more depth and is not fully understood yet. It seems that most users have applied an empiric screening approach identifying the ideal catalyst/base/solvent combination delivering the best yields for their own substrate. It appears that the success of these systems originates from the use of more reactive catalysts to accomplish the coupling before the concomitant hydrolysis reaction consumes the substrate significantly. In the future, a more in-depth analysis could reveal how the interplay of base, solvent and temperature is connected to the rate of triflate hydrolysis. Once conditions are found that consistently leave the triflate group untouched across a wider range of substrates, a versatile Pd catalyst that is less dependent on the specific substrate might be identified. A general trend seems to be that stronger bases and polar solvents facilitate the cross-coupling reaction already at lower temperatures, but at the same time triflate hydrolysis is also enhanced under these conditions.

The use of hydrolytically more stable nonaflates offers a very attractive alternative to triflates, which should deserve more attention as the current examples and our own experience indicate that the coupling yields are consistently better and at lower reagent costs.

Another strategic alternative is the conversion of the triflate substrate to a halide. Here considerable progress has been achieved over the last few years providing now good methods for the conversion of alkenyltriflates and some methods for aryltriflates. As these transformations require additional reaction steps, these approaches will be limited to special cases, in which the direct halogenation of the original substrate is not possible by established methods.

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