Université de Strasbourg

UNIVERSITÉ DE STRASBOURG

EDSC École Doctorale des Sciences Chimiques

ÉCOLE DOCTORALE 222

Laboratoire de Catalyse Chimique

Institut de Science et d'Ingénierie Supramoléculaires

THÈSE

présentée par :

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soutenue le : **03 Mai 2021**

pour obtenir le grade de : **Docteur de l'université de Strasbourg**

Discipline/ Spécialité : Chimie organique

The Suzuki Cross-Coupling of Aryl Sulfones and Sulfonyl Fluorides

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18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane	Et	Ethyl
acac	Acetylacetonate	g	Gram(s)
Ac	Acetyl	GC/MS	Gas chromatography – mass spectrometry
AcO	Acetate	h	Hour(s)
AcOH	Acetic acid	HOMO	Highest occupied molecular orbital
Am	Amyl	HRMS	High-resolution mass spectrometry
aq.	aqueous	Hz	Hertz
Ar	Aryl/Arene	*i*	*iso*
B3LYP	Becke-3-Lee-Yang-Parr	L	Liter / Ligand
BDE	Bond-dissociation energy	LUMO	Lowest unoccupied molecular orbital
Bu	Butyl	M	Molar / metal
Bn	Benzyl	*m*	Meta
°C	Degree Celsius	Me	Methyl
cat	Catalytic quantity	mg	Milligram
cod/COD	1,3-cyclooctadiene	mol%	Molar percent
Cy	Cyclohexyl	mmol	Millimole
dba	dibenzylideneacetone	mp	Melting point
DFT	Density Functional Theory	mL	Milliliter
Diglyme	2-Methoxyethyl ether	NCarb	*N*-Carbazole
DMF	Dimethyl formamide	Nu	Nucleophile
DMSO	Dimethyl sulfoxide	*o*	*ortho*
equiv	Equivalent	OA	Oxidative addition
EI	Electron impact	OTf	Triflate
ESI	Electrospray Ionization	OMs	Mesylate

p	*para*
ppb	Parts per billion
ppm	Parts per million
Pr	Propyl
PivOH	Pivalic acid
Py	Pyridyl/Pyridine
PyFluor	2-PyridineSO_2F
quant.	Quantitative
R^2	Coefficient of determination
ref	Reference
rt	Room temperature
s	Second(s)
S_EAr	Electrophilic aromatic substitution
SMC	Suzuki-Miyaura Coupling
S_NAr	Nucleophilic aromatic substitution
SuFEx	Sulfur Fluoride Exchange
t	*tert*
t	Time
T	Temperature
TC	Thiophene-2-carboxylate
TFA	Trfluoroacetic acid
THF	Tetrahydrofuran
Tol	Tolyl
Ts	*p*-toluenesulfonyl, tosyl
p-TsOH	*p*-toluenesulfonic acid
TS	Transition state
µ	Micro
v/v	Ratio by volume
w/w	Ratio by weight (mass)
X	Halide

ACKNOWLEDGEMENTS

I would firstly like to sincerely thank Prof. Joseph Moran for the opportunity to work on this project. His support and advice have been valuable to me during academic discussions, and I have learned a lot from him about presenting research the right way in academic papers or oral presentations. I also thank him for always trying to keep the work environment pleasant and not stressful despite the challenges we all face.

I would also like to express my gratitude toward Dr. Pawel Dydio, for the discussions that helped bring my projects forward, Prof. Chris Rowley, for helping me with the DFT and taking the time to teach me the basics, and Dr. David Leboeuf, for his advice on my last project.

I would also like to thank all the colleagues I have had throughout these years: Kamila, for tutoring me during my master's, and helping me get the MRT fellowship for my PhD; Abhijit, for helping me with my first project and for inviting me to your wedding in India; Cyprien, for your humor and your help in my second project, it was great to spend time with you; Daria, even though your internship was cut short by the pandemic, you were very hardworking and helpful; Lucas, with whom I've shared almost my entire time during my PhD, for the interesting discussions, your nice taste in music and all the fun we've had; Vuk, who always kept the lab organized, thank you for your good spirits, it was always entertaining to have you around; Anton, for winning at life; Jing, for always sharing your food with me; Shaofei, for teaching me interesting Chinese expressions; Robin, our favorite analytical person; Élodie, for your down to earth discussions; Joris, for the fun we've had during lunch; Ankita and Harpreet, for our nice coffee breaks in lab III18; Sophia, for your obsession with tidiness; Émilie, for making lab life more lively; Nick, for your valuable advice and for always inviting me to gatherings; Marie, for your help and advice; Florent, for your showmanship and unconventional way of seeing things;

Edward, Sreejith, Jan, Corinna, Quentin, Robert, Stefania, Andrei and Capucine for contributing to the lovely atmosphere.

Thanks also to the analytical team, Jean-Louis Schmitt, Cyrille Antheaume and Wahnyalo (our latest addition to the group), for going the extra mile to get an HRMS of a compound that won't ionize, help in the determination of a structure via NMR and most importantly care for the often-capricious analytical machines.

Lastly, thank you, Dr. Laurence Grimaud, Dr. Manuel Van Gemmeren and Prof. Patrick Pale, for taking the time to evaluate my manuscript and being part of my jury.

RESUME

1) Introduction

Cette thèse, divisée en trois chapitres, décrit le développement de deux méthodes de synthèse de molécules biaryliques en utilisant des électrophiles alternatifs dans la réaction de Suzuki catalysée au palladium.

La formation de liaisons carbone-carbone est une propriété essentielle à l'apparition de la vie sur terre, ainsi qu'aux avancées technologiques majeures, notamment en chimie pharmaceutique et en chimie des matériaux. Les méthodes de synthèse des liaisons carbone-carbone sont ainsi devenues indissociables de notre vie courante.

Une des méthodes les plus répandues pour former des liaisons carbone-carbone est la réaction de Suzuki-Miyaura.[1–3] En utilisant un catalyseur au palladium, une liaison est formée entre une molécule halogénée et une molécule borylée. La flexibilité de cette réaction a poussé les chimistes à développer des méthodes pour étendre son champ d'applications. Récemment, des méthodes substituant les halogènes par des composés alternatifs, notamment des arènes nitrés, ont été décrites.[4]

Ma thèse a porté sur le développement de catalyseurs permettant le couplage de Suzuki-Miyaura en utilisant des arènes soufrés (sulfones)[5] et sulfofluorés (fluorures de sulfonyle). Ces derniers présentent l'avantage d'être réactif en absence de base qui est normalement requise pour cette réaction.

Les sulfones ont attiré beaucoup d'attention de la part des scientifiques grâce à leur réactivité dans la réaction de Suzuki-Miyaura.[6–11] Ceci est dû à leur stabilité et à leur rôle de groupement directeur. Les sulfones aromatiques permettent des réactions de substitution électrophiles aromatiques *méta*-sélectives (par exemple, des nitrations, halogénations ou réactions de Friedel-Crafts).[12] Les sulfones permettent également des fonctionnalisations *ortho*-sélectives via lithiation,[7,13] et *para*-sélectives via alkylation catalysée au nickel.[14] L'hydrogène en α des sulfones benzyliques présente aussi des avantages : cette acidité peut donner lieu à des arylations, alkylations et fluorinations facilement.[6,8,10,15]

Les sulfones sont donc des groupements fonctionnels idéaux pour les réactions de couplage ; ils peuvent de plus être utilisés comme groupement directeur pour induire diverses transformations de manière sélective.

Les fluorures de sulfonyle sont une autre classe de molécules soufrées très robustes (à l'instar des autres halogénures de sulfonyle). Ils sont principalement utilisés dans des réactions dites « click » (c'est-à-dire des réactions très efficaces et sélectives) dans une branche de la chimie développée par Sharpless et baptisée SuFEx.[16,17] L'avantage de ces molécules est de ne réagir que dans des conditions réactionnelles très spécifiques qui sont orthogonales à beaucoup d'autres conditions réactionnelles, notamment la catalyse par métaux de transition. Cette thèse montre que ce n'est pas toujours le cas, puisqu'une méthode de synthèse a été développée pour le couplage de Suzuki-Miyaura à partir de ces molécules.

Parallèlement à ces travaux, mon étude sur la formation catalytique de liaisons carbone-carbone a permis des découvertes sur des possibles scénarios quant à l'origine de la vie sur terre (présenté en annexe). Il a été montré que des voies métaboliques pouvaient être reproduites sans enzymes, à partir de minéraux et de CO_2 dans des conditions proches de celles existant peu après la formation de la Terre.[18]

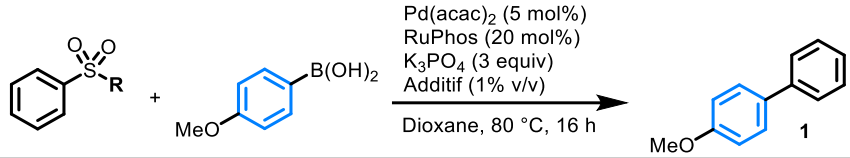
2) Résultats et discussion

a) La réaction de Suzuki-Miyaura en employant des sulfones (hétéro)aromatiques comme électrophiles

Nos premières études se sont concentrées sur l'identification d'arylsulfones capables de servir de partenaires de couplage (tableau 1). Lorsque le RuPhos a été utilisé comme ligand en présence de K_3PO_4, de $Pd(acac)_2$ catalytique et de DMSO, la diphénylsulfone a subi un couplage avec l'acide 4-méthoxyphénylboronique à 130 °C pour un faible rendement (entrée 1). La phénylméthyl sulfone et ses analogues mono- et di-fluorés ne se sont pas montré réactifs (entrées 2-4) ; en revanche, la trifluorométhylphénylsulfone a subi un couplage avec d'excellents rendements à une température modérée de 80 °C (entrée 5). La présence de DMSO comme additif s'est avérée importante pour avoir des rendements élevés (entrée 6). D'autres solvants polaires ont eu un effet similaire, bien que moindre (entrées 7-8). En revanche, un ligand sulfoxide bidentate a inhibé la réaction (entrée 9). Le DMSO n'a pas pu être

utilisé comme solvant (entrée 10), mais la réaction a pu être réalisée efficacement en l'absence de DMSO en utilisant de l'eau micellaire (entrée 11). Des groupements fonctionnels apparentés, tels que les trifluorométhylsulfoxydes ou les trifluorocétones, n'ont pas subi de couplage dans ces conditions.

Tableau 1 : Évaluation des paramètres réactionnels



Entrée	R	additif	Rendement 1 (%)[a]
1	Ph	DMSO	14[b]
2	CH_3	DMSO	<1
3	CH_2F	DMSO	<1
4	CHF_2	DMSO	<1
5	CF_3	DMSO	95
6	CF_3	-	55
7	CF_3	H_2O[c]	38
8	CF_3	HMPA	77
9	CF_3	$(PhSOCH_2)_2$[d]	5
10	CF_3	-	<1[e]
11	CF_3	-	90[f]

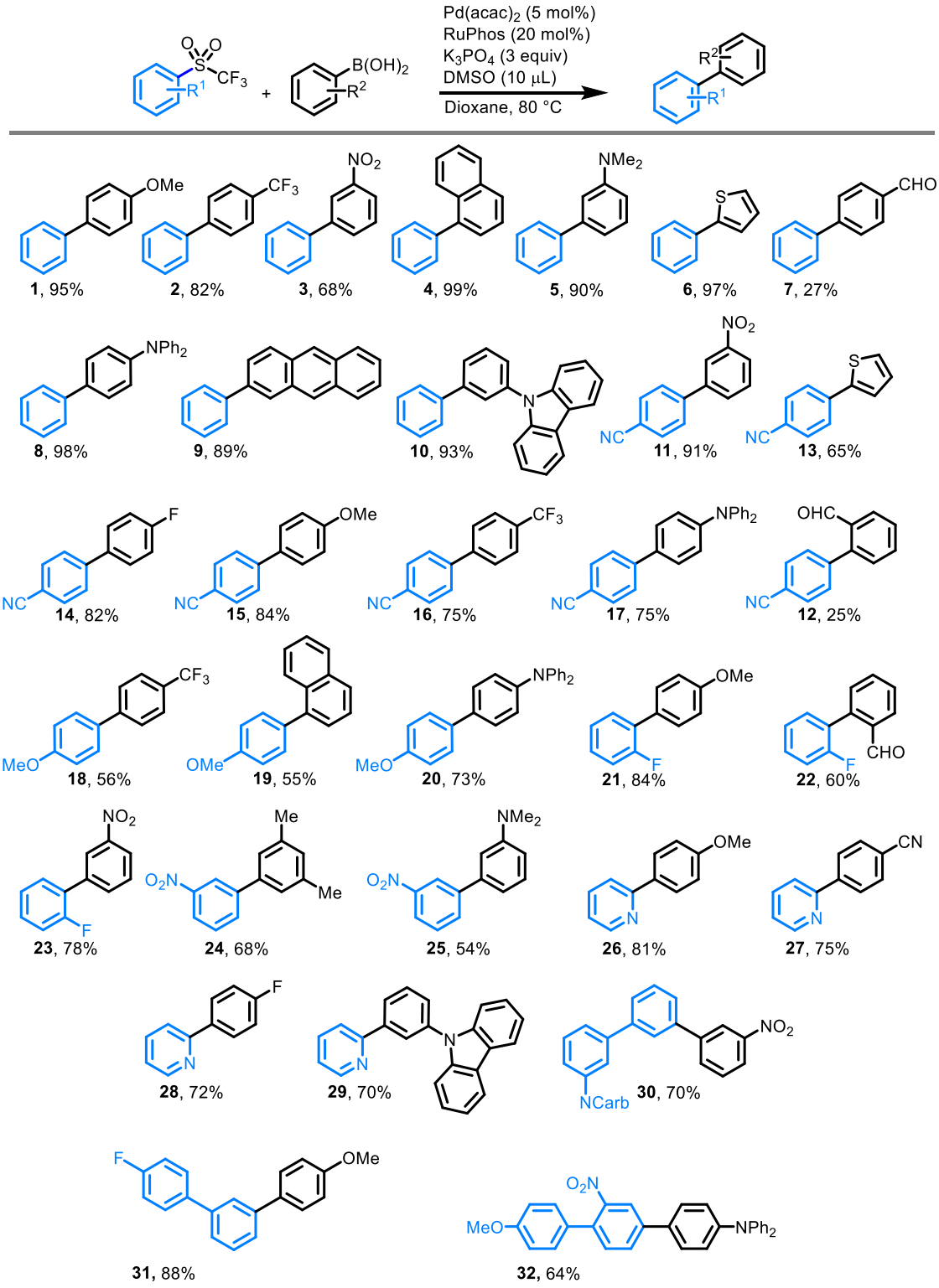
[a] Rendement isolé. [b] 130 °C. [c] 0.2% (v/v). [d] 50 mol%. [e] DMSO en tant que solvant. [f] Tocopherol methoxypolyéthylène glycol succinate (micelles) dans l'eau (2 % v/v) en tant que solvant. acac = acétylacétonate; DMSO = diméthyle sulfoxyde; HMPA = hexaméthylphosphoramide; RuPhos = 2-dicyclohéxylphosphino-2′,6′-diisopropoxybiphényl.

Les conditions optimisées ont ensuite été appliquées à une variété d'arylsulfones et d'acides arylboroniques (tableau 2). Les groupements électrodonneurs ou électroattracteurs ont été bien tolérés sur l'acide boronique ou sur la sulfone. Le couplage a été sélectif pour les sulfones par rapport aux groupes nitro (**3a**, **11a**, **23a-25a**, **31a**), ce qui ouvre la possibilité d'un couplage séquentiel utilisant la réaction de Suzuki sur les nitroarènes décrite récemment.[4] Les acides boroniques encombrés stériquement ont couplé avec d'excellents rendements (**8a-10a**, **17a**, **21a** et **29a**). Les acides boroniques dérivés du thiophène ont également été bien tolérés (**6a** et **13a**) à l'instar des acides boroniques dérivés de la pyridine.

La substitution par un fluor en *ortho* sur la sulfone n'a pas non plus altéré la réactivité (**20a**, **22a**, **23a**). Les 2-pyridyl-sulfones ont également couplé avec de bons rendements (**26a-29a**). Les sulfones substituées par des aryles en *meta* et *para* ont également couplé avec de très bons rendements (**30a** et **31a**). La principale limitation du champ d'application de cette méthode concerne les acides boroniques portant des

groupements aldéhydes, pour lesquels la réaction s'est produite avec des rendements nettement inférieurs (produits **7a**, **12a** et **22a**).

Tableau 2 : Champ d'application de la réaction



En profitant des conditions réactionnelles très différentes requises pour le couplage avec des chlorures d'aryle (22 °C, en utilisant le XPhos comme ligand), des arylsulfones (80 °C, en utilisant le RuPhos comme ligand) et des nitroarènes (130 °C, en utilisant le BrettPhos comme ligand), nous avons développé un protocole de couplage séquentiel pour la synthèse de terphényles et de quaterphényles non symétriques (schéma 1). Le couplage du groupement chloro d'une 2-chloro phénylsulfone avec de l'acide 3-nitrophénylboronique a donné le biphényle **s4**.

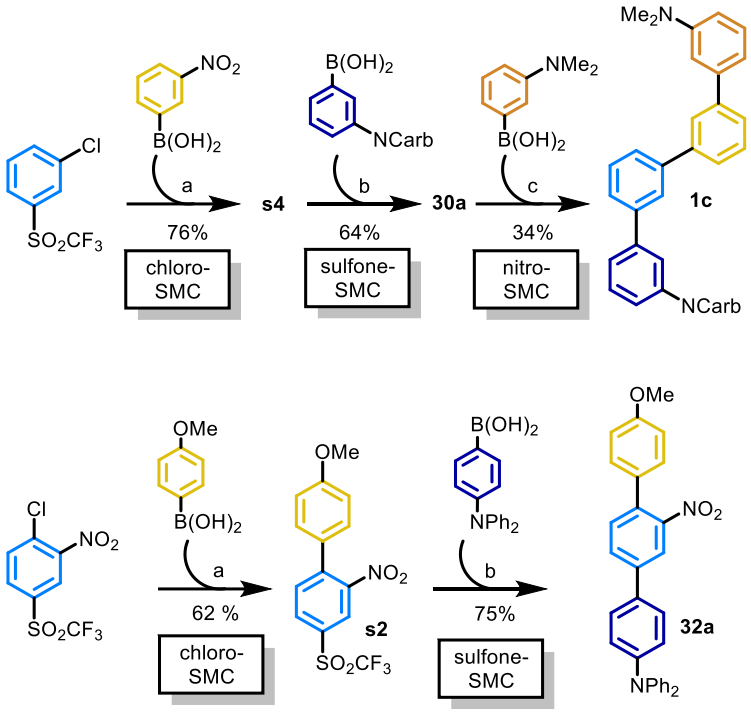


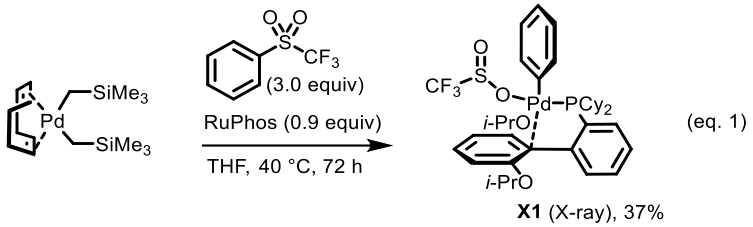
Schéma 1 : Couplage séquentiel pour la synthèse de ter- et quaterphényles

a: $Pd(OAc)_2$ (1 mol %), XPhos (3 mol%), K_3PO_4 (3 equiv), THF, 22 °C, 17 h; b: conditions standard; c: $Pd(acac)_2$ (5 mol%), BrettPhos (20 mol%), 18-crown-6 (10 mol%), K_3PO_4 (3 equiv), dioxane, 130 °C, 48 h. NCarb = *N*-carbazole.

Ensuite, le couplage du groupe sulfone avec de l'acide 4-*N*-carbazolephénylboronique a conduit au terphényle **30a**, avant un couplage final du groupe nitro pour donner le quaterphényle **1c**. Les groupes chloro, sulfone et nitro peuvent aussi être différenciés quand ils sont sur le même noyau aromatique, comme le montre un couplage chloro-sélectif du 1-chloro-2-nitro-4-((trifluorométhyl)sulfonyl)benzène pour donner le biphényle **s2**, suivie d'un couplage sélectif aux sulfones pour donner le produit **32a**.

Pour mieux comprendre le mécanisme, une réaction stœchiométrique entre le (1,5-cyclooctadiène)bis(triméthylsilylméthyl)palladium, un précurseur de Pd(0), et le $PhSO_2CF_3$ en présence de RuPhos a été effectuée pour isoler l'intermédiaire

réactionnel (produit d'addition oxydante) **X1** (eq. 1). La structure a été élucidée par diffraction aux rayons X et a révélé qu'après l'addition oxydante, le palladium est lié à l'oxygène du sulfinate. La structure est similaire à ce qui a été observé pour l'addition oxydante des halogénures d'aryles aux nitroarènes,[4] le palladium adoptant une géométrie « carrée plan ». L'extraction d'un mélange réactionnel brut typique (plus précisément, celui décrit dans le tableau 1, entrée 5) dans le D_2O a révélé la présence de trifluorométhanesulfinate comme étant le seul composé visible par RMN du ^{19}F. Par conséquent, bien que l'addition oxydante dans les chlorures de sulfonyle soit connue pour libérer du SO_2 et le chlorure, ici le groupe partant reste intact sous forme de trifluorométhanesulfinate.



(eq. 1)

L'intermédiaire **X1** a réagi avec l'acide 4-méthoxyphénylboronique à 25 °C (dans des conditions analogues à nos réactions de couplage) pour donner le composé **1** dans des rendements quasi quantitatifs, ce qui suggère que l'addition oxydante est l'étape limitante. Aucune différence significative de rendement n'a été observée en l'absence de DMSO : l'ajout du solvant joue vraisemblablement un rôle lors de l'addition oxydante ou lors d'une étape antérieure (pour la formation du catalyseur initial, par exemple).

Pour conclure, nous avons décrit le couplage de Suzuki des arylsulfones et une addition oxydante relativement rare du palladium dans la liaison C–S d'une sulfone. Les trifluorométhylsulfones présentent un niveau intermédiaire de réactivité de couplage entre celui des nitroarènes et des halogénures d'aryle, ce qui permet de synthétiser facilement des teraryles et des quaterphényles par couplage séquentiel de ces groupements fonctionnels.

b) La réaction de Suzuki en employant fluorures de sulfonyle (hétéro)aromatiques comme électrophiles

Nos premières investigations se sont concentrées sur l'identification de fluorures de sulfonyle capables de servir comme partenaires de couplage électrophiles. Lorsque le RuPhos a été utilisé comme ligand avec le $Pd(acac)_2$ en l'absence de base, le *p*-

tolylSO_2F a subi un couplage avec l'acide 4-méthoxyphénylboronique à 130 °C mais avec de faibles rendements. Malheureusement, les tentatives pour optimiser ce système catalytique n'ont pas eu d'effets bénéfiques.

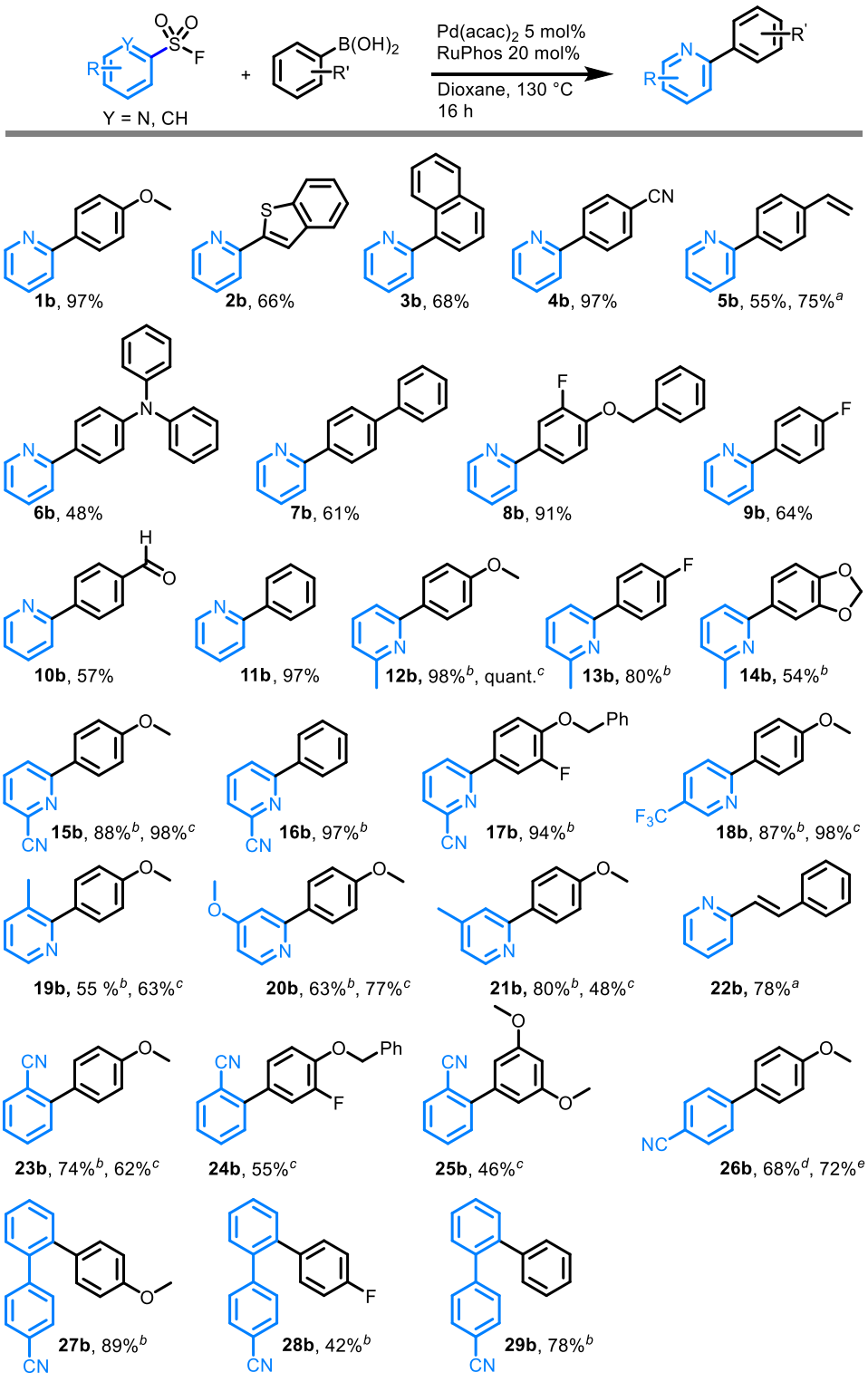
La 2-pyridineSO_2F (PyFluor) a ensuite été étudiée et, à notre grande satisfaction, a subi un couplage sans base dans les conditions décrites précédemment (tableau 4). Ces conditions se sont avérées optimales et ont ensuite été appliquées à une variété de fluorures d'arylsulfonyle et d'acides arylboroniques (tableau 3). Les groupements électrodonneurs ou attracteurs sur l'acide boronique ont bien été tolérés. La réaction a également bien fonctionné pour les acides boroniques portant des amines, des éthers benzyliques, des aldéhydes et des aldéhydes protégés.

Le dérivé 6-méthyle du PyFluor a réagi plus modestement. En raison de son effet positif sur le couplage des sulfones,[19] le Cu(IPr)Cl a été testé comme additif. Combiné au bifluorure de potassium, le Cu(IPr)Cl a conduit au couplage avec un excellent rendement (tableau 4). Il est intéressant de noter que l'ajout de bifluorure de potassium seul a légèrement inhibé la réaction, tandis que le Cu(IPr)Cl seul a donné des rendements très élevés, ce qui laisse supposer un effet synergique entre les deux espèces.

Ensuite, des efforts ont été faits pour trouver d'autres conditions permettant de réduire la charge du ligand. Un excès de RuPhos moins important (10 mol%) a été nécessaire lors de l'utilisation de PdG3-RuPhos [(2-Dicyclohéxylphosphino-2′,6′-diisopropoxy-1,1′-biphényl)[2-(2′-amino-1,1′-biphényl)]palladium(II) methanesulfonate] au lieu de $Pd(acac)_2$: une partie de l'excès de ligand est probablement nécessaire pour réduire le précatalyseur Pd(II) en une espèce Pd(0) active. Les autres fluorures de sulfonyle hétérocycliques n'ont pas réagi, ce qui nous amène à émettre l'hypothèse que le groupement 2-pyridyle oriente le Pd dans la liaison S-F proximale. Cela expliquerait la performance plus faible du dérivé 6-méthyle, qui est légèrement plus encombré au niveau de l'azote. Le dérivé 6-MeO a conduit à une faible conversion en raison de son fort encombrement stérique par rapport à l'azote : la 2-MeO-pyridine existe principalement dans la conformation *cis* qui est encombrée.[20]

Les fluorures d'arylsulfonyle non hétérocycliques ont également donné de bons résultats dans le cas d'une substitution par des groupements cyano ou aryle en position *ortho,* probablement en raison des effets de groupe directeur.

Tableau 3 : Champ d'application de la réaction



[a]6 h. [b]Additifs: Cu(IPr)Cl (2.5 mol%) et KHF_2 (50 mol%). [c]Avec PdG3-RuPhos (5 mol%), RuPhos (10 mol%) en tant que catalyseurs. [d]Avec $Co(acac)_3$ à la place de Cu(IPr)Cl. [e]Avec PdG3-RuPhos (5 mol%), RuPhos (10 mol%) en tant que catalyseurs.

Le dérivé *para*-cyano a couplé avec de bons rendements lorsque $Co(acac)_3$ a été utilisé comme additif au lieu de Cu(IPr)Cl, ce qui montre que les groupements directeurs ne sont pas forcément nécessaires pour coupler des fluorures de sulfonyle. L'activité du cobalt dans la réduction des sulfones a déjà été décrite, ce qui peut expliquer son implication dans l'activation de la liaison C–S.[21] Cependant, l'ajout de $Co(acac)_3$ à d'autres substrats a conduit à des rendements plus faibles par rapport au co-catalyseur Cu(IPr)Cl. Enfin, l'utilisation du PdG3-RuPhos comme alternative a généralement conduit à des rendements équivalents ou légèrement supérieurs, sauf pour le dérivé 4-picolyl où il a conduit à un rendement modéré.

Les premières études sur le mécanisme de cette réaction ont été réalisées en soumettant le PyFluor à ses conditions de couplage standard en présence d'un autre électrophile efficace pour la réaction de Suzuki (PhCl ou $PhSO_2CF_3$). Le couplage n'a été observé que sur le PyFluor ; l'autre substrat est resté intact à la fin de la réaction, bien que la température soit beaucoup plus élevée que celle généralement requise pour le couplage des chlorures d'aryle à l'aide de ligands de type Buchwald.[5] Le bromobenzène, plus réactif, a inhibé la réaction, mais aucun couplage n'a été observé sur ce substrat. Ces résultats indiquent que la formation de l'intermédiaire Pd-F est irréversible ou que l'étape de transmétallation se produit relativement rapidement après sa formation. Ils confirment également que cette réaction est exempte de base : le groupe pyridine sur le substrat ou le produit de couplage croisé ne semble pas suffisamment basique pour engendrer la transmetalation avec les autres substrats.

En résumé, malgré leur stabilité généralement admise pour la catalyse par les métaux de transition, les fluorures d'arylsulfonyle ne sont pas inertes en ce qui concerne l'addition oxydante : Ils peuvent être utilisés comme électrophiles dans la réaction de Suzuki même en utilisant des catalyseurs simples tels que $Pd(PPh_3)_4$. Nous avons montré que le couplage se produit sans aucune base exogène et même dans des conditions fortement acides. Nous prévoyons que ces résultats contribueront à de nouveaux développements dans la synthèse divergente à partir des fluorures de sulfonyle, ainsi qu'à éclairer les réactions catalysées par les métaux de transition qui ont échoué, supposant l'orthogonalité des fluorures de sulfonyle par rapport à ces conditions réactionnelles.

3) Conclusion générale

Pour conclure, cette thèse décrit le couplage Suzuki de deux électrophiles robustes à base de souffre (les sulfones et les fluorures de sulfonyle), qui offrent des avantages synthétiques distincts par rapport aux électrophiles développés précédemment pour cette réaction. Ils présentent tous deux un ordre de réactivité distinct qui se différencie facilement des autres électrophiles, ce qui a été exploité dans la synthèse de molécules polyaromatiques. Les sulfones peuvent en outre être utilisées comme groupe directeur pour une variété de transformations avant leur effacement ultérieure par couplage. Ceci conduit à un avantage synthétique significatif par rapport à d'autres groupes directeurs qui sont généralement gênants à éliminer ou à exploiter dans une fonctionnalisation ultérieure. Le couplage des fluorures de sulfonyle présente l'avantage majeur d'être complémentaire à la formation de la liaison S - N très bien établie dans la chimie SuFEx, faisant du groupe -SO_2F un point de divergence dans la synthèse de liaison C–C et S–N.

I. Introduction

1.1 Background: Carbon-Carbon bond formation

Carbon is a unique element due to its ability to form stable bonds with itself and other atoms in long and ramified chains. This leads to an almost infinite possibility of carbon-based, or *organic*, molecules. The properties of carbon are also at the root of the emergence of life: The genetic information, structural components, as well as the energy of living organisms depend on the carbon-carbon bond. In consequence, before the advent of organic synthesis in the early 1800s, organic molecules were strictly defined as being derived from living organisms. In the modern era, organic matter was extended from living or life-derived materials to man-made synthetic matter – which are now ubiquitous in our daily lives. Pharmaceuticals, dyes, synthetic fabrics, and plastics are all based on the study of the carbon-carbon bond: an essential field of chemistry known as *organic chemistry*. The high stability of the carbon-carbon bond, however, has made the synthesis of organic molecules exceedingly challenging, leading chemists to continuously develop new methods for their construction since the mid-1800s.

The Wöhler synthesis in 1828 converting inorganic cyanate into urea is widely regarded as the starting point of organic chemistry.[22] The second half of the 19th century then saw many milestones in organic chemistry and C–C bond forming reactions such as electrophilic aromatic substitution (used in the synthesis of salicylic acid)[23,24] aldol condensation,[25,26] culminating with the Grignard reaction in 1900.[27] The uses of magnesium in C–C bond formation, however, predates the Grignard reaction and was already reported in 1859 with the pinacol reaction, the earliest example of a coupling reaction.[28]

1.2 History of Coupling Reactions

A coupling reaction can be defined as a reaction joining two molecular fragments with the aid of a metal. Using a reducing metal, the pinacol reaction combines two aldehydes to form a 1,2-diol linkage. In spite of its archaic nature, it has found uses as a key step in the total synthesis of Taxol, an important anti-cancer drug.[29] Its modernized variant, the McMurry reaction, uses a high-valent titanium salt and a reductant to combine the C–C bond formation with a de-oxygenation step, forming the corresponding alkene.[30,31] It has found widespread use in the synthesis of natural products as well as unusual macrocyclic molecules, notably in Feringa's molecular motors.[32,33]

In 1869, ten years after the discovery of the pinacol reaction, Glaser reported the oxidative homocoupling of terminal alkynes to form symmetrical diynes in a reaction mediated by copper, using oxygen or air as an oxidant.[34] Ullman later discovered the homocoupling of aryl halides in 1901 using stoichiometric copper.[35] It is the earliest reported method for the formation of biaryls. Unfortunately, the high reaction temperatures and the lack of selectivity to form unsymmetrical biaryls limit its scope: like the earlier Glaser coupling, it is mostly useful in the synthesis of symmetrical molecules.

Apart from a major improvement in the coupling of alkynes – the Cadiot–Chodkiewicz coupling,[36] a cross-coupling version of the earlier Glaser coupling – the 20th century saw little breakthrough in coupling chemistry until the 70s, where all the essential cross-coupling reactions we know today were developed in a single decade: from the Kumada coupling in 1972 to the Suzuki reaction in 1979. Cross-coupling reactions have had a vast impact on organic synthesis and were the object of the 2010 Nobel prize in chemistry, awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.[37]

- The Kumada coupling

The Kumada coupling can be touted as the first general-purpose cross-coupling reaction. It employs a transition-metal catalyst to cross-couple an organomagnesium halide (a Grignard reagent) with an organohalide, typically sp^2 or sp^3 hybridized.

While Kharash and Fields discovered the coupling of Grignard reagents with organohalides using various catalytic metal salts as early as 1941,[38] Kumada, and to a lesser extent, Corriu, greatly enhanced its scope and applicability as a synthetic method by using nickel catalysts.[39,40] In Kumada's initial report, various aryl and alkyl Grignard reagents were cross-coupled to alkenic and arylic halides in excellent yields. Even with the inherent limitations imposed by the high reactivity of Grignard reactants, the Kumada coupling has been widely employed and explored in recent years, leading to an ever more versatile synthetic method. Asymmetric cross-couplings starting from racemic compounds have been disclosed, and its scope has been extended to functional groups that are typically sensitive to Grignard reagents (such as esters), thanks to Knochel's pioneering work.[41–44] The *in-situ* formation of Grignard reagents and subsequent coupling has even been reported in aqueous media,[45] showing that the Kumada coupling is still far from its full potential.

- The Heck reaction

The Heck reaction is a palladium catalyzed cross-coupling between an alkene and, typically, an aryl or alkenyl halide, although the scope of this reaction has been extended to several other functional groups including acyl and sulfonyl chlorides as well as alkyl halides bearing no β-hydrogen.[46] It was first reported in 1971 by Mizoroki[47] and later by Heck in 1972,[48] building on previous reports of the same reaction using stoichiometric palladium.[49,50] Because of its wide scope, this reaction revolutionized the synthesis of alkenes and is one of the most widely used methods for the formation of C–C bonds via transition-metal catalysis. It has seen extensive use as a key step in the total synthesis of natural products, mainly in its intramolecular variant,[51] as well as in the pharmaceutical, agrochemical and polymer industries.[52,53]

- The Sonogashira reaction

The Sonogashira reaction can be considered as the alkynyl analogue of the Heck reaction: it couples an aryl or vinyl halide to a terminal alkyne. Like the older work by Glaser on alkyne coupling presented previously, it employs a copper catalyst but also requires palladium. This reaction was discovered independently by Sonogashira,

Cassar, and Heck in 1975, a few years after Heck's initial publication on the coupling of alkenes.[54–56] While Sonogashira published his results one month after the initial reports by Cassar and Heck, his method employing copper as a co-catalyst allowed for the reaction to proceed under much milder conditions, at room temperature instead of 100 °C. The "Sonogashira reaction" then became a blanket term to describe couplings with terminal alkynes, even those that were later optimized to avoid the addition of copper, building on Cassar's and Heck's works rather than Sonogahira's. It remains a highly relevant synthetic method today, as exemplified by its use in the industrial production of the antifungal terbinafine (Lamisil ®).[52,53] Therefore, it continues to be the focus of studies to find alternative catalysts, notably to avoid the Glaser-type side products that spoil the often costly alkyne starting materials. Thus, much effort has been made to avoid the use of copper, but methods using catalytic copper only, avoiding the use of expensive palladium, have also emerged.[57–59]

- The Negishi coupling

This method can be seen as an improvement of the earlier Kumada coupling, employing the more selective organozinc species as an alternative to Grignard reagents. The coupling of aryl and benzylic zinc compounds was first reported in 1977,[60] followed shortly by a publication describing its applications in the coupling of alkynes, displaying tolerance to esters.[61] Overall, compared to the Kumada coupling, the Negishi coupling displays a lower sensitivity to air and moisture and a higher functional group tolerance. Unlike the Kumada coupling, early versions of the method were already tolerant to oxo, nitrile, and ester groups.[37] Highlighting the importance of this reaction: despite being largely superseded by the more versatile Stille and Suzuki couplings, its higher reactivity makes the Negishi coupling superior to the latter for the synthesis of some complex natural products,[62–64] and there is at least one example of its superiority to the Suzuki coupling on an industrial reaction. In the synthesis of a phosphodiesterase inhibitor on a 4.5 kg scale by Novartis, the Negishi coupling was more succesful.[53,65] Negishi studied many aspects of palladium catalyzed reactions, discovering the coupling of many alkyne metal derivatives with aryl halides. Most importantly, he discovered the reactivity of organotin, organoboron

and organosilicon species in 1977,[66] the principles of which were used in the later Stille, Suzuki and Hiyama couplings.

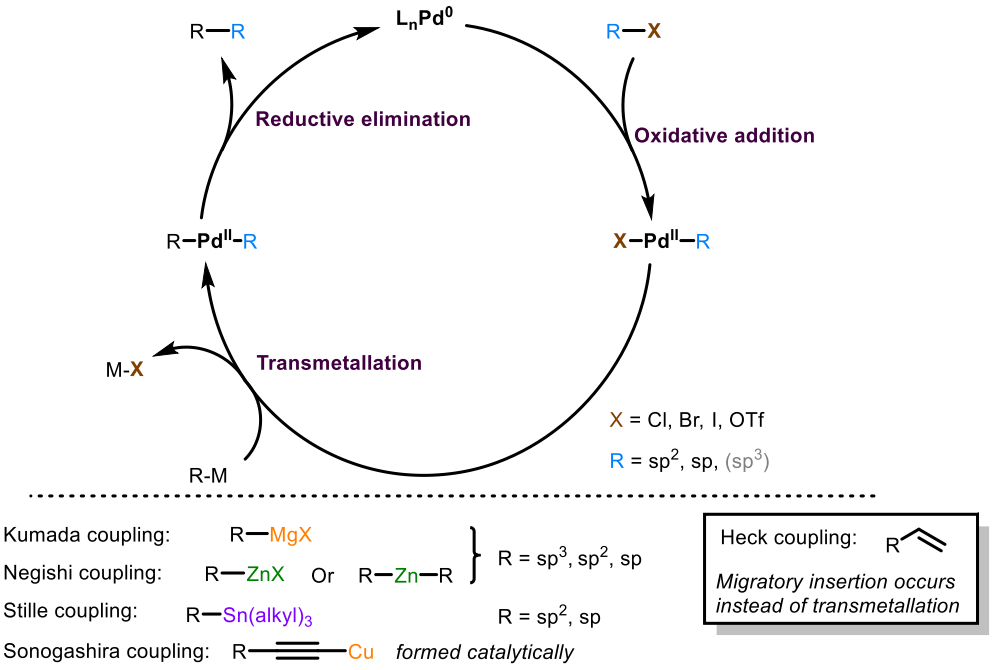


Figure I.1: General mechanism and summary of cross-coupling reactions

- The Stille coupling

The Stille coupling is a cross-coupling reaction typically occurring between an organotin (or stannane) compound and a halide. Building on a report from 1976 involving the palladium catalyzed homocoupling of aryl stannanes formed *in situ*,[67] Migita and Kosugi reported several Pd-catalyzed cross-coupling reactions with stannanes in 1977. The alkylation, allylation and arylation of acyl chlorides was reported, as well as the allylation of several aryl halides.[68–70] Stille later improved those methodologies and started elucidating their mechanism in 1978 and ’79. The coupling reaction occurred in very good yields under milder conditions, using low catalyst loadings.[71–73] The main advantage of the Stille reaction over the Negishi coupling is its relative lack of sensitivity to air and moisture, as well as the stability, easy preparation, and purification of stannanes. Its main disadvantage is the use of tin compounds, the toxicity of which has caused the Stille coupling to dwindle in favor of the non-toxic organoboron compounds of the Suzuki reaction. However, the high

selectivity and versatility of this reaction is still relevant in industry and total synthesis today, where the Negishi and Suzuki couplings sometimes fail to achieve the anticipated results.[74,75] Scientists at Pfizer reported that the Stille coupling was the only suitable coupling method in the large-scale synthesis of an imidazole−thienopyridine intermediate for a potential anticancer drug, despite the toxicity of tin which makes this reaction generally less suited for pharmaceutical compounds.[76]

1.3 The Suzuki Cross Coupling, background

The Suzuki reaction is a palladium catalyzed cross-coupling reaction between an organoboron reagent, typically a boronic acid, and, usually, an organohalide (-I, -Br, -Cl) or triflate (-OTf). It is one of the preferred methods for the formation of C–C bonds, mostly in the synthesis of biaryls.[1–3]

The first reports of the Suzuki reaction date back to June 1979,[77,78] disclosing a palladium catalyzed cross-coupling reaction between alkenyl boron compounds and alkynyl, alkenyl or aryl halides, yielding enynes, dienes or styrenes, respectively (Figure I.2 A). The scope of this reaction quickly grew to include allylic and benzylic bromides,[79] and by 1981 Suzuki reported what is today the most common use of the Suzuki reaction: the formation of biaryls using boronic acids (Figure I.2 B).[80]

Since its early discovery, the Suzuki reaction has been one of the most valuable methods for the formation of biaryls and by the year 2014 it became the second most common synthetic method used in total synthesis or medicinal chemistry papers.[81]

This is largely due to the use of boronic acids as nucleophiles, which present substantial advantages over the other nucleophiles in alternative cross-coupling reactions. The toxicity of stannanes in the Stille coupling and their lower reactivity are major drawbacks, just like the sensitivity and low selectivity (*i.e*. lower scope) of the organomagnesium and organozinc compounds used in the Kumada and Negishi couplings. Boronic acids on the other hand are non-toxic and are stable to air and moisture.[82]

Another important property of boronic acids that has led to the extensive use of the Suzuki coupling is that they are almost always solids and have a long shelf life. Along with their lack of toxicity, it has led to the vast industrial production of these derivatives due to their ease of transport, storage, and handling. To give a relevant example, there are as of today [15-01-2021] 647 different commercially available boronic acids on the Sigma-Aldrich website.[83]

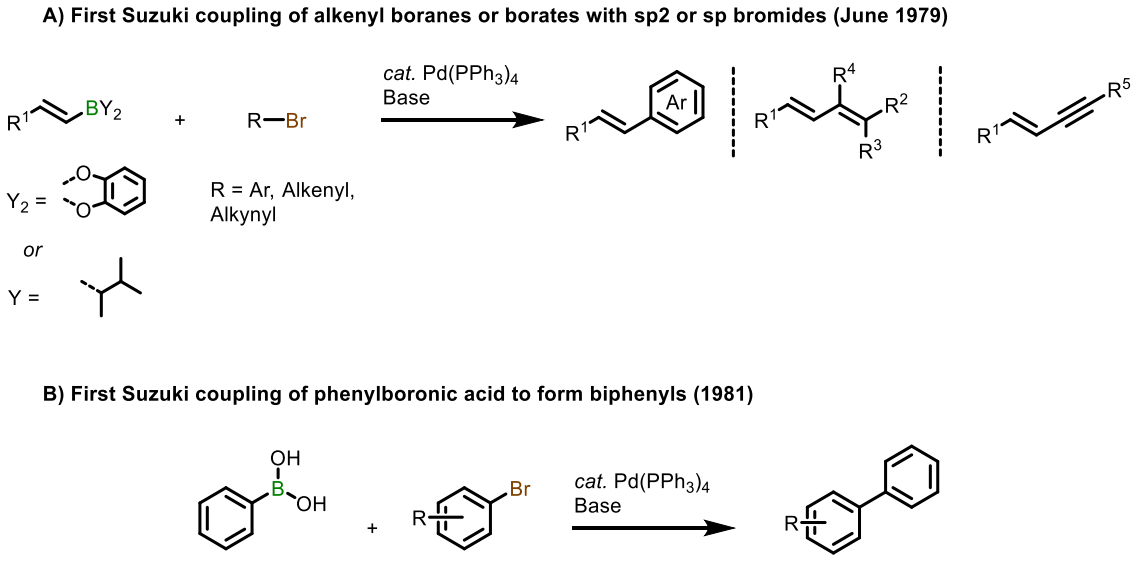


Figure I.2: Early reports of the Suzuki reaction.

The high number of commercially available boronic acids has driven its development in academia, and numerous improvements have been made since its initial discovery. First, the scope of the reaction has greatly improved. Early reports focused on sp^2 (or sp) hybridized coupling partners, but the scope of this reaction has been extended to enable alkyl-alkyl or alkyl-aryl couplings in excellent yields, selectivity, and in mild conditions, as illustrated by its use in natural product synthesis.[1,84–86] It has also been extended to substrates such as heterocycles, and coupling can occur at room temperature with hindered substrates and challenging electrophiles using very low catalyst loadings.[87] In-depth discussion of challenging and alternative electrophiles for the Suzuki reaction is made in chapter 1.6. The high versatility and reliability of this reaction has made it easily scalable and it is now routinely used in industrial processes.[52,53,88,89]

Many alternative catalysts have also emerged as cheaper alternatives to palladium. The nickel catalyzed variation is now well established,[90–92] and copper-catalyzed variations have also appeared,[93] as well as a few reports using cobalt,[94–96] and even iron.[97–99]

It would be unfair to not put the previous paragraphs into context by mentioning the drawbacks, or limitations of this reaction. The main limitations of boronic acids lies in their protolytic deboronation (Figure I.3 A).

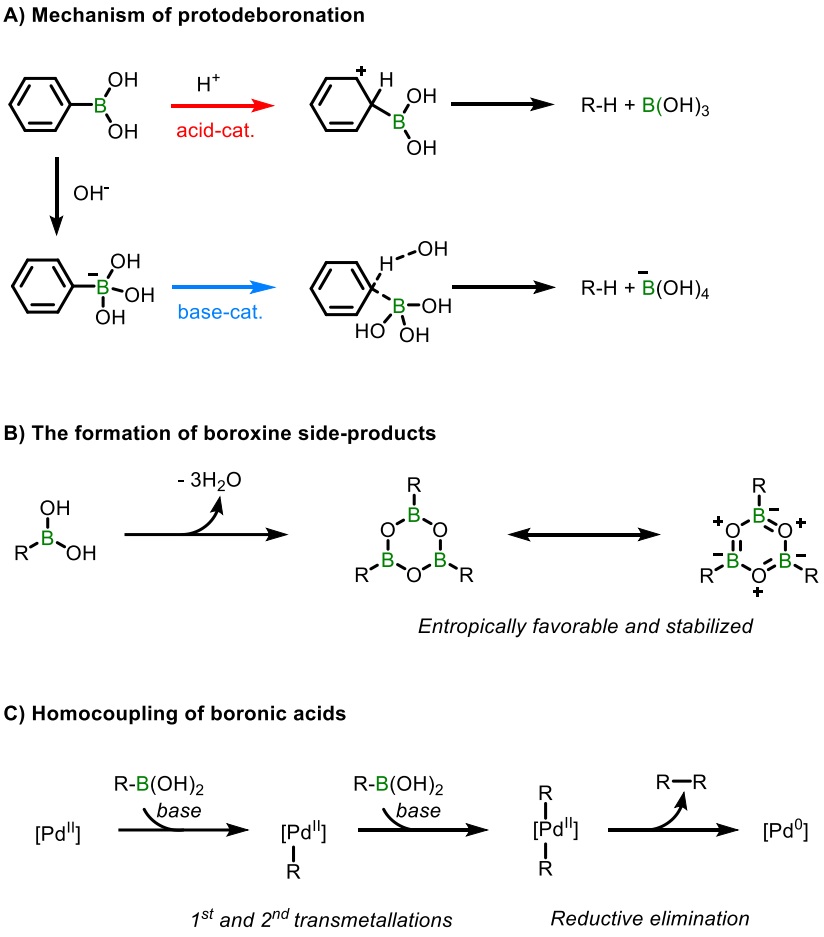


Figure I.3: Main side reactions related to boronic acids

In basic or acidic media, boronic acids slowly decompose to the parent arene, and heterocyclic boronic acids are especially sensitive.[82,100–102] The preparation of these substrates can also cause some issues: their anhydrides, or boroxines, typically form during their synthesis (Figure I.3 B) and it can be difficult to separate them from the wanted compounds.[82,89] Although they are similarly reactive in the Suzuki coupling,[103] their much higher molar mass can make stoichiometry calculations less precise.[82,89] Boronic acids are also somewhat prone to homocoupling in the presence of air (Scheme 3C) or oxidation to the corresponding phenol.[82] These side reactions can be circumvented by the use of other boron reagents such as boronic esters, boronates or trifluoroborates.[82] As mentioned previously, there are rare cases where the Negishi and Stille coupling are still preferred to the Suzuki reaction. Still, the limitations of the Suzuki reaction are trivial in comparison to these earlier methods, which justifies its more widespread use today.

1.4 Mechanism of the Suzuki reaction

1.4.1 General mechanism

The mechanism of the Suzuki reaction occurs in a catalytic cycle.[2,3,104,105] Like the other palladium catalyzed cross-coupling reactions discussed in chapter 1.2, three major steps are responsible for the formation of the C–C bond: oxidative addition, transmetalation and reductive elimination, as depicted in Figure I.4.[87,104] For clarity, and because the present thesis is about biaryls, the mechanism uses the coupling between bromobenzene and phenylboronic acid as a representative example, as will the following discussion. The reader should bear in mind that this reaction is of course a much more powerful synthetic method than what can be inferred from this example and should refer to the previous subchapter for a broader overview of this reaction.

The first step is the oxidative addition of a palladium (0) catalyst into the aryl halide bond. In this step, the palladium formally "gives" one electron to the aryl group and to the halide, forming a palladium (II) complex, bound to the halide and the aryl group. Hence the name *oxidative* addition. With the aid of the base or fluoride, a transmetalation occurs.[2,87] In essence, the phenyl group attached to the boron atom gets transferred to the palladium (II) center, substituting the halide or the oxygen species bound to the palladium.

The role of the base is essential for the transmetalation to occur and there are two major pathways in which it has been postulated to be involved. It can either "activate" the boronic acid by forming a boronate or form an oxo-palladium species via ligand substitution, which enhances the rate of transmetalation.[3,82,106] The concurrence of these two pathways was also suggested, depending for the most part on the conditions used.[82] Lastly, the reductive elimination forms the biaryl linkage and regenerates the Pd(0) catalyst. Each step has been shown to occur in a variety of ways, depending on substrate, catalyst or conditions used. The next subchapters will focus on the precise mechanism of each step.

The rate-determining step of the Suzuki reaction was initially thought to be the oxidative addition for aryl bromides, and for aryl iodides, transmetalation.[105] Later studies however, veered towards transmetalation,[107] or reductive elimination.[108]

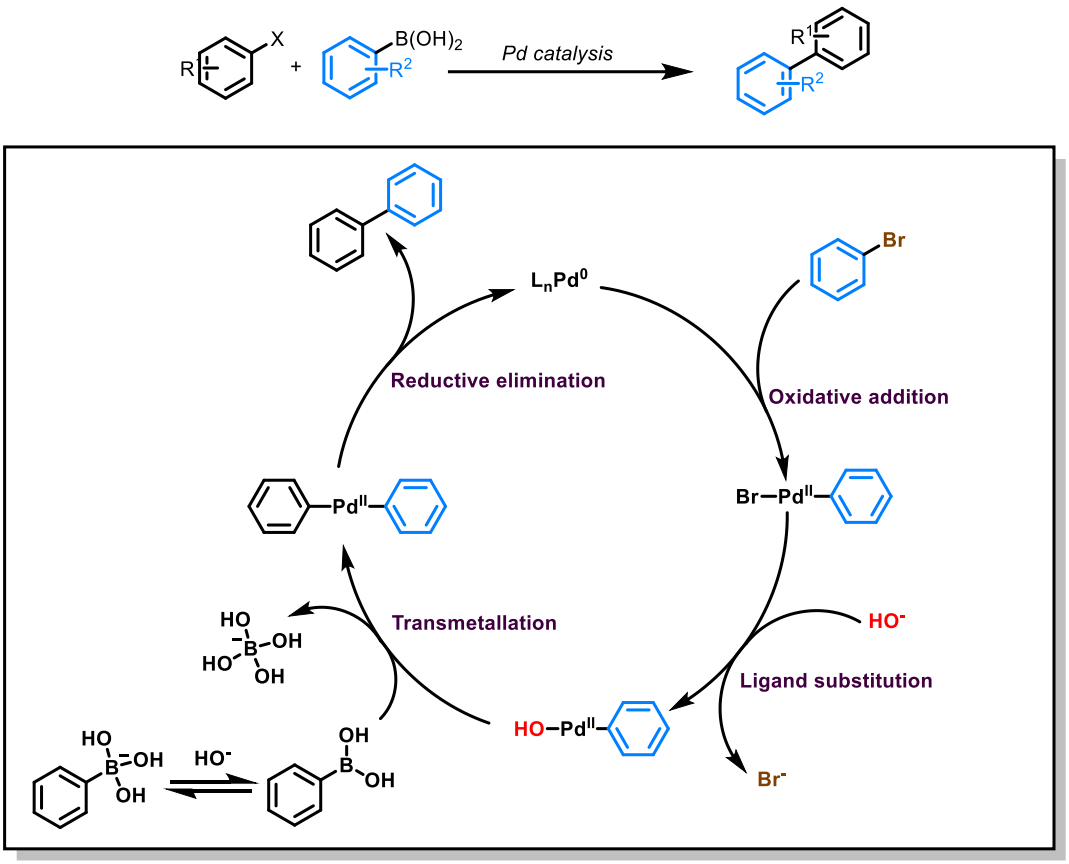


Figure I.4 Catalytic cycle of the Suzuki reaction using a representative example and general scheme of the reaction (ligands omitted for clarity).

Even for the more challenging aryl chlorides, according to a recent study, oxidative addition is not rate-limiting.[109]

An initial mono-ligated palladium (0) complex has been suggested to be the active catalyst for this reaction.[110] Starting from a palladium (II) precatalyst such as $Pd(OAc)_2$ is common and forming the active species requires its reduction. It usually happens through the homocoupling side-reaction of boronic acids (depicted in Figure I.3 C)[82] or by the base-mediated oxidation of a phosphine ligand to form a phosphine oxide.[111,112] The following step involves the spontaneous de-ligation of the stable tetra-coordinated palladium complexes into unstable, transient di-ligated or monoligated species.[113] Therefore, the ligands used in this reaction must be sufficiently labile. This explains the use of bulky phosphine ligands, which have been shown to exhibit a more rapid catalyst initiation.[110] The choice of precatalyst, the order of addition of reagents, as well as the mode of reduction and the presence of base have all been shown to have

an impact on catalytic activity by changing the way that the precatalytic species is formed.[110,111,114,115]

1.4.2 Oxidative addition

In this step, the Pd^0 catalyst oxidatively inserts into the aryl halide bond to form an R-Pd(II)-X complex.[2] Due to its occurrence in all palladium-catalyzed cross-coupling reactions, many studies have focused on elucidating its mechanism.

Several different pathways are thought to be involved in its mechanism, depending on the substrates used.[116–120] According to recent hypotheses, it can either start from a monoligated Pd(0) complex,[110,115,121] or a diligated species.[115,117–119] The precise identity of these catalysts has been shown to have a large impact on the mechanism of the oxidative addition and thus the reaction outcome.[122–124] In polar solvents, the active species has been suggested to be the anionic form of the monoligated complexes *e.g.* $[ClPd(PR_3)]^-$.[122,123,125,126] Although technically diligated, these anionic species will be referred to as "monoligated" in the following discussion, in contrast to the diligated species (*i.e.* bearing two phosphines), which have also been investigated in anionic form.[118,122]

The most widely accepted mechanism for this step is the concerted addition of the Pd(0) center into the aryl halide bond, which can occur via a 3-centered transition state.[116,119,127] A similar concerted mechanism involving a 2-centered transition state was also postulated (Figure I.5).[116]

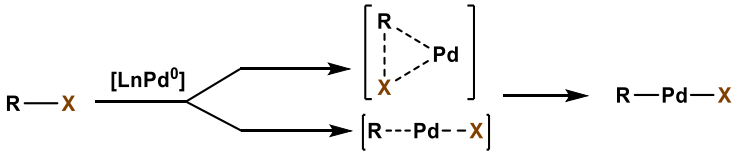


Figure I.5: Concerted pathway for oxidative addition

A third option for the transition state in the concerted oxidative addition mechanism involves a pre-coordination of the halide to the palladium center (Figure I.6).[118,127]

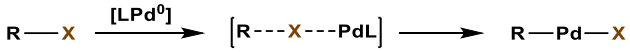


Figure I.6: Oxidative addition via pre-coordination to the halide

A computational study by Ziegler on the oxidative addition of Pd^0 to an aryl halide did not find the widely accepted 3-centered transition state (located in the gas phase) viable.[119] The catalyst considered was a Pd^0 species chelated to the unhindered bisphosphines 1,2-bis(dimethylphosphino)ethane (dmpe) or 2,2′-bis(dimethylphosphino)-1,1′-biphenyl (bimep). Taking solvation effects into account, an alternative two-step ionic mechanism was suggested (Figure I.7).

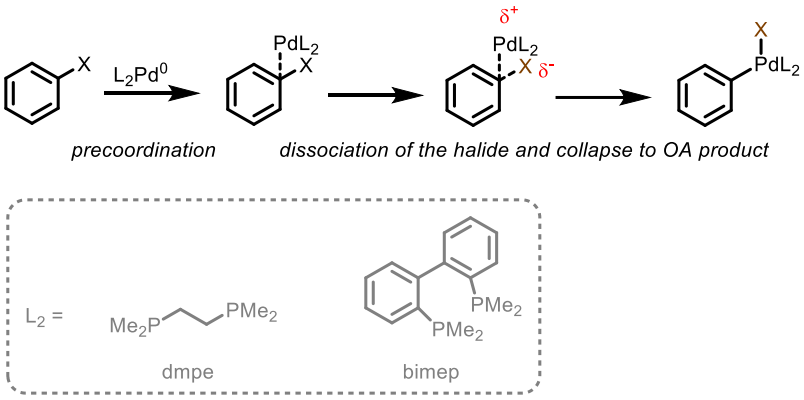


Figure I.7: Alternative ionic mechanism of the 3-centered OA transition state

However, these ligands, and methyl phosphines in general, are uncommon in cross-coupling reactions. A more recent DFT study by Schoenebeck investigating the more hindered and common ligand P^tBu_3 found that considering solvation, the concerted mechanism could be located by DFT for the oxidative addition into aryl chlorides or triflates.[125]

This is corroborated by another study exploring the selectivity of the Suzuki coupling of Csp^3-Br versus Csp^2-Br electrophiles.[128] It was found that hindered phosphines favored a concerted oxidative addition process into Csp^2-Br bonds while less hindered ligands favored an ionic oxidative addition mechanism in the Csp^3-Br bonds.[128]

More insight into the mechanism is given by the study of the selective Suzuki reaction on a bifunctional arene bearing both an -OTf and a -Cl leaving group.[123,124] Fu and coworkers noted that switching the ligand from P^tBu_3 to PCy_3 led to exclusive coupling on either the chloride or triflate, respectively.[129] It was shown that bulky phosphines (P^tBu_3) favor a monoligated intermediate and that less bulky phosphines (PCy_3) led to a diligated active catalyst. Monoligated catalysts favored oxidative addition into aryl chlorides, whose bond-dissociation energy is lower; diligated catalysts favored

oxidative addition into triflates due to the more prominent interactions with the leaving group.[123,124]

A recent study by Grimaud and coworkers describes a different oxidative addition mechanism involving two Pd(0) centers on aryl iodides, when using nitrogenated ligands.[130] First, a Pd(0) complex coordinates the iodide, as depicted in Figure I.6. A second Pd(0) complex then oxidatively inserts into the resulting weaker bond through a 3-centered concerted mechanism as shown in Figure I.5 (top arrow). The authors stress that this second-order kinetics is only observed for electron rich iodoarenes or those bearing mild electron-withdrawing groups. Highly activated iodoarenes or bromoarenes undergo oxidative addition without pre-coordination of a second palladium complex to the halide of the electrophile.

Thus, the consensus points to both the ionic-type mechanism and the three-centered concerted mechanism being viable mechanisms. The former is favored by bulky ligands (which leads to monoligated palladium catalysts) and by the diligated palladium species formed with less hindered ligands. The ionic mechanism on arenes reported by Ziegler[119] was challenged by later studies but appears to be a viable mechanism for alkyl bromides.[128]

Another proposed mechanism for the oxidative addition is the SNAr-type, which appears limited to *ortho*-nitro or *ortho*-carboxy substituted aryl halides, due to their coordinating effects on the palladium center,[120,131] although other coordinating electron-withdrawing groups could lead to a similar mechanism (Figure I.8).

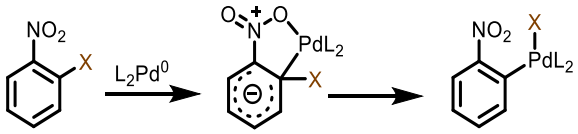


Figure I.8: SNAr-type mechanism for the oxidative addition into *ortho*-nitro aryl halides

The oxidative addition is a fundamental step in the Suzuki reaction and often dictates the reaction outcome. It can occur through different mechanisms, influenced not only by the type of substrate but also the major catalytic species formed during the reaction, explaining the seemingly unpredictable differences in reactivity for some substrates or resulting from slight changes in the reaction conditions.

1.4.3 Transmetalation and role of the base

As opposed to the oxidative addition and reductive elimination that occur in most cross-coupling reactions, the transmetalation from boron to palladium is unique to the Suzuki reaction. After oxidative addition, the transmetalation of the organoboron species to palladium forms a palladium complex substituted by two organic groups *i.e.*, a diaryl palladium complex (Figure I.4).

Three different mechanisms have been suggested for the transmetalation step (Figure I.9).[82] Two possible active palladium complexes are considered: the palladium halide complex [LnPdAr(Cl)], direct oxidative addition adduct, and an oxo-palladium complex [LnPdAr(OH)], resulting from a ligand substitution by the base on the first complex. The possible boron species are the parent boronic acid $ArB(OH)_2$ and the boronate $ArB(OH)_3^-$ generated by reaction with the base.

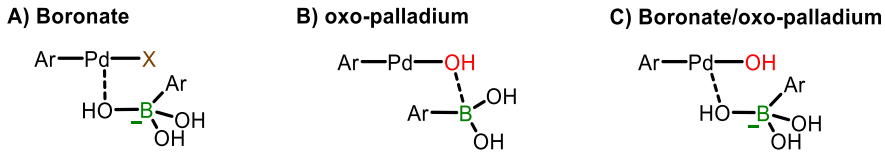


Figure I.9: Different suggested mechanisms for transmetalation

Since its early discovery, it is well established that the Suzuki reaction does not occur in the absence of base, despite the absence of proton transfers during its mechanism.[1,3] The resulting hypothesis claimed that the base was required during the transmetalation step, either by forming a (presumably) more reactive boronate or a more reactive oxo-palladium complex.[1,3,105] Several computational studies have corroborated the claim of a more reactive boronate, seeing pathway A as more viable.[106,132]

However, experimental evidence conducted by Hartwig contradicted these claims. Using stoichiometric palladium, transmetalation occurred at a much faster rate – 4 orders of magnitude – starting from the oxo-palladium complex than from the boronate and palladium halide complex (Figure I.10).[82,133] The ready formation of the oxo-palladium species with the base was also demonstrated, in an equilibrium with the palladium-halide complex (Figure I.10).

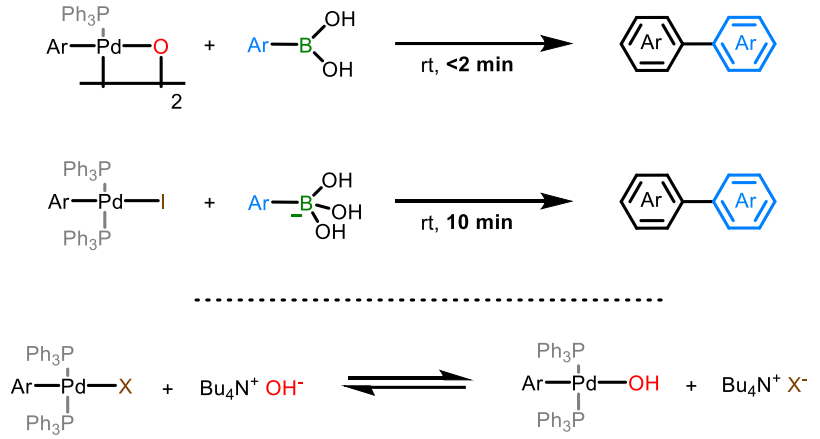


Figure I.10: Hartwig's study demonstrates the higher viability of the oxo-Pd pathway and the formation of the oxo-Pd in equilibrium with the Pd-halide complex

A study by Larina on homocoupling supported these claims: adding the boronic acid to a palladium complex pre-reacted with a base led to faster coupling than pre-reacting the base with the boronic acid, suggesting an inhibitory effect of boronates on transmetalation (Figure I.11).[82,134]

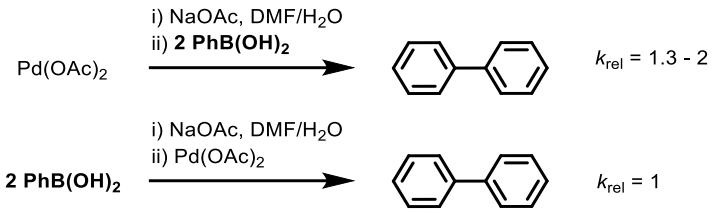


Figure I.11: Larina's study on homocoupling: pre-reacting the base with the boronic acid leads to a slower reaction, indicative of slower transmetalation

The most convincing experimental evidence stems from the groundbreaking work by Jutand using electrochemical techniques, elucidating the various (beneficial and antagonistic) roles of the base and the mechanism of transmetalation in the Suzuki reaction, using a large excess of boron reagents to simulate catalytic conditions.[107,135,136]

Transmetalation was observed from the boronic acid to the palladium halide complex [ArPdBr(PPh_3)$_2$] using base (Figure I.12 A) or to the oxo-palladium complex [ArPd(OH)(PPh_3)$_2$] with or without base (Figure I.12 B). However, past a certain ratio of base relative to the boronic acid, a decrease in reactivity was observed.

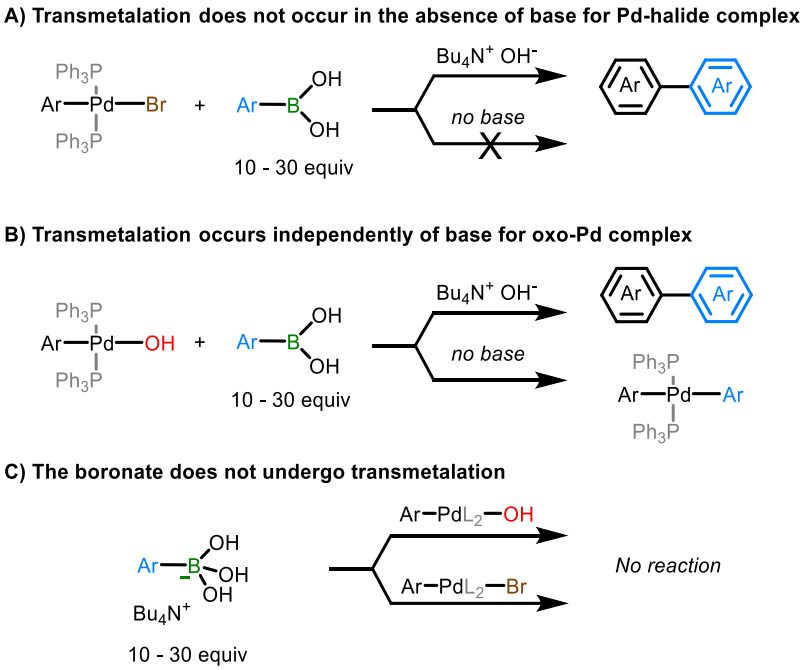


Figure I.12: Summary of Jutand's 2011 experiments

These findings suggest that the palladium halide complex is not the reactive species in the reaction and that the excess base inhibits the reaction shifting the equilibrium toward the formation of the unreactive boronate. These findings were confirmed by the absence of transmetalation using a preformed boronate on either of these complexes (Figure I.12 C).

Although transmetalation readily occurs from the boronic acid to the oxo-palladium complex in the absence of base, the reductive elimination does not happen immediately (Figure I.12 B): The base is also seemingly involved in the reductive elimination step which will be discussed in its dedicated subchapter.

Finally, an excess of bromide ions (shifting the equilibrium toward the palladium halide complex) also inhibited the reaction. This "halide inhibition effect" was also described in a recent study.[137] The halide salts generated as a by-product of the reaction itself were found to have a detrimental effect on the reaction – this was particularly the case with bromide and iodide (see Figure I.14).

These experiments, along with the previously exposed findings by Hartwig and Larina, provide strong evidence for the mechanism of the transmetalation from the trivalent boronic acid to the oxo-palladium species corresponding to Figure I.9 B.

The strong difference in reactivity for these two pathways was exploited in the cross-coupling reactions of allyl(BPin), reacting either as a Heck or Suzuki coupling partner depending on the base and solvent system.[138] It was shown that conditions favoring the formation of the oxo-palladium complex led to the Suzuki coupling while conditions favoring the palladium-halide complex as a major species led to the Heck coupling products (Figure I.13). These findings were confirmed by stoichiometric experiments using different palladium complexes and by studying the anion metathesis via ^{31}P NMR. It confirms the higher rate of transmetalation from boron to Pd induced by oxo-palladium complexes.

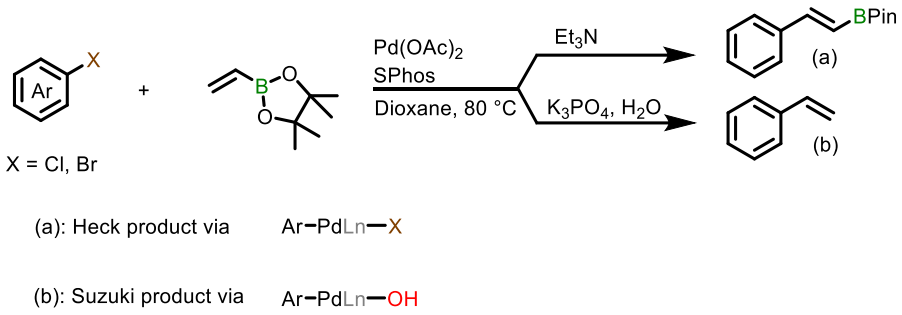


Figure I.13: Divergent cross-coupling exploiting on the different transmetalation rates

Further studies by Jutand focused on the more common bases used in the Suzuki reaction such as fluorides and carbonates.[107,136,139] Carbonates and phosphates have been shown to form oxo-palladium species by generating small amounts of hydroxide ions *in situ*.[137,140] Their corresponding cation was shown to have a negative influence on the reaction, by coordinating the oxygen of the reactive [Pd-OH] complex. The inhibitory effect increased in the following order: $n\text{Bu}_4\text{N}^+ < \text{K}^+ < \text{Cs}^+ < \text{Na}^+$ (Figure I.14). Thallium and silver bases are particularly active because of the insolubility of their halide salts: [Pd-OH] forms irreversibly.[141]

Hydroxide ions were also shown to inhibit the reaction by sequestering the boronic acids as unreactive boronates. Fluoride ions form the similarly reactive [Pd-F] complexes and were shown to have the same inhibitory effect as hydroxide ions (formation of unreactive fluoroboronates) but to a lesser extent.

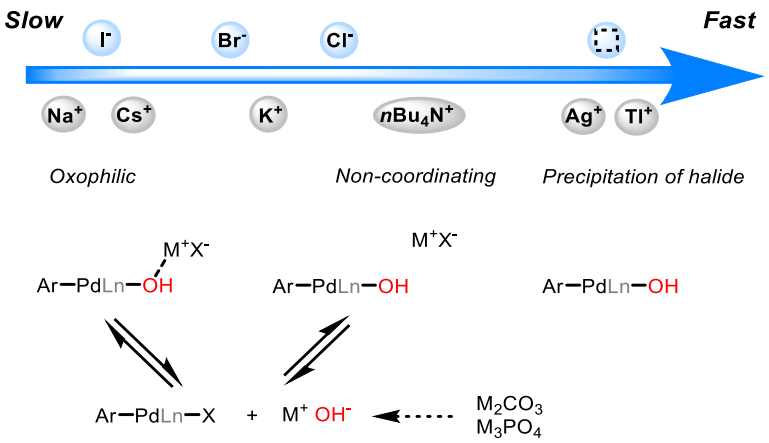


Figure I.14: Relative rate of transmetalation: inhibitory effects of base cation and halide

These studies provide evidence for the pathway B of transmetalation, which was further confirmed by Denmark's recent work on elucidating the precise structures of transmetalation intermediates.[142,143] Using rapid-injection NMR and computational studies, a viable mechanism for the transmetalation of aryl boronic acids on palladium was established (Figure I.15). 4-Fluorophenyl groups were used as the corresponding aryl groups on the palladium complexes and the boronic acid due to the possibility of analysis using ^{19}F NMR. Triisopropylphosphine was selected as the ligand due to its ability to form stable palladium hydroxide complexes, and to simplify ^{1}H NMR analysis. The elucidated structure of a transmetalation intermediate containing a trivalent boron center (Figure I.15, 3) supported the case that boronic acids need not be "activated" by base prior to transmetalation.

The mechanism differed slightly starting from a mono- or binuclear (dimer) palladium complex (Figure I.15 i and ii). The binuclear complex generated the intermediate **1a** after the addition of a boronic acid, which is in equilibrium with the 8-B-4 intermediate **2**.

Starting from the palladium hydroxide complex from pathway (ii), the intermediate **1** was generated, which was sufficiently stable at low temperatures for its analysis via NMR.

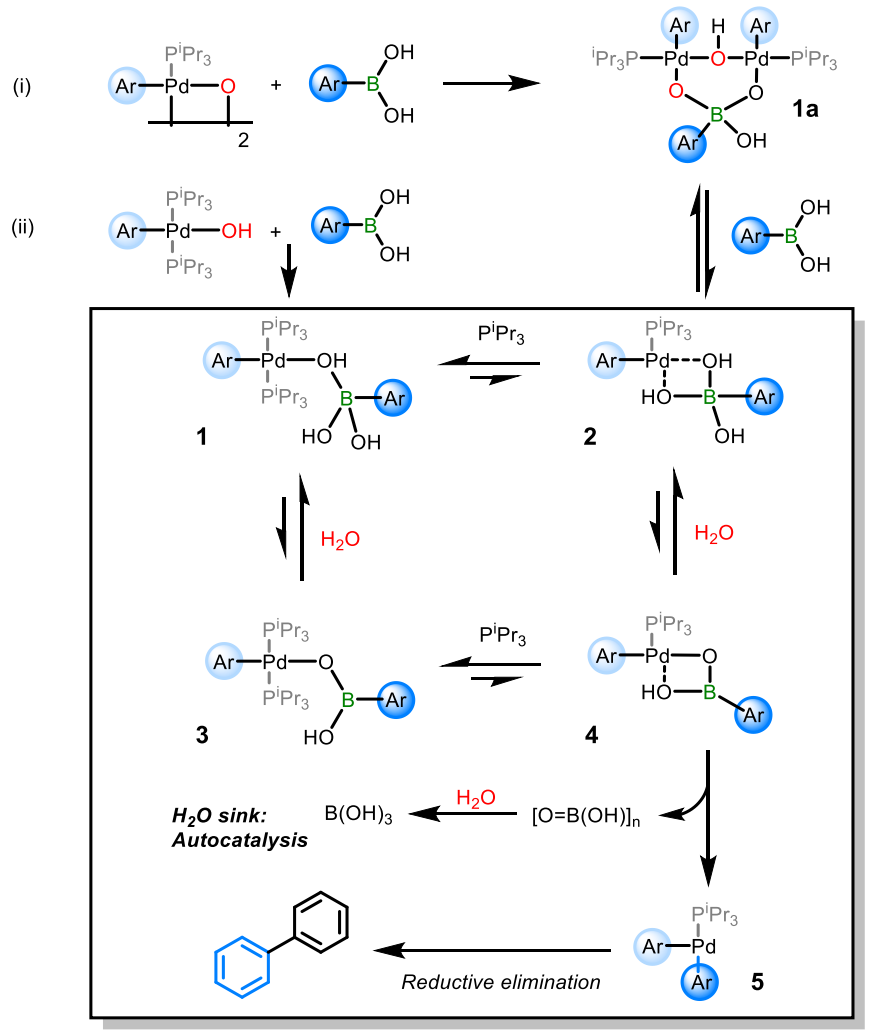


Figure I.15: Denmark's elucidated transmetalation mechanism

The structure of **1** is in equilibrium with the 8-B-4 intermediate **2** via loss of a phosphine ligand, and with the 6-B-3 intermediate **3** via loss of water. Kinetic data indicated that transmetalation required a loss of phosphine to form the putative intermediate **4**, which is consistent with earlier computational studies[144] indicating a high barrier for the transmetalation starting from intermediates such as **3**. For systems with excess phosphine, transmetalation then occurs from intermediate **4**, releasing metaboric acid that acts as the water sink, driving the equilibrium forward. This mechanism is consistent with the observed autocatalytic nature of the reaction. With bulkier ligands, transmetalation is postulated to occur through intermediate **2**.

The precise mechanism of the transfer of the aryl group from boron to palladium was studied computationally starting from intermediate **2** or **4** (Figure I.15), which is shown in Figure I.16.

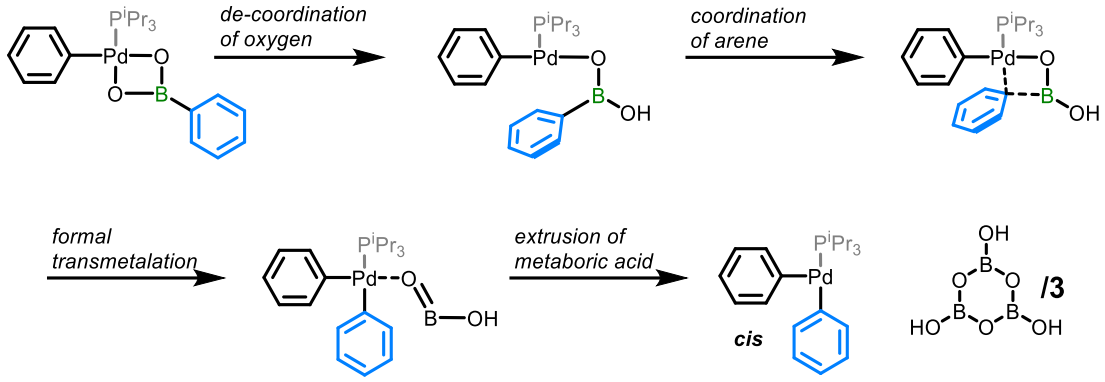


Figure I.16: Transmetalation via 6-B-3 intermediate (in presence of excess phosphine). The same steps have been located via DFT for the mechanism via the 8-B-4 intermediate.

The first step is the de-coordination of one of the boron oxygens to create a trivalent palladium center with an empty coordination site – it then coordinates the aryl group before extrusion of boric or metaboric acid to form the preferred *cis* di-aryl complex.

These results are put in perspective by a recent study following a Suzuki reaction in real-time by ESI-MS spectrometry.[145] Under catalytic conditions, the authors could not detect any oxo- or fluoro-palladium complexes but observed a cationic palladium complex which they postulate to act as the intermediary between the palladium halide complex and the unidentified transient reaction species. While the study does not exclude the action of an elusive oxo-palladium, the concurrence of several different pathways is suggested.

1.4.4 Transmetalation in base-free Suzuki couplings

To tackle the base-catalyzed deboronation side-reaction (Figure I.3), to which some substrates are especially sensitive, some rare methods were developed to avoid the addition of base to the reaction mixture.

The unusual reactivity of cationic palladium complexes was first reported in the ligandless and base-free coupling of arenediazoniums and boronic acids or trifluoroborates.[146,147] A recently disclosed synthetic method supports the claims of the formation of a reactive cationic palladium intermediate after oxidative addition to aryl diazoniums.[148] The base-free cross-coupling of diazonium tetrafluoroborates with boronic acids allowed the coupling of base-sensitive boronic acids such as the

pentafuorophenyl derivative. Mechanistic experiments revealed the formation of a reactive monoligated cationic palladium complex to which transmetalation readily occurs from boronic acids, avoiding an oxo-palladium intermediate and the use of base altogether (Figure I.17 A).

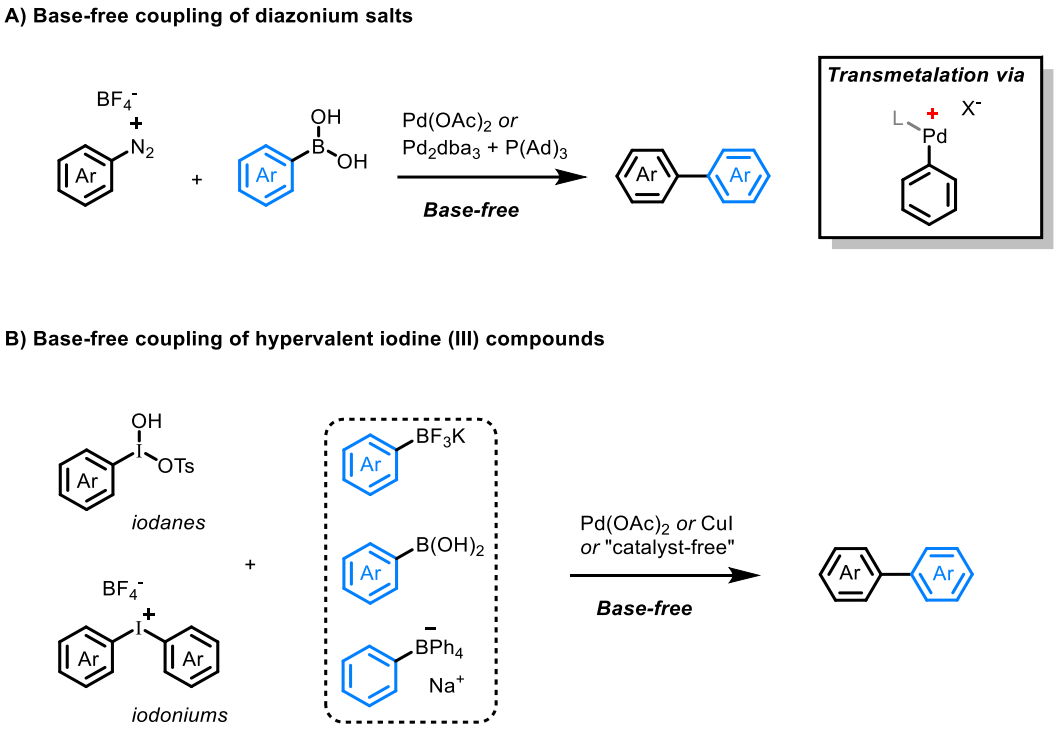


Figure I.17: Base-free cross-coupling of diazoniums and hypervalent iodine (III) compounds – transmetalation via cationic complex

Hypervalent aryl iodine (III) compounds – iodonium salts and iodanes – were also found to react in base-free conditions and transmetalation was also postulated to occur through a cationic palladium (Figure I.17 B).[149,150] Some examples of base-free coupling occurred on diphenyliodonium tetrafluoroborate with boronic acids using palladium[150] or copper.[151] Unfortunately, because the addition of base slightly enhanced the yields, the results of the base-free couplings were not explored in the synthetic scope. The base-free coupling of aryl trifluoroborates was studied more deeply and found to occur with both iodoniums and iodanes using palladium acetate alone.[152]

Tetraphenylborates were also efficient coupling partners in the base-free coupling of iodoniums,[149] even occurring with two equivalents of a strong acid,[153] or under microwave irradiation in neat conditions, presumably without any catalyst.[154] While

several papers were published on the alleged catalyst-free conditions, they were all by the same team and unfortunately, no further studies appeared. While it is possible that iodoniums don't require palladium to couple, in an analogous fashion to the Gomberg-Bachman reaction,[155] coupling might occur with trace palladium on the reaction apparatus.[149]

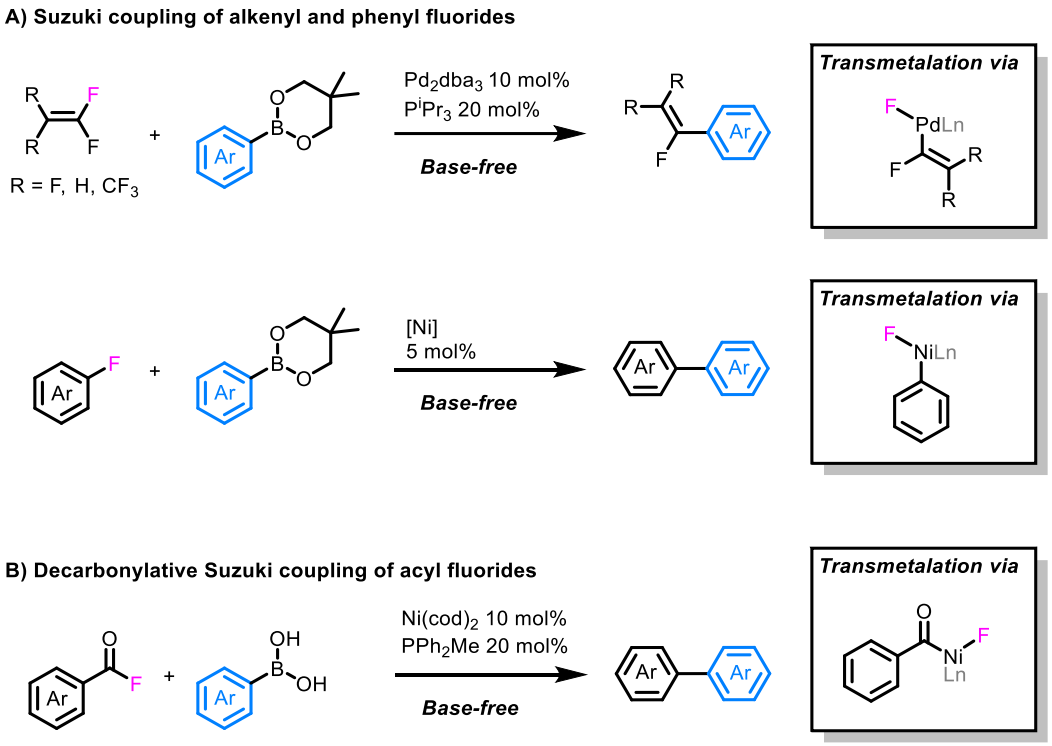


Figure I.18: Base-free couplings exploiting fluoride leaving groups to form reactive palladium fluoride complexes

The high coupling reactivity of these compounds – often coupling at room temperature using low catalyst loadings without base or ligand – warrants further discussion. Reviews were published on the coupling of diazonium salts and iodoniums,[149,156] and in-depth discussion will follow in subchapter 1.6.2.

Similarly, aryl triflates were postulated by Miyaura and Suzuki to form a cationic palladium intermediate after oxidative addition,[1] and there is one report of a base-free coupling on aryl triflates with aryl trifluoroborates under microwave irradiation.[157] Another example on the base-free coupling of triflates occurs with trifluoromethyl alkenyl triflates and boronic acids. It requires a substantially higher catalyst loading and reaction temperature than what is usually the case for triflates,[158] which indicates that base-free coupling is not favorable for these substrates.

Other work on base-free Suzuki couplings focused on fluorinated substrates to create a reactive palladium fluoride complex after oxidative addition. This type of reaction was first reported on tetrafluoroethane using palladium, and on fluorobenzene with a nickel catalyst (Figure I.18 A). Experiments confirmed the formation of Pd-F and Ni-F intermediates, which are reactive towards transmetalation.[159] Exploiting this principle, the nickel-catalyzed decarbonylative cross-coupling of carbonyl fluorides was recently reported. Biaryls were formed via transmetalation on a nickel fluoride intermediate.[160] A subsequent DFT study found that transmetalation likely occurs on the acyl nickel fluoride before extrusion of CO (Figure I.18 B).[161]

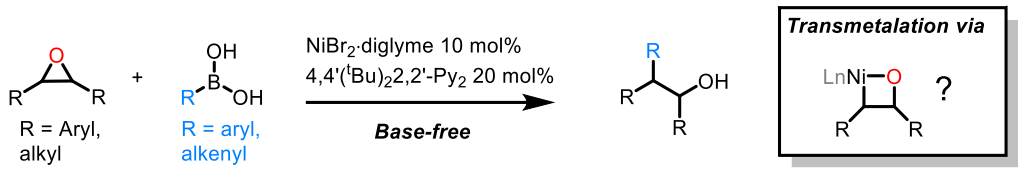


Figure I.19: Base-free Suzuki coupling of epoxides – undisclosed mechanism

The base-free nickel-catalyzed Suzuki coupling of epoxides is another example of base-free Suzuki coupling and was postulated to occur through a radical mechanism due to the observed scrambling on chiral substrates.[162] However, the radical mechanism might only be involved in the oxidative addition and the transmetalation could occur through a nickel-oxetane type structure, analogous to the reactive Pd-alkoxide complexes (Figure I.19).

A specific example of a base-free Suzuki coupling is an unusual example using twisted difluoroacetamides as the electrophiles.[163] The transmetalation was found to occur via a difluoroacyl-palladium complex with the glutarimidate leaving group acting as the base. Although not discussed by the authors, it might occur through its oxyanion (Figure I.20).

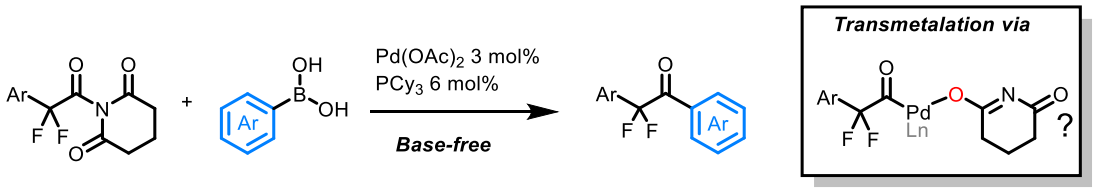


Figure I.20: Base-free Suzuki coupling of fluoroacetamides

A different mechanism for transmetalation has been proposed for the base-free coupling of the very exotic pentavalent triarylantimony diacetate electrophiles.[164,165] After oxidative addition, the ancillary acetate bound to the antimony leaving group was hypothesized by the authors to coordinate the boron, inducing transmetalation (Figure I.21). This was rationalized by the absence of cross-coupling using the corresponding diaryl antimony(V) chloride and Ar_3Sb(III). The reaction was also tolerant to aryl bromides, reinforcing the plausibility of a distinctive transmetalation mechanism.

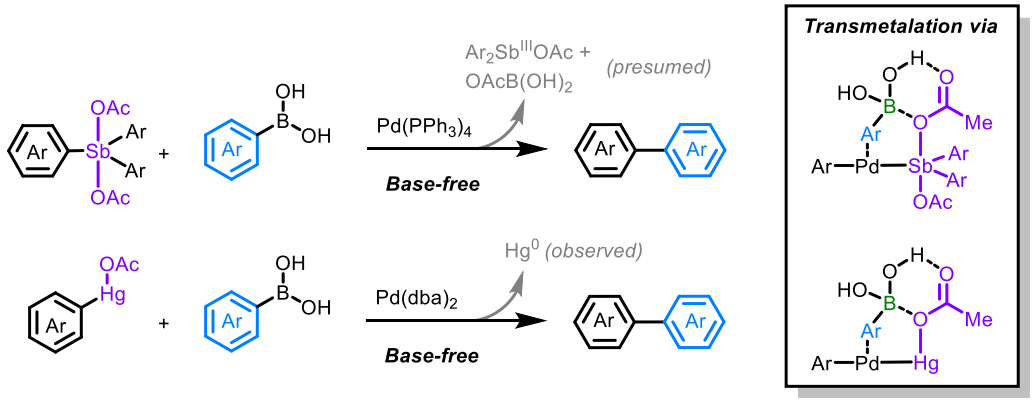


Figure I.21: Base-free Suzuki coupling of electrophiles with ancillary acetate

A similar reaction was reported in the base- and ligand-free coupling of arylmercuric acetates (Figure I.21).[166] These unusual electrophiles displayed a high reactivity, achieving high yields at room temperature in relatively short reaction times (3 h). Although not discussed by the authors, it can be postulated that the acetate on the mercury plays a similar role in transmetalation as what was hypothesized with the pentavalent antimony compounds: no coupling occurred on the analogous mercuric chlorides and bromides.

Metallic mercury was also observed at the end of the reaction, proving that oxidative addition takes place at the C–Hg bond. Thus, coupling likely does not occur oxidatively after two transmetalations from the boronic acid and the aryl mercuric acetate.

Suzuki couplings can also occur efficiently without exogenous base using specific activated organoboron reagents. For example, there have been several reports of "base-free" couplings using tetra-arylborates.[153,157,167–169] The transmetalation of these

compounds is not discussed in any of the papers on these couplings, but the high apparent reactivity of tetra-arylborates suggests that transmetalation might be favorable without necessarily arising from an oxo-palladium complex.

Finally, the structure of the electrophilic substrate, but also specific catalysts and exposure to air, can lead to cross-coupling in the absence of exogenous base. Using a preformed palladium hydroxide-NHC complex (*i.e.* a catalytic equivalent of base), cross-coupling could proceed satisfactorily between aryl chlorides and boronic acids, but base-free coupling only proceeded under air.[170] Under inert atmospheres, the reaction proceeded smoothly only with added base. Oxygen might be involved in a mechanism analogous to the one discussed for ligandless couplings in chapter 1.5.2.

1.4.5 Reductive elimination

The reductive elimination is the last step in the catalytic cycle of the Suzuki reaction. After transmetalation, the two aryl groups are coupled and the Pd(II) is reduced to regenerate the Pd(0) catalyst. Generally, reductive elimination has been described as the mechanistic reverse of oxidative addition, passing through the same types of transition states.[171] Some studies support this claim, by proposing a 3-centered concerted mechanism starting from a *cis* diaryl palladium complex (Figure I.22) which would be analogous to the mechanism of oxidative addition presented in Figure I.4.[122,172,173]

Monoligated trivalent palladium complexes have been shown to favor reductive elimination (Figure I.22, ii),[172,173] with the most reactivity being observed for alkenes and arenes – alkyl groups being far less reactive due to the lack of π-interactions between the two substrates.[173] Predictably, for biaryls, the fastest reductive eliminations occurs when one aryl group is electron-poor and the other electron rich.[172]

Kinetic experiments led by Jutand in her work elucidating transmetalation revealed that the base also had a positive effect on the rate of transmetalation and an alternative mechanism of reductive elimination was postulated.[107,135] The hydroxide – or fluoride – ion coordinates to the palladium to form a pentavalent complex, bypassing the need for the slow *cis-trans* isomerization of the aryl groups (Figure I.22, iii).

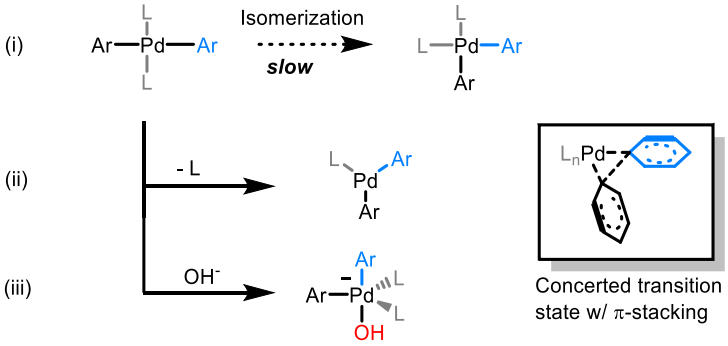


Figure I.22: Different pathways for accessing the reductive elimination transition step

These hypotheses assume the formation of a trans complex after transmetalation. However, Denmark's recent DFT studies on transmetalation indicate that the formation of a *cis* di-aryl palladium complex after transmetalation (Figure I.16) is more favorable.

Because of Jutand's observations on the role of the base, reductive elimination might still occur through a pentavalent intermediate, but not necessarily to bypass isomerization.

Finally, using nitrogenated ligands, some evidence supports the hypothesis of the induction of reductive elimination after a second oxidative addition step to form a palladium(IV) complex.[174,175] Another study on biaryl formation even reported this effect after reacting a diaryl palladium(II) complex with the oxidant H_2O_2.[176] Its occurrence in the Suzuki reaction remains doubtful however, due the particularity of the systems studied in these examples.

1.4.6 Detailed catalytic cycle

To summarize the previous discussion and give a clear overview of the current consensus on the underlying mechanisms of the Suzuki reaction, a detailed catalytic cycle is presented in Figure I.23.

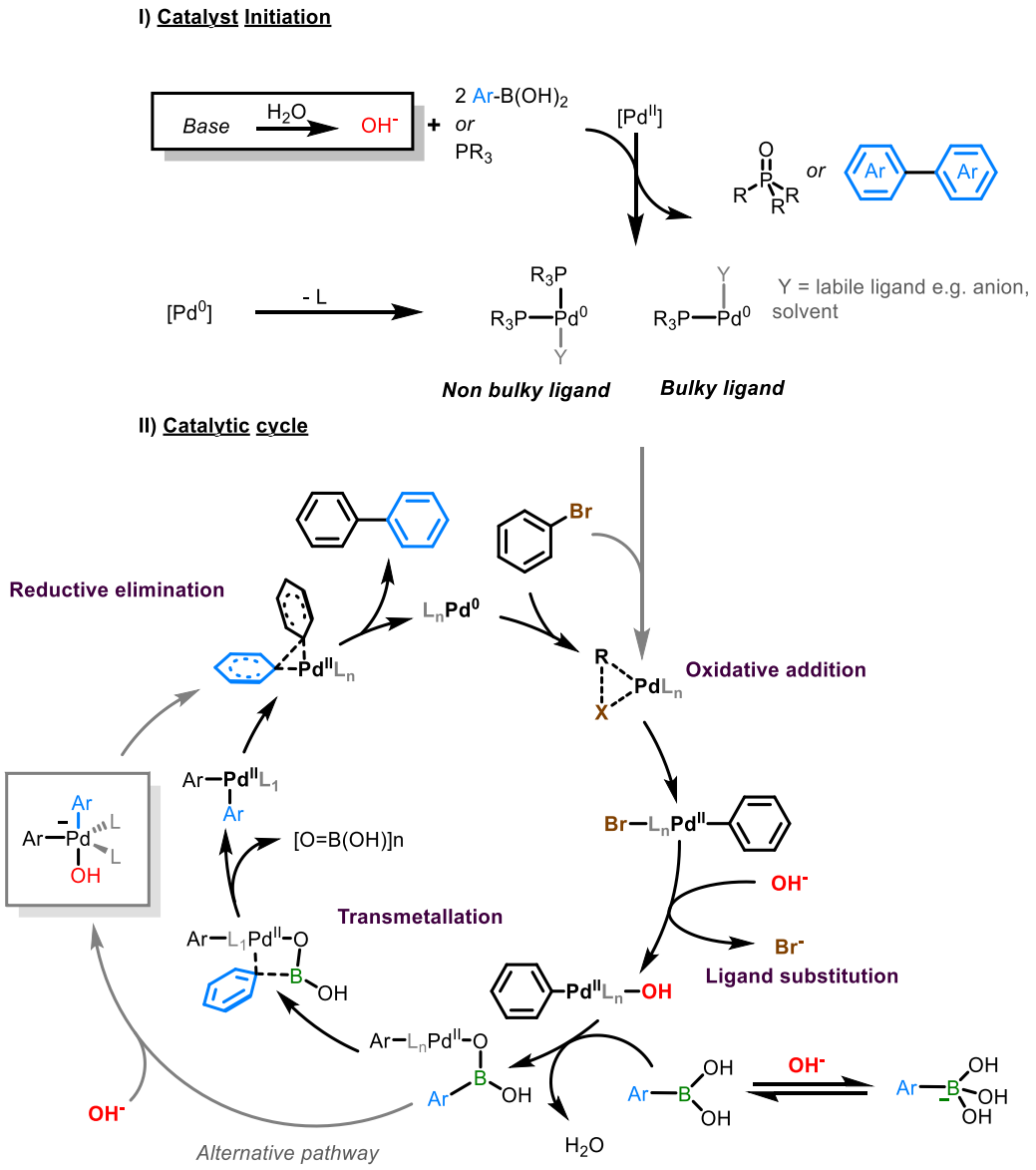


Figure I.23: A more accurate representation of the Suzuki cross-coupling mechanism summarizing the previous discussion. The hydroxide ion can be substituted for a fluoride ion.

1.5 Catalysts and ligands

Being one of the most developed reactions in organic chemistry, numerous catalytic systems have emerged, varying ligands, palladium sources, using alternative metals and developing efficient heterogeneous systems. Even minute, almost undetectable amounts of catalyst – several ppb – have resulted in efficient coupling.[177] As mentioned in subchapter 1.3, alternative transition-metals are used efficiently for this reaction, providing a cheaper alternative to the costly palladium catalysts. The use of nickel is well established, [90–99] and some reports using copper as the sole catalyst have also appeared,[93] as well as cobalt,[94–96] and iron.[97–99] However, as of today, palladium remains the most widely studied and used catalyst due to its high reliability and efficiency.[177]

Heterogenous catalysts have also emerged as advantageous systems, due to their easy separation from the reaction mixture and high reusability, in contrast to homogeneous catalysts.[177–179] Because only homogeneous catalysts were used in the present thesis, the following chapter will focus on homogenous, *i.e.* soluble, catalysts.

1.5.1 Precatalysts

Early reports of the Suzuki reaction typically relied on Pd(0) sources such as $Pd(PPh_3)_4$, which is still valuable today for the coupling of bromoarenes and boronic acids bearing no demanding steric or electronic factors.[1,2] Most other Pd(0) complexes are usually not bench stable, with the exception of dibenzylideneacetone (dba) complexes. Pd(II) complexes are more common: $Pd(OAc)_2$ is one of the most frequently used palladium sources.[180]

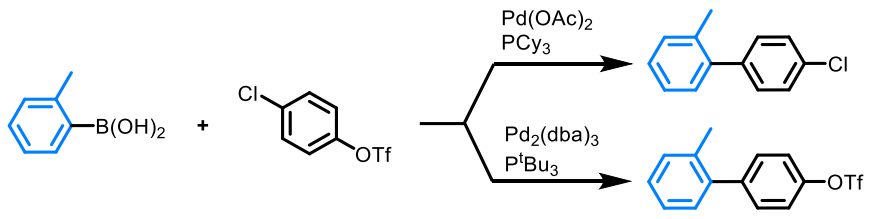


Figure I.24: Greg Fu's discovery of catalyst-induced chemoselectivity in the Suzuki reaction

The role of the palladium source is discussed in Chapter 1.4 as an important factor in forming low-ligated palladium(0) complexes, which are the true active species in the catalytic cycle. This can be emphasized by Fu's famous experiment where either a chloride or a triflate were coupled by slightly varying the precatalyst and ligand (Figure I.24).[129] The difference in reactivity was explained by the formation of monoligated Pd(0) in the conditions coupling chlorides; a diligated complex was formed in the other case.[124]

The formation of these complexes arises either by the de-ligation of tetracoordinated Pd(0) complexes such as $Pd(PPh_3)_4$ or are formed transiently after the reduction of Pd(II) precatalysts.[110–113,181,182] Grimaud and coworkers proposed two mechanisms for the reduction of Pd(II) precatalysts through phosphine ligand oxidation (Figure I.25 and Figure I.29).

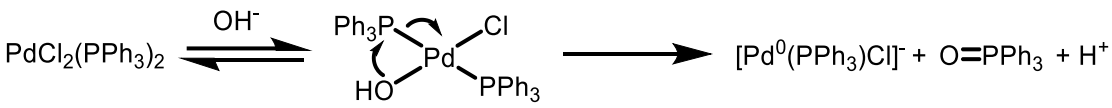


Figure I.25: Mechanism for the reduction of Pd(II) precatalysts by phosphine ligand oxidation

Regrettably, the reversible deligation step is unfavorable and the reduction of Pd(II) occurs via several concurrent pathways, leading to different catalytically active Pd(I) and Pd(0) species (Figure I.26, I).[82,114] For the catalyst initiation step to proceed more efficiently, palladacycles emerged as an alternative class of precatalysts. They generate the active species via a pathway emulating the catalytic cycle, bypassing the drawbacks associated with the other methods. Palladacycles are organopalladium (II) heterocycles, containing a palladium atom in the ring (Figure I.26, II).

They are bound to an anionic (X) carbon ligand and a nitrogen or a phosphorous L ligand. In the Suzuki reaction, early versions of these precatalysts were activated after transmetalation and reductive elimination to form a Pd(0) catalyst ligated to a single biaryl-based ligand (Figure I.26, II). The stability of biaryl ligands is well documented and is the foundation of the "Buchwald ligands", a class of ligands that display very favorable properties in terms of activity and stability – they will be discussed in their corresponding subchapter 1.5.3.[87]

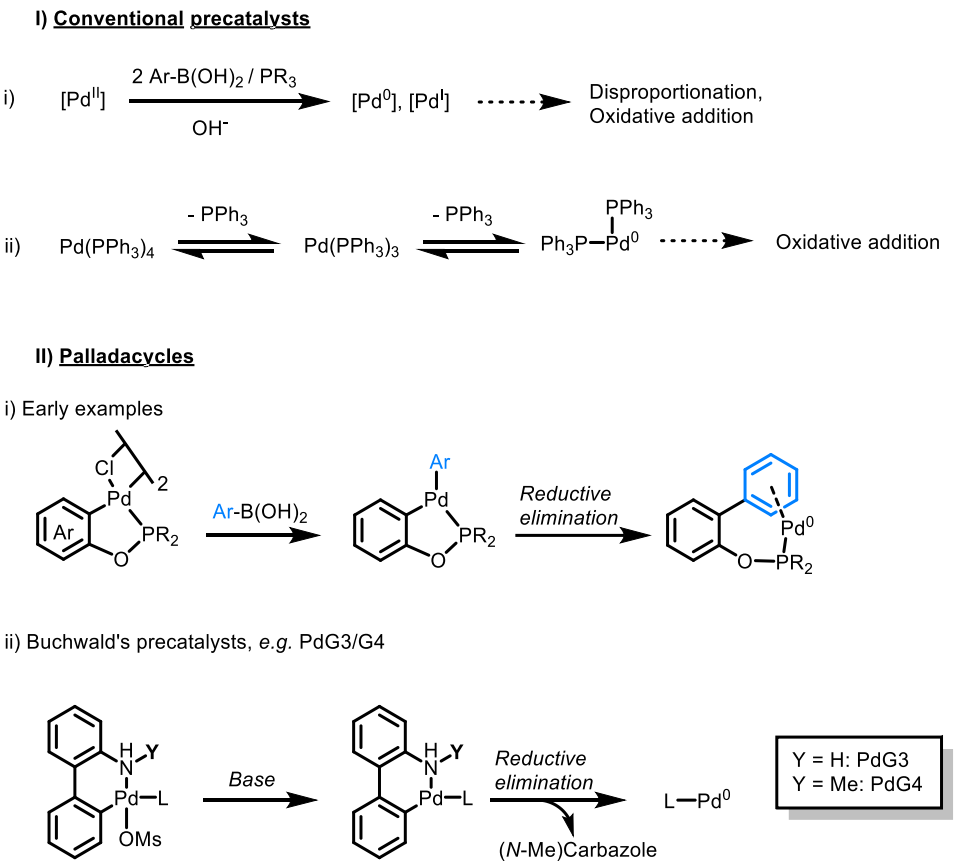


Figure I.26: Advantages of palladacycles for catalyst initiation

The Buchwald group also capitalized on the benefits of palladacycles by developing their own class of precatalysts, baptized "PdG1-G4".[183–185] These are beneficial over the previous versions of palladacycles because they reductively eliminate directly from the precatalyst, avoiding the transmetalation step (Figure I.26, II). Another key advantage is their commercial availability: a comprehensive review of these precatalysts can be found on the Sigma website.[186]

1.5.2 Ligand-free coupling

The Suzuki coupling is, in many cases, known to avoid the use of complex precatalysts and ligands altogether, allowing for atom economy in the reduction of waste as well as cost reduction. These reactions usually take place under air, in protic solvents, and often with the addition of water or in fully aqueous conditions. Even relatively challenging substrates like aryl chlorides or hindered molecules can cross-couple in short reaction times.[179,187–193]

By far the most commonly used precatalyst for this reaction is $Pd(OAc)_2$. Several studies focused on elucidating the catalyst activation of this unusual reaction. Palladium acetate readily hydrolyses to form palladium hydroxide complexes,[194] which are then reduced via homocoupling of boronic acids.[187] Interestingly, it was found that the presence of oxygen was beneficial for the reaction. While initial reaction rates are slower in the presence of O_2, the reaction reaches higher yields because the reaction under N_2 plateaus quickly. Water is necessary for the formation of palladium hydroxides and oxygen inhibits the aggregation of palladium into inactive nanoparticles by its adsorption on palladium.[187,193] Some other studies have postulated that the active species in ligand-free Suzuki reactions are three- or four- centered – Pd_3 and Pd_4 – palladium clusters.[195,196] These highly active species were found to be stabilized by water – after synthesis, they could be stored in aqueous media for extended periods. DFT studies indicated that energy barriers for Pd_3 and Pd_4 are very close, with the rate-limiting steps being transmetalation in the absence of base. Using base, the rate-limiting step was oxidative addition.[196]

1.5.3 Buchwald Ligands

Defining factors for an efficient catalytic system are ready formation of reactive low-ligated species and stability of the catalyst over time (preventing its aggregation). Dialkylbiarylphosphine developed by the Buchwald group (“Buchwald ligands”) were a major step forward for the Suzuki reaction, and in transition-metal catalyzed reactions in general, by successfully addressing these two factors.[87,127,140,197]

Buchwald ligands are bulky monodentate and electron-rich phosphine ligands that display a high stability to air and heat in solid form and in solution, as opposed to other efficient ligands such as P^tBu_3. Their convenient large-scale preparation accounts for their widespread commercial availability, contributing to their high popularity.

Their biaryl structure is responsible for their resistance to oxidation and the stabilization of L_1Pd species, through coordination at the ipso carbon, and has also been shown to enhance the rate of reductive elimination. Substitution at the *ortho* position of the bottom ring prevent the formation of palladacycles (Figure I.27, II, i) and their bulkiness favor the formation of $[L_1Pd]$ by increasing the overall bulkiness of the ligand.

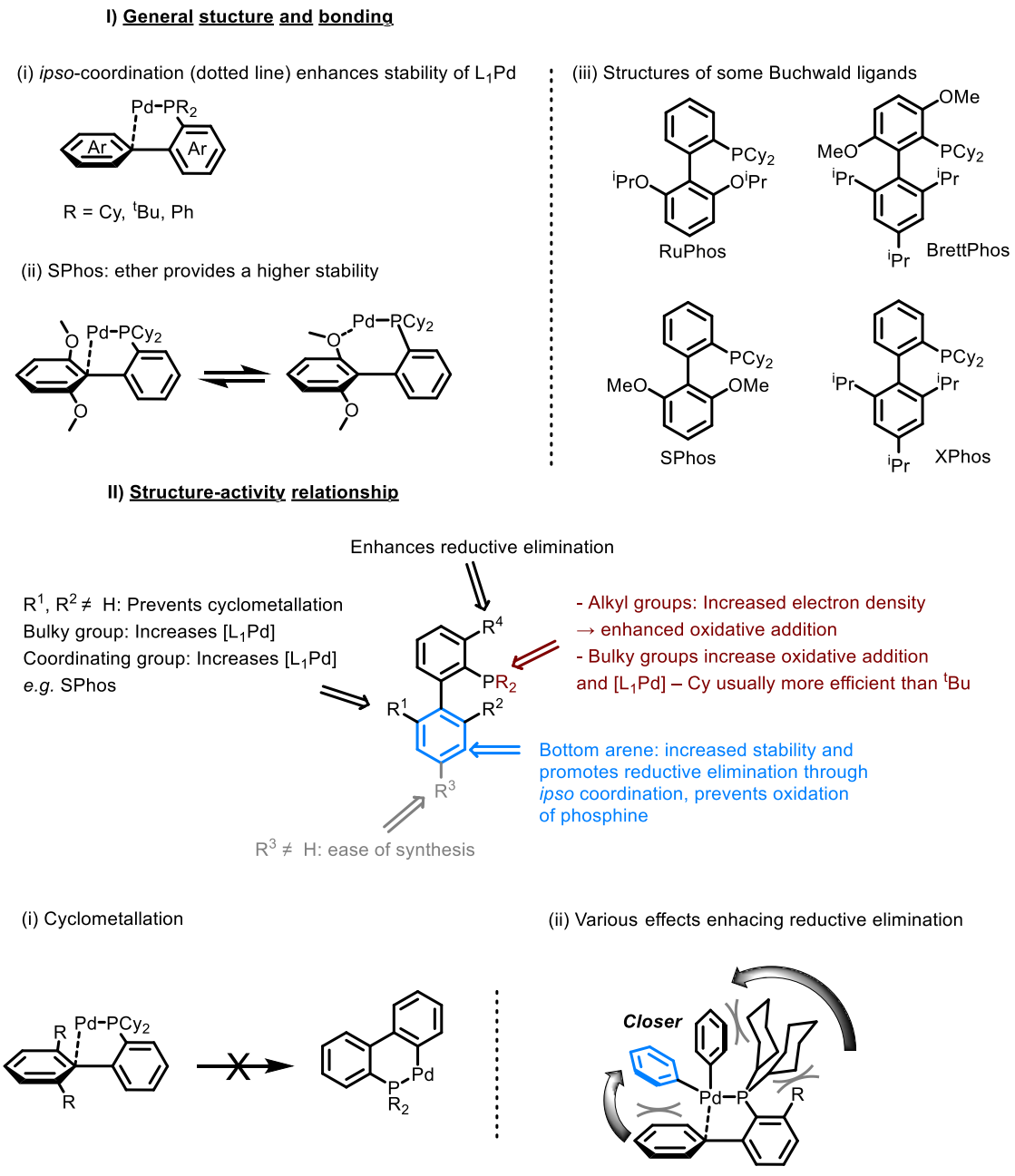


Figure I.27: General properties of Buchwald ligands

Ether substituents on ligands such as SPhos further stabilize [L_1Pd] by providing an alternative coordination to the oxygen as well as the ipso carbon of the bottom ring (Figure I.27).[87,197] Similarly to Fu's electron rich PCy_3 or P^tBu_3 ligands for chloride activation,[129] the phosphine is typically substituted with cyclohexyl or *tert*-butyl groups which support oxidative addition through their electron-donating properties. On the top ring, substitution *ortho* to the phosphine carbon favors the conformation of the phosphine over the bottom ring which promotes reductive elimination by bringing the two arenes together (Figure I.27, II).[87]

An interesting side-reaction occurring on the Buchwald ligand palladium complexes with RuPhos and SPhos was recently reported by Bedford and coworkers.[198] While substitution on the 2',6' positions of Buchwald ligands prevents the formation of 6-membered palladacycles on the bottom ring (Figure I.27, II, i), Bedford's work described the facile formation of 4-membered palladacycles on the top ring (Figure I.28, A). This reaction occurred in significant yields (21 – 33%) after heating a mixture of $Pd(OAc)_2$ and SPhos or RuPhos in toluene at 60 °C for only 2 h.

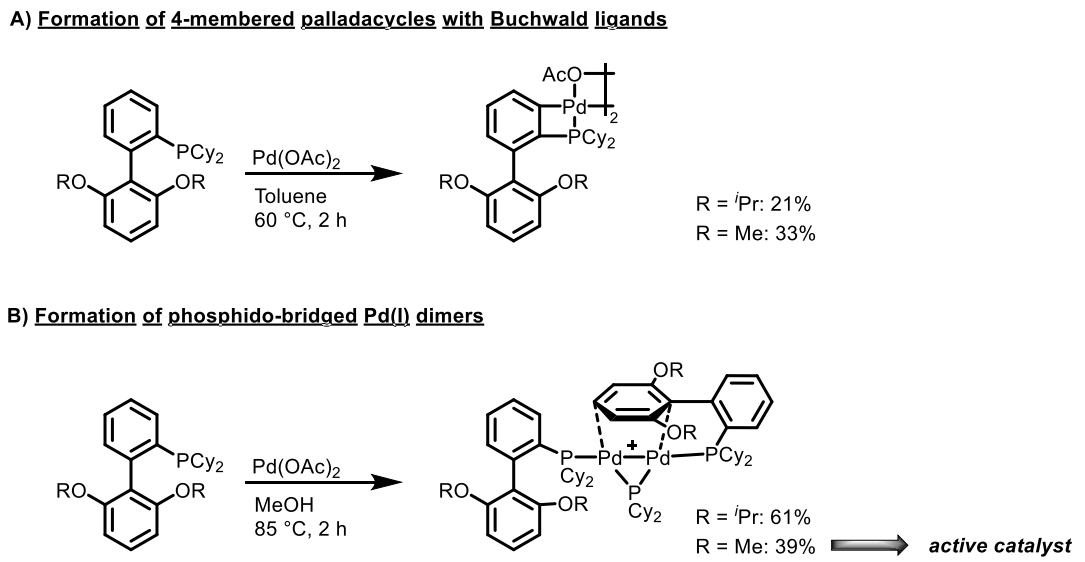


Figure I.28: Bedford's work on the facile formation of unusual complexes from Buchwald ligands and $Pd(OAc)_2$

In methanol, some of the ligand decomposes though P-C bond dissociation to yield a dinuclear Pd(I) complex bridged by the phosphide $P(Cy)_2^-$ and the bottom arene of the Buchwald ligand (Figure I.28, B). The corresponding complex with SPhos was used successfully in a Buchwald-Hartwig amination reaction.

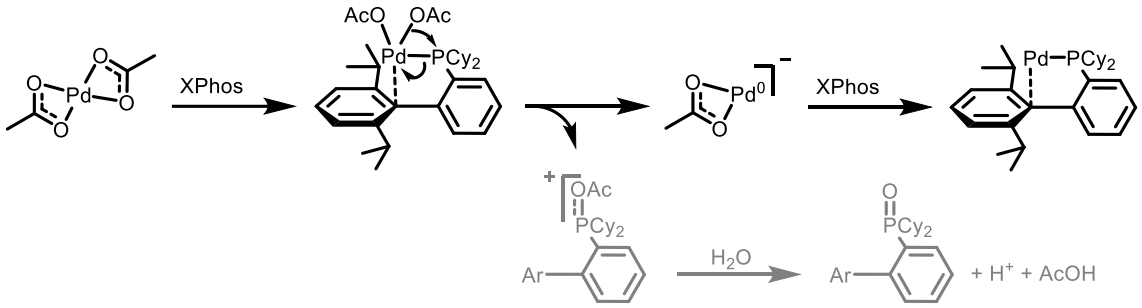


Figure I.29: Mechanism of reduction of $Pd(OAc)_2$ through oxidation of Buchwald ligand XPhos

The facile formation of these types of phosphide complexes, which is especially favored with RuPhos, might play a significant role in reactions employing Buchwald ligands at high temperatures. The same is true for the aforementioned 4-membered palladacycles.

A recent study elucidated the mechanism of the formation of active Pd(0) complexes starting from the common Pd(II) precursor $Pd(OAc)_2$ and XPhos (Figure I.29).[182] Using electrochemical techniques, it was claimed that the initial step is the formation of a $Pd(II)(OAc)_2$XPhos complex. Then, through an intramolecular electron transfer, the complex is reduced to a transient anionic $[Pd(0)OAc]^-$ complex which then gets ligated to XPhos to form Pd(0)XPhos. In agreement with Buchwald's research, the latter monoligated complex is responsible for the oxidative addition and it occurs at room temperature even for the less reactive aryl chlorides. The diligated complex $Pd(0)(XPhos)_2$ was found to be unreactive.

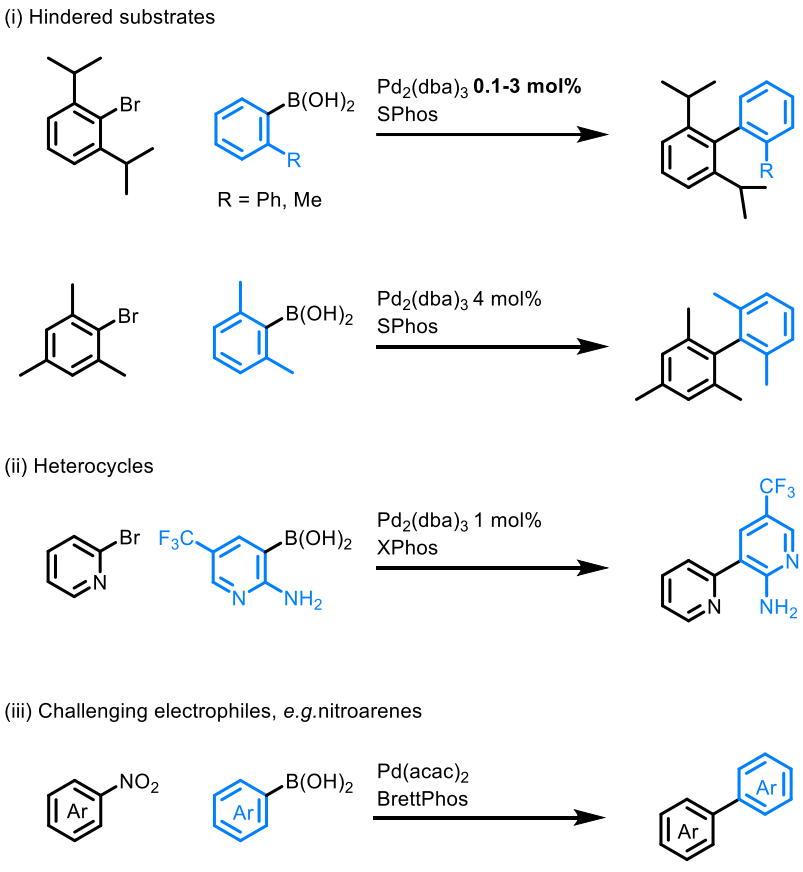


Figure I.30: Examples of challenging couplings with Buchwald ligands. The structures of the corresponding ligands are found in Figure I.27

These ligands were used in the Suzuki reaction to synthesize hindered tetra-*ortho* substituted biphenyls and enabled the coupling of challenging heterocyclic substrates (Figure I.30). In general, most aryl chlorides, bromides and triflates couple using very low catalyst loadings and at room temperature.[87,140,197] Further illustrating their high catalytic activity, Buchwald ligands were used to couple challenging new electrophiles such as nitroarenes (Figure I.30) and sulfones.[4,5,11]

1.5.4 Other phosphine ligands

The high utility of phosphine ligands is due to their strong sigma-donating ability, increasing the electron density at the palladium center and favoring oxidative addition. Π-backbonding contributes to the electronic effects of phosphine ligands, allowing them to act as an electron shuttle. Their stability and the commercial availability of a wide array of phosphine ligands made it possible for chemists to fine-tune electronic and steric parameters of organometallic complexes by varying the phosphines used.[199–201]

Despite the higher versatility of Buchwald ligands presented earlier, other phosphine ligands have remained useful, as demonstrated by their use in recent industrial reactions.[52] The comparable reactivity induced by other phosphine ligands at a lower cost makes these older phosphines superior for some reactions.

Entry	Ligand	Price per mol of phosphorous (€)
1	SPhos	10279
2	P^tBu_3	1036
3	dppf	2703
4	PCy_3	202
5	PPh_3	60.3

Table I.1: Relative price of various phosphine ligands (Strem Chemicals)

Comparing the prices listed on the Strem website for 100 g of a given ligand (14/12/2020), SPhos is 10 times more expensive per mole of phosphorous than P^tBu_3, which also displays a high coupling activity (Table I.1, entries 1 and 2).[129] The high price of dppf (entry 3) is offset by its seemingly high reliability in industrial settings.[52]

Tricyclohexylphosphine also displays high coupling activity[129] at a much lower price (entry 4), and the low-cost PPh_3 (entry 5) still finds many uses in Suzuki couplings.[53]

In coupling reactions, the main drawback of phosphines is their tendency for oxidation and "ligand scrambling" – a side reaction in which the aryl groups of the ligand get transferred to the coupling product, which is especially favored with PPh_3.[202] The main upcoming challenge, however, is the high demand and limited supply of phosphorous worldwide, with some estimating that a significant portion of phosphorous mines will be depleted in the coming decades, leading to phosphorous shortages and thus possibly a high inflation of the price of these ligands.[203–205]

1.5.5 NHC Ligands

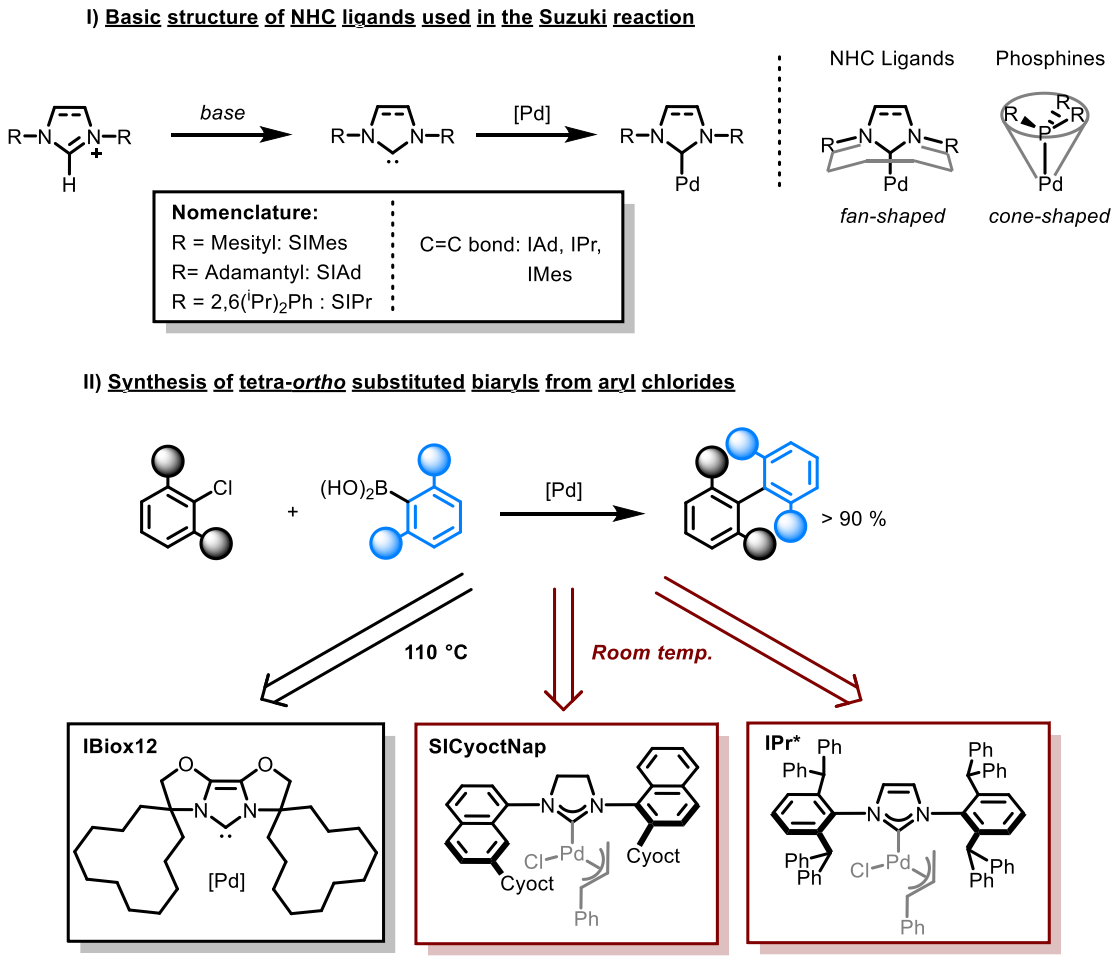


Figure I.31: Basic structure of NHC ligands and examples of challenging reactions

N-Heterocyclic carbene (NHC) ligands have the advantage of being more conveniently synthesized from abundant aldehydes and amines. They are stronger

sigma donors, their steric properties are also tunable by varying the *N*-substituents,[199,206] and they are more tolerant to oxidation.[207,208] NHC ligands used in the Suzuki reaction are mostly based on imidazolium or dehydro-imidazolium structures and they have a different spatial arrangement: they are fan-shaped rather than cone-shaped (Figure I.31, I).[199,206]

The strong sigma donation and high steric bulk, favoring the formation of reactive monoligated palladium, makes them efficient ligands for the Suzuki reaction, even for challenging substrates. Their favorable properties were fist demonstrated using the 1,3 substituted imidazoliums **IPr** and **IAd**: cross-coupling of aryl chlorides was achieved at room temperature.[209,210]

The synthesis of the challenging tetra-*ortho* substituted biaryls from aryl chlorides was achieved using the very hindered oxazo-imidazolium IBiox12 ligand (Figure I.31, II).[206] This type of challenging coupling was improved using catalysts bearing the **IPr*** (the asterisk is part of name) and **SIOctNap** ligands: though the earlier **IBiox12** ligand required relatively high catalyst loadings and temperatures, the newer catalysts afforded the coupling products at room temperature with loadings as low as 0.5 mol% for some substrates.[211,212]

Other carbene ligands that have been developed for the synthesis of hindered biphenyls are mostly based on 1,3 substituted imidazoliums, but no recent improvements have been made compared to the highly active **IPr*** and **SIOctNap** ligands.[213]

Another interesting class of NHC ligands that have been used successfully in the Suzuki coupling are biphenyl-based pyridimidazolium structures: essentially the NHC analogues of Buchwald ligands.[206,214] Their application in the Suzuki reaction was first reported by Glorius, where hindered aryl chlorides were successfully coupled to form di- and tri-*ortho* substituted biaryls,[214] using an NHC analogue of the previously reported DPEPhos by Buchwald (Figure I.32, I).[214,215] These types of ligands have seldom been used in cross-couplings until their recent applications in the cross-couplings of challenging electrophiles such as nitroarenes, where they showed superior activity to Buchwald ligands,[216,217] and for the cross-coupling of sulfoxides (Figure I.32, II).[218]

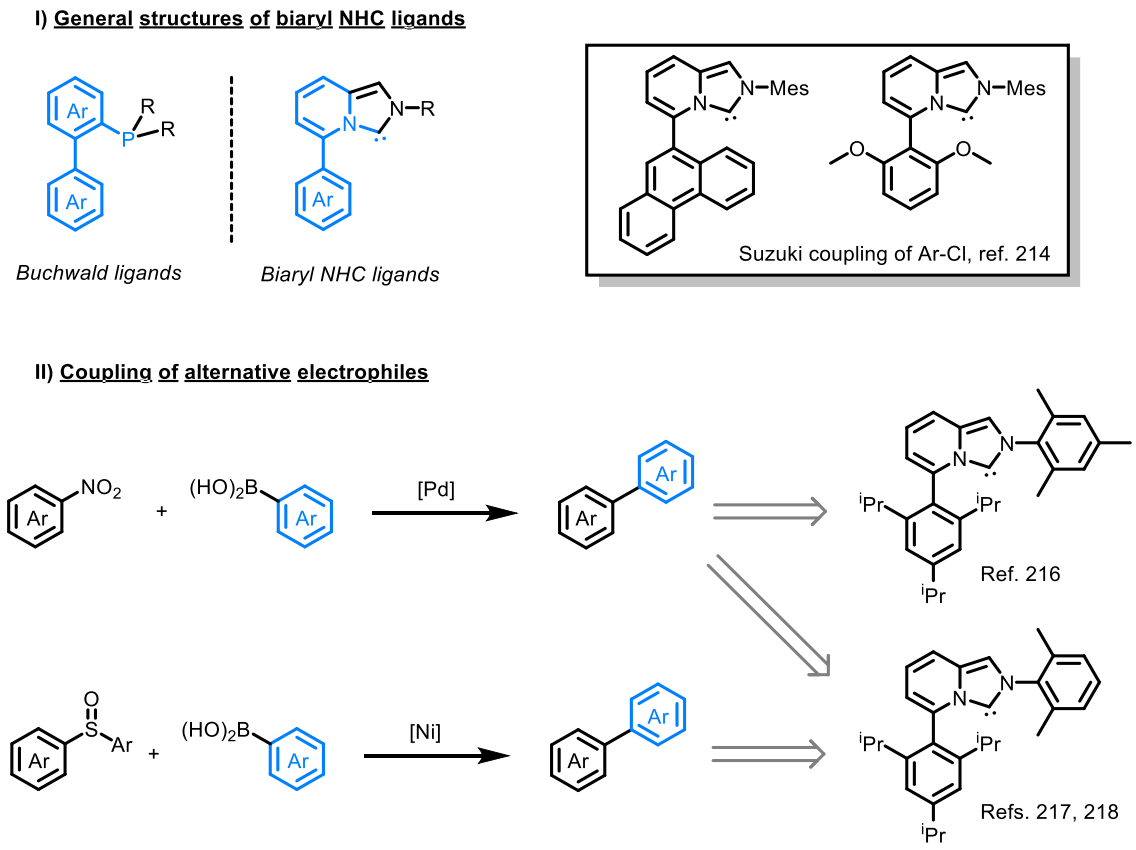


Figure I.32: Biaryl NHC ligands analogous to Buchwald ligands and their uses

1.6 Electrophiles in the Suzuki reaction

In today's state-of-the art, the standard electrophilic coupling partners in the Suzuki reaction is typically a halide (-I, -Br, -Cl) or pseudohalide (-OTf). To broaden the scope of this reaction, substantial efforts were undertaken to find alternative electrophiles that can present improvements such as a lower reactivity towards other reaction conditions, the possibility to act as a directing group, accessing other structures as end-products, or promoting the base-free couplings presented in subchapter 1.4.4.

1.6.1 Halides and pseudohalides

The order of reactivity of aryl halides is usually F << Cl < Br < I, which is consistent with their respective bond dissociation energies (BDE, kcal/mol) of 126, 96, 81 and 65.[219] This trend was confirmed by several reported syntheses of terphenyls starting from polyhalogenated arenes.[220,221] In these experiments, arenes bearing both an iodide and a bromide were first coupled on the iodide and then the bromide (Figure I.33). One-pot sequences were also reported.[220] Similarly, in Suzuki's first report of the cross-coupling of bromoarenes, it was noted that chloroarenes did not react and *p*-ClPhBr was successfully coupled on the bromide, leaving the chloride intact.[80]

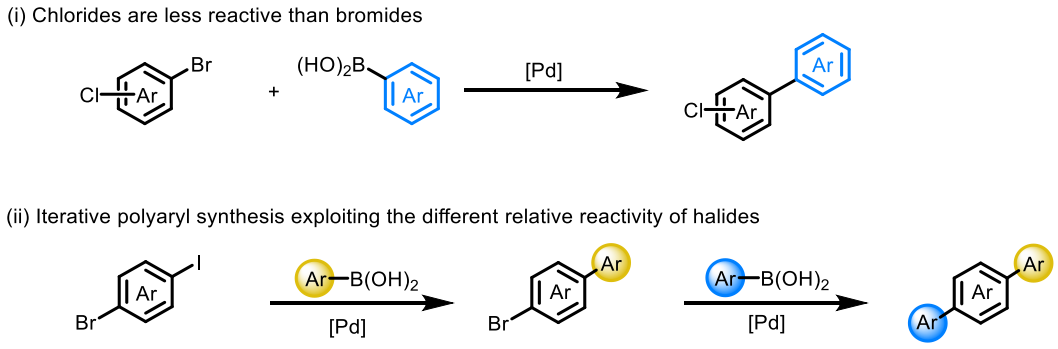


Figure I.33: Experiments showcasing the relative order of reactivity for halides

In the same paper, iodides seemed less reactive than bromides, leading to lower yields under the same reaction conditions. Fu also noted that using his newly developed method, iodides reacted slower than bromides.[129] It was later postulated that, while iodides and activated bromides undergo very rapid oxidative addition, the rate-

determining transmetalation makes the reaction more dependent on the base and solvent system, explaining the sometimes lower reactivity of iodides.[107] This was later experimentally confirmed by studying the inhibitory roles of various halide ions on transmetalation. Using Pd/SPhos in THF/H_2O with K_3PO_4, the reactivity trend was reversed, leading to the following observed reactivity: PhI < PhBr < PhCl. For PhI, the initial conversion was very rapid, due to the easier oxidative addition, but stalled after a few minutes. This was explained by the increasing inhibitory effect of their respective halide ions (accumulating over time) in transmetalation (see Figure I.14). Switching to the less polar solvent toluene led to a better reactivity for iodides, due to the lower solubility of KI.[137]

Amongst the various available aryl halides, chloroarenes are the most advantageous. They combine reactivity (now trivial with the use of modern ligands) with cheap price. bromides and iodides are more pricey, and fluorides are both costly and unreactive.[222] Triflates are also advantageous, being readily available from abundant phenols. However, they aren't very stable as they are susceptible to hydrolysis.[223]

Initial reports of the Suzuki coupling of aryl and alkenyl triflates indicate that triflates possess a reactivity intermediate to those of chlorides and bromides, leading to: Cl < OTf < Br < I.[223,224] Arenes bearing both a triflate and bromide or iodide are first coupled on the latter. It was found that the addition of lithium chloride enhances the reaction,[225] presumably by stabilizing the cationic palladium triflate with a halide ion, preventing catalyst decomposition.[1]

This relative reactivity was challenged by Jutand, who observed a slightly faster oxidative addition for triflates than for bromides using a Pd(0) complex,[226] a trend also observed in a palladium-catalyzed Sonogashira-type reaction.[227] A study by Brown found that the lower reactivity of triflates relative to bromides is exclusive to the Suzuki reaction. Using an arene substituted by both a bromide and a triflate, the Heck, Stille, Negishi and Buchwald-Hartwig amination reactions usually favor coupling on the triflate. One hypothesis is a sequestrating effect of the bromide by the boron, due to the affinity of boranes towards bromides (in contrast, triflate ions are exceptionally poor Lewis bases).[228]

Fu's experiments using bulky electron-rich monophosphines on palladium found triflates to be even less reactive than chlorides when using P^tBu_3 (Figure I.34): the

relative reactivity of triflates to chlorides thus can't be reliably established.[129] For the Suzuki reaction, OTf < Br and Cl < Br but OTf ~ Cl depending on the conditions. Shoenebeck elucidated the reason for the trend inversion of triflates and chlorides depending on the catalyst used. Starting from *p*-ClPhOTf, monoligated systems (formed with P^tBu_3) favor insertion into the Ar-Cl bond, whose BDE is lower (90.6 kcal/mol) than the Ar-OTf bond (101.5 kcal/mol). Diligated catalysts (formed with PCy_3) favor oxidative addition at the site with greatest HOMO-LUMO interactions, found at the Ar-OTf bond (Figure I.34).[124]

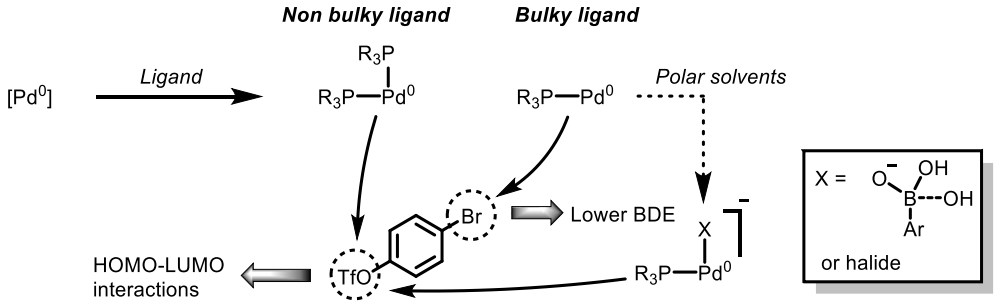


Figure I.34: Influence of catalyst on chemoselectivity

In polar solvents, Schoenebeck found that with P^tBu_3, which normally favors coupling on the chloride, insertion was favored on the triflate.[123] This selectivity inversion is allegedly due to the formation of anionic palladium complexes in polar solvents, which favor oxidative addition in triflates rather than chlorides (Figure I.34). This further explains the higher reactivity in the coupling of triflates when adding halide ions, such as LiCl in one of the first reports of the Suzuki coupling on triflates.[225] In the absence of added halides, an anionic palladium complex can be formed through coordination with a boronate (Figure I.34).[123]

As discussed in subchapter 1.4.4, the least reactive of the aryl halides – aryl fluorides – are also successful coupling partners in the Suzuki reaction, enabling base-free couplings through the formation of a Pd-F intermediate after oxidative addition (Figure I.18).[159] Unfortunately, this base-free approach suffers from a narrow scope and an earlier paper disclosed a more generally applicable synthetic method using nickel and a zirconium additive. Interestingly, in this case, coupling did not occur without added fluoride.[229]

1.6.2 Highly reactive electrophiles: diazoniums and iodoniums

Apart from their high reactivity, diazoniums have the advantage of being conveniently prepared from anilines (one of the most abundant classes of arenes) in short reaction times without a purification step.[149] They are also often more economical than halides since many aryl halides are synthesized from diazoniums through the Sandmeyer reaction (Figure I.35).[230] As discussed in chapter 1.4.4, diazoniums couple in base-free conditions (transmetalation occurs through a cationic palladium complex) and ligands are often avoided as well: another selling point for diazoniums.[149,156]

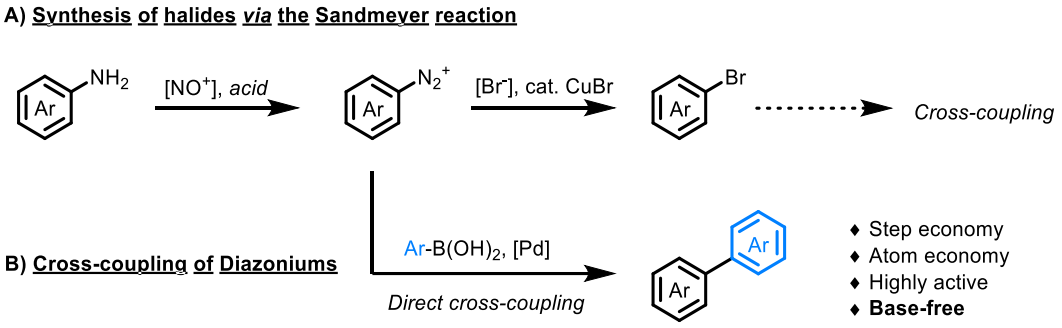


Figure I.35: Coupling of halides vs direct coupling of diazoniums

Their main drawback lies in their liability to explosively decompose. However, this instability is mostly seen in diazoniums whose counteranion is nucleophilic, such as acetates or halides. The use of tosylates or tetrafluoroborates enables their purification and storage as stable compounds.[149] Their relative safety is demonstrated by their use in the industrial synthesis of Prosulfuron via the palladium-catalyzed Heck reaction.[156,231] In the Suzuki reaction, diazoniums were investigated in the synthesis of a precursor compound to several pharmaceutically active molecules and a reaction was safely conducted in near-kilogram scale.[230]

The high reactivity of diazoniums in the Suzuki reaction is illustrated by their efficient coupling, in their first report, at room temperature in base-free and ligandless conditions.[147] A later report by Andrus revealed efficient cross-coupling at temperatures as low as 0 °C using the NHC ligand SIPr, still in the absence of base, in short reaction times (Figure I.36 A).[232] In the same paper, it was revealed that room temperature couplings tolerated palladium loadings as low as 100 ppm.

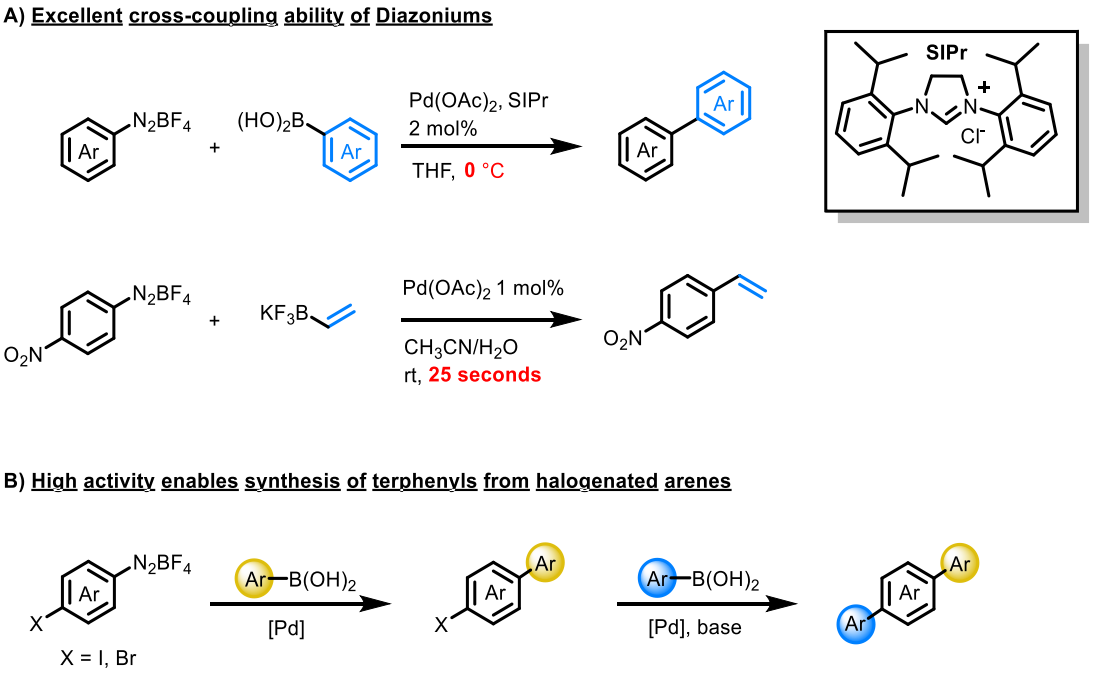


Figure I.36: High coupling activity of diazoniums

A more recent study revealed a Suzuki coupling of a diazonium reaching 97% yield in only 25 seconds (Figure I.36 A).[233] Diazoniums can thus be considered as the most reactive of the electrophiles used in the Suzuki reaction. Their higher reactivity relative to bromides and iodides was demonstrated in several papers,[149,156,234–237] and was exploited in the synthesis of unsymmetrical terphenyls starting from halogenated arene diazonium compounds (Figure I.36 B).[235,236]

To bypass the hazards associated with diazonium salts, the use of anilines and acetanilides as starting materials was also reported, in a one-pot procedure involving diazotization with BF_3 etherate and subsequent cross-coupling (Figure I.37).[149,156,232,238] The diazotization was first performed at 0 °C, after which the catalyst was added and the reaction was warmed to room temperature. Similarly, a procedure by Wang was developed using acetic acid for the diazotization step.[239] The previous procedure with BF_3 requires the addition of the catalyst after completion of the first step but Wang's procedure occurs with a single addition step. Unfortunately, while slightly more convenient, this procedure requires higher catalyst loadings (5 mol% *vs* 1 mol%) and reaction temperatures (90 °C *vs* r.t.). However, Wang's procedure still proceeded satisfactorily without the addition of acid.

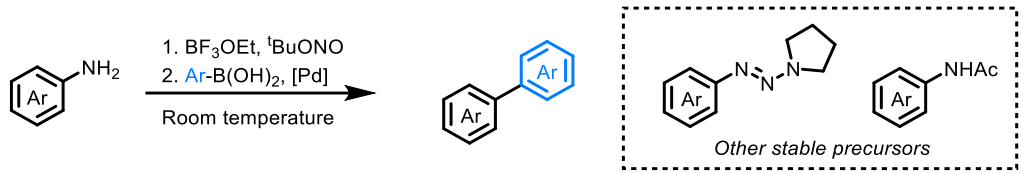


Figure I.37: Anilines as starting materials and other stable diazonium precursors

Other procedures were developed to avoid the use of added acid in the one pot procedures from anilines but they require a coordinating group *ortho* to the aniline, limiting their scope.[240,241]

Triazenes were also efficiently used as stable precursors to diazoniums in base-free Suzuki couplings employing BF_3 etherate as the Lewis acid necessary for their conversion to the corresponding diazoniums (Figure I.37).[242,243] Cross-coupling could occur in excellent yields after only 10 minutes at room temperature.[242] However, bromides and iodides were not well tolerated. Using a supported catalyst, iodides and bromides were successfully added to the scope of aryl triazenes.[244] Triazenes are tolerant to strong bases and nucleophiles and display orthogonal reactivity to standard Suzuki coupling conditions until converted to their corresponding diazonium by reaction with a Lewis or Brønsted acid.[156] These properties were elegantly exploited in the synthesis or polyfunctionalized aryl triazenes bearing a boronate ester which were subsequently used for the synthesis of terphenyls via sequential Suzuki cross-couplings.[243]

While diazoniums are highly active electrophiles for the Suzuki reaction, their scope remains limited to aryl compounds (heteroaryl substrates have also been used in the Similar Heck reaction, but the alkyl and alkenyl derivatives are not stable).[149] Iodoniums, which were discussed in chapter 1.4.4 due to their ability to couple without base (Figure I.17 B), are also highly reactive electrophiles that have unfortunately not received as much attention. They can be used to introduce alkenyl moieties and were shown to couple efficiently at room temperature without ligands or base.[150] They are also tolerant to bromides[157] and iodides – the leaving group is an aryl iodide.[149]

While more expensive and less atom-economic, iodoniums are bench-stable and can be used to introduce alkynes and alkenes. The poor atom economy of iodoniums is due to the generation of one equivalent of aryl iodide as a byproduct. However, the

valuable aryl iodide could be recovered or can undergo coupling as well, when harsher conditions are applied.[149]

1.6.3 C–O bond activation in the Suzuki reaction

Phenol-based electrophiles for the Suzuki reaction – encompassing triflates – are among the most diverse due to their convenient syntheses from widespread reagents. Their use in palladium catalyzed coupling reactions was recently reviewed.[245]

Triflates, covered in chapter 1.6.1, are the most prominent of these derivatives. However, substantial efforts were made to find suitable alternatives due to their cost and sensitivity.[245]

A suitable alternative are nonaflates (nonafluoro-butanesulfonates, ONf – Figure I.38). Whereas the synthesis of triflates require the sensitive and costly triflic anhydride, nonaflates have the advantage of being conveniently prepared from the bench-stable and relatively inexpensive $C_4F_9SO_2F$ (NfF). The NfF reagent is stable to air and water but reacts with phenoxides efficiently, generating fluoride as the byproduct – a less wasteful reaction than what is seen with triflic anhydride.[246,247]

Compared to triflates, nonaflates have been shown to have a higher coupling activity but also a higher stability, producing less byproducts resulting from side-reactions and accounting for simpler purification and storage.[247–249] In a representative case study, triflated and nonaflated coumarin derivatives were compared in their reactivity to several cross-coupling reactions. In the Suzuki reaction, the triflated substrate led to the desulfonation product as a major product but the nonaflated substrate could be used to synthesize various cross-coupled coumarin derivatives (Figure I.38).[249]

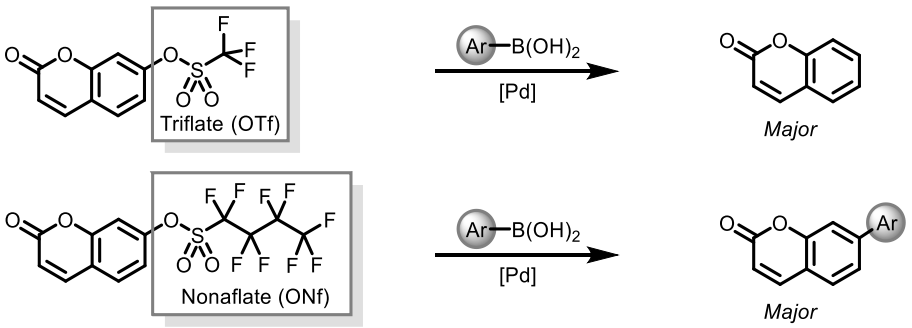


Figure I.38: Nonaflate and its higher stability compared to triflates.

A downside to the use of nonaflates is their low atom economy. Another alternative to triflates are the more economical fluorosulfates. Although their application in cross-coupling date from 1990, they have seen little use until recent years due to their synthesis involving highly toxic fluorosulfonic anhydride.[250]

To improve their usability, the Sharpless group developed a new synthetic method involving the low-cost and less toxic sulfuryl fluoride (used as a fumigant). Aryl fluorosulfates were efficient coupling partners for the Suzuki reaction in aqueous ligandless conditions at room temperature,[190] and a one-pot reaction starting from phenols was also reported (Figure I.39).[251] The order of reactivity of fluorosulfates was reported to be Br > OSO2F > Cl, which was exploited in the synthesis of polyaromatics via sequential Suzuki reactions on polyfunctionalized pyridines.[252]

A more recent study by Schoenebeck confirmed this trend for Negishi couplings using polyhalogenated arenes. A transition state was located by DFT for the oxidative addition in fluorosulfates which is analogous to those of triflates and nonaflates, leading to the conclusion that fluorosulfates are an excellent but cheaper substitute for these groups.[253]

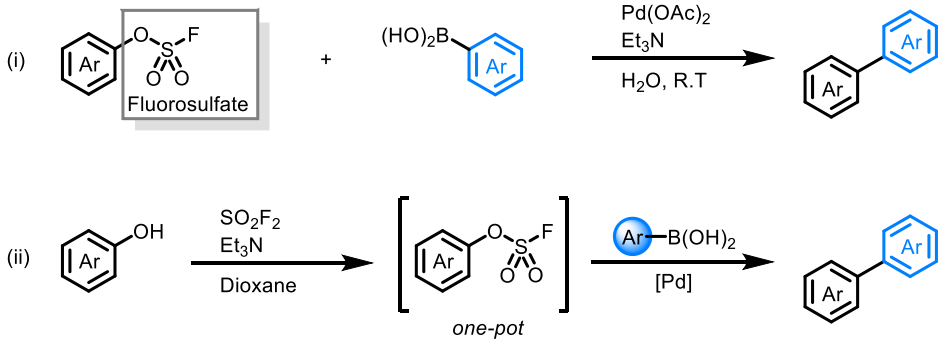


Figure I.39: Structure of fluorosulfates and selected examples of Suzuki reactions

The use of hydrocarbon-based sulfonates such as mesylates and tosylates is well established in organic chemistry and their synthesis is trivial from innocuous reagents, which makes them attractive alternatives to the aforementioned fluorinated sulfonates.

The reactivity of activated aryl mesylates and *p*-fluorobenzenesulfonates was first reported by Percec in 1995.[254] The reaction was low yielding and saw little improvements until the Buchwald group disclosed a general procedure for the cross-coupling of tosylates using XPhos (Figure I.40).[255]

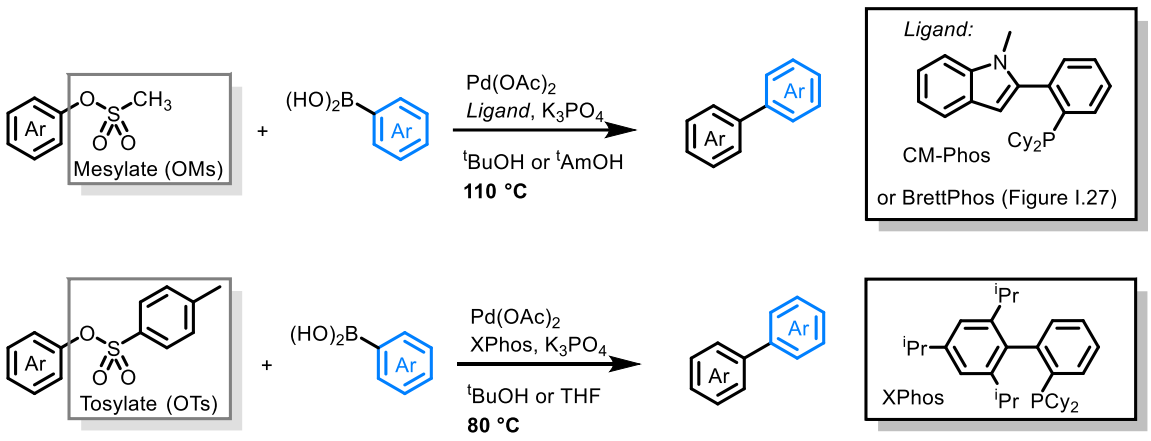


Figure I.40: Selected examples of methodologies for the Suzuki coupling of mesylates and tosylates

The reaction is run in *tert*-butanol, which is unusual for cross-coupling reactions. The role of this solvent was attributed to a better solubility of the starting material and the boronic acid, leading to a faster coupling rate relative to protodeboronation for sensitive boronic acids.

Efficient procedures for the coupling of mesylates were discovered by the group of Kwong using CM-Phos, and Buchwald later extended the scope to heteroaromatics and hindered substrates with BrettPhos, also using tertiary alcohols as solvents.[256,257] *Tert*-Amyl alcohol was used by Buchwald as an improvement due to its higher boiling point and higher convenience – ^{t}BuOH is often solid at room temperature.

Other examples of electrophiles based on the -OSO_2R moiety include nosylates (ONs, R = 4-NO_2Ph),[258] imidazolylsulfonates[259] and pentafluorobenzenesulfonates.[260]

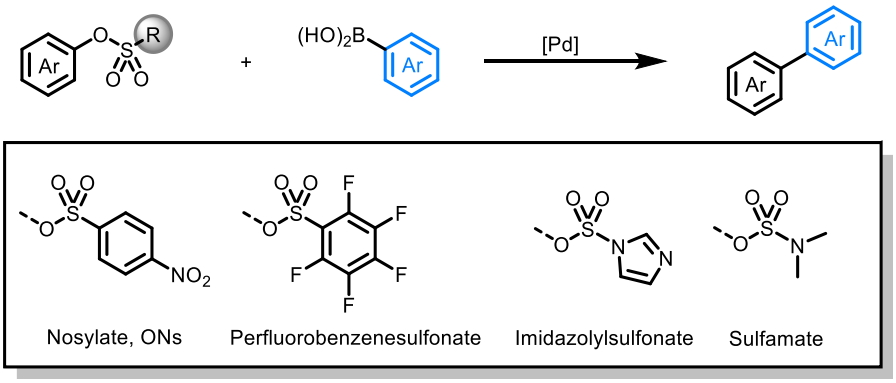


Figure I.41: Other sulfonyl-based electrophiles in the Suzuki reaction

The latter are highly active coupling partners, achieving high yields at room temperature. Imidazolylsulfonates on the other hand have been shown by kinetic experiments to have a similar reactivity to triflates; tosylates remained intact in their reaction conditions.[259] The latter substrates also have the advantage of having their leaving group decompose to the innocuous imidazolium sulfate unlike aryl and alkyl sulfonates which are suspected of genotoxicity.[259]

Sulfamates are a distinct subcategory in $ROSO_2X$-based electrophiles, being neither fluorinated nor hydrocarbon based ($X = NMe_2$). The use of sulfamates in the Suzuki reaction was first described in a nickel-catalyzed reaction but required rather harsh reaction conditions.[261] A later report employing palladium showed the Suzuki coupling of sulfamates at room temperature employing a (η^3-1-^{t}Bu-indenyl)-based precatalyst ligated to XPhos.[262] However, the substrate scope was rather narrow and unsubstituted phenyl sulfamate required heating at 80 °C. In contrast, the earlier nickel-catalyzed reaction had a more complete scope and an earlier palladium catalyzed method with a wider scope required a similarly high temperature of 110 °C.[263]

Sulfonate-based leaving groups are highly developed in the Suzuki reaction and many methods involving superior alternatives to triflates are now available. The most promising electrophiles appear to be fluorosulfates, due to their high atom economy (highest among the sulfonates) and high reactivity as well as their relative stability.

Phosphate esters have also been used sparingly in the Suzuki reaction for the coupling of vinyl substrates. The first report appeared in 1999 and required relatively mild conditions.[264] Soon after its publication, this new method was used in the total synthesis of ciguatoxin.[265] Several complex α-oxo vinyl phosphate were coupled to sp^3 carbons from carbohydrates, illustrating the wide scope of this reaction (Figure I.42 A).

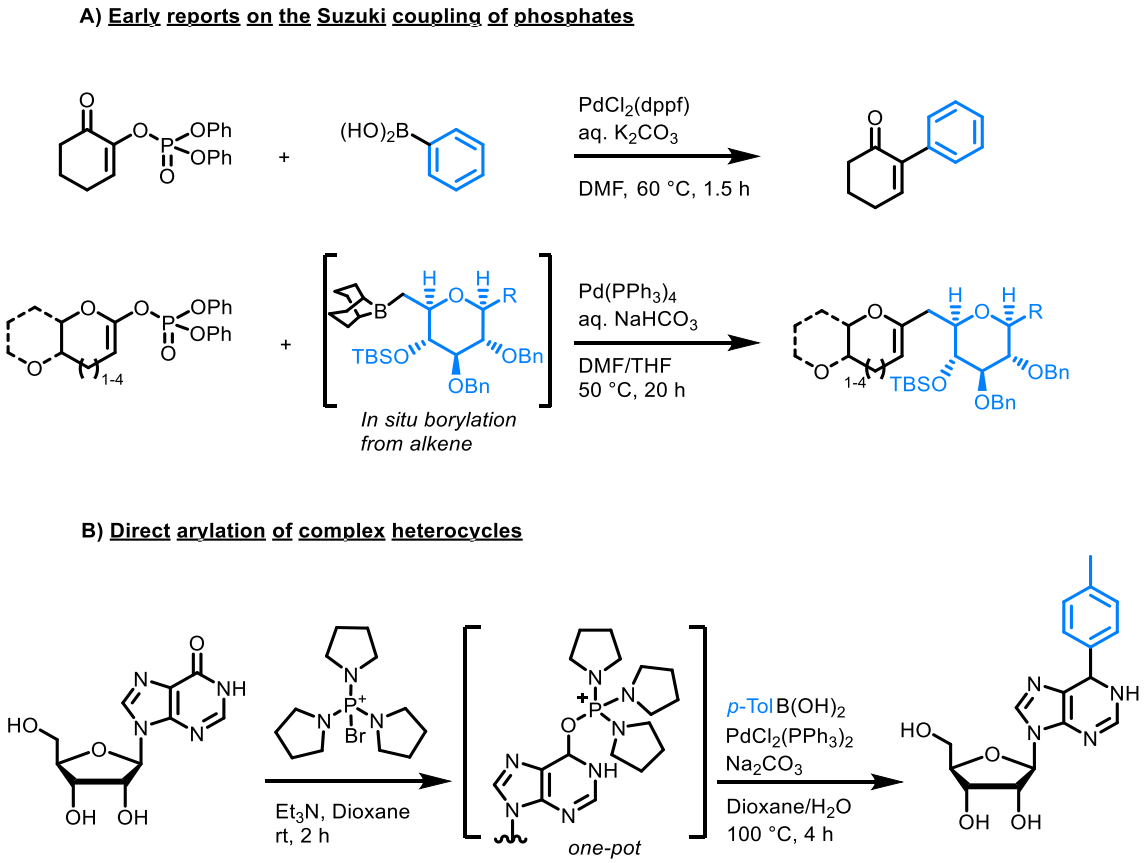


Figure I.42: Examples of Suzuki couplings on vinyl phosphates and phosphoniums

The orthogonality of phosphorylation reactions towards heterocycles has driven the use of these functional groups in methodologies for the arylation of heterocycles.[245,266,267] The most representative example is a method applied for the arylation of heteroarenes, used in the one-pot arylation of the unactivated and unprotected nucleobase inosine, via the in-situ formation of a phosphonium ether (Figure I.42 B).[267]

Enol phosphinates (-$OP(O)Ph_2$ instead of -$OP(O)(OPh)_2$) have also appeared in the Suzuki reaction, coupling efficiently in short reaction times.[268]

Despite the relatively early discovery of the reactivity of phosphates in the Suzuki reaction, and its impressive scope, aryl phosphates have remained largely unexplored in palladium catalyzed cross-coupling reactions. Only one report on the nickel catalyzed Suzuki reaction of aryl phosphates has appeared.[269]

The coupling of esters is also efficient, as demonstrated by the wide scope of a one-pot reaction involving pivalate esterification and coupling starting from phenols (Figure I.43 A).[270] Switching the ligand enabled selective synthesis of biaryls or ketones/benzophenones. In this study, this class of substrates was shown to be less reactive than bromides but tolerant to chlorides and tosylates. Earlier methods enabled the arylation of allylic esters,[271] or the synthesis of benzophenones from aryl esters (Figure I.43 B).[272–275] The Suzuki coupling of the more atom economical acyl fluorides, however, was also developed for the synthesis of similar ketones.[276] Methods employing nickel could also be used for biaryl formation such as in the procedures of Love and Yamaguchi (Figure I.43 B).[275,277–279]

Palladium catalysis is lacking compared to nickel in the coupling of other carbon-based leaving groups: carbonates, and carbamates. Using palladium, only benzylic coupling was achieved from carbonates.[280,281]

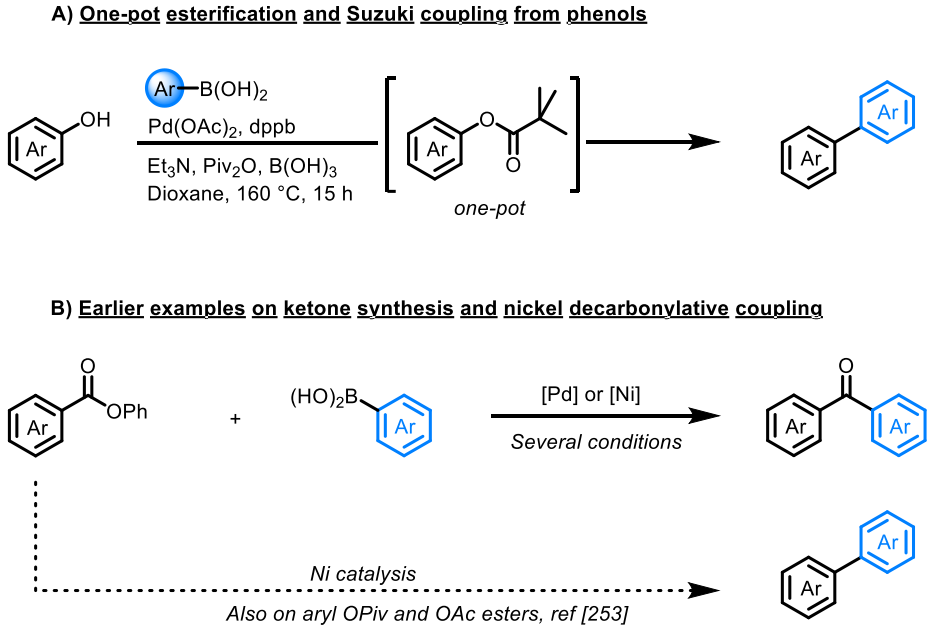


Figure I.43: Suzuki couplings on aryl esters

The benzylic carbonate coupling has recently been used in a process development reaction for the synthesis of a pharmaceutical molecule in near-kilogram scale,

highlighting its importance (Figure I.44 A).[282] Halides could not be used because of the amide-diamide side-chain – benzyl carbonates were an efficient alternative. Nickel on the other hand has been used to form biaryls from carbonates, as well as from carbamates, which have yet to be used in the palladium catalyzed Suzuki reaction (Figure I.44 B).[261]

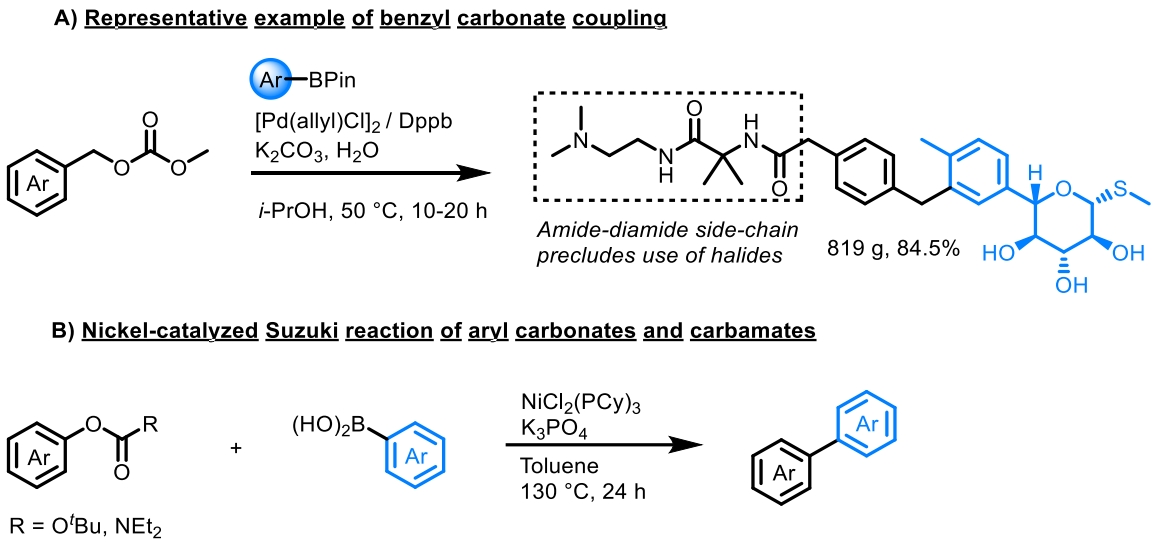


Figure I.44: Suzuki couplings on carbonates and carbamates

Finally, using nickel, the Suzuki coupling has even been reported on aryl methyl ethers on molecules such as anisole without any activating or directing group (Figure I.45).[283]

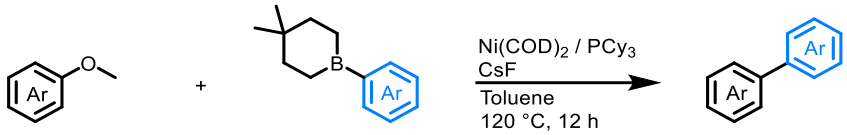


Figure I.45: Nickel-catalyzed Suzuki cross-coupling on methyl ethers

1.6.4 Nitrogen-based electrophiles

Similarly to esters, amides have also been used as successful coupling partners in the Suzuki reaction.[275,284] Amides could be used as coupling partners when their electronic and steric properties led to them adopting a twisted conformation. By deconjugating the nitrogen lone-pair with the adjacent carbonyl, the C-N bond is weakened, and oxidative addition becomes possible (Figure I.46 A). Glutarimides, *N*-tosylated or Boc protected amides have been cross-coupled successfully.

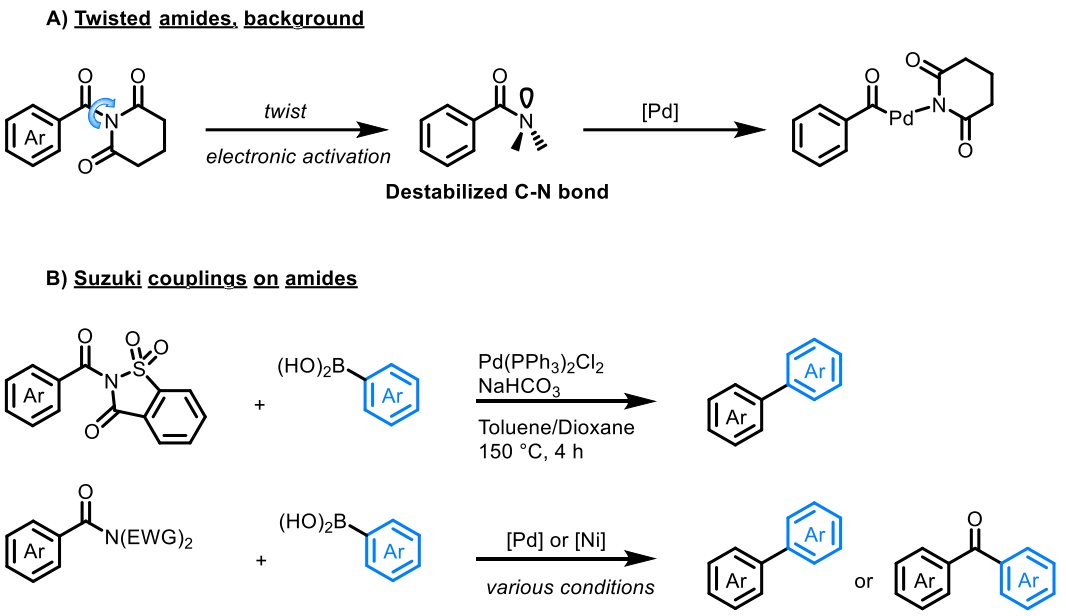


Figure I.46: Twisted amides in the Suzuki reaction

In earlier reports, palladium catalysis only yielded ketones,[284] but nickel enabled the decarbonylative version of this coupling to afford biphenyls (Figure I.46 B).[285,286] In this respect, the coupling reactivity of twisted amides appears to be very similar to that of esters. A recent paper, however, elucidated the palladium-catalyzed decarbonylative coupling of saccharin-based amides (Figure I.46 B).[287]

Aryl trimethyl ammonium salts are another class of nitrogen-based electrophiles which bear the advantage of being conveniently prepared from abundant anilines. Though suffering from lower atom-economy compared to diazonium salts, these electrophiles avoid the associated safety risks. Biaryl formation was only reported using nickel,[288] but palladium can be used to couple benzylic substrates (Figure I.47).[289] Aryl chlorides are tolerant to the palladium-catalyzed variation on benzylic substrates.

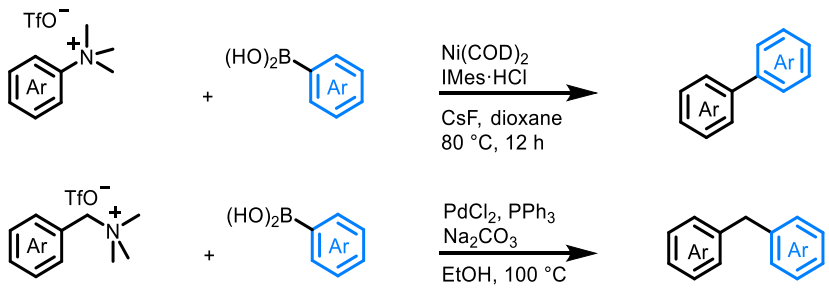


Figure I.47: Suzuki coupling of aryl and benzylic trimethyl ammoniums

An unusual example is in the cross-coupling of aryl hydrazines, where the reaction proceeds not with base but with addition of acid and under air. It was found that both the acid and oxygen are necessary to favor the formation of N_2 and O_2 as the leaving group (Figure I.48).[290] Another team independently discovered the equivalent reaction using base – air was also required in this reaction.[291]

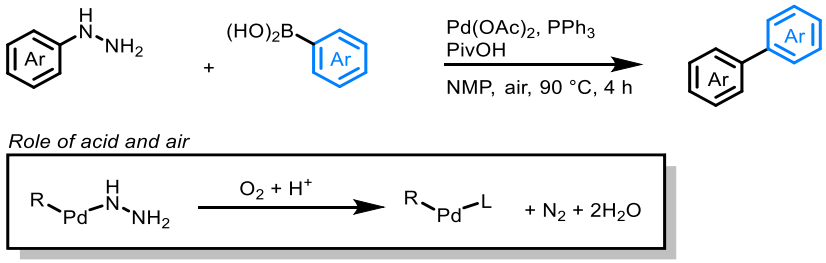


Figure I.48: Suzuki coupling requiring acid and oxygen: aryl hydrazines

Nitroarenes are the most economical class of nitrogenated electrophiles, due to their ready availability by direct nitration of arenes. Most anilines are prepared by reduction of nitroarenes. Besides their advantage from an economical point of view, nitroarenes are a useful scaffold because of their ability to act as *meta* directing groups for S_EAr reactions such as nitration, halogenation, sulfonylation and Friedel-Crafts reactions. Nitroarenes usually tolerate many reaction conditions and are not often thought of as a potential leaving group even though their use as such has been documented as early as 1891 and in several other S_NAr reactions.[292,293]

As electrophiles for the Suzuki reaction, they have remained elusive until a report by Nakao and coworkers in 2017, where various nitroarenes were coupled using the Buchwald ligand BrettPhos under high temperatures (Figure I.49).[4] This procedure required high ligand loadings, but a later version using an NHC equivalent of BrettPhos (see chapter 1.5.5, Figure I.32) led to similar results using much lower catalyst loadings.[216,217]

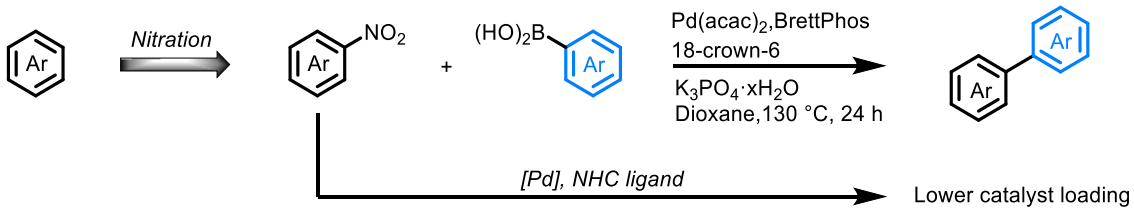


Figure I.49: The Suzuki coupling of nitroarenes

1.6.5 Sulfur-based electrophiles

Thioesters are the most widespread sulfur electrophiles in cross-coupling reactions with organoborons due to the discovery of the Liebeskind-Srogl reaction. This copper-mediated and palladium-catalyzed reaction, similar to the Suzuki reaction, is used in the synthesis of ketones. Several reviews have been published on this reaction and it will not be covered here.[294,295] Similarly, thioamides and thioureas were recently shown to couple in a silver-mediated reaction.[296]

The similar thioethers have been used to some extent in the Suzuki coupling, but their lower reactivity has largely limited their use to heteroaromatic substrates such as indoles and furans bearing *ortho* directing groups or to tetrazines.[297]

A few examples of aryl thioester coupling have appeared, such as the rhodium-catalyzed Suzuki reaction of *ortho*-keto aryl thioethers, reported independently by Shi and Willis,[298,299] and the copper-mediated palladium-catalyzed coupling of *ortho*-nitro derivatives (Figure I.50).[300] Shi's rhodium catalyzed method and the copper mediated reaction of nitrated substrates both require high catalyst loadings (10 – 20 mol%) and superstoichiometric additives, indicative of the low reactivity of these types of substrates. Willis' method however employed lower loadings and the method was found to be orthogonal to aryl halides (-Br, -Cl) and alkyl iodides (Figure I.50).

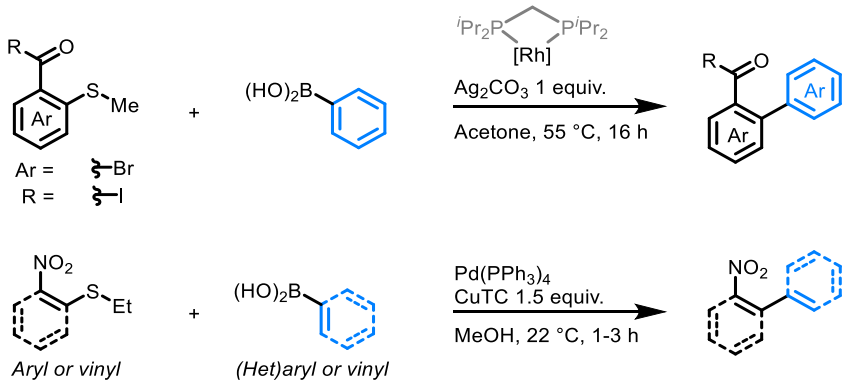


Figure I.50: The Suzuki coupling of aryl and vinyl thioethers

Tetramethylene sulfoniums were first reported by Liebeskind and Srogl as more reactive C–S functional groups for cross-coupling reactions.[301] These sulfoniums were conveniently prepared from tetrahydrothiophene and an alkyl halide or from a thiophenol and 1,4-dibromobutane and are bench-stable compounds. They couple under relatively mild conditions and are tolerant to benzylic and (hetero)aromatic substrates (Figure I.51). This methodology was applied in a recent paper on the Suzuki

coupling of various azulene sulfonium derivatives, where it was found to be superior to the more classical halides or triflates due to their easier preparation. The scope included various sensitive heteroaromatic boronic acids.[302] Tetramethylene sulfoniums were also employed in a base-free coupling with sodium tetra-arylborates.[169]

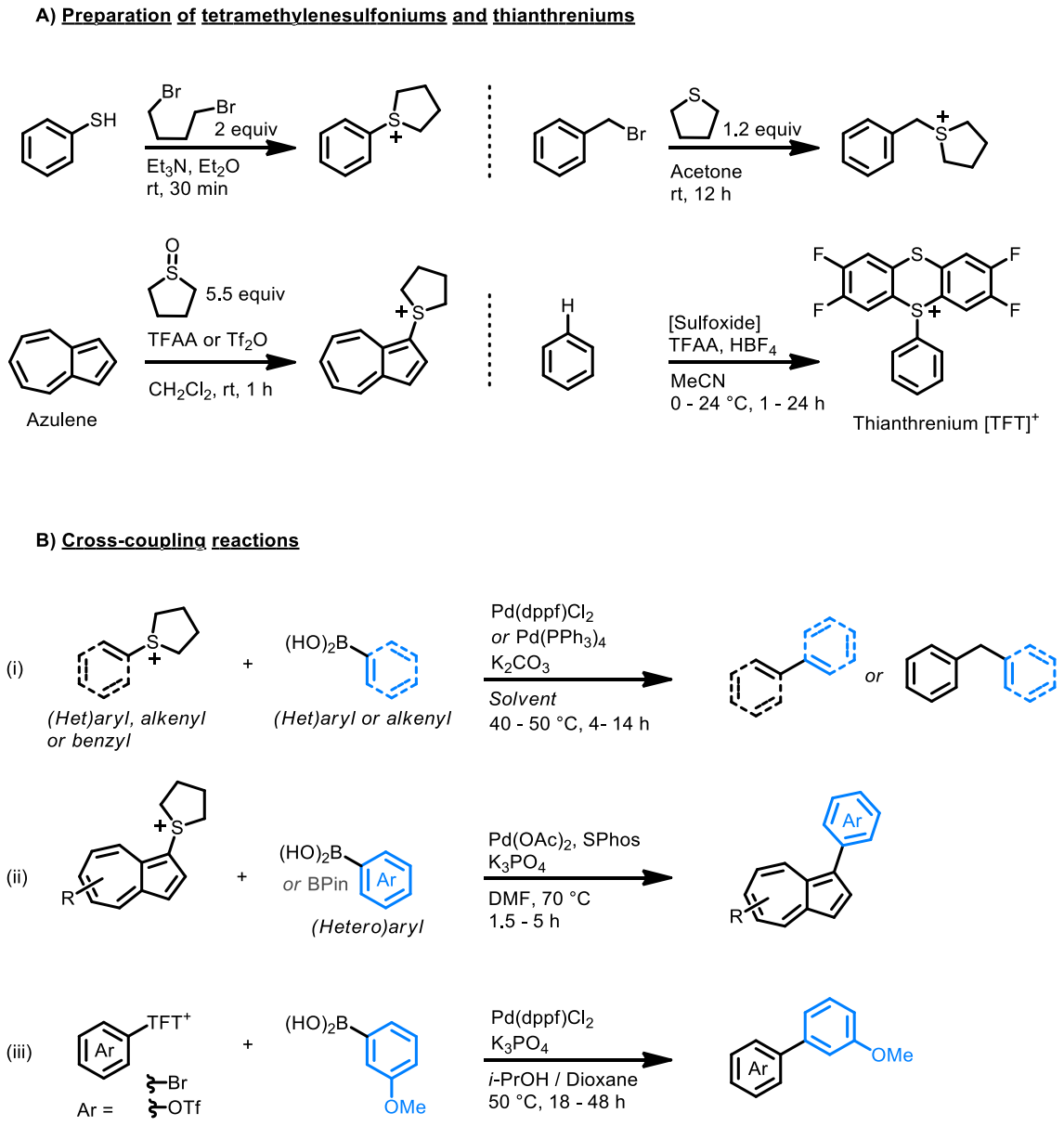


Figure I.51: Structures, preparation, and Suzuki reactions of various sulfoniums

Other types of sulfoniums were also described, such as the (alkyl)diaryl or triaryl derivatives but these were of no real improvement as they required higher catalyst loadings, reaction temperatures, reaction times, displayed a lower atom economy and are harder to synthesize.[297]

The recently disclosed thianthrenium derivatives display a similar profile as another class of bench-stable but reactive ionic sulfur compounds (Figure I.51).[303]

They cross-coupled under similar reaction conditions and were shown to be tolerant to aryl bromides and triflates but only one boronic acid was surveyed (3-methoxybenzene). From an atom economy perspective, they are inferior to the aforementioned sulfoniums due to the very large size of the tetrafluorothianthrene moiety. To tackle atom-economy issues, the thianthrene leaving group was shown to be recoverable, and after oxidation, it could be used in the synthesis of new thianthrenated molecules. A major advantage of the use of this functional group is that their installation is highly regioselective.

Diaryl sulfoxides have also been used as electrophiles in the Suzuki reaction, under palladium or nickel catalysis.[218,304] Both methods required the strong base *tert*-butoxide and used NHC ligands, but the palladium-catalyzed version required milder condition and showed some tolerance towards aryl chlorides (Figure I.52).

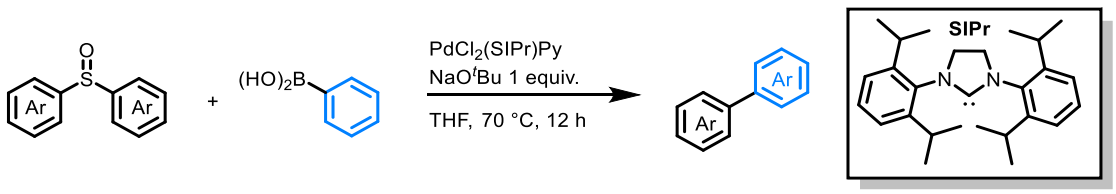


Figure I.52: The Suzuki coupling of diaryl sulfoxides

Sulfonyl chlorides displayed a reactivity between aryl bromides and iodides in the Suzuki reaction, using relatively low catalyst loadings with the NHC ligand SIPr (Figure I.53).[305] Sulfonyl chlorides were also reported to couple with aryl tetrafluoroborates under similar conditions in DMSO, in a reaction tolerant to 4-iodophenylboronic acid (Figure I.53).[306]

The scope was extended in the reaction with tetrafluoroborates, displaying higher yields with alkenyl substrates and successfully coupling various heteroarenes on the boron or sulfonyl substrate.

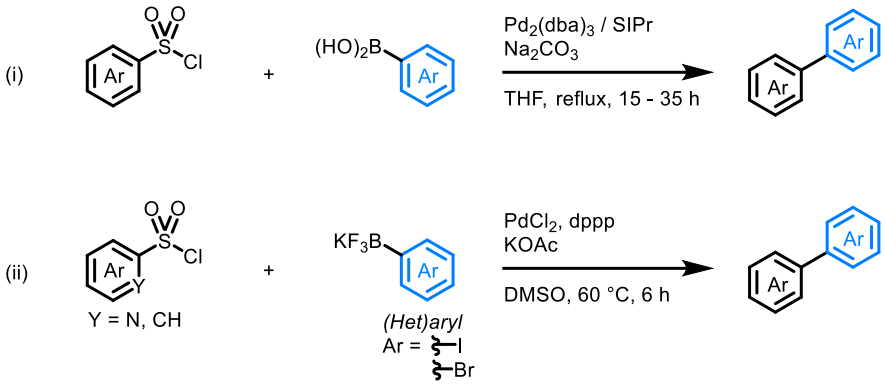


Figure I.53: The Suzuki coupling of sulfonyl chlorides: orthogonality to iodides and bromides

The similar sulfonyl hydrazides were also described in the paper about the Suzuki coupling of aryl hydrazines (Figure I.54).[291] Unfortunately, only two examples were described and the conditions don't appear optimized for sulfonyl hydrazides.

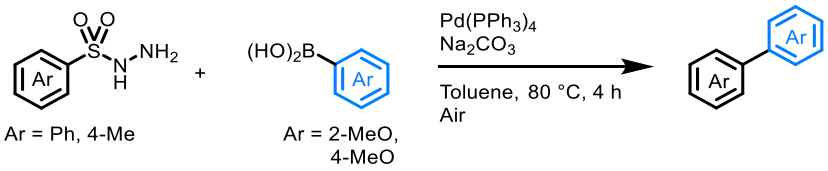


Figure I.54: The Suzuki coupling of sulfonyl hydrazides

Sulfonyl fluorides are another interesting class of sulfur-based molecules. Unlike other sulfonyl halides, they are highly stable (they are inert to hydrolysis and reduction) and have been described as being inert to transition-metal catalysis.[16,17] Their main application is in SuFex chemistry, a branch of "click chemistry", where they undergo nucleophilic substitution only under very specific reaction conditions.

Contrary to the claims of inertness towards transition-metal catalysis, they were shown to undergo Suzuki coupling as an unexpected di-addition product of 4- and 5- bromo 2-pyridine sulfonyl fluoride with 2-thiophene boronic acid. Under the same conditions, other boronic acids did not lead to SO_2F coupling (Figure I.55).[307]

Sulfonyl fluorides are the focus of Chapter 3 of the present thesis, where a method was developed for their cross-coupling under base-free conditions.

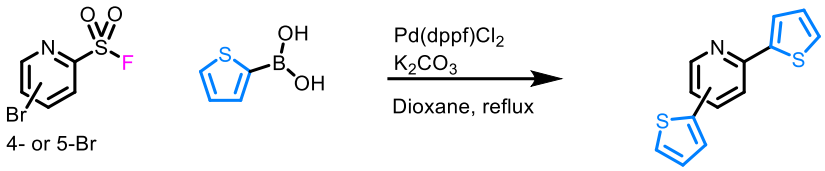


Figure I.55: First report of an unexpected sulfonyl fluoride Suzuki coupling

Sulfones have gotten considerable attention as electrophiles for the Suzuki reaction in recent years.[5,6,8–11,15,19] Like nitroarenes, aryl sulfones can be used as a *meta* directing group for S_EAr reactions,[12] but also for selective *ortho* functionalization via lithiation[7,13] and *para* functionalization via nickel catalysis (Figure I.56).[14] They also appear more robust than nitroarenes: even the highly activated trifluoromethyl sulfones display a lower leaving group ability in S_NAr reactions.[293]

Benzylic sulfones are also an interesting functional group because of the induced acidity of the adjacent protons, leading to possible functionalizations such as arylation,[6,8,10] alkylation[6] or fluorination (Figure I.56).[15]

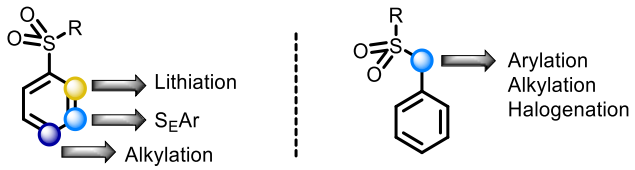


Figure I.56: Sulfones as a synthetic handle for various transformations

Crudden and coworkers demonstrated the synthetic utility of benzyl sulfones in a series of papers reporting their Suzuki couplings. Benzylic sulfones were first used in the Suzuki reaction as part of a sequence to produce triarylmethanes from methyl phenyl sulfone (Figure I.57).[8] The first two arylations were done through deprotonation of the benzylic hydrogens and coupling with aryl halides. The activated phenylsulfonyl group could then be coupled to various boronic acids using SIPr and palladium. Using the more activating 3,5-bis(CF_3)phenylsulfonyl group, simple benzylic sulfones could be coupled under similar conditions,[6] and a nickel-catalyzed version also appeared, using the unactivated phenylsulfonyl leaving group (Figure I.57).[10] Finally, a recent paper described the benzylic fluorination of benzyl trifluromethyl sulfone (SO_2CF_3) and subsequent Suzuki coupling (Figure I.57).[15]

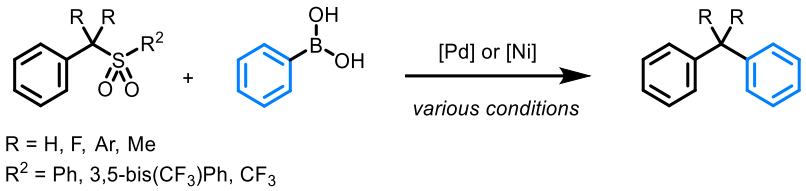


Figure I.57: Crudden's work on benzylic sulfones

Various other procedures emerged, such as the coupling of tetrazolic sulfones[11] or vinyl sulfones (Figure I.58).[9]

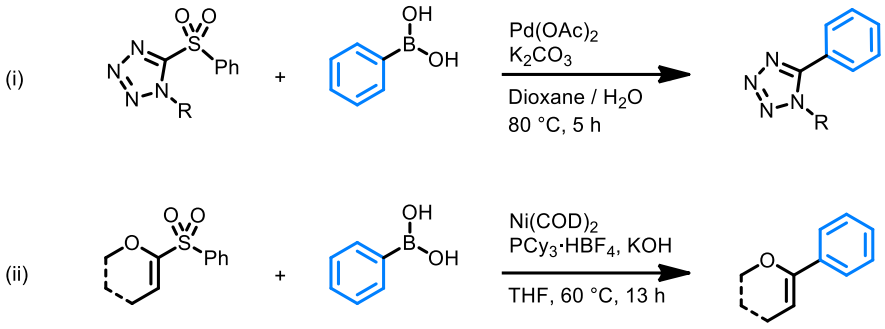


Figure I.58: Coupling of tetrazolic and α-oxo vinylsulfones

A general procedure for the synthesis of biaryls remained elusive however, until a method that will be the subject of the second chapter of the present thesis was disclosed (Figure I.59).[5] Trifluromethyl sulfones were shown to have an intermediate reactivity between aryl (pseudo)halides and nitroarenes, enabling the synthesis of ter- and quarterphenyls via iterative Suzuki reactions.

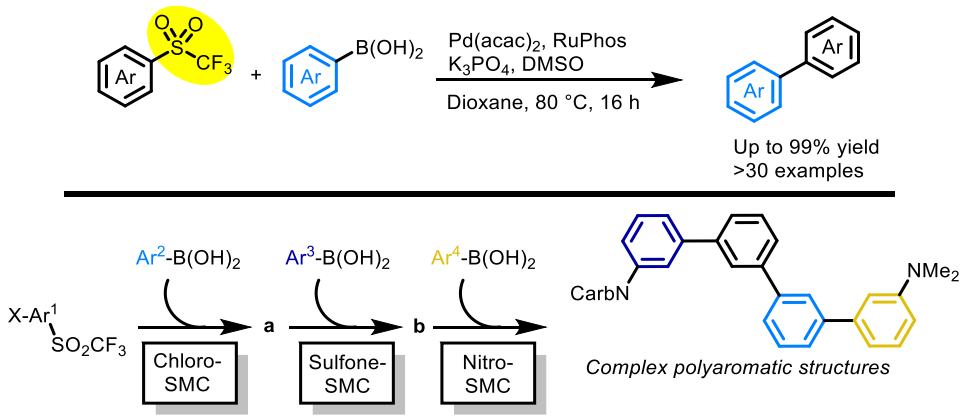


Figure I.59: Our work on the coupling of aryl sulfones

1.6.6 Unusual electrophiles

Some other unusual functional groups were used as electrophiles for the Suzuki reaction. Several procedures were published employing butyl telluride ethers.[308,309] In a silver-mediated reaction with aryl tetrafluoroborates, aryl tellurides were shown to display a higher reactivity than chlorides, bromides and even iodides (Figure I.60).[308] Iodobiphenyls could be synthesized in moderate yields and other halogenated substrates led to excellent yields. The coupling of styryl tellurides proceeded under similar conditions, using ultrasound instead of heating.[309] Vinyl tellurides were also employed in the synthesis of enynes, by coupling with alkynyl trifluoroborates.[310] The drawbacks to these electrophiles are the high catalyst loadings and superstoichiometric silver additives. However, only rudimentary palladium catalysts were screened, and better performances might be possible with the use of more performant ligands (see chapter 1.5).

Diaryl (or di-alkenyl) telluride (IV) dichlorides were also successful in the Suzuki coupling (Figure I.60).[311] Both arenes from the starting tellurium compound were successfully incorporated into the end product in high yields. The addition of silver was not necessary here, but the same comment can be made about the high palladium loadings and the absence of modern ligands.

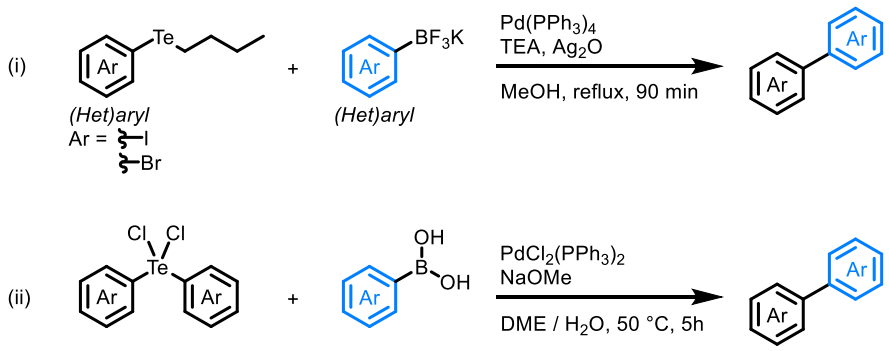


Figure I.60: Structure and coupling reaction of various telluride electrophiles

The related selenides were relatively unexplored, and only appeared in one recent paper.[312] Butyl selenide ethers were efficient coupling partners for alkynic, alkenic and hetroarylic substrates in a reaction mediated by copper acetate (Scheme 57). Selenide trichlorides were ineffective, yielding the corresponding aryl selenoethers. A single example of the use of a selenoxide for the formation of biaryls has been

described but the original article doesn't explicitly mention whether the reaction requires addition of base. (Figure I.61).

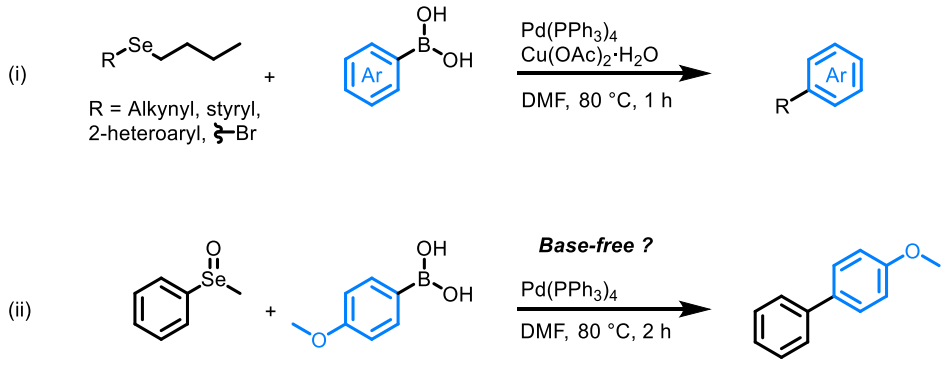


Figure I.61: Reactivity of various selenides in the Suzuki reaction

A Suzuki-type reaction was also reported after oxidative addition into the C–C bond of a ketone, to yield aryl ketones via rhodium catalysis and under acidic rather than basic conditions (Figure I.62).[313]

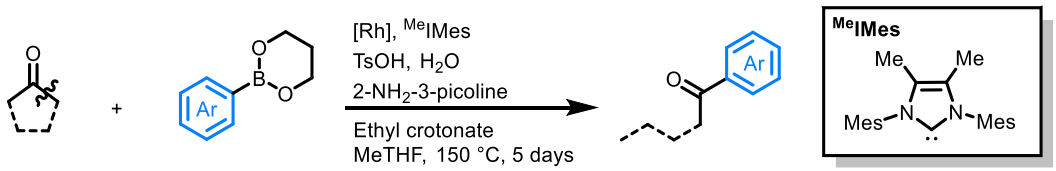


Figure I.62: C–C bond activation of ketones in a Suzuki-type reaction

This reaction occurs with aryl boronate esters as coupling partners and requires several unusual substoichiometric additives: 2-amino-3-picoline, ethyl crotonate and TsOH. Ethyl crotonate was hypothesized to act as a π-acid to promote reductive elimination. The role of the other additives was not discussed, but the acid (as well as the excess water) is likely involved in the protonation of the carbanion leaving group.

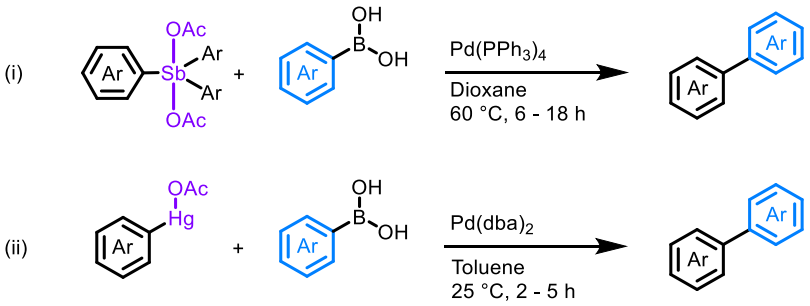


Figure I.63: Base-free coupling of aryl mercury and aryl antimony acetates

Other unusual electrophiles were discussed in chapter 1.4.4 because they couple under base-free conditions: triaryl antimony (V) acetates and aryl mercuric acetates (Figure I.63).[164–166]

The variety of available electrophiles for the Suzuki reaction has expanded enormously since its initial discovery, which offers a significant synthetic advantage. Chemists can now choose from any of the dozens of electrophiles best suited to their needs.

1.7 Aim of the thesis

The aim of this thesis was to discover an electrophile for the Suzuki reaction with an intermediate reactivity to enable the synthesis of polyaromatic molecules via sequences of Suzuki reactions. Ideally, this new electrophile should be inert to the cross-coupling conditions of most major Suzuki electrophiles like (pseudo)halides, yet still reactive enough to be a useful synthetic method. Other factors considered in the selection of the electrophile were the atom economy of the overall process and the possibility that the new electrophile could act as a transient directing group, cleavable by cross-coupling, which would give it a significant synthetic advantage.

Trifluoromethyl sulfones were selected as the prime candidate to fit these criteria, due to their high stability, atom economy (one atom less than triflates) and the sulfone directing group effects for selective *ortho*-, *meta*- and *para*- functionalization. The goal was to access polyaromatic molecules such as terphenyls or quaterphenyls starting from simple polyfunctionalized arenes. In parallel, attention was directed towards the synthesis of polyfunctionalized arenes starting from simple molecules such as $PhSO_2CF_3$, taking advantage of the sulfone's capabilities as a directing group prior to its use as an electrophile for the Suzuki reaction.

Due to their similarity with trifluoromethyl sulfones and their widespread use in SuFex chemistry, sulfonyl fluorides were also investigated as an electrophile in the base-free Suzuki coupling due to their potentially labile fluoride. Like sulfones, sulfonyl fluorides are a very stable functional group. Developing a Suzuki coupling of sulfonyl fluorides would endow this functional group with a unique strategic advantage for divergent synthesis, as any sulfonyl fluoride group could be a potential handle for S–N or C–C bond formation.

II. The Suzuki Coupling of (Hetero)aryl Sulfones[†]

Due to their many uses in organic synthesis, sulfones and other sulfur-bearing functional groups have been extensively studied for their role in cross-coupling reactions.[5,6,8–11,15,19] Their high synthetic usefulness stems from their ability to act as directing groups for *ortho*-metallation and selective *meta* and *para* functionalization on arenes, and α-functionalization on benzylic sulfones (Figure II.1).[6–8,10,12–15]

In comparison, most of the other electrophiles (pseudo/halides or SO_2Cl) induce virtually no selectivity or are too sensitive for S_EAr or *ortho*-metallation reaction conditions. Nitroarenes are a notable exception but are limited to S_EAr and their SMC requires high temperatures (130 °C).[314]

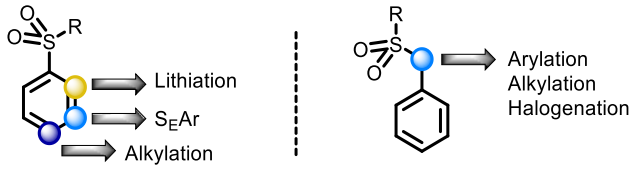


Figure II.1: Sulfones as a synthetic handle for various transformations

Furthermore, using existing electrophiles, it can be challenging to orchestrate iterative sequences of Suzuki reactions to achieve polyaromatic molecules. For instance, the order of reactivity of triflates and chlorides varies with the ligand or solvent system.[123,129]

Developing an alternative electrophile that remains virtually inert to the conditions used for the cross-coupling of the more common (pseudo)halide electrophiles and that can act as a directing group for diverse functionalizations is thus highly desirable.

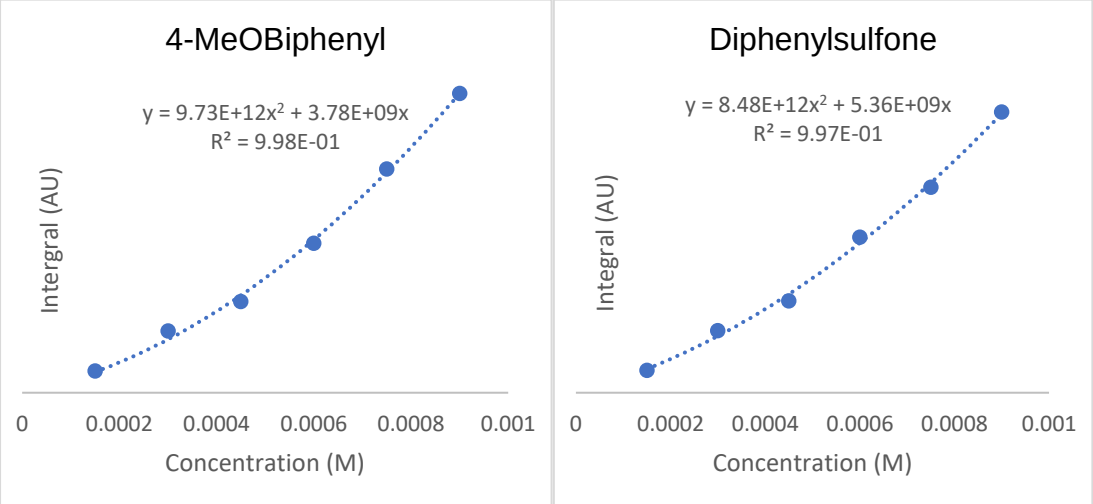
This chapter describes the development of a general method for the cross-coupling of aryl trifluoromethyl sulfones with aryl boronic acids, the usefulness of which is highlighted in the synthesis of several polyaromatic molecules, exploiting the large reactivity differences between trifluoromethyl sulfones and (pseudo)halides.

[†] Portions of this chapter have been published.[5]

2.1 Screening methodology

The reaction between diphenylsulfone and 4-methoxybenzeneboronic acid was first investigated as a model reaction in the Suzuki coupling of aryl sulfones. To get a rough idea of the relative performance of various reaction conditions, the reaction outcome was first evaluated using calibrated GC/MS response factors for the product, 4-methoxybiphenyl and the substrate (diphenylsufone).

A calibration curve was drawn using 6 different concentrations of the products. Two runs were done for each concentration, using the GC/MS integral to establish a response factor of a given concentration, with response factor = concentration/integral. The calibration curve was then drawn using a polynomial model fit (Graph 1).



Graph II.1: GC/MS calibration curves of the product and substrate

During this calibration, it was discovered that diphenyl sulfone and 4-methoxybiphenyl shared a very similar response factor. Therefore, the ratio of the uncorrected integrals of the coupling product to the starting material could be used as a rough measure of conversion – diphenylsulfone essentially acting as an internal standard due to the low conversions observed. The reliability of this method was deemed suitable as a quick screening method: the ratios in percentage were very close (within 1-2%) to the GC calibrated yields using the response factor of the product and were more reproducible.

The same method was then applied to the other screened reactions to obtain the *relative* performance of each reaction. The reactions displaying a significant conversion, or the ones evaluating important reaction parameters, were verified by obtaining an isolated yield.

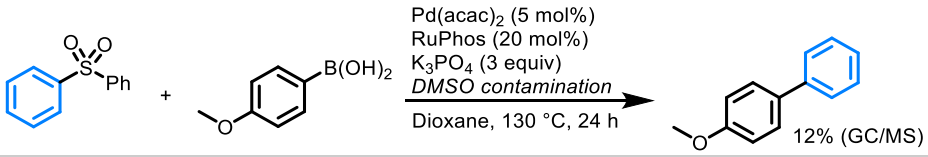
2.2 Identification of a viable sulfone substrate

2.2.1 Initial screening with diphenyl sulfone

Because of the unreactive nature of sulfones as electrophiles for the Suzuki reaction, the first conditions screened were similar to the ones described in the optimization of the Suzuki coupling of nitroarenes.[314] Therefore, a reaction temperature of 130 °C was first applied, using dioxane as the solvent and K_3PO_4 as the base. The ligands and palladium sources originally assayed were those found to be the most efficient for the nitroarene Suzuki coupling.

Using $Pd(acac)_2$ and RuPhos in dioxane produced the best results, but even heating at 130 °C for an extended period (24 h) led to a low conversion (entry 1). Attempts to vary the conditions led to worse results and often did not lead to any coupling at all. Factors evaluated were base (Table II.1, entries 2, 3, 6, 7), solvent effects (entries 4, 5), ligand loading (entry 8), ligand (entries 8 – 13), palladium source (entries 14, 15), and reaction temperature (entry 16). Finally, the very active Ni(0) catalyst $Ni(COD)_2$ was tried but it failed to achieve the anticipated result (entry 17). Using conditions analogous to the ones reported by Crudden[6] on the coupling of benzylic sulfones (SIPr as ligand, ethanol as solvent) also led to a lower performance (entry 11).

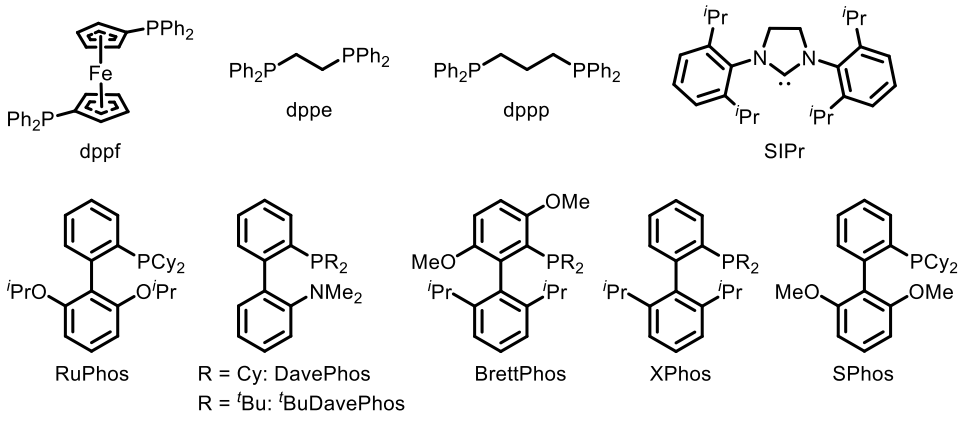
An intriguing discovery was made during the optimization (entries 1 – 3). It was discovered that the potassium phosphate used in the initial reaction was contaminated with a small amount of DMSO.



Entry	Variations from condition	Conversion (%)[a]
1	No variation	12
2	Clean K_3PO_4 instead of contaminated K_3PO_4	7
3	Clean K_3PO_4 + 10 µL DMSO	14[b]
4	Toluene instead of Dioxane	3
5	Ethanol instead of Dioxane	3
6	K_2CO_3 instead of K_3PO_4	2
7	NaOEt instead of K_3PO_4	n.d
8	10 mol% RuPhos	8
9	SPhos instead of RuPhos	1
10	SIPr·HBF_4 instead of RuPhos	3
11	SIPr·HBF_4 instead of RuPhos, Ethanol as solvent	6
12	Xphos or BrettPhos instead of RuPhos	n.d
13	Dppe or dppf instead of RuPhos	n.d.[c]
14	$Pd_2(dba)_3$[d], $Pd_2(allyl)_2Cl_2$[d] or $Pd(OAc)_2$ instead of $Pd(acac)_2$	n.d.
15	$Pd(F_6acac)_2$ instead of $Pd(acac)_2$	11
16	100 °C instead of 130 °C	8
17	$Ni(COD)_2$ instead of $Pd(acac)_2$	n.d.[e]

Conditions: 0.2 mmol $PhSO_2Ph$, 0.3 mmol 4-MeOPhB$(OH)_2$, 0.6 mmol K_3PO_4 (contaminated with DMSO), 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 1 mL Dioxane, N_2, 130 °C, 24 h. [a]GC/MS ratio of product to substrate. [b]Isolated yield. [c]10 mol% ligand (bidentate). [d]2.5 mol%. [e]The reaction was performed in a nitrogen-filled glovebox. N.d: Not detected.

Table II.1: Optimization of the reaction of $PhSO_2Ph$



Proton NMR analysis confirmed the presence of DMSO in the base as shown by a singlet at 2.62 ppm. Best results were finally obtained using clean K_3PO_4 and adding 10 μL of DMSO (entry 3).

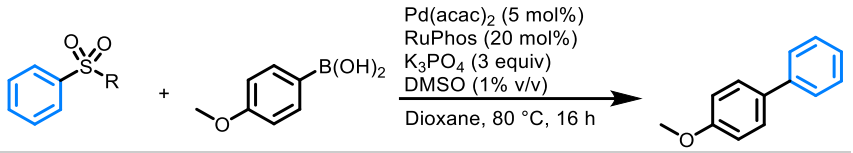
DMSO has recently been shown to act as a ligand in a palladium-catalyzed Heck reaction where it favors the formation of anionic palladium catalysts,[315] but its role as an additive had never been reported. The alleged mechanism of action of DMSO will be discussed more thoroughly in chapter 2.2.3: it is assumed to act in the catalyst initiation step. All reactions in table II.1, unless otherwise indicated, were made using the same batch of base.

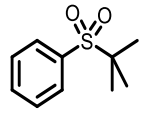
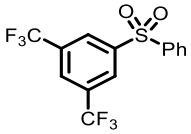
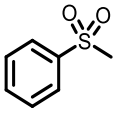
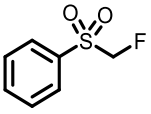
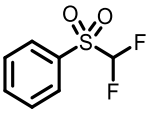
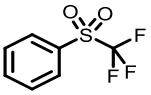
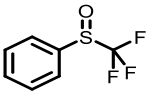
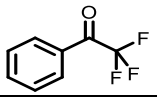
2.2.2 Substrate variations and discovery of optimal substrate

Due to the apparent low reactivity of diphenyl sulfone, attempts were made to vary the substrate. Using the optimized conditions from table II.1, other aryl sulfones were screened. Phenyl *tert*-butyl sulfone, known to participate in the Kumada cross-coupling,[316] didn't react (table II.2, entry 1). A strongly activated unsymmetrical diaryl sulfone, bearing the very electron-poor 3,5-bis(trifluoromethyl)phenyl ring, did cross-couple to some extent on the electron poor ring (entry 2). The same type of regioselectivity was also observed in the Suzuki cross-coupling of diaryl sulfoxides.[304]

The degree of fluorine substitution was varied on the methyl group of phenyl methyl sulfone, to study the effects of increasing electron withdrawal. Phenyl methyl sulfone was unreactive using this catalytic system (entry 3). Its mono- and di- fluorinated counterparts did not cross-couple at all and did not significantly decompose (as seen on GC/MS analysis) (entries 4 and 5). Due to the strong electron-withdrawing properties of the CF_3 group, high conversions were observed with phenyl trifluoromethyl sulfone at a lower temperature (entry 6). The sulfoxide and ketone analogues of $PhSO_2CF_3$ proved unreactive in these conditions (entries 7 and 8).

Aryl trifluoromethyl sulfones are thus ideal sulfone substrates for the Suzuki reaction, displaying fair atom-economy (compared to tosylates and triflates), high coupling activity and being relatively inert to relatively harsh reaction conditions such as S_NAr,[293] lithiation,[13] and S_EAr.[5]



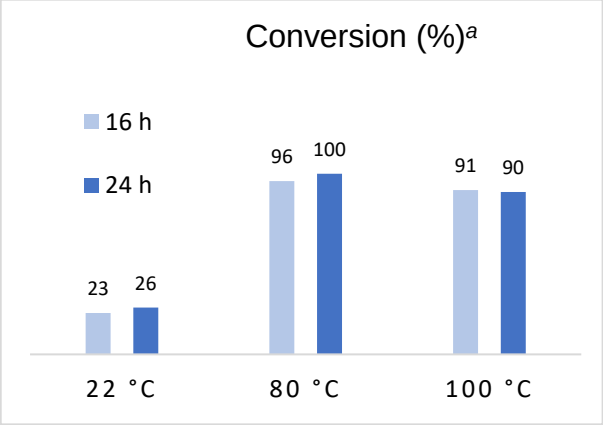
Entry	Substrate	Yield (%)[a]
1		n.d.[b]
2		25[c]
3		n.d.
4		n.d.
5		n.d.
6		95
7		n.d.
8		n.d.

Conditions: 0.2 mmol $PhSO_2CF_3$, 0.3 mmol 4-MeO(C_6H_4)B($OH)_2$, 0.6 mmol K_3PO_4, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 1 mL Dioxane, 10 µL DMSO, N_2, 80 °C, 16 h. [a]Isolated yield. [b]130 °C. [c]Product: 4'-methoxy-3,5-bis(trifluoromethyl)-1,1'-biphenyl. N.d: Not detected.

Table II.2: Selection of sulfone coupling partner

2.2.3 Optimization with $PhSO_2CF_3$

First, to optimize the reaction with $PhSO_2CF_3$, the reaction temperature and reaction times were screened (Graph 2.2). A maximum conversion was reached at 80 °C, and no significant difference in reactivity was observed between 16 and 24 h for all reaction temperatures screened. The poorer yields at higher temperatures might be attributed to a faster catalyst decomposition.



Conditions: 0.2 mmol $PhSO_2CF_3$, 0.3 mmol 4-MeOPhB(OH)$_2$, 0.6 mmol K_3PO_4 (contaminated with DMSO), 5 mol% Pd(acac)$_2$, 20 mol% RuPhos, 1 mL Dioxane, T °C, t h. [a]GC/MS ratio of product to substrate.

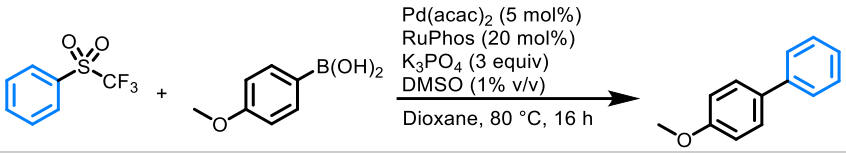
Graph II.2: Temperature screen

The optimization of $PhSO_2CF_3$ (Table II.3) followed a similar trend to diphenyl sulfone (Table II.1). Adding 10 µL DMSO to clean K_3PO_4 proved to be the best conditions, achieving an isolated yield of 95% after 16 h at 80 °C (table II.3, entry 1). The presence of coordinating substituents on the Buchwald ligands (an ether, in the case of RuPhos; a dimethylamino group, in the case of DavePhos) on the bottom ring seemed beneficial for the reactivity (entries 1 – 3). This effect is most likely due to a stabilizing effect for the palladium, as described by Buchwald (see Figure I.27).[197]

However, XPhos, which bears no coordinating substituents, led to similar yields in the absence of DMSO (entry 4). BrettPhos, which is similar to XPhos but is substituted with two methoxy groups on the top ring, inhibited the reactivity (entry 5). The bidendate ligand dppp was ineffective (entry 6).

The addition of DMSO was beneficial but using it as a solvent completely shut down the reactivity (entries 1, 7 and 11). Except for toluene, which achieved high yields, varying the solvent had a significant deleterious effect on the reaction (entries 8 – 11).

Though less effective than Pd(acac)$_2$, the more common Pd(OAc)$_2$ still carried out the reaction (entry 12), in contrast to the Pd(0) precatalyst $Pd_2(dba)_3$ which did not furnish any coupling product (entry 13). The lower activity of Pd(OAc)$_2$ compared to Pd(acac)$_2$ might be due to the stronger ligating properties of acetylacetonate, which could stabilize the palladium or could form anionic palladium complexes more readily.



Entry	Variations from standard conditions	Yield (%)[a]
1	No variation	95
2	^{t}BuDavePhos instead of RuPhos	70
3	DavePhos instead of RuPhos	81
4	XPhos instead of RuPhos, no DMSO	55
5	BrettPhos instead of RuPhos	19
6	Dppp[b] instead of RuPhos, no DMSO	n.d.
7	No DMSO	55
8	Toluene instead of dioxane	83
9	THF instead of dioxane	52
10	Trifluorotoluene instead of dioxane	65
11	DMSO instead of dioxane	n.d.
12	$Pd(OAc)_2$ instead of $Pd(acac)_2$	65
13	$Pd_2(dba)_3$[c] instead of $Pd(acac)_2$	n.d.
14	NaOEt instead of K_3PO_4	n.d.
15	CsF instead of K_3PO_4	57
16	K_2CO_3 instead of K_3PO_4	79

Conditions: 0.2 mmol $PhSO_2CF_3$, 0.3 mmol 4-MeO(C_6H_4)B(OH)$_2$, 0.6 mmol K_3PO_4, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 1 mL Dioxane, 10 µL DMSO, N_2, 80 °C, 16 h. [a]Isolated yield. [b]10 mol% ligand (bidentate). [c]2.5 mol%. N.d: Not detected.

Table II.3: Optimization of the reaction of $PhSO_2CF_3$

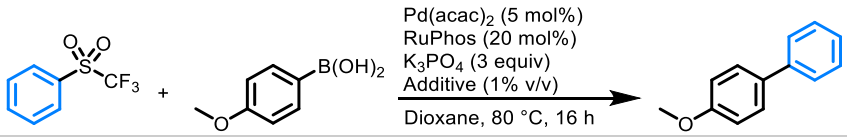
Anionic complexes are known to favor oxidative addition into triflates,[123] and due to their similar structure, the same might be true for trifluoromethyl sulfones. Weak bases with a potassium counterion provided the best results, which is consistent with Jutand's observations on cation inhibition (entries 14 – 16, see Figure I.14).[136]

The significant effect of $Pd(acac)_2$ *vs* $Pd(OAc)_2$ might also be due to a more facile reduction of Pd(II) to Pd(0). Grimaud's postulated mechanism on the reduction of $Pd(OAc)_2$(XPhos) to Pd(0)XPhos (Figure I.29) indicates that the more nucleophilic

oxyanion on acetylacetonate would favor the oxidation of the phosphine and thus reduction of palladium.

A point to consider about the high catalytic activity of RuPhos in these conditions is that it may be due to the formation of phosphide bridged Pd(I) dimers (which were shown to be active catalysts), as was described by Bedford to be especially favored with RuPhos at 80 °C (see Figure I.28). However, the higher yields observed with RuPhos might simply be due to the increased bulk of the ligand, which favors the formation of monoligated complexes. The ether substituents of RuPhos could coordinate to Pd, stabilizing the complex and increasing the catalyst lifetime (see Figure I.27).

The effect of additives was evaluated and is summarized in Table II.4. Without DMSO, the yield dropped significantly (entries 1 and 2). A similar additive effect with 18-crown-6 was described in the Suzuki coupling of nitroarenes (which requires similar reaction conditions). This additive is known to bind potassium and thus might help in solubilizing the base or prevent the antagonistic effect of the potassium ion on transmetalation (see Figure I.14). DMSO might thus play a role in solubilizing the inorganic base. Other conditions capable of solubilizing the base, such as using the highly polar solvent HMPA as an additive, also significantly enhanced the yield (albeit to a lesser extent) (entry 3). Excellent yields could also be obtained using micellar water as solvent (entry 4).



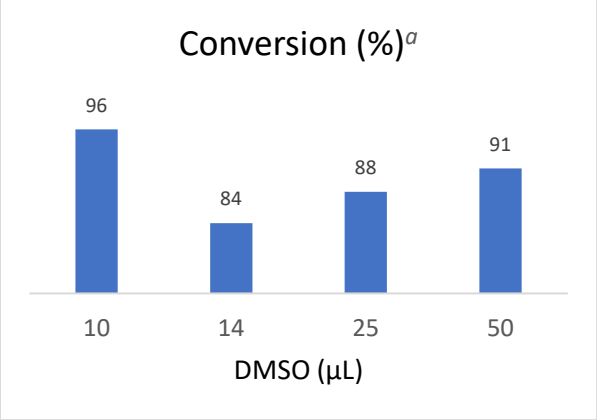
Entry	Variations from standard conditions	Yield (%)[a]
1	None	95
2	No DMSO	55
3	HMPA instead of DMSO	77
4	TPGS (2% w/w) in H_2O as solvent, no DMSO	90
5	H_2O 0.2% v/v instead of DMSO	38
6	$(PhSOCH_2)_2$ 50 mol% instead of DMSO	5

Conditions: 0.2 mmol $PhSO_2CF_3$, 0.3 mmol 4-MeO(C_6H_4)B($OH)_2$, 0.6 mmol K_3PO_4, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 1 mL Dioxane, 10 µL DMSO, N_2, 80 °C, 16 h. [a]Isolated yield. TPGS: DL-α-Tocopherol methoxypolyethylene glycol succinate.

Table II.4: Evaluation of the effect of DMSO addition

Addition of small amounts of water inhibited the reaction, thus the additive effect is probably not due to the water content of these polar solvents (entry 5). To investigate a possible ligand effect of DMSO, a comparable molar amount of a sulfoxide ligand was investigated, but it inhibited the reaction (entry 6). The addition of DMSO has been shown to favor the formation of anionic palladium catalysts,[315] which Schoenebeck has shown to be more active on the oxidative addition of the structurally related aryl triflates.[123]

The amount of DMSO addition was investigated (Graph II.3). Interestingly, the performance of the system dips when 14 µL (1 molar equivalent relative to the sulfone) of DMSO is added. Past this point, the conversion increases proportionally to the amount of DMSO added. The best results were achieved with 10 µL (1 % v/v). Amounts beyond 50 µL were not investigated due to the significant proportion of equivalents of DMSO which might have caused problems during purification. Similarly, amounts lower than 10 µL were not investigated because of the precision of the measurement becoming too low: DMSO was added via micro-syringe after the vacuum/nitrogen cycles and 10 µL was the lowest volume which could be measured reliably.



Conditions: 0.2 mmol $PhSO_2CF_3$, 0.3 mmol 4-$MeOPhB(OH)_2$, 0.6 mmol K_3PO_4, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, *x* µL DMSO, 1 mL Dioxane, 80 °C, 16 h. [a]GC/MS ratio of product to substrate.

Graph II.3: Evaluation of additive loading

Another hypothesis concerning the effect of the addition of low amounts of DMSO in the reaction mixture can be drawn from an interesting paper by Hunter and coworkers that reports an increased polarity of a solvent mixture relative to either of its components – the stability of an H-bonded complex was significantly impacted.[317] Therefore, weak interactions might significantly change in the solvent system presented herein.

This type of effect would account for a higher solubility of ionic compounds such as the base, which could have several effects:

- A higher concentration of [Pd-OH], increasing the rate of transmetalation.
- A more facile reduction of Pd(II) to Pd(0) during catalyst initiation (via base-mediated phosphine oxidation or transmetalation-mediated homocoupling or reduction from trace dimethyl sulfide)
- Formation of anionic palladium complexes, which might favor oxidative addition into Ar-SO_2CF_3 (similarly to what is observed with triflates)

2.3 Mechanistic experiments

2.3.1 Isolation of oxidative addition intermediate

To gain more insight into the reaction, a reaction between a palladium(0) precursor, (1,5-cyclooctadiene)bis(trimethylsilylmethyl)palladium, and $PhSO_2CF_3$ was undertaken to isolate the oxidative addition intermediate X1 (Figure II.2).

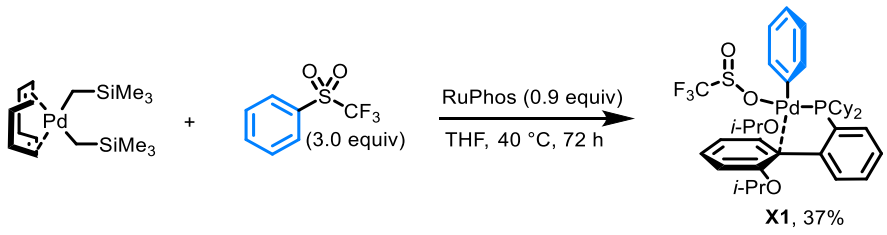


Figure II.2: Isolation of reaction intermediate **X1**

The structure of X1 was confirmed by single crystal X-ray diffraction which revealed a square planar geometry,[318] with the palladium bound to the oxygen of the sulfinate leaving group. This rearrangement from the S-bound intermediate arising after

oxidative addition might be to minimize dipole in the apolar crystallization solvent. By comparison, the similar palladium (2-pyridyl)sulfinate complexes were isolated as S-bound.[319] The structure of X1 was otherwise similar to what has been reported for oxidative addition into aryl halides or nitroarenes, using Buchwald ligands.[314,320]

A typical reaction mixture was extracted with D_2O, and ^{19}F NMR revealed the presence of trifluoromethane sulfinate as the only visible compound. Along with structural data, this confirms that the reaction does not occur via release of SO_2 like the similar sulfonyl chlorides.[305]

Several mechanistic experiments were conducted with **X1** (Figure II.3). First, a stoichiometric reaction with **X1** and 4-MeO(C_6H_4)B(OH)$_2$ was undertaken at room temperature under otherwise standard conditions. The coupling product was obtained in near quantitative yields, which confirms that **X1** is an active reaction intermediate. The lower reaction temperature also suggests that oxidative addition is most likely the rate-limiting step of this reaction. Slightly higher yields were obtained in an analogous reaction without adding DMSO: the additive is thus probably not involved in the transmetalation or reductive elimination step but rather during oxidative addition or an earlier step such as catalyst initiation. Catalytic **X1** was then used in two experiments under otherwise standard conditions to evaluate the need for ligand oversaturation (optimal reaction conditions require 20 mol% of RuPhos relative to 5 mol% of Pd) and to gain more insight into the role of DMSO.

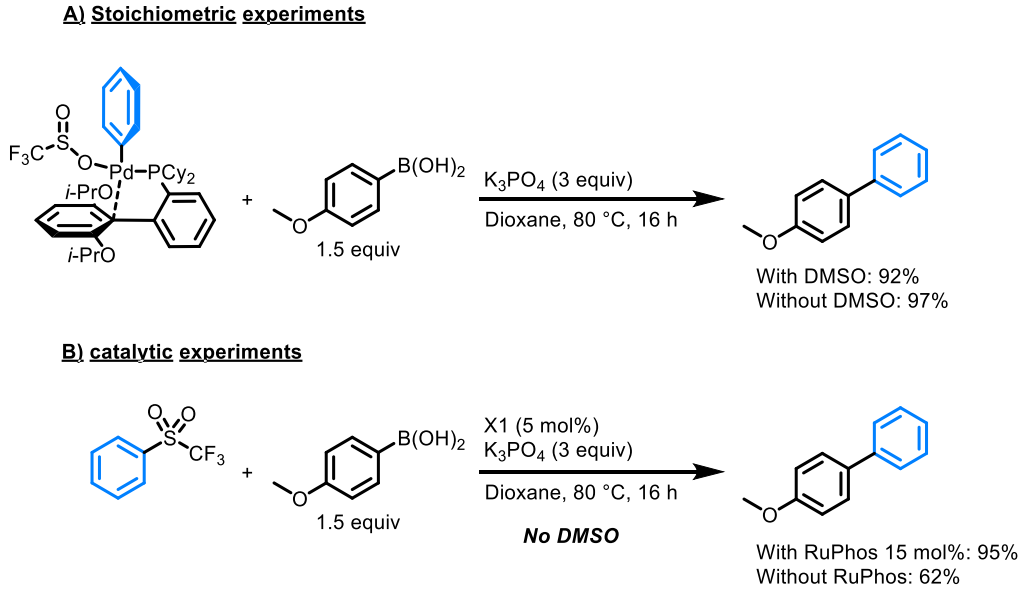


Figure II.3: Mechanistic experiments with intermediate **X1**

Near quantitative yields were obtained without the addition of DMSO, but a lower performance was observed without the addition of excess ligand. Therefore, excess RuPhos is likely involved in delaying catalyst decomposition and DMSO is likely involved in catalyst initiation but not oxidative addition, transmetalation or reductive elimination. It may be involved in the reduction of Pd(II) through trace dimethyl sulfide or via rate-enhancement of base-mediated phosphine oxidation. It could also be involved in the stabilization of the initial mono-ligated palladium complex before the first oxidative addition.

These conclusions are in contrast with Yorimitsu's later work on the coupling of sulfones via rhodium co-catalysis, where it was postulated that reductive elimination and transmetalation are most likely rate-limiting.[19]

2.3.2 DFT calculations

To complement our experimental observations, DFT calculations were undertaken with collaborator Chris Rowley (Figure II.4). The experiments described above support oxidative addition as being turnover-limiting, as is expected with a challenging electrophiles.[4,129] The Gibbs energy profiles for the insertion of the catalyst into the C–S bond were calculated using the B3LYP-D3-def2-TZVP model, comparing $PhSO_2Ph$ with $PhSO_2CF_3$.

The first step is a ligand substitution of the solvent dioxane with the substrate to form a π-complex, which is slightly favored for $PhSO_2CF_3$. The Gibbs energy for the transition state corresponding to oxidative addition into the C–S bond has an activation energy that is 5.8 $kcal \cdot mol^{-1}$ higher for $PhSO_2Ph$ than for $PhSO_2CF_3$, which is consistent with the observed experimental trend (Table II.1, entry 3 *vs* Table II.2, entry 6) and coincides with the increased polarization of the C–S bond for the trifluoromethyl derivative. The located transition state for the oxidative addition corresponds to the 3-centered concerted mechanism (see chapter 1.4.2). and starts from a monoligated Pd(0) complex.

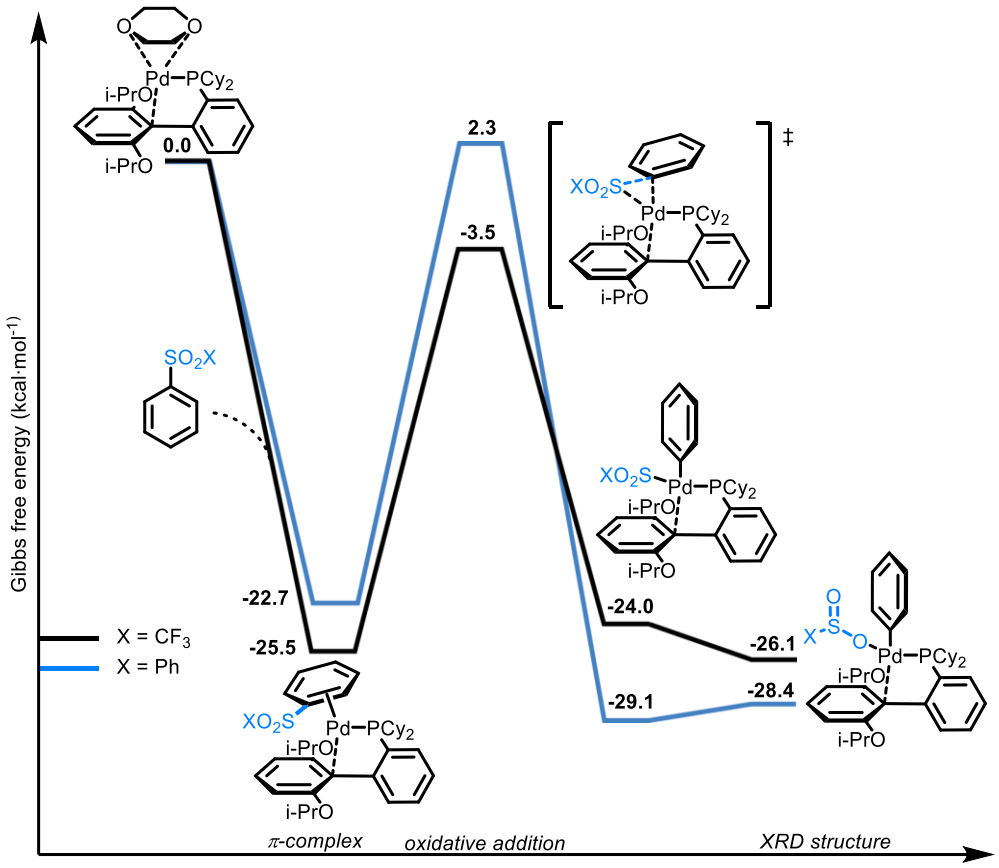


Figure II.4: Calculated Gibbs energies for the oxidative addition of sulfones to monoligated Pd^0(RuPhos)

Finally, formation of the O-bound sulfinate after oxidative addition was found to be favorable for the trifluoromethyl substrate. This provides a further explanation as to why the reaction intermediate was isolated as O-bound (Figure II.2), while the similar 2-pyridyl complex was reported as S-bound.[319]

2.3.3 Competition experiments to establish relative reactivity

The relative reactivity of aryl sulfones relative to other electrophiles in the Suzuki reaction was determined to be -Br > -Cl >> $-SO_2CF_3$ > -OTs >> NO_2, through several competition experiments (Figure II.5). One equivalent of $4MeO(C_6H_4)B(OH)_2$ was reacted with an equivalent 1:1 mixture of $PhSO_2CF_3$ and a) *p*-tolyl chloride, b) *p*-nitrotoluene, c) and d) *p*-tolyl tosylate. The conditions used (catalyst and solvent) corresponded to our optimized conditions for sulfones or conditions efficient for the other respective functional groups. The composition of the reaction mixture was then

analyzed by GC/MS. Trifluoromethyl sulfones were found to be inert under the conditions required to couple aryl chlorides.

Likewise, nitroarenes and aryl tosylates were not reactive in the conditions required to couple aryl trifluoromethyl sulfones. However, the conditions described by Buchwald to couple tosylates (Figure II.5, d)[257] were also efficient for sulfones, despite using a precatalyst and ligand that displayed low efficiency in our optimization (BrettPhos and $Pd(OAc)_2$, see Table II.3).

The relative proportions of products indicate that sulfones display a relative reaction rate at least two orders of magnitude slower than chlorides and at least two orders faster than nitroarenes. Tosylates are closer in reactivity: sulfones are 20 to >99 times more reactive depending on the conditions used.

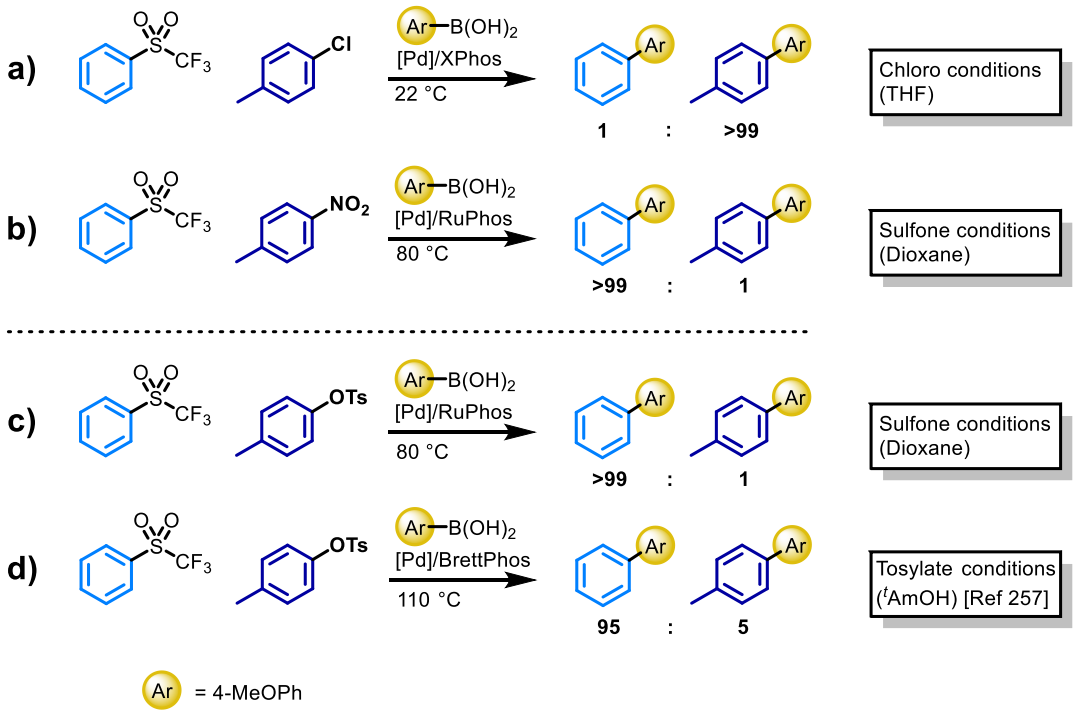


Figure II.5: Competition experiments to establish relative reactivity

2.4 Sulfones as a directing group

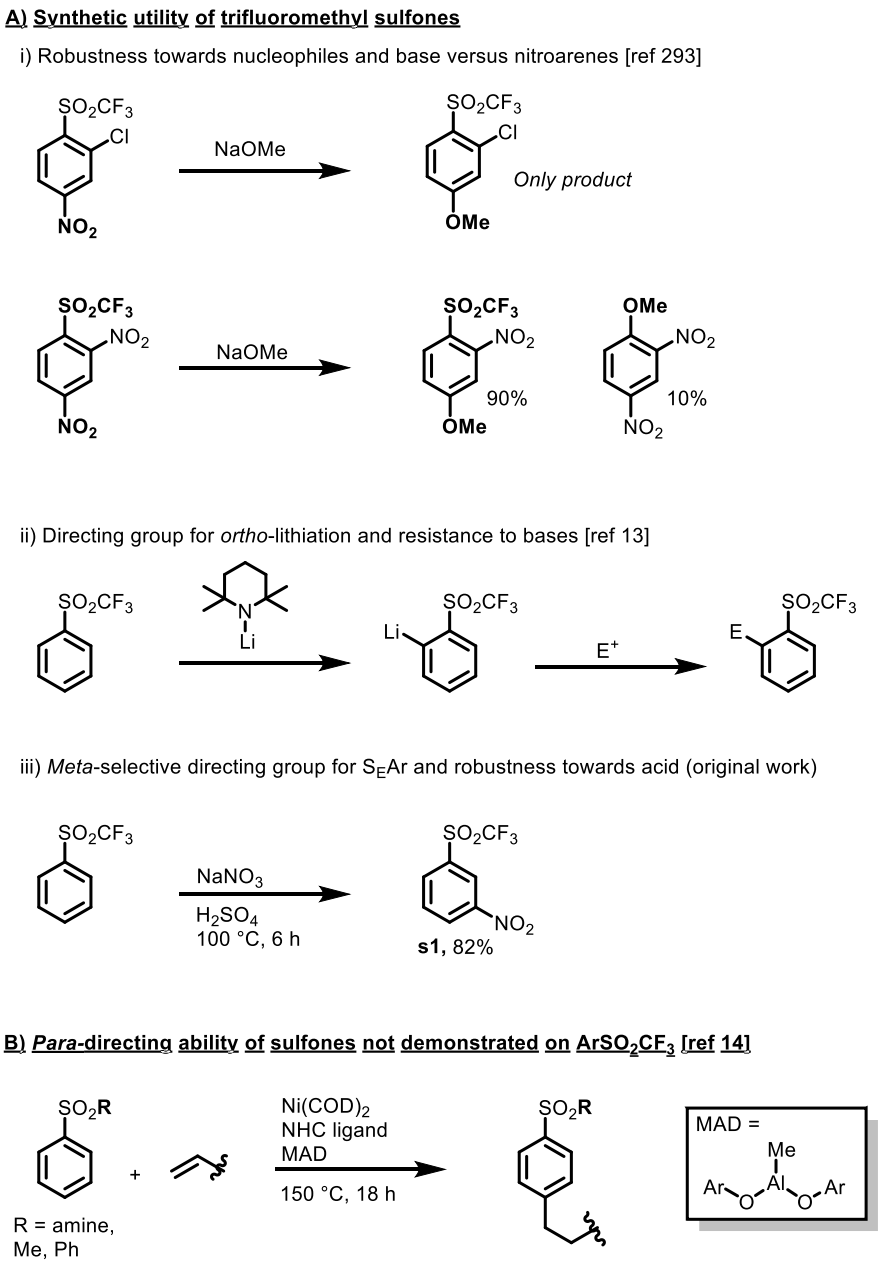


Figure II.6: Aryl sulfones are a robust directing group for all three positions of an arene

The advantages of sulfones as a directing group were briefly introduced in Figure I.56 and are summarized in Figure II.6. Aryl trifluoromethyl sulfones in particular were shown to be resistant to S_NAr reactions (as opposed to nitro groups)[293] and to act as a directing group for ortho-lithiation.[13] In the present study, their orthogonality to harsh

S_EAr conditions (sulfuric acid as the solvent, 100 °C) and their strong *meta* directing effect was reported in a nitration reaction.

The *para* selective alkylation was reported on aryl sulfonamides, methyl phenyl sulfone and diphenyl sulfone.[14] Although not included in their scope, there is no indication that these reaction conditions would preclude trifluoromethyl sulfones.

2.5 Orthogonal coupling

Having established the relative reaction rate of trifluoromethyl sulfones in the Suzuki reaction, a protocol was established for the synthesis of polyaromatic molecules via sequential coupling reactions. (Figure II.7).

Haloarenes coupled at room temperature using the ligand XPhos in THF. Sulfones required a higher temperature of 80 °C and the ligand RuPhos in dioxane with DMSO as an additive. Finally, nitroarenes required a much higher temperature of 130 °C, BrettPhos as a ligand as well as the additive 18-crown-6.

The relative rate of reactivity of sulfones in the Suzuki coupling are best illustrated in sequence a) of Figure II.7. Starting from the polyfunctionalized arene 1-Cl-2-NO_2-4-(C_6H_3)SO_2CF_3, a terphenyl was obtained in good yields after a sequence of two coupling reactions. The first coupling of the chloro group with 4-MeO(C_6H_4)$B(OH)_2$ afforded biphenyl **s2**, followed by sulfone-selective coupling to afford terphenyl **32a**. As was predicted during the competition experiments, nitro-substitution did not significantly impact the reaction.

Sequence b) displays a sequence starting from 3-Br(C_6H_4)SO_2CF_3. As can be expected from the reaction with the less reactive chlorides, coupling on the bromide left the sulfone largely intact. The sulfone coupling then occurred in excellent yields.

Sequence c) differs from the previous two sequences in that the use of nitro-coupling was also demonstrated in a sequence. First, chloro-coupling on 3-Cl(C_6H_4)SO_2CF_3 with 3-NO_2(C_6H_4)$B(OH)_2$ afforded biaryl **s4** in a very good yield. The resulting biaryl was subjected to sulfone-coupling conditions to afford biaryl **30a** in good yields

despite the high molar mass of the resulting product. Nitro-coupling only occurred in mediocre yields even after an extended reaction time to afford quaterphenyl **1c**. The lower yield could be attributed to the very high molar mass of the starting material **30a**, substantially lowering its mobility in the reaction medium. The robustness of the presented sulfone-Suzuki method is well illustrated in this set of experiments: the order of reactivity is well established with other Suzuki electrophiles and polyfunctional biarylic sulfones are coupled in very high yields using the standard conditions.

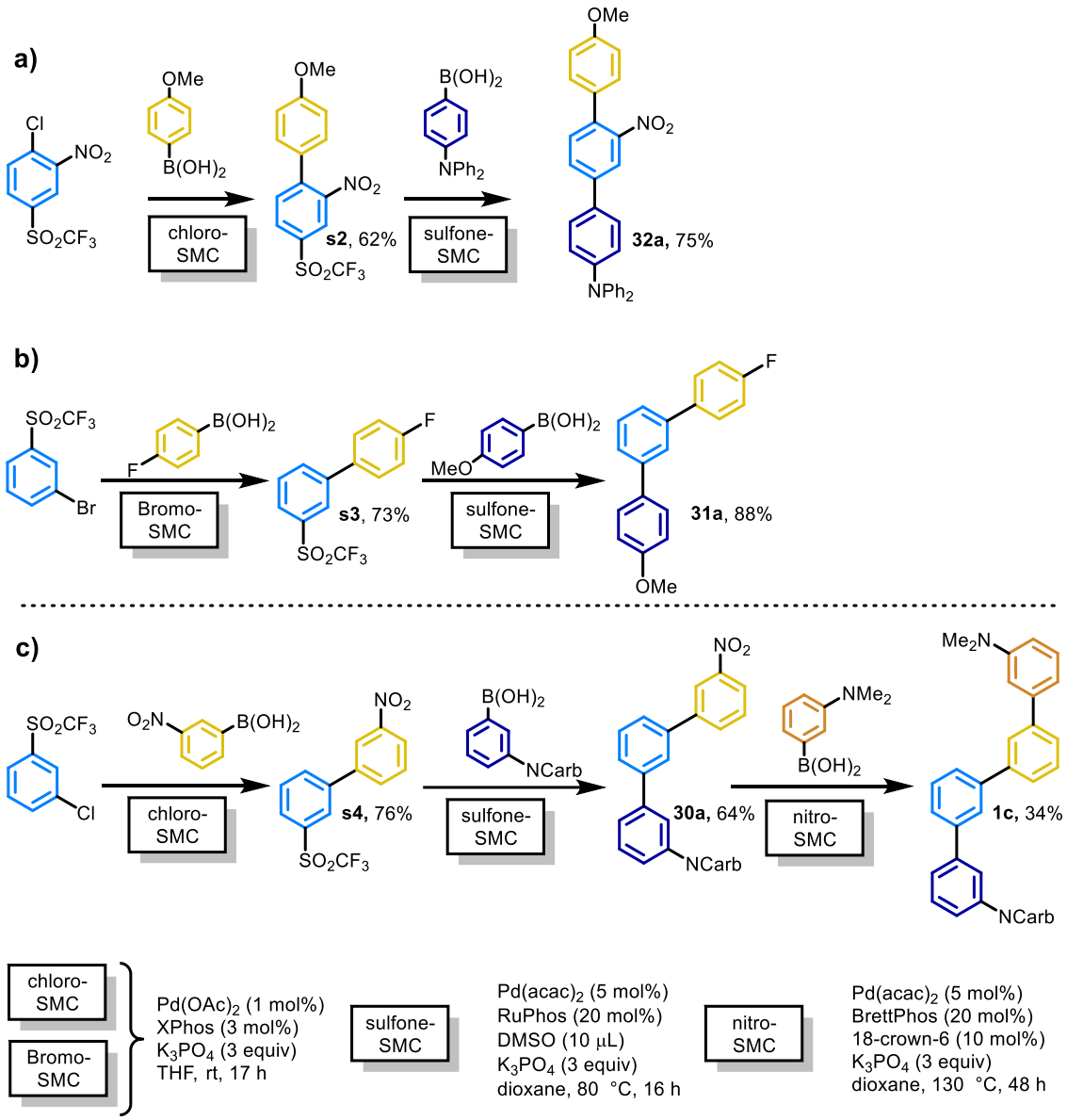


Figure II.7: Synthesis of non-symmetric terphenyls and quaterphenyls by taking advantage of the relative reactivity of different electrophiles

Compounds **31a** and **32a** are analogues of active molecules against leukemia,[321] which illustrates the usefulness of sulfones to synthesize terphenyls (Figure II.8).

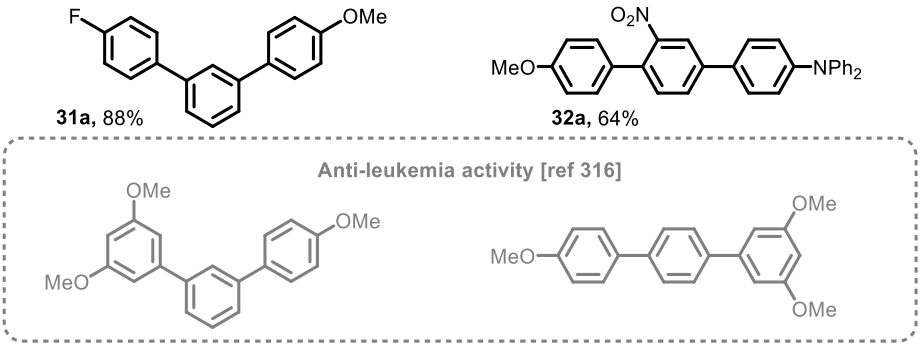


Figure II.8: Terphenyls synthesized using the present method have analogous structures to active molecules

2.6 Substrate Scope

The applicability of this reaction was evaluated by varying the substituents on the aryl sulfone and the boronic acid (Table II.5). On the sulfone coupling-partner, the parent phenyl compound achieved excellent yields (**1a** – **10a**). Electron-withdrawing groups such as cyano, fluoro, and nitro were well tolerated (entries **11a** – **17a**, **21a** – **25a**). Electron-donating groups were evaluated using the 4-MeO derivative, which was found to impair reactivity slightly compared to the parent phenyl compound or its electron-poor counterparts (**18a** – **20a**). Heterocyclic derivatives coupled smoothly (**26a** – **29a**) and *para* and *ortho* biphenylic derivatives were already showcased in Figure II.7: they reacted in high to very high yields (**29a** – **32a**).

On the boronic acid coupling partner, the electron-rich 4-methoxy derivative produced high yields (**1a**, **15a**, **21a**, **26a**, **31a**), but electron-poor boronic acids, even the very activated 4-CF_3 derivative, were also very well tolerated (**2a**, **3a**, **11a**, **14a**, **16a**, **18a**, **23a**, **27a**, **28a**, **30a**). Compound **18a**, which results from the coupling of electron-rich 4-MeO(C_6H_4)SO_2CF_3 and electron-poor 4-CF_3(C_6H_4)$B(OH)_2$, was formed in worse yields even though reductive elimination is favored in such cases.[172] This indicates that reductive elimination is likely not rate-limiting but is more likely to be oxidative addition.

The reaction also tolerated steric hindrance on the boronic acid such as for the 2-napthyl and 2-CHO derivatives (**4a**, **19a**, **22a**). Bulky boronic acids (phenanthryl, diphenylaminophenyl and phenylcarbazole) reacted well (**8a**, **9a**, **10a**, **17a**, **20a**, **29a**, **32a**), and the more coordinating 3-NMe_2 group did not impair the reactivity (**5a**, **25a**).

2-Thienyl boronic was also an efficient coupling partner in this reaction (**6a**, **13a**). The main limitation in the scope of boronic acids seems to occur with 2- or 4-carboxaldehyde substitution which mostly led to low yields (**7a**, **12a**).

When using 2-F(C_6H_4)SO_2CF_3, 2-CHO(C_6H_4)$B(OH)_2$ could be used as a nucleophile to achieve a good yield of 60% (**22a**). The significant effect of 2-F *vs* 4-CN substitution on the sulfone when coupling with this specific boronic acid (**12a**, **22a**) could not be rationalized.

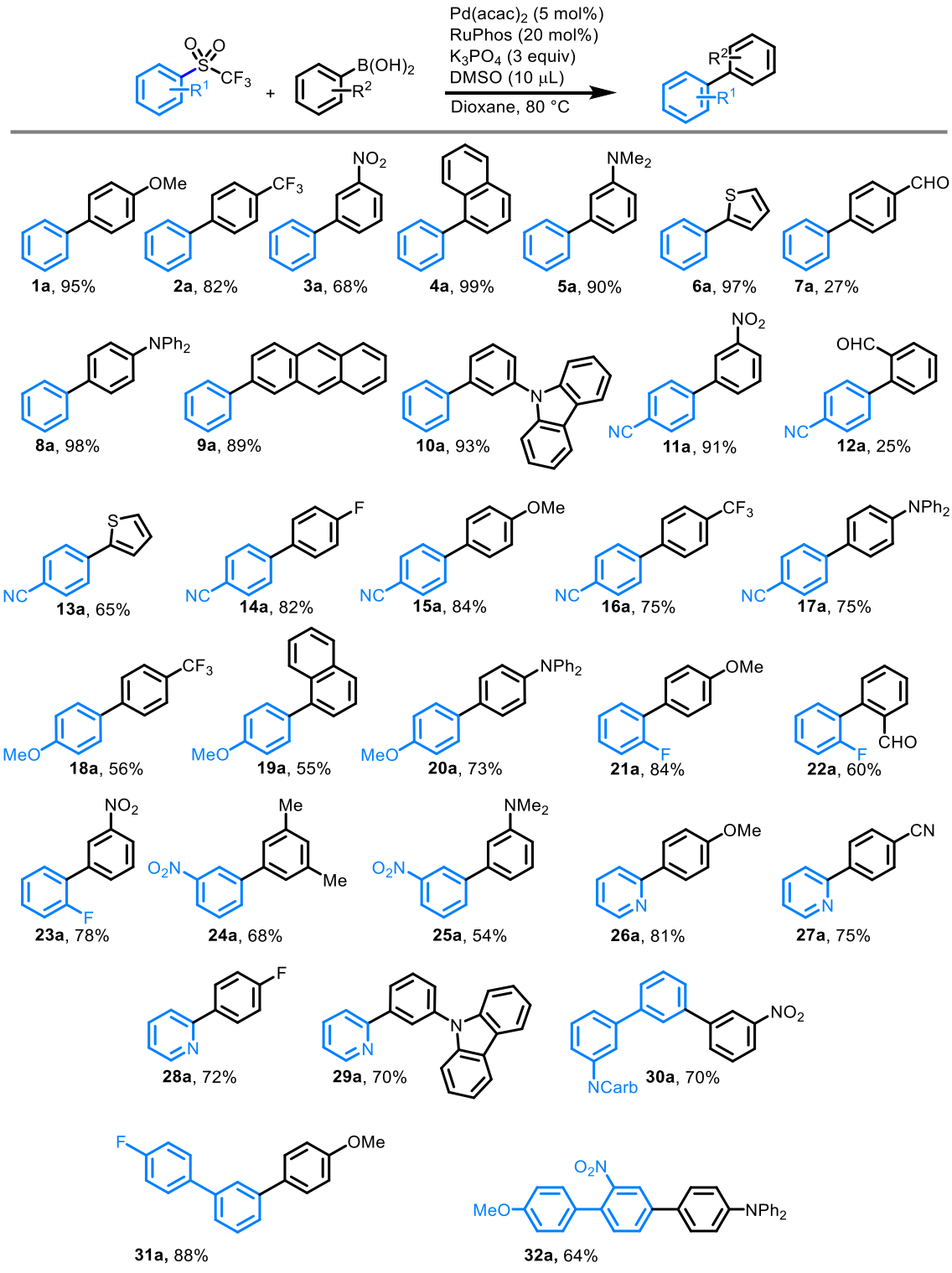


Table II.5: Aryl substrate scope

2.7 Conclusion to chapter II

In summary, a general method was developed for the Suzuki coupling of aryl trifluoromethyl sulfones. Their directing ability and robustness were demonstrated in a selective nitration reaction. More importantly, the vast difference in reactivity between halides, sulfones and nitroarenes was demonstrated and exploited in the synthesis of polyaromatic molecules via sequential Suzuki reactions, which is particularly attractive because of the wide potential applications of terphenyls (Figure II.9).[220,322] Mechanistic experiments indicate that oxidative addition is probably rate-limiting and occurs in the aryl-sulfur bond, leaving the leaving group intact as a sulfinate.

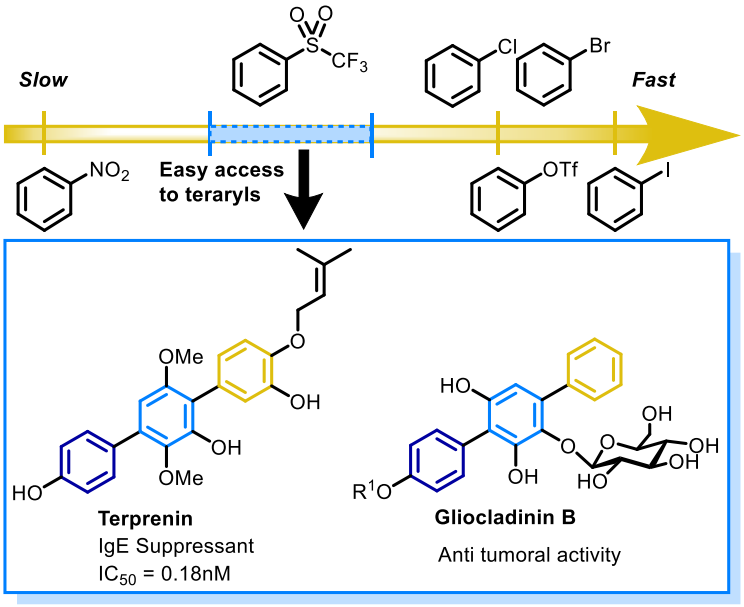


Figure II.9: Order of reactivity of aryl sulfones in the Suzuki reaction, facilitating access to terphenyls

III. The Suzuki Coupling of Sulfonyl Fluorides[‡]

Sulfonyl fluorides have received significant attention since their recent re-discovery by Sharpless as "click-able" reagents in SuFEx chemistry, which has been described as one of the most powerful reactions in click chemistry.[16,323] Despite their structural similarity to sulfonyl chlorides, the higher energy of the S–F bond confers sulfonyl fluorides a unique reactivity.[17] They undergo rapid and selective nucleophilic substitution under specific reaction conditions, and can be used for S–N, S–O and also S–C bond formation, which is challenging with sulfonyl chlorides due to their vulnerability to reduction by carbon nucleophiles.[16]

As highlighted in Sharpless' and Arvidsson's recent reviews, sulfonyl fluorides are largely inert to hydrolysis, reduction, and transition metal catalysis.[16,17,323] Indeed, the SO_2F group is often installed through transition-metal catalyzed processes,[324–336] and has been reported as a bystander in several Suzuki-Miyaura couplings (SMC).[17,307,337,338]

Inspired by Sanford's base-free Ni-catalyzed decarbonylative Suzuki coupling of carbonyl fluorides (see Figure I.18),[160] we envisaged that sulfonyl fluorides could react in an analogous desulfonative pathway under Pd-catalysis (Figure III.1).

This chapter describes the discovery and development of the Suzuki reaction of aryl sulfonyl fluorides, which can undergo coupling under base-free conditions. The usefulness of this reaction is highlighted by a divergent synthesis of two relevant biologically active molecules via C–C (Suzuki) or S–N (SuFEx) bond formation.

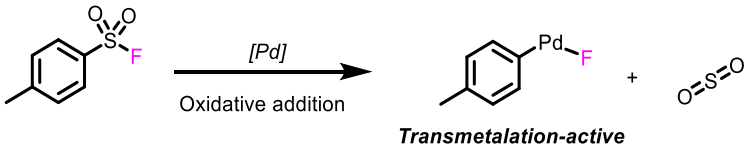


Figure III.1: Hypothesis of sulfonyl fluorides acting as base-free electrophiles in the Suzuki reaction

[‡] A manuscript in preparation includes portions of this chapter.

3.1 Screening methodology

The coupling between *p*-tolylSO$_2$F and 4-MeO(C$_6$H$_4$)B(OH)$_2$ was first investigated as a model reaction (Figure III.2). Like in the previous chapter, in the early discovery phase, conversion was estimated using the uncorrected GC/MS ratios of the integrals of the product *vs* the starting material. This method was reliable to establish the relative performance (or inefficacy) of various reaction conditions, and the reactions displaying a high conversion were isolated to obtain a precise measurement.

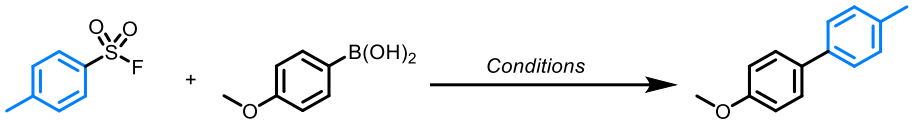


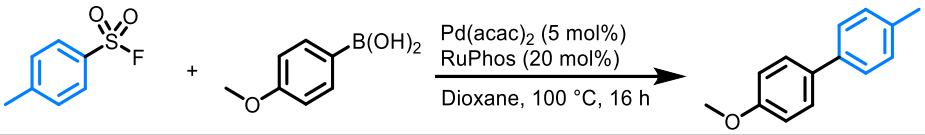
Figure III.2: Model reaction for the early stages of reaction development

3.2 Optimization of substrate

3.2.1 Initial screening with *p*-TolSO$_2$F

Because of the similar nature of sulfonyl fluorides relative to trifluoromethyl sulfones, the conditions that were first tried were analogous to the standard conditions described in the previous chapter, albeit without the addition of base. In accordance with the previous research, out of the species screened, Pd(acac)$_2$, RuPhos and dioxane provided the best results (Table III.1).

Varying the palladium source had a significant detrimental effect on the reaction (entries 2, 3). Interestingly, the addition of DMSO completely shut down the reactivity for this substrate (entry 4). This reaction was also more efficient without base than with base (entry 5). Other Buchwald ligands were screened but apart from XPhos, this usually led to a significant decline in reactivity (entries 6 – 9).

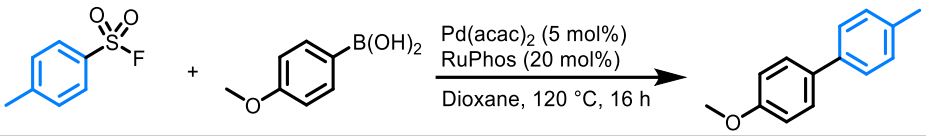


Entry	Variation from conditions	Conversion (%)[a]
1	No variation	12
2	Pd(PPh$_3$)$_4$ instead of Pd(acac)$_2$/RuPhos	trace
3	PdCl$_2$ instead of Pd(acac)$_2$	n.d.
4	+ 10 uL DMSO	n.d.
5	+ 3 equiv K$_3$PO$_4$	5
6	XPhos instead of RuPhos	11
7	BrettPhos instead of RuPhos	2
8	CPhos instead of RuPhos	4
9	DavePhos instead of RuPhos	5

Conditions: 0.2 mmol *p*-TolSO$_2$F, 0.3 mmol 4-MeO(C$_6$H$_4$)B(OH)$_2$, 5 mol% Pd(acac)$_2$, 20 mol% RuPhos, 1 mL Dioxane, N$_2$, 100 °C, 16 h. [a]GC/MS ratio of product to substrate.

Table III.1: Preliminary optimization of the reaction for *p*-TolSO$_2$F

After obtaining these preliminary results, a screen of additives was undertaken at a higher temperature to try to enhance the yields (Table III.2). Calcium salts were first screened due to their documented activity in SuFex chemistry, but completely shut down the reaction (entries 1 – 3).[339,340] Other Lewis acidic additives inhibited the reaction (entries 4, 5). Copper or rhodium additives, efficient in the cross-coupling of sulfones were also screened.[19] Apart from Cu(IPr)Cl, these additives also strongly inhibited the reaction (entries 6 – 8). Pd-PEPPSI(IPr), efficient in the cross-coupling of sulfones,[6,19] did not lead to any cross-coupling, indicating that the activity of Cu(IPr)Cl is not caused by the IPr ligand (entry 7).

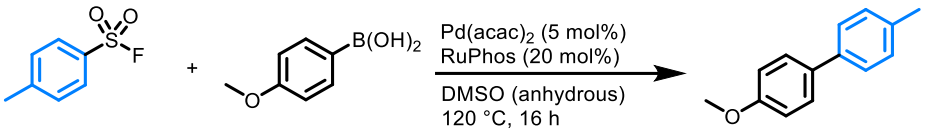


Entry	Variation from conditions	Conversion (%)[a]
1	+ $Ca(OH)_2$ 5 mol%	n.d.
2	+ $Ca(NTf)_2$ 5 mol%	n.d.
3	+ 1 equiv $Ca(NTf)_2$	n.d.
4	+ SbF_3 5 mol%	2
5	+ FeF_3 5 mol%	n.d.
6	+ $[RhCl(cod)_2]$ 2.5 mol%	trace
7	+ CuTC	trace
8	+ Cu(IPr)Cl	8
9	Pd-PEPPSI(IPr) instead of $Pd(acac)_2$ +/- $[RhCl(cod)_2]$ 2.5 mol%	n.d.

Conditions: 0.2 mmol *p*-$TolSO_2F$, 0.3 mmol 4-$MeO(C_6H_4)B(OH)_2$, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 1 mL Dioxane, N_2, 120 °C, 16 h. [a]GC/MS ratio of product to substrate. CuTC = copper thiophene carboxylate. Cu(IPr)Cl = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I). Pd-PEPPSI(IPr) = [1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride.

Table III.2: Additive screen for *p*-$TolSO_2F$

Next, the addition of KHF_2, also used in SuFex chemistry, was investigated (Table III.3).[341] The reaction reported in this SuFex reaction was run in anhydrous DMSO. Thus, DMSO was used to evaluate these conditions.



Entry	Variation from conditions	Conversion (%)[a]
1	No additives	n.d.
2	+ KHF_2 0.5 equiv	3
3	+ Cu(IPr)Cl 2.5 mol%	2
4	+ KHF_2 0.5 equiv + Cu(IPr)Cl 2.5 mol%	13
5	+ KHF_2 0.25 equiv + Cu(IPr)Cl 2.5 mol%	2
6	+ KHF_2 2 equiv + Cu(IPr)Cl 2.5 mol%	n.d.
7	+ KHF_2 0.5 equiv + Cu(IPr)Cl 1.25 mol%	5
8	Entry 4, 0.5 mL solvent	17
9	+ KHF_2 0.5 equiv + Cu(IPr)Cl 2.5 mol%, dioxane as solvent	13[b]

Conditions: 0.2 mmol *p*-TolSO_2F, 0.3 mmol 4-MeO(C_6H_4)B($OH)_2$, 5 mol% Pd(acac)$_2$, 20 mol% RuPhos, 1 mL DMSO, N_2, 120 °C, 16 h. [a]GC/MS ratio of product to substrate. [b]Reproduced twice.

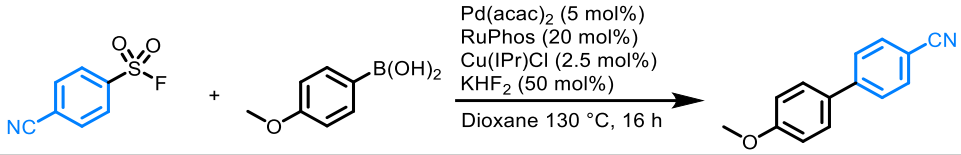
Table III.3: Synergy between Cu(IPr)Cl and KHF_2 as additives

The addition of either KHF_2 or Cu(IPr)Cl alone only led to very minor improvements relative to the reaction in the absence of any additive (entries 1 – 3). The combination of these additives led to a major improvement, hinting at a possible synergy between the two species (entry 4). 50 mol% KHF_2 was optimal in these conditions. Lowering or increasing the loading had a significant negative effect (entries 5, 6). A lower loading of Cu(IPr)Cl also inhibited the reaction (entry 7). Doubling the concentration of the reaction led to improved yields (entry 8). The conditions using KHF_2 and Cu(IPr)Cl could be reliably reproduced using dioxane instead of DMSO (entry 9).

3.2.2 Optimization on activated arenes

Due to the low reactivity of the tolyl substrate, further investigations were carried out on the more activated *p*-CN(C_6H_4)SO_2F (Table III.4). This reaction was first investigated using 0.5 mL solvent due to the higher observed activity at this concentration (see previous paragraph). A more significant improvement was observed when using Cu(IPr)Cl as an additive using this substrate (entries 1, 2).

However, the copper catalyst did not lead to any coupling products in the absence of palladium (entry 3). Similarly, the activity of the copper catalyst is probably not due to its NHC ligand: adding SIPr inhibited the reaction (entry 4). Because boronic acids form tetrafluoroborates by reaction with KHF_2,[342] $4MeO(C_6H_4)BF_3K$ was investigated instead of $4MeO(C_6H_4)B(OH)_2$, without adding any KHF_2 and it led to a higher conversion (entry 5). CuCl, another Cu(I) additive, completely inhibited the reaction (entry 6) and using a very high catalyst loading slightly inhibited the reaction (entry 7). The use of the cobalt salt $Co(acac)_3$ instead of Cu(IPr)Cl provided better results (entry 8). Cobalt catalysts have previously been implicated in the reduction of sulfones, hinting to its possible role interacting with the C–S bond.[21] However, the isolated product could not be separated from some impurities. Optimal conditions were finally achieved with 1 mL solvent and using a boronic acid (entry 9).

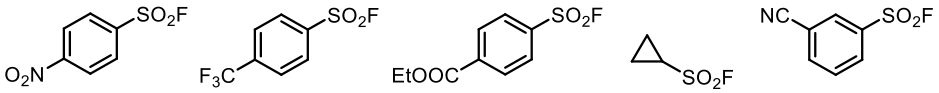


Entry	Variation from conditions	Conversion (%)[a]
1	No change	53
2	No Cu, No KHF_2	15
3	No Pd	n.d.
4	$SIPr{\cdot}HBF_4$ 2.5 mol% + K_3PO_4 5 mol% instead of Cu	n.d.
5	$4\text{-}MeO(C_6H_4)BF_3K$ instead of $-B(OH)_2$, no KHF_2	78
6	Entry 5, CuCl instead of Cu(IPr)Cl	n.d
7	Entry 5, 50 mol% Pd, 1 equiv RuPhos, 25 mol% Cu	69
8	Entry 5, $Co(acac)_3$ instead of Cu(IPr)Cl	80, 69[b,c]
9	$Co(acac)_3$ instead of Cu(IPr)Cl, 1 mL solvent	68[b]

Conditions: 0.2 mmol $4\text{-}CN(C_6H_4)SO_2F$, 0.3 mmol $4\text{-}MeO(C_6H_4)B(OH)_2$, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 0.5 mL Dioxane, N_2, 130 °C, 16 h. [a]GC/MS ratio of product to substrate. [b]Isolated yield. [c]Some impurities could not be separated from the product.

Table III.4: optimization with activated aryl sulfonyl fluorides

A) Other unsuccesful carbocyclic substrates



B) Other succesful activated arenes

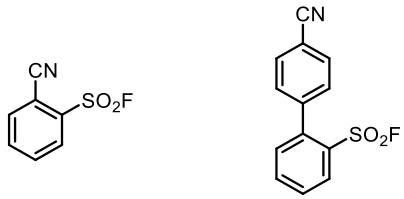
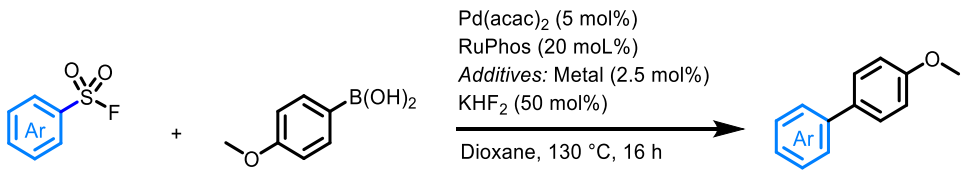
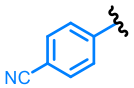
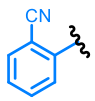
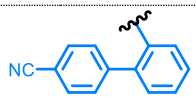


Figure III.3: Structures of other carbocyclic aryl sulfonyl fluorides and their coupling ability

Unexpectedly, other activated arenes such as 4-$CF_3(C_6H_4)SO_2F$, 4-$COOEt(C_6H_4)SO_2F$ and 4-$NO_2(C_6H_4)SO_2F$ were unreactive. The low reactivity of the 4-nitro derivative may be due to nitro activation competing with our desired coupling under these conditions: although no nitro-coupled product was observed, the coupling of nitroarenes also occurs at 130°C and the released NO_2 could lead to catalyst decomposition.[314]



Entry	Substrate	Conditions	Yield (%)[a]
1		No additives	15[b]
2		Cu(IPr)Cl + KHF_2	53[b]
3		$Co(acac)_3$ + KHF_2	68
4		No additives	65
5		Cu(IPr)Cl + KHF_2	74
6		$Co(acac)_3$ + KHF_2	65[c]
7		Cu(IPr)Cl + KHF_2	89

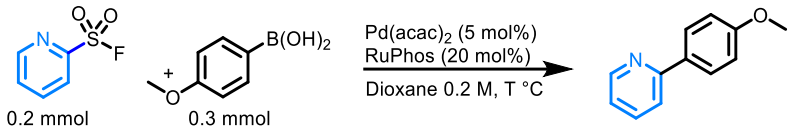
Conditions: 0.2 mmol $ArSO_2F$, 0.3 mmol 4-$MeO(C_6H_4)B(OH)_2$, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 0.5 mL Dioxane, N_2, 130 °C, 16 h. [a]Isolated yield. [b]GC/MS ratio of product to substrate. [c]Some impurities could not be separated from the product.

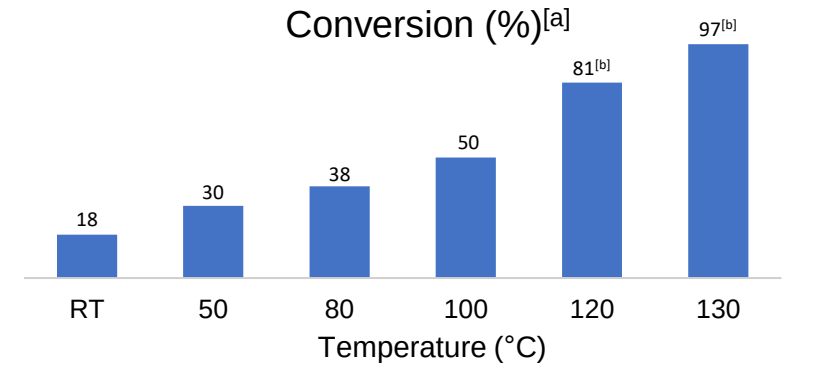
Table III.5: additives for the coupling of carbocyclic sulfonyl fluorides

The low reactivity of the *meta* cyano derivative relative to its *ortho* and *para* counterparts is consistent with the theoretical electron-withdrawing effects. The cyclopropane derivative also did not lead to cross-coupling and did not decompose in these conditions, as observed by GC/MS analysis.

The optimal conditions for carbocyclic sulfonyl fluorides are summarized in Table III.5. The *para* cyano derivative achieves optimal yields when using $Co(acac)_3$ as an additive (entries 1 – 3), but its *ortho* equivalent performs best with the addition of Cu(IPr)Cl (entries 4 – 6). Interestingly, for the latter substrate, the base-free conditions are rather efficient as well. Finally the ortho-biaryl substrate presented in entry 7 achieves excellent yields using Cu(IPr)Cl.

3.2.3 Heterocyclic substrates





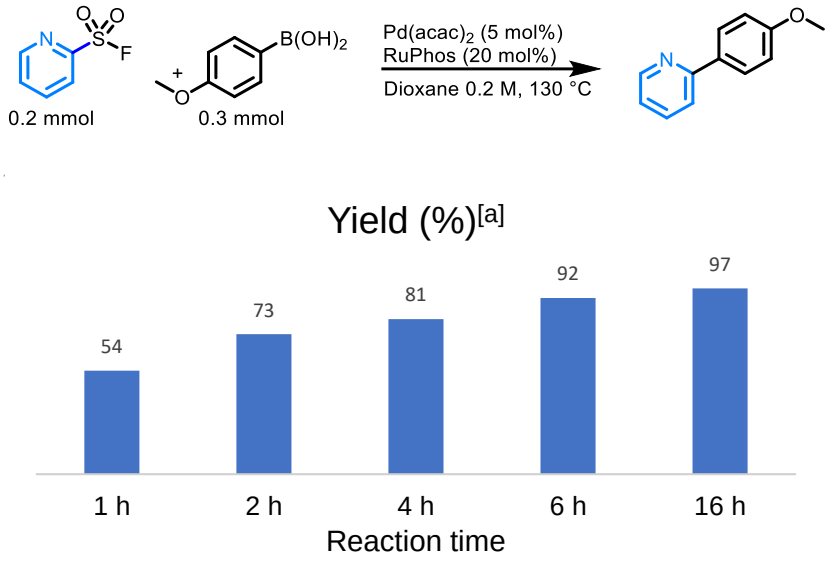
Conditions: 0.2 mmol 2-$PySO_2F$, 0.3 mmol 4-$MeO(C_6H_4)B(OH)_2$, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 1 mL Dioxane, T °C, 16 h. [a]GC/MS ratio of product to substrate. [b]Isolated yield.

Graph III.1: Temperature screen

In parallel, heteroaryl sulfonyl fluorides were investigated as potentially more reactive substrates. The higher reactivity of 2-pyridine sulfonyl fluoride, also known as PyFluor, was already known in deoxyfluorination reactions,[343] and 2-pyridyl substrates are generally less challenging electrophiles (the Suzuki reaction on

chlorides was first limited to electron-poor arenes or 2-pyridyl chlorides). It was also hypothesized that the 2-pyridyl group could direct the palladium to the S–F bond. Thus, it was postulated that PyFluor could display a higher reactivity than the highly challenging *p*-TolSO$_2$F. Satisfactorily, the pre-optimized conditions for the coupling of *p*-TolSO$_2$F (Table III.1, entry 1) resulted in high conversions for PyFluor and the optimal reaction temperature was determined to be 130 °C (Graph III.1). Cross-coupling occurred to some extent at room temperature, although only trace amounts of coupling product (< 10%) could be isolated.

Next, a time-course experiment was undertaken. Consistently with our assumptions, the optimal reaction time was found to be 16 h, although most of the reaction was completed in under 6 h (Graph III.2). To ensure completion of the reaction, and because most biphenyl products are thermally stable, the reactions were usually left to run overnight (16 h).

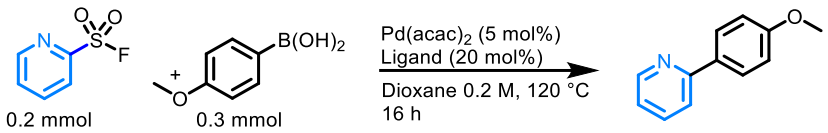


Conditions: 0.2 mmol 2-PySO$_2$F, 0.3 mmol 4-MeO(C$_6$H$_4$)B(OH)$_2$, 5 mol% Pd(acac)$_2$, 20 mol% RuPhos, 1 mL Dioxane, 130 °C, t h. [a]Isolated yield.

Graph III.2: Time-course experiments

Next, to ensure that the previous optimization done on *p*-TolSO$_2$F fits with this heterocyclic substrate, several ligands were screened at 120 °C instead of 130 °C to make ligand performance more apparent than if the reaction proceeds to full conversion (Table III.6). In general, Buchwald ligands bearing ether groups (SPhos

and RuPhos) led to high conversions (entries 1 and 2), likely due to the stabilizing effects of the coordination of the Pd to the oxygen as well as the arene (see Figure I.27). More importantly, because of the high temperatures, the activity of the catalyst could be (partly) explained by the facile formation of Pd(I) phosphide complexes from RuPhos and SPhos at high temperatures (see Figure I.28).[198] DavePhos, which also bears a coordinating substituent (NMe_2) was also moderately efficient (entry 3).



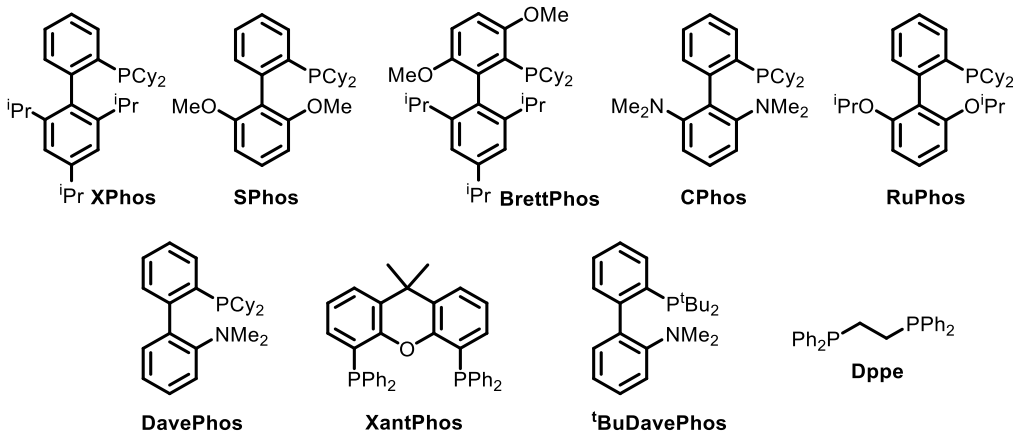
Entry	Ligand (20 mol%)	Conversion[a] (%)
1	RuPhos	90
2	SPhos	86
3	DavePhos	63
4	XPhos	45
5	^{t}BuDavePhos	36
6	BrettPhos	56
7	CPhos	44
8	$Pd(PPh_3)_4$ (5 mol%)	67
9	XantPhos	27
10	Dppe (10 mol%)	15
11	PCy_3	5
12	PhS(O)EtS(O)Ph (10 mol%)	n.d.

[a]GCMS conversion. Conditions: PyFluor 0.2 mmol, $4MeO(C_6H_4)B(OH)_2$ 0.3 mmol, $Pd(acac)_2$ 5 mol%, Ligand 20 mol%, dioxane 1 mL, 120 °C, 16h. N.d.: Not detected

.

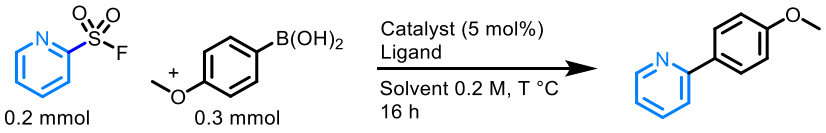
Table III.6: Ligand optimization of 2-$PySO_2F$

XPhos, which has a similar bulk to RuPhos and bears electron donating substituents (^{i}Pr) produced much lower yields, indicating the need for coordinating substituents to stabilize the Pd complex (entry 4). *Tert*-Butyl phosphine derivatives of Buchwald ligands were less efficient (entry 5). BrettPhos, useful in the coupling of nitroarenes,[314] also failed to achieve high conversions (entry 6) and CPhos was about as efficient as XPhos (entry 7). Unsurprisingly, the "first-generation" catalyst $Pd(PPh_3)_4$, useful in the coupling of sulfonyl chlorides,[305] achieved relatively high conversions (entry 8). Other simple phosphine ligands displayed a low activity (entries 9 – 11).



The bis-sulfoxide ligand PhS(O)EtS(O)Ph completely inhibited the reaction (entry 12), similarly to what was observed in the coupling of sulfones.

Next, solvents and various metals were investigated to see if they could lead to a successful coupling (Table III.7). A lower temperature of 100 °C or 120 °C was used to better evaluate reactivity differences. Toluene led to lower yields compared to dioxane (entries 1 and 2) but trifluorotoluene was an acceptable substitute to dioxane (entry 3). Nickel catalysts were unreactive in the conditions tried (entries 4 – 6). Surprisingly, a cobalt(III) salt in combination with XantPhos led to some cross-coupling product (entry 7), which is in agreement with the observation of its positive effect as a adjuvant for the coupling of *p*-CN(C_6H_4)SO_2F (see Table III.5).

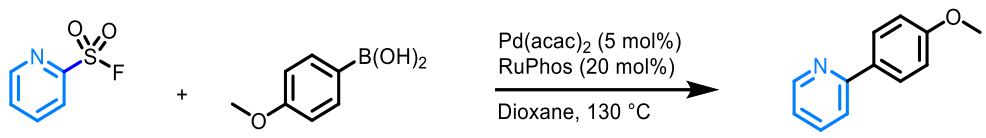


Entry	T °C	Catalyst	Ligand /mol%	Solvent	Conversion[a] (%)
1	100	$Pd(acac)_2$	RuPhos (20)	Dioxane	55
2	100	$Pd(acac)_2$	RuPhos (20)	Toluene	37
3	100	$Pd(acac)_2$	RuPhos (20)	$PhCF_3$	46
4	100	$NiCl_2(PCy_3)_2$	-	Dioxane	n.d.
5	120	*trans*-$(PCy_2Ph)_2$-Ni(o-tolyl)Cl	-	Dioxane	trace
6	120	$Ni(acac)_2$	PCy_3 (20)	Dioxane	n.d.
7	120	$Co(acac)_3$	XantPhos (10)	Dioxane	12

[a]GCMS conversion. Conditions: PyFluor 0.2 mmol, $4MeO(C_6H_4)B(OH)_2$ 0.3 mmol, *catalyst 5* mol%, *ligand* x mol%, solvent 1 mL, T °C, 16 h. N.d.: Not detected.

Table III.7: Catalyst and solvent optimization the coupling of PyFluor

The optimization, mostly based on GC/MS conversions, was reproduced by isolating the yields when varying significant reaction parameters (Table III.8). When RuPhos was used as a ligand with catalytic $Pd(acac)_2$ in absence of base, 2-$PySO_2F$ (PyFluor) underwent coupling with 4-methoxybenzeneboronic acid at 130 °C in excellent yields without addition of any base (Table 1, entry 1). $Pd(PPh_3)_4$, previously used in the SMC coupling of sulfonyl chlorides,[305] was somewhat effective (entry 2). Changing the Pd source to $Pd(OAc)_2$ led to a significant decline in yield (entry 3), similarly to what was observed in the previous chapter: $Pd(acac)_2$ might lead to a more facile reduction of Pd(II) via phosphine oxidation or might favor the formation of a more active anionic catalyst. The ligand loading was also an important feature of this reaction: lowering it led to decreased yield, highlighting the importance of oversaturation, which likely prevents catalyst decomposition (entry 4).[5] Other Buchwald ligands, such as SPhos and XPhos, were not as successful (entries 5, 6). Toluene was a less adapted solvent, whereas trifluorotoluene was an acceptable substitute for dioxane (entries 9, 10).

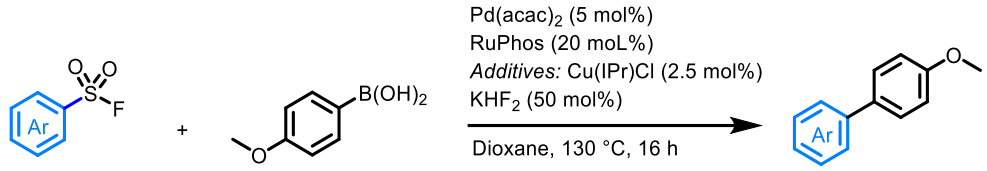


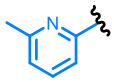
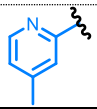
Entry	Variations from standard conditions	Yield 1 (%)[a]
1	None	97
2	$Pd(PPh_3)_4$ as only catalyst	49
3	$Pd(OAc)_2$ instead of $Pd(acac)_2$	57
4	RuPhos 15 mol% instead of 20 mol%	77
5	SPhos instead of RuPhos	67
6	XPhos instead of RuPhos	59
7	Toluene instead of Dioxane	67
8	$PhCF_3$ instead of Dioxane	90

Reaction conditions: 0.2 mmol 2-$PySO_2F$, 0.3 mmol 4-$MeO(C_6H_4)B(OH)_2$, $Pd(acac)_2$ (5 mol%), RuPhos (20 mol%), Dioxane 1 mL, 130 °C, 16 h. [a]Isolated yield.

Table III.8: Summary of optimization for PyFuor coupling

Next, to evaluate the scope of this reaction on heterocyclic substrates, substituted 2-pyridyl sulfonyl fluorides were investigated (Table III.9). Interestingly, like their carbocyclic counterparts (see Table III.5), they required a copper additive to cross-couple in high yields. The 6-Me and 4-Me derivatives of PyFluor were subjected to standard conditions (*i.e.* Table III.8, entry 1) or to the addition of Cu(IPr)Cl and KHF_2.



Entry	Substrate	Conditions	Yield (%)[a]
1		No additives	30
2		$Cu(IPr)Cl + KHF_2$	98
3		No additives	33
4		$Cu(IPr)Cl + KHF_2$	80

Conditions: 0.2 mmol $ArSO_2F$, 0.3 mmol 4-$MeO(C_6H_4)B(OH)_2$, 5 mol% $Pd(acac)_2$, 20 mol% RuPhos, 0.5 mL Dioxane, N_2, 130 °C, 16 h. [a]Isolated yield. [b]GC/MS ratio of product to substrate. [c]Some impurities could not be separated from the product.

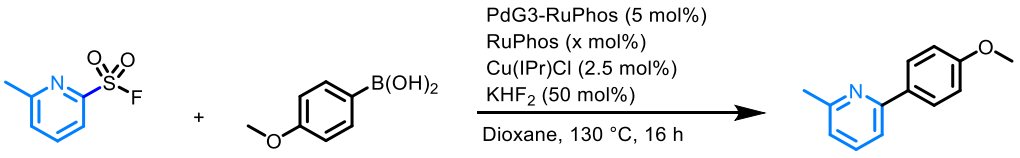
Table III.9: Influence of additives on substituted pyridines

It was initially hypothesized that the 6-methyl derivative of PyFluor exhibited a lower coupling reactivity because it disturbed a potential directing ability of the nitrogen into

the S–F bond (Table III.9, entries 1 and 2). However, very similar results were obtained using the 4-methyl derivative, which is unhindered at its nitrogen (entries 3 and 4). For these two different substituted 2-$PySO_2F$ substrate, the addition of Cu(IPr)Cl and KHF_2 resulted in excellent to near quantitative yields.

3.3 Optimization of ligand loading

Because of the high excess ligand used in our standard conditions (20 mol%), efforts were made to lower the ligand loading in our reaction using 6-$MePySO_2F$ as a model substrate (Table III.10). Using the Buchwald palladacycle PdG3-RuPhos (see Figure I.26**:** Advantages of palladacycles for catalyst initiation, less excess ligand was required. Only 10 mol% excess ligand (amounting to 15 mol% total RuPhos) was required to achieve quantitative yields (entries 1 – 3). A higher excess led to diminished yields (entry 4).



Entry	PdG3-RuPhos + added ligand	Yield[a] (%)
1	No added RuPhos	43
2	RuPhos 5 mol%	83
3	RuPhos 10 mol%	>99
4	RuPhos 15 mol%	90
5	RuPhos 10 mol%, PdG4-RuPhos instead of PdG3-RuPhos	75
6	RuPhos 10 mol%, no Cu(IPr)Cl, no KHF_2	60
7	RuPhos 10 mol%, no Cu(IPr)Cl	46
8	RuPhos 10 mol%, no KHF_2	80

[a]Isolated yield. Conditions: 6-Me-2-$PySO_2F$ 0.2 mmol, 4MeO(C_6H_4)$B(OH)_2$ 0.3 mmol, PdG3-RuPhos 5 mol%, RuPhos x mol%, Cu(IPr)Cl 2.5 mol%, KHF_2 50 mol%, dioxane 1 mL, 130 °C, 16h. PdG3 = 2-(2-amino-1,1-biphenyl)]palladium(II) methanesulfonate; PdG4 = 2-(2-methylamino-1,1-biphenyl)]palladium(II) methanesulfonate

Table III.10: Alternative conditions to lower the ligand loading and controls for the role of additives.

Therefore, it was hypothesized that part of the excess RuPhos was required to reduce the $Pd(acac)_2$ precatalyst (used in standard conditions) to the active Pd(0) species (see Figure I.29**:** Mechanism of reduction of $Pd(OAc)_2$ through oxidation of Buchwald ligand XPhos). The similar PdG4-RuPhos was also an efficient precatalyst for the reaction (entry 5).

During the course of this experiment, more investigations were also undertaken to understand the role of the Cu(IPr)Cl and KHF_2 additives. Interestingly, using KHF_2 as the sole additive led to slightly diminished yields compared to not using either additive (entries 6 and 7). Using Cu(IPr)Cl alone still leads to high yields (entry 8), but the best yields are obtained with the combination of both additives (entry 3). This hints to a synergistic effect between KHF_2 and Cu(IPr)Cl.

A lower ligand loading was also used in the large-scale cross-coupling of 2-$PySO_2F$ with 4-$MeO(C_6H_4)SO_2F$ (Figure III.4). At a 2 mmol scale, the ligand loading could be reduced to 5 mol% and the Pd and Cu loadings to 2.5 and 1.25 mol%, respectively.

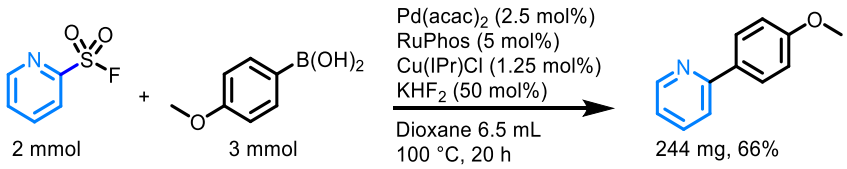


Figure III.4: Large-scale coupling of PyFluor

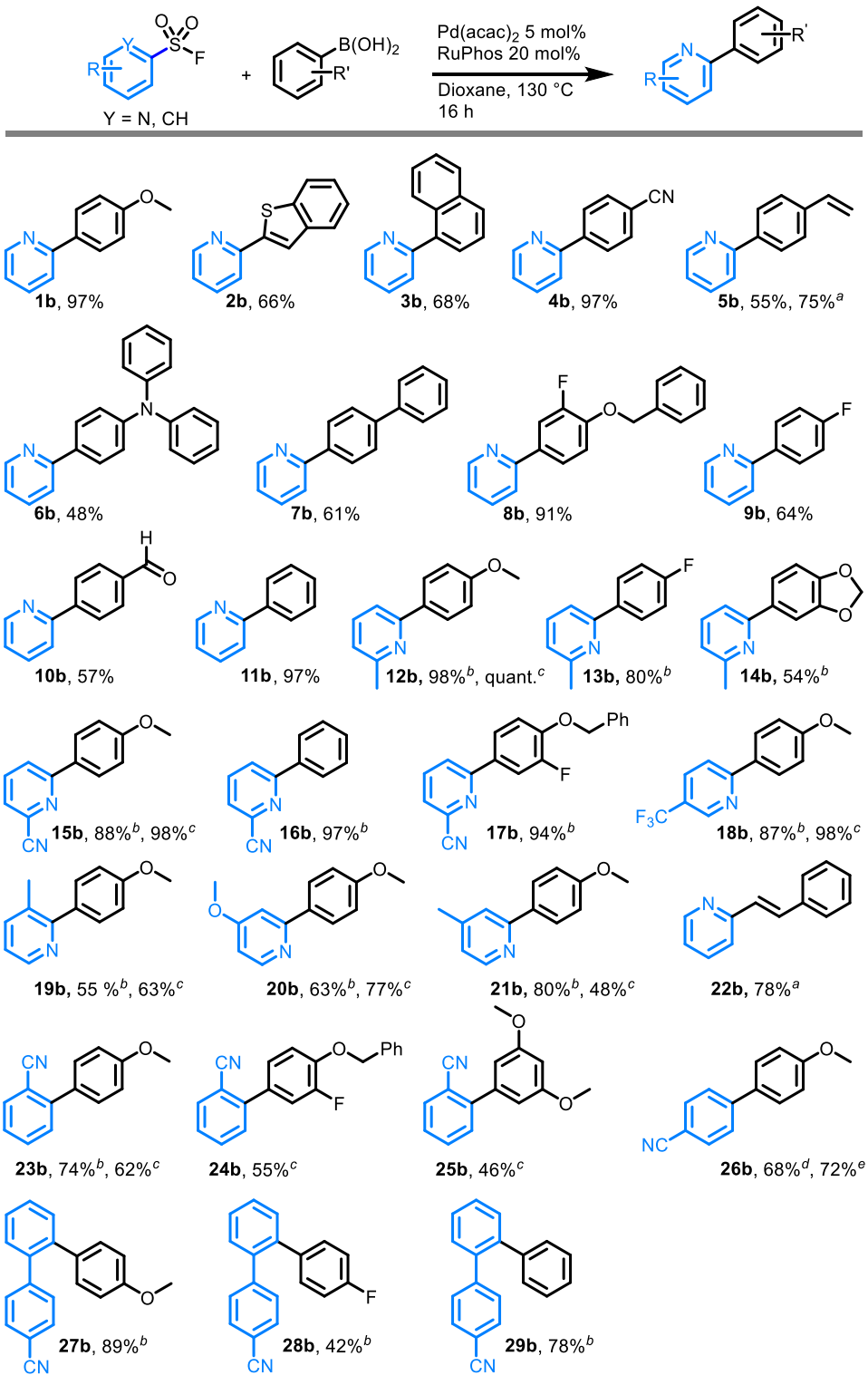
Despite the reactivity of PyFluor in the absence of Cu(IPr)Cl and KHF_2, these enhanced conditions were used because the reaction temperature could not be raised above the boiling point of the solvent due to a lack of suitable reaction apparatus for larger-scale reactions under pressure

3.4 Substrate scope

The optimized conditions were then applied to a variety of aryl sulfonyl fluorides and aryl boronic acids (Table III.11). For the coupling of PyFluor under base-free conditions, electron donating or withdrawing groups were well-tolerated on the boronic acid. 2-Benzothienyl boronic acid was also well-tolerated (**2b**) but pyridyl boronic acids were unreactive. Hindrance in 2-naphthyl boronic acid did not seem to impair reactivity (**3b**). The reaction was also tolerant to vinyl substitution, and high yields were obtained after a shorter reaction time (**5b**), indicating product decomposition during prolonged exposure to the reaction conditions. Other functional groups were also tolerated on the boronic acid, like diarylamino (**6b**), benzyl ethers (**8b**, **17b**, **24b**), aldehyde (**10b**), and a methylene dioxy group (**14b**). Alkenyl boronic acids were also suitable coupling partners in this reaction under standard base-free conditions (**22b**).

Other substituted pyridines displayed good reactivity using Cu(IPr)Cl and KHF_2 as additives (see Table III.9), and were tolertant to electron-donating and electron-withdrawing groups (**12b** – **21b**). The cross-coupling was also tolerant to substitution *ortho* to the sulfonyl fluoride leaving group (**19b**).

Other heterocyclic sulfonyl fluorides such as the 4-pyridyl derivative did not react, hinting to a specific effect of the 2-nitrogen: it might act as a directing goup into the proximal S–F bond. However, other hetyerocycles bearing a proximal nitrogen such as the 2- or 8-quinoline derivatives did not react or led to low conversions (Figure III.5). The lower reactivity of 4-Me$PySO_2F$ (Table III.9), which has similar electronic and steric properties to 2-$PySO_2F$ was also more challenging to couple, which weakens the directing nitrogen hypothesis. Interestingly, 5-chloro-PyFluor did not couple on the chloride using standard base-free conditions (as in Table III.8), but was also unreactive on the sulfonyl fluoride. Using the conditions with KHF_2 and Cu(IPr)Cl (see Table III.9), coupling occurred on both functional groups, but only to a small extent.



[a]6 h. [b]additives: Cu(IPr)Cl (2.5 mol%), KHF_2 (50 mol%). [c]*a* using PdG3-RuPhos (5 mol%), RuPhos (10 mol%) as catalysts. [d]*a* using $Co(acac)_3$ instead of Cu(IPr)Cl. [e]*c* using PdG3-RuPhos (5 mol%), RuPhos (10 mol%) as catalysts.

Table III.11: Substrate scope of $ArSO_2F$ coupling

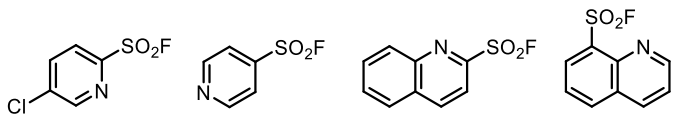


Figure III.5: Unsuccessful heterocyclic substrates

Non-heterocyclic aryl sulfonyl fluorides cross-coupled in good yields when substituted with cyano or aryl groups (**23b** – **29b**). However, other activated arenes displayed low reactivity (Figure III.3). The *para*-cyano derivative coupled in good yields, when $Co(acac)_3$ was used as an adjuvant instead of Cu(IPr)Cl (Table III.5), showing that directing groups are not a requirement for the succesful coupling of sulfonyl fluorides (**26b**). The activity of cobalt in the reduction of sulfones was reported, hinting to its possible role interacting with the C–S bond.[21] The mild activity of this cobalt salt in the cross-coupling of PyFluor (Table III.7) supports this claim. The addition of $Co(acac)_3$ to other substrates led to lower yields compared to the copper co-catalyst Cu(IPr)Cl (Table III.5, entry 6). Ortho-aryl substitution was also well tolerated (**27b** – **29b**) and the resulting terphenyl structures are analogues of biologically active molecules.[321] This was exploited in a representative example of a divergent synthesis in Figure III.6.

3.5 Divergent synthesis

To illustrate the usefulness of the present method, a representative divergent synthesis was undertaken to synthesize two analogues of biologically active compounds from a single sulfonyl fluoride substrate. Starting from biphenyl **s5**, conveniently prepared from the commercial 2-$Br(C_6H_4)SO_2F$, a Suzuki coupling can be undertaken to create an analogue of an anti-leukemia compound,[321] or a SuFEx reaction can be undertaken to form an analogue of the novel opioid antidepressant PF-4455242 under development by Pfizer (Figure III.6).[305] This kind of reactivity is not accessible from aryl halides, and the corresponding aryl sulfonyl chloride starting material is not trivial to synthesize.

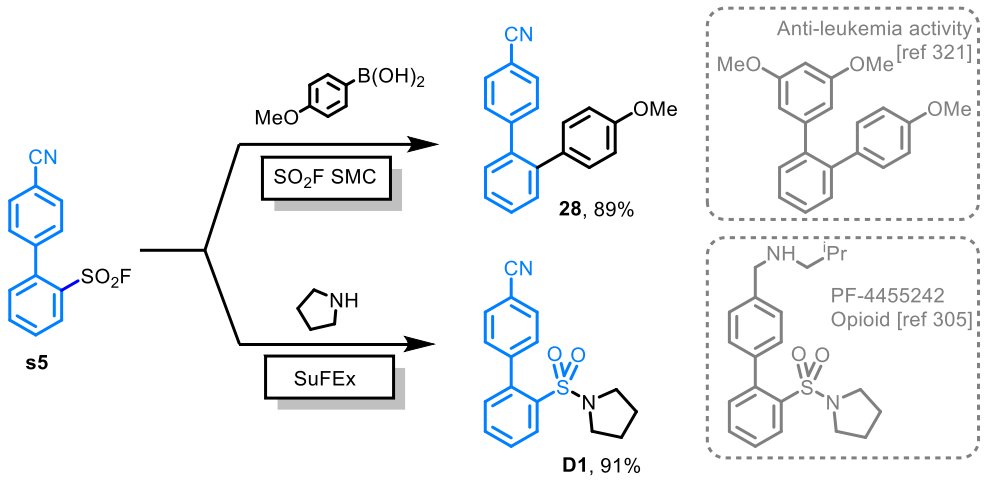


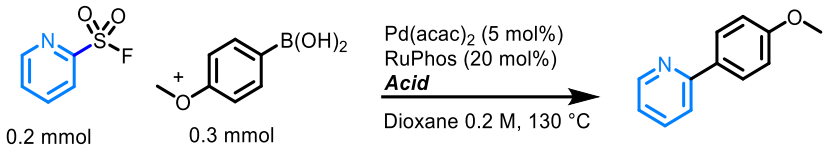
Figure III.6: Divergent synthesis from sulfonyl fluorides illustrating the complementarity between SuFEx chemistry and the Suzuki coupling

Using this method, sulfonyl fluorides can be used as a hydrolytically stable (and otherwise very stable) functional group for the installation of S–N and C–C bonds. It is thus a method that can be complementary to SuFEx chemistry.[16,17]

3.6 Mechanistic experiments

3.6.1 Base-free quality of the reaction and mechanism of transmetalation

To probe the base-free quality of this reaction, the tolerance to added acids were investigated. Three acids were screened by increasing acidity (Table III.12). 1 equiv. camphor sulfonic acid (CSA) inhibits the reaction only mildly, however excess CSA had a detrimental effect on the reactivity (entries 1 and 2). To our delight, tolerance was observed for the addition of TFA, where 1.5 equiv. still led to moderate yields (entries 3 and 4). The bigger inhibitory effect of CSA might be due to the interaction of the sulfonyl group with the catalyst. The stronger *p*TsOH completely inhibited the reaction at a stoichiometric loading (entry 5). These results further confirm the "base-free" character of this reaction (the pyridyl motif on the product or the substrate does not act as a base to promote transmetalation).



Entry	Acid (1equiv)	pKa	Yield (%)[a]
1	Camphor sulfonic acid (CSA)	1.2	65
2	CSA (1.5 equiv)		14
3	TFA	0.23	77
4	TFA (1.5 equiv)		46
5	*p*TsOH	-2.8	Trace

Conditions: PyFluor 0.2 mmol, 4MeO(C_6H_4)B(OH)$_2$ 0.3 mmol, Pd(acac)$_2$ 5 mol%, RuPhos 20 mol%, *acid* 1 or 1.5 equiv, dioxane 1 mL, 130 °C, 16 h.

Table III.12: Tolerance of the reaction to various acids

This is a rare example of a Suzuki reaction run with added acids, being only described on aryl diazoniums,[239] aryl hydrazines[290] and ketones (using rhodium catalysis).[313] However, the acids used in those examples are simple alkyl carboxylic acids of considerably weaker acidity that TFA.

Competition experiments were next carried out. Subjecting PyFluor to its standard cross-coupling conditions, but in the presence of other SMC electrophiles such as PhCl or $PhSO_2CF_3$, led only to coupling of PyFluor. The other substrate was still observed at the end of the reaction, despite the reaction temperature being much higher than is generally required for the coupling of aryl chlorides (or sulfones) using Buchwald ligands (Figure III.7).[5,87] Performing the same competition experiment with the more electrophilic bromobenzene inhibited the reaction; no cross-coupling was observed on either substrate. The more reactive aryl bromides might sequester all the palladium as oxidative addition products. Unfortunately, despite these promising results, 5-Cl-2-$PySO_2F$ could not be used for cross-coupling on either functional group (see Figure III.5).

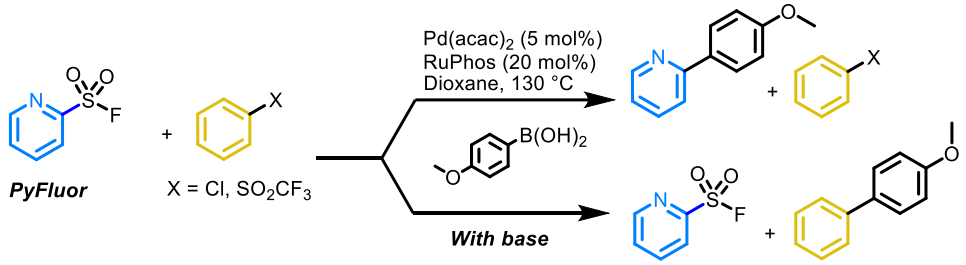


Figure III.7: Orthogonality with chlorides and sulfones – the pyridyl substrate and the product do not act a base for the SMC reaction.

Taken together, these experiments suggest that the pyridyl group on the substrate or product does not act as a base to facilitate transmetalation, but rather that a Pd-F intermediate is involved.[139] It also suggests that the Pd-F intermediate is either formed irreversibly or that the subsequent transmetalation step occurs relatively quickly after its formation.

Next, PyFluor was reacted with 1 equiv of $LiBF_4$ as a fluoride scavenger (LiF is a highly insoluble salt) under otherwise standard conditions (Figure III.8). Only trace amounts of coupling were observed via TLC, but no product could be isolated.

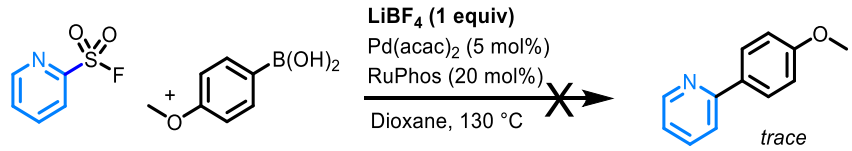


Figure III.8: Fluoride scavenging experiment

This supports the hypothesis that transmetalation occurs through a Pd-F intermediate (and thus release of SO_2 gas) and rules out a cationic transmetalation as is observed for diazoniums (see Figure I.17).

To further probe the mechanism, the fate of the leaving group was examined by extracting a typical reaction mixture (specifically, the conditions described in Table III.8, entry 1) in D_2O. ^{1}B NMR revealed the presence of $B(OH)_3$, HBF_4 and BF_3. ^{19}F NMR of the same extract confirmed the presence of these species, along with unassigned peaks which might correspond to SO_2F^- (fluorosulfite) and other fluoroborated molecules. HRMS analysis of this mixture confirmed the presence of these species, along with other fluoroborated products ($B(OH)_2O^-$, $BF(OH)O^-$, BF_2O^-, BF_4^-). This, along with the observed inhibition of the reaction when using $LiBF_4$ (Figure III.8), further corroborates that the reaction proceeds through a Pd-F intermediate and indicates that fluoride ions liberated during the reaction are scavenged by boron after transmetalation.

3.6.2 Role of the copper additive

For substituted pyridyl sulfonyl fluorides and carbocyclic sulfonyl fluorides, the addition of Cu(IPr)Cl enhanced the yields (see Tables III.9 and III.10). To investigate the role of the copper additive in the reaction, PyFluor was reacted with either PdG4-RuPhos alone (50 mol%) or with PdG4-RuPhos (50 mol%) and Cu(IPr)Cl (25 mol%) in dioxane (0.5 M) at 130 °C (Figure III.9). In the absence of Cu(IPr)Cl, unreacted PyFluor was the major reaction component, as revealed by ^{19}F NMR after 2 h. However only trace PyFluor was observed in the reaction using Cu(IPr)Cl, indicating a decomposition of the substrate. No 2-fluoropyridine was observed. PdG4, also useful as a precatalyst (see Table III.10), was chosen to prevent C–N cross-coupling with the carbazole leaving group of PdG3 (see Figure I.26).

In the absence of PdG4-RuPhos, Cu(IPr)Cl does not react with PyFluor, implying a possible synergistic effect between the two species. Cu(IPr)Cl is thus likely involved in the desulfonation step (SO_2 release), which happens after oxidative addition of the palladium.

This is supported by a report describing the desulfonation of vinyl sulfonyl fluorides using a copper catalyst and B_2Pin_2 as a reductant.[344] The inactivity of Pd-NHC catalysts in this reaction (Table III.4) excludes the role of Cu(IPr)Cl as a mere ligand source.

However, interactions with the boron substrate or the fluoride ion cannot be excluded: several copper species have been reported to act as a fluorination catalyst for halides and borylated substrates.[345,346]

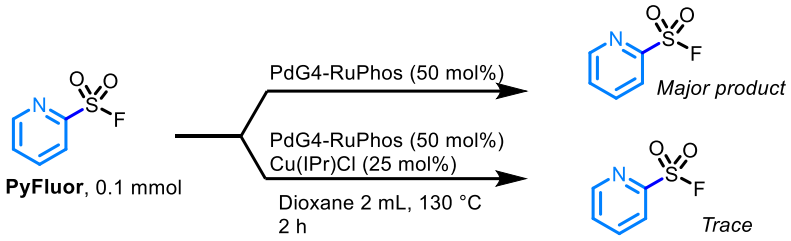


Figure III.9: Control experiments to investigate the role of the Cu(IPr)Cl additive

3.6.3 DFT Studies

DFT studies are currently underway with collaborator Chris Rowley and will be available in the corresponding publication

3.6.4 Proposed mechanism

The various proposed mechanisms are represented in Figure III.10. Because of the higher activity of 2-pyridyl and 2-CN or 2-Ar substrates, a reasonable hypothesis would be a directing action into the S-F bond of the sulfonyl fluoride. After desulfonation, transmetalation would occur through a Pd-F intermediate.

However, undirected oxidative addition in the C–S bond, as is known to occur with the similar $ArSO_2CF_3$ sulfones presented in the previous chapter is also likely, and the higher activity of the 2-substituted substrates might be due to other effects.

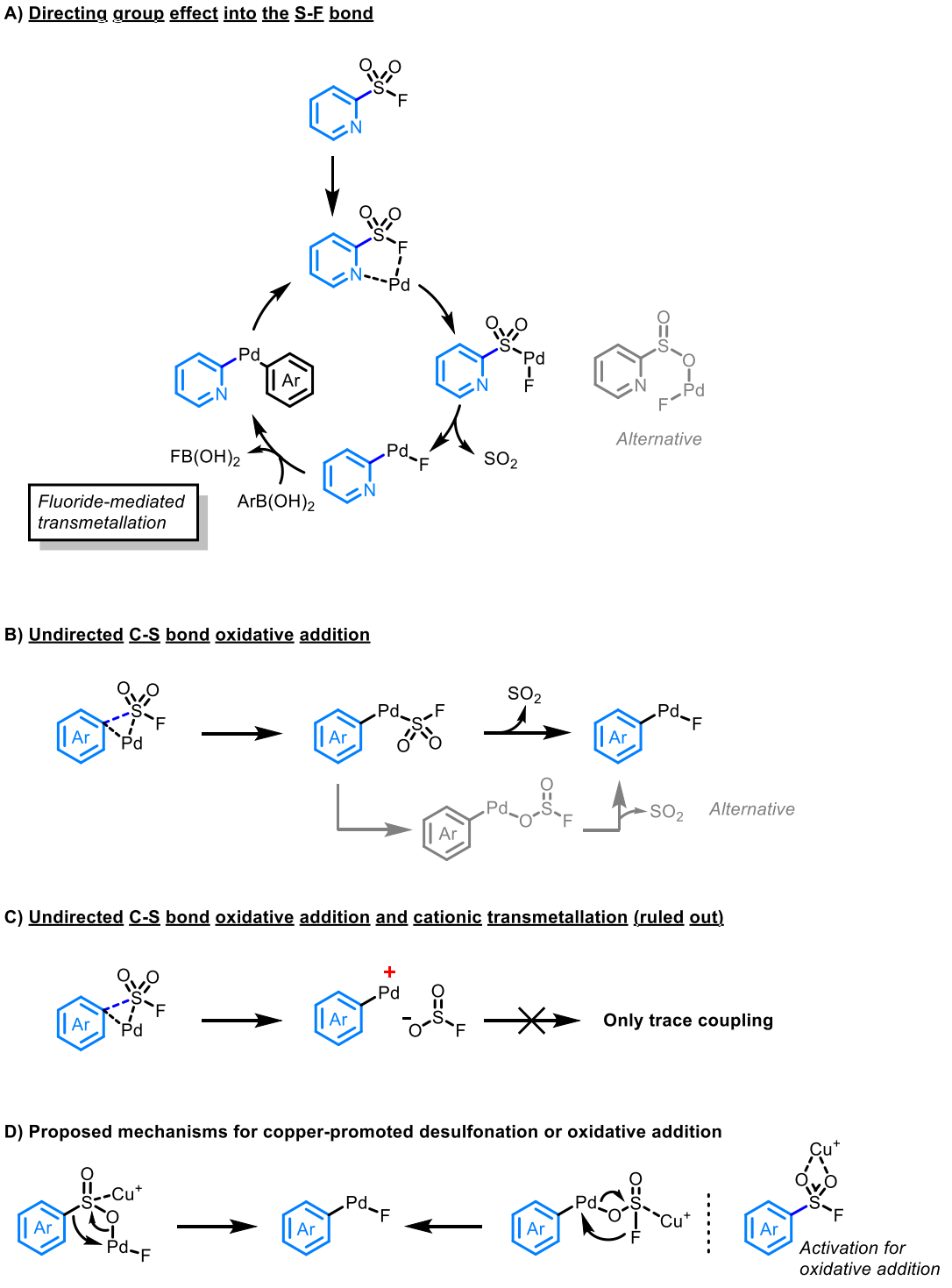


Figure III.10: Different proposed mechanisms for the cross-coupling of sulfonyl fluorides (ligands omitted for clarity)

A transmetalation from a cationic intermediate was ruled out: the addition of a lithium salt inhibits the reaction, and the reaction is enhanced by the addition of KHF_2, a fluoride source (Tables III.9 and 10).

The role of the copper additive Cu(IPr)Cl in the mechanism was postulated to occur through the O-bound palladium sulfinate. The thiophilic Cu(I) would coordinate to the lone pair on the sulfur, thereby reducing its electron density and facilitating the transfer of electrons from the palladium bound oxygen, liberating a fluoride or the arene to coordinate the palladium (Figure III.10 C).

3.7 Conclusion to chapter III

In summary, despite their widely reported stability in the face of transition-metal catalysis,[17] aryl sulfonyl fluorides can be used as electrophiles in the Suzuki reaction. Mechanistic experiments suggest that the coupling occurs via SO_2 release and that the fluoride leaving group can act as the base for the transmetalation step, although more challenging substrates necessitated added fluoride in the form of KHF_2 to couple in high yields. The turnover-limiting step is likely oxidative addition or desulfonation, but it remains unclear whether oxidative addition occurs in the C–S bond or in the S–F bond (likely directed by nitrogen in the latter case). DFT studies are ongoing and should be available at the time of the PhD defense. The usefulness of this method was demonstrated in a divergent synthesis, where two analogues of biologically active molecules could be prepared from a single substrate, either through C–C or S–N bond formation. This type of divergent reactivity is not accessible from other Suzuki electrophiles, which enables further developments in the divergent synthesis using the well-established SuFEx chemistry.[16]

IV. Conclusion and outlook

The construction of carbon-carbon bonds is a vital feature of organic synthesis, being essential for many of the technological achievements in the pharmaceutical, agrochemical as well as materials sciences. Throughout the last 200 years, much effort has been dedicated to developing new efficient methods for the formation of these C–C bonds, and the 20th century saw great progress in this field mainly due to the advent of transition-metal catalyzed cross-coupling reactions.

Of the cross-coupling reactions, the Suzuki reaction is one of the preferred methodologies for the formation of carbon-carbon bonds due to the use of bench-stable, non-toxic, and solid organoboron reagents as nucleophiles. The electrophilic coupling partner is usually a halide (-Cl, -Br, -I) or pseudohalide (-OTf). Because of the many advantages of organoboron compounds and the large occurrence of the Suzuki reaction, finding alternative electrophiles has been the focus of significant research to widen its scope (see chapter 1.6).

In the first part of this thesis, a method was developed to couple aryl trifluoromethyl sulfones (-SO_2CF_3), a functional group similar to triflates (-OSO_2CF_3) but markedly more stable. Triflates are susceptible to hydrolysis and are highly reactive towards oxidative addition.[223,226] In contrast, sulfones are hydrolytically stable, even in strongly acidic or basic conditions,[5,293] and can be used as a directing group for various transformations (Figure IV.1, see text surrounding Figure I.56).

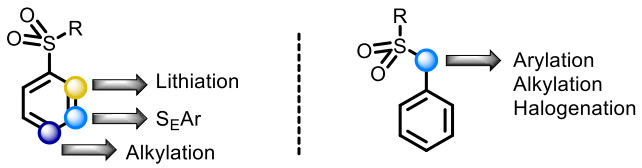


Figure IV.1: Sulfones as a synthetic handle for various transformations

This research mostly focused on aryl sulfones, which displayed an intermediate reactivity between (pseudo)halides and nitroarenes in the Suzuki reaction. Its coupling conditions were easily differentiated from halides and triflates, leading to the facile synthesis of polyaromatic molecules via short coupling sequences.

Mechanistic experiments showed that oxidative addition is likely rate-limiting and occurs in the C–S bond, with the leaving group rearranging to form the O-bound sulfinate Pd complex. Unlike what is observed in the coupling of sulfonyl chlorides,[305] no release of SO_2 occurs.

This reaction was mostly possible due to a serendipitous discovery of the action of a small amount of added DMSO in the reaction mixture. This additive was postulated to facilitate the reduction of Pd(II) to Pd(0) via base-mediated phosphine oxidation or direct reduction from trace dimethyl sulfide. Another possibility would be the stabilization of the initial mono-ligated Pd(0) complex, thus favouring the initial oxidative addition step.

This new method is an important development in the Suzuki reaction, due to its complementary reactivity to other Suzuki electrophiles which facilitates access to unsymmetrical polyaromatics such as terphenyls. The usefulness of the present method was demonstrated by synthesizing analogues of biologically active terphenyls through an iterative sequence of cross-couplings.

The high-stability and directing ability of sulfones also confers them an advantage. Compared to other known Suzuki electrophiles, more divergent syntheses are accessible from a single substrate with a low degree of functionalization. This is especially relevant because the high biological activity of trifluoromethyl sulfones is likely.[347]

Therefore, the Suzuki coupling of sulfones fills a void in the scope of this reaction and it is anticipated that this method will be useful in the synthesis of specific substrates.

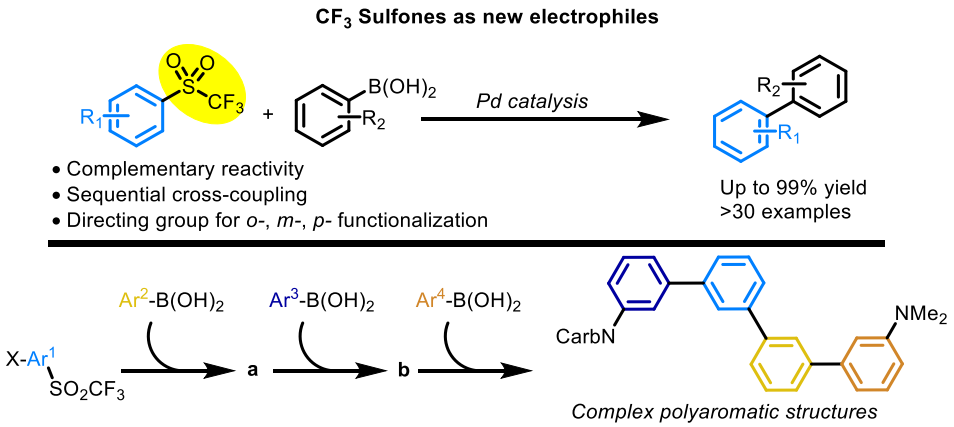


Figure IV.2: Summary of the work on the coupling of sulfones

To continue the work on the coupling of robust C–S based electrophiles in the Suzuki reaction, the second part of this thesis focused on aryl sulfonyl fluorides (-SO_2F). In contrast to other sulfonyl halides, sulfonyl fluorides are hydrolytically stable and only undergo substitution under very specific reaction conditions.[16,17] The principle of this peculiar reactivity is exploited in a branch of S–N bond forming click-chemistry known as SuFEx chemistry.

Similarly to previous work on the coupling of fluorinated electrophiles (see chapter 1.4.4), it was postulated that sulfonyl fluorides could undergo base-free coupling using the fluoride leaving group of the -SO_2F to mediate transmetalation after release of SO_2 (similarly to what is known to occur in the Suzuki coupling of sulfonyl chlorides).[305]

Sulfonyl fluorides were found to be much less reactive than sulfones in the Suzuki reaction. However, cross-coupling proceeded smoothly for activated arenes, despite the widely held belief that sulfonyl fluorides are inert to transition-metal catalysis.[17] 2-Pyridine sulfonyl fluoride, also known as PyFluor,[343] and 2-$CN(C_6H_4)SO_2F$ could undergo cross-coupling without the addition of exogenous base using conditions similar to the ones elucidated for the coupling of sulfones, the main difference being the higher temperature.

Other substrates underwent significant cross-coupling only with the addition of a copper (or in a specific case, cobalt) co-catalyst and using 50 mol% KHF_2 (which represents one equivalent of fluoride base).

Mechanistic experiments supported the assertion that the fluoride leaving group of the SO_2F motif was implicated in mediating the transmetalation and the copper additive was postulated to exert its action in the desulfonation step.

Despite suffering from some limitations in the substrate scope, this method represents the first cross-coupling to be reported on this functional group (with the exception of one example in one report where SO_2F coupling occurred as a side-product,[307] see Figure I.55**:** First report of an unexpected sulfonyl fluoride Suzuki coupling).

The usefulness of this method was highlighted in a divergent synthesis, producing two analogues of biologically active molecules from a single aryl sulfonyl fluoride (Figure IV.3**:** Divergent synthesis from sulfonyl fluorides, highlighting the usefulness of the present method). The sulfonyl fluoride group can thus be used as a handle for S–N or

C–C bond formation. Despite the limitations in scope with respect to the Suzuki reaction, we anticipate that the widespread popularity of SuFEx chemistry will contribute to the use of this new C–C coupling method to access more scaffolds starting from a single substrate.

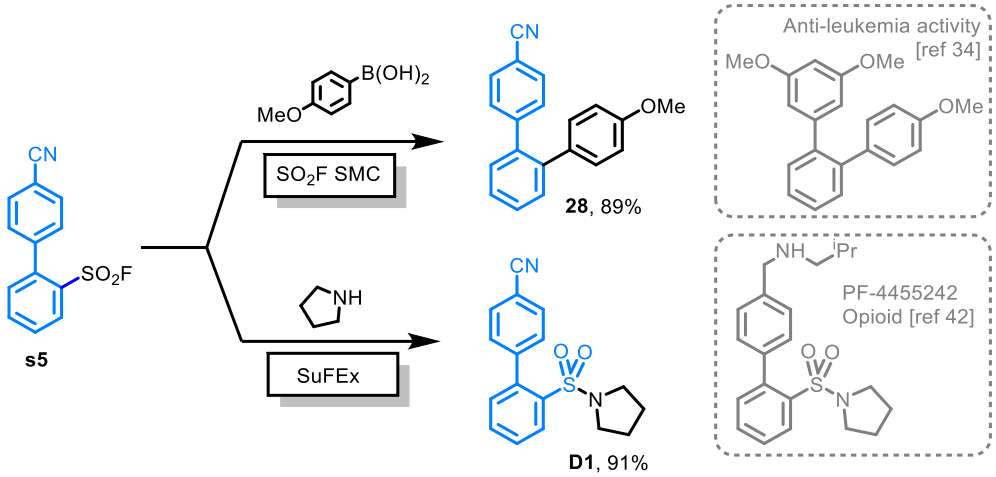


Figure IV.3: Divergent synthesis from sulfonyl fluorides, highlighting the usefulness of the present method

The base-free properties of this reaction as well as its orthogonality with the more reactive aryl chlorides add to the potential usefulness of this functional group in divergent synthesis starting from complex molecules. However, the low reactivity of unactivated arene sulfonyl fluorides should be the focus of further studies to find more performant catalytic systems.

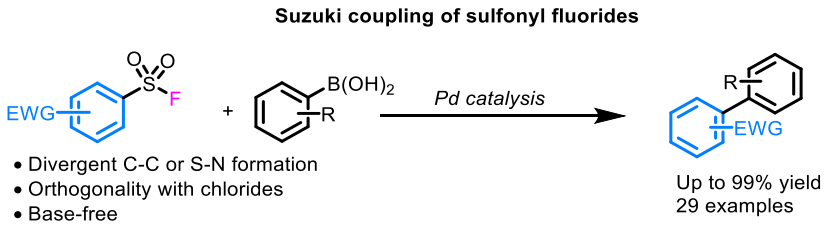


Figure IV.4: Summary of the coupling of sulfonyl fluorides

In summary, this thesis described the Suzuki coupling of two robust C–S based electrophiles (sulfones and sulfonyl fluorides) that offer distinct synthetic advantages compared to the previously developed coupling partners for this reaction. They both display a distinct order of reactivity that is easily differentiated from other electrophiles, which was exploited in the synthesis of polyaromatic molecules. Sulfones can moreover be used as a directing group for a variety of transformations

before its subsequent erasure via cross-coupling. This leads to a significant synthetic advantage relative to other directing group which are usually bothersome to eliminate or exploit in further functionalization. The coupling of sulfonyl fluorides has the major advantage of being complementary to the very well-established S–N bond formation in SuFEx chemistry, setting up the sulfonyl fluoride group as a point of divergence in synthesis via C–C bond formation.

V. Experimental

5.1 General information

All cross-coupling reactions were performed in 10 mL sealed microwave tubes under a nitrogen atmosphere using commercial anhydrous solvents. Purification of reaction products was carried out by flash column chromatography using Biotage KP-Sil (40-63 μm) or Büchi FlashPure (40 μm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F254 (E. Merck), cut to size. Visualization was accomplished with UV light.

^{1}H NMR spectra were recorded on a Bruker Avance500 (500 MHz) or Avance400 (400 MHz) spectrometer at ambient temperature unless otherwise noted and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants in Hz. **^{13}C NMR** spectra were recorded on a Bruker Avance500 (125 MHz) or Avance 400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). **^{19}F NMR** spectra were recorded on a Bruker Avance400 (376 MHz) spectrometer.

High resolution mass spectrometry (HRMS) analysis was performed on a Thermo Scientific Exactive Plus EMR (ESI-Orbitrap).

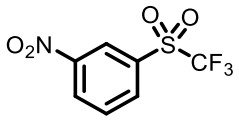
Gas chromatography–mass spectrometry (GC/MS) analysis was performed on a GC System 7820A (G4320) coupled to an MSD block 5977E (G7036A). An Agilent High Resolution Gas Chromatography Column (PN 19091S – 433UI, HP – 5MS UI, 28 m×0.250 mm, 0.25 Micron, SN USD 489634H) was used. Hydrogen (99.999 % purity) was the carrier gas, supplied at a constant flow rate of 1.5 $mL \cdot min^{-1}$. Samples were prepared in ethyl acetate (200 μL sample volume). The analysis was carried out on a 1 μL injection volume (splitless mode). The injection port temperature was 250 °C, and the column oven temperature program was 60 °C for 1 min and then increased to 310 °C with a 30 $°C \cdot min^{-1}$ ramp, followed by a 3 min hold (for total running time of 12.33 min). The mass spectrometer was turned on after a 2 min delay

and was operated at the electron ionization mode with a quadrupole temperature of 150 °C. Data was acquired in the full-scan mode (50-500).
Data analysis and integration were performed using Agilent MassHunter Workstationv.B.06.00software.

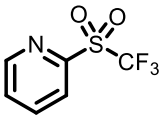
Materials: All commercially available starting materials and solvents were purchased from *Sigma-Aldrich, TCI, fluorochem, abcr, Alfa Aesar* or *Fisher Scientific* and were used without further purification.

5.2 The Suzuki coupling of sulfones

5.2.1 Preparation of starting materials

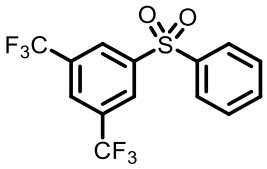


3-Nitrophenyltrifluoromethyl sulfone (s1)
A screw-capped tube was charged with Phenyl trifluoromethyl sulfone (148 µL, 1.00 mmol), $NaNO_3$ (128 mg, 1.50 mmol) and concentrated H_2SO_4 (400 µL). The reaction mixture was stirred at 100 °C for 4 h to afford 3-nitrophenyltrifluoromethylsulfone (210 mg, 82%) after column chromatography (EtOAc:Petroleum ether 8:2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.89 (t, *J* = 2.0 Hz, 1H), 8.71 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H), 8.38 (d, J= 8.0 Hz, 1H), 7.96 (t, *J* = 8.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 136.0 (q, *J* = 0.7 Hz), 133.7 (q, *J* = 1.6 Hz), 131.5, 130.9, 126.0 (q, *J* = 0.8 Hz), 119.6 (q, *J* = 325.9 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -77.51. Spectral data are in agreement with the literature.[348]



2-Pyridyltrifluormethylsulfone

This compound was prepared using a modified literature procedure.[349] A microwave tube was charged with PyFluor (209 mg, 1.3 mmol), KHF_2 (100 mg, 1.3 mmol) and was evacuated and backfilled with nitrogen three times. Then, anhydrous DMF (2.0 mL) and $TMSCF_3$ (1.30 mmol, 192 µL) were added via syringe. The reaction mixture was stirred at room temperature for 2 h, extracted into toluene and washed with water and brine. Purification by column chromatography afforded 2-pyridyltrifluormethylsulfone (233 mg, 85%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.91 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.29 – 8.20 (m, 1H), 8.10 (td, *J* = 7.8, 1.7 Hz, 1H), 7.75 (ddd, *J* = 7.8, 4.7, 1.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.5, 151.3 (q, *J* = 1.9 Hz), 138.7, 129.6, 126.3 (q, *J* = 1.0 Hz), 119.8 (q, *J* = 327.7 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -75.57. Spectral data are in agreement with the literature.[349]

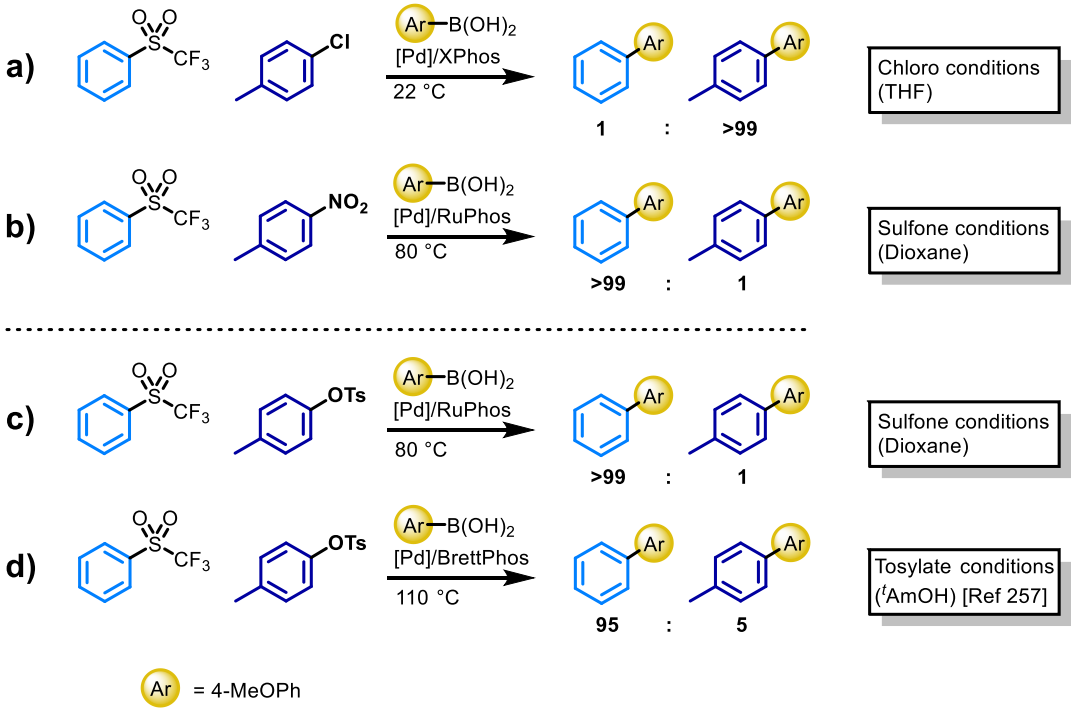


1-(phenylsulfonyl)-3,5-bis(trifluoromethyl)benzene

Following a literature modified procedure,[350] 1-iodo-3,5bis(trifluoromethyl)benzene (68 mg, 35 µL, 0.20 mmol), sodium benzenesulfinate (99 mg, 0.60 mmol, 3.0 equiv), Cs_2CO_3 (65 mg, 0.20 mmol, 1.0 equiv) and anhydrous DMSO (2.0 mL) were added to five quartz tubes under a stream of argon. The reaction mixtures were then stirred at room temperature under the irradiation of UV light (352 nm, 80 W) for 24 h. The five reaction mixtures were then quenched with water and the mixture was extracted with dichloromethane three times. The combined organic phases were washed with a saturated brine solution and dried over anhydrous Na_2SO_4. Then, the solution was concentrated *in vacuo* and purified by column chromatography over silica (using a mixture of petroleum ether and ethyl acetate as eluents, R_f 0.46 petroleum ether:ethyl acetate 9:1) to afford the title compound as a white crystalline solid, m.p. 61 °C (80 mg, 23%). **HRMS(ESI):** calculated: 354.0149; found: 354.0328 (M+). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 8.05 (s, 1H), 7.99 (dd, *J* = 7.2, 1.8 Hz, 2H), 7.67 (t, *J* =

7.4 Hz, 1H), 7.59 (dd, *J* = 8.4, 6.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.7, 139.7, 134.4, 133.2 (d, *J* = 34.6 Hz), 129.9, 129.5, 128.1, 126.9 (dt, *J* = 7.2, 3.7 Hz), 122.3 (d, *J* = 273.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.9.

5.2.2 Competition experiments



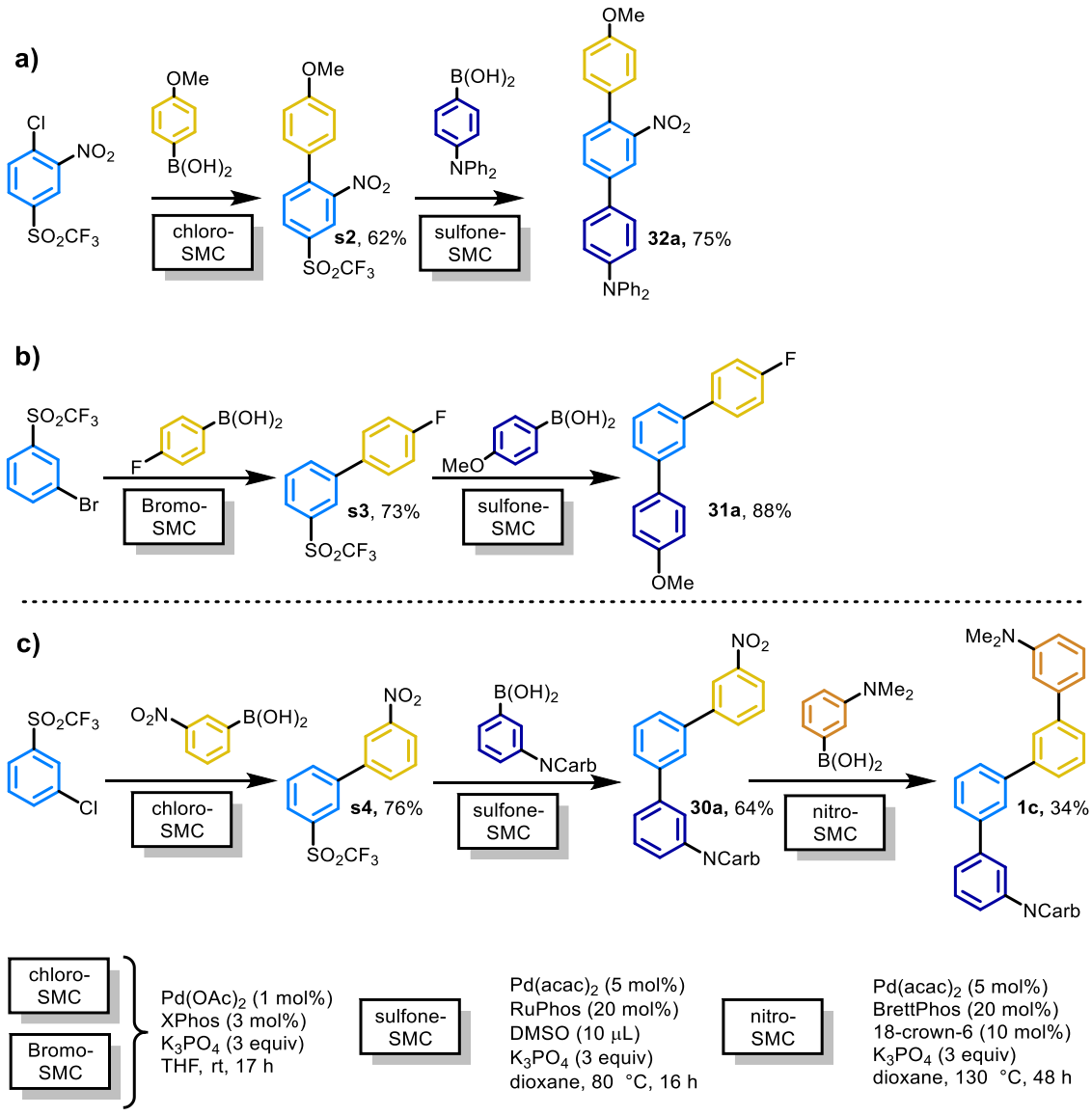
a) A microwave vial was charged with $Pd(OAc)_2$ (1.3 mg, 3 mol%.), XPhos (8.6 mg, 9 mol%), 4-methoxyphenylboronic acid (30 mg, 0.20 mmol) and K_3PO_4 (126 mg, 0.60 mmol). Then, the vial was evacuated and backfilled with nitrogen three times, followed by the addition of 1.0 ml anhydrous THF, phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) and 4-chlorotoluene (24 µL, 0.20 mmol). The reaction mixture was stirred at 22 ˚C for 16 h, diluted in EtOAc and filtered through a plug of silica. The relative product ratios were determined by GC/MS.

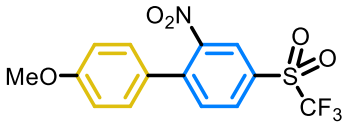
b) An analogous procedure to the one above was used, with $Pd(acac)_2$ (3.0 mg, 5 mol%) and RuPhos (18.6 mg, 20 mol%) as the catalyst, 4-nitrotoluene (27.4 mg, 0.20 mmol) as the competition substrate, anhydrous dioxane as solvent and 80 ˚C as the reaction temperature. The relative product ratios were determined by GC/MS.

c) An analogous procedure to the one above (**b**) was used, using *p*-tolyl 4-methylbenzene-sulfonate (52.5 mg, 0.20 mmol) as the competition substrate. The relative product ratios were determined by GC/MS.

d) A microwave vial was charged with $Pd(OAc)_2$ (0.9 mg, 2 mol%.), BrettPhos (4.3 mg, 4 mol%), 4-methoxyphenylboronic acid (30 mg, 0.20 mmol), *p*-tolyl 4-methylbenzene-sulfonate (52.5 mg, 0.20 mmol) and K_3PO_4 (126 mg, 0.60 mmol). Then, the vial was evacuated and backfilled with nitrogen three times, followed by the addition of 0.4 ml anhydrous *t*-amyl alcohol and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol). The reaction mixture was stirred at 22 ˚C for 16 h, diluted in EtOAc and filtered through a plug of silica. The relative product ratios were determined by GC/MS.

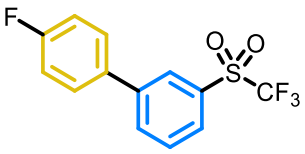
5.2.3 Sequential coupling: molecules that are not part of the scope





4'-Methoxy-2-nitro-4-((trifluoromethyl)sulfonyl)-1,1'-biphenyl (s2)

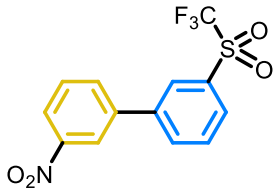
4-Methoxyphenylboronic acid (91 mg, 0.60 mmol), $Pd(OAc)_2$ (1 mg, 1 mol%), XPhos (6 mg, 3 mol%) and K_3PO_4 (254 mg, 1.20 mmol) were weighed into a microwave vial, sealed and placed under vacuum for 15 min. Then the vial was filled with N_2 followed by the addition of 2.0 ml anhydrous THF and 1-chloro-2-nitro-4-((trifluoromethyl)sulfonyl)benzene (116 mg, 0.40 mmol). The solutions were stirred at ambient temperature for 16 h. The reaction was determined to be complete by TLC. After the reaction, the crude mixture was filtered through a bed of Celite and washed with dichloromethane. Then, the solution was concentrated *in vacuo* and purified by column chromatography over silica (using petroleum ether and dichloromethane as eluents, R_f 0.40 petroleum ether : dichloromethane 3:1) to afford **s2** as a colorless oil (87 mg, 62%). **HRMS (ESI):** calculated:361.0232; found: 361.0226 (M+). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 1.9 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.1, 149.5, 143.83, 133.7, 133.4, 130.6 (q, *J* = 1.6 Hz), 129.3, 126.7, 126.6, 119.6 (q, 327 Hz), 114.9, 55.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -77.6.



4'-Fluoro-3-((trifluoromethyl)sulfonyl)-1,1'-biphenyl (s3)

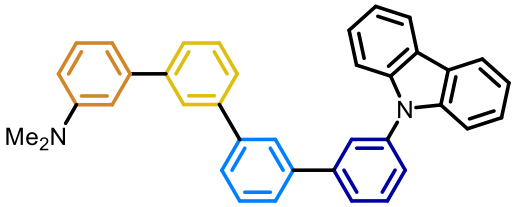
4-Flurophenylboronic acid (168 mg 1.20 mmol), $Pd(OAc)_2$ (2.0 mg, 1 mol %.), XPhos (12 mg, 3 mol %) and K_3PO_4 (508 mg, 2.40 mmol) were charged into a microwave vial. Then, the vial was evacuated and backfilled with nitrogen three times, followed by the addition of 8.0 ml anhydrous THF and 1-bromo-3-((trifluoromethyl)sulfonyl)benzene (250 mg, 0.80 mmol). The solutions were stirred at rt. for 16h. The reaction was determined to be complete by TLC. After the reaction, the crude mixture was filtered through a bed of celite and washed with dichloromethane. Then, the solution was concentrated *in vacuo* and purified by column chromatography over silica (using a mixture of petroleum ether and

dichloromethane as eluents, R_f 0.33 petroleum ether : dichloromethane 4:1) to afford **s3** as a white solid (87 mg, 73%). **HRMS (ESI):** calculated: 304.0181; found: 304.0174 (M+). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.0 Hz, 1H), 8.04 – 7.97 (m, 2H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.24 – 7.16 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.3 (d, *J* = 249.2 Hz), 142.3 (d, *J* = 27.1 Hz), 134.9, 134.4 (d, *J* = 14.8 Hz), 133.9, 132.1, 130.3 (d, *J* = 25.4 Hz), 129.2, 129.0 (dd, *J* = 8.3, 5.5 Hz), 128.9, 126.8 (d, *J* = 26.2 Hz), 119.8 (d, *J* = 325.9 Hz), 116.2 (d, *J* = 4.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.2, -112.9.



3'-Nitro-3-((trifluoromethyl)sulfonyl)-1,1'-biphenyl (s4)

3-Nitrophenylboronic acid (91 mg, 0.60 mmol), $Pd(OAc)_2$ (1 mg, 1 mol%), XPhos (6 mg, 3 mol%) and K_3PO_4 (254 mg, 1.20 mmol) were weighed into a microwave vial, sealed and placed under vacuum for 15 min. Then the vial was filled with N_2 followed by the addition of 2.0 ml anhydrous THF and 3-chloro-phenyl trifluoromethyl sulfone (116 mg, 0.40 mmol). The solutions were stirred at ambient temperature (roughly 22 ºC) for 16 h. The reaction was determined to be complete by TLC. The reaction crude mixture was filtered through a bed of Celite and washed with dichloromethane. Then, the solution was concentrated *in vacuo* and purified by column chromatography over silica (using petroleum ether and dichloromethane as eluents, R_f 0.50 petroleum ether: dichloromethane 4:1) to afford **s4** as a colorless oil (87 mg, 62%). **HRMS (ESI):** calculated: 331.0126; found: 331.0121 (M+). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.48 (t, *J* = 1.9 Hz, 1H), 8.34 – 8.30 (m, 1H), 8.28 – 8.24 (m, 1H), 8.15 – 8.07 (m, 2H), 7.97 – 7.94 (m, 1H), 7.86 (s, 1H), 7.71 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.9, 141.0, 139.9, 135.1, 134.1, 133.1, 130.9, 130.5 (m), 129.1, 128.2, 127.0, 123.6, 122.2. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -78.0.

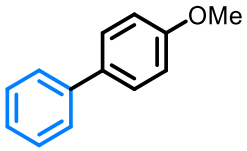


4'''-(9*H*-Carbazol-9-yl)-*N*,*N*-dimethyl-[1,1':3',1'':3'',1'''-quaterphenyl]-4-amine (1c)

Following the reported reaction procedure[314] compound **1b (**50 mg, 0.11 mmol) reacted with 3-(*N*,*N*-dimethylamino)phenylboronic acid (28 mg, 0.17 mmol) and was purified by column chromatography over silica (with a mixture of petroleum ether and ethyl acetate, R_f 0.58 petroleum ether : ethyl acetate 4:1) to afford **1c** as a yellow oil (20 mg, 34%). **HRMS (ESI):** calculated: 515.2487; found: 515.2481 (M+H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (d, J = 7.7 Hz, 2H), 7.93 – 7.83 (m, 3H), 7.79 – 7.75 (m, 1H), 7.72 – 7.64 (m, 3H), 7.63 – 7.55 (m, 4H), 7.51 (dd, J = 15.1, 7.8 Hz, 3H), 7.45 – 7.40 (m, 2H), 7.35 – 7.28 (m, 3H), 7.05 – 6.92 (m, 2H), 6.77 (d, J = 7.3 Hz, 1H), 3.01 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.0, 143.1, 142.2, 142.2, 141.3, 140.9, 140.7, 138.3, 130.3, 129.5, 129.4, 129.1, 126.8, 126.6, 126.4, 126.3, 126.2, 126.1, 126.0, 125.8, 123.4, 120.3, 120.0, 115.9, 111.8, 111.6, 109.8, 40.8.

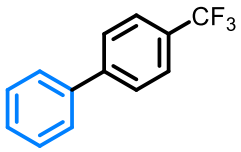
5.2.4 Substrate scope

General procedure: Boronic acid (0.30 mmol), $Pd(acac)_2$ (5 mol%), RuPhos (20 mol%) and K_3PO_4 (0.60 mmol) were weighed into a microwave vial, which was sealed, evacuated, and backfilled with nitrogen 3 times. Then, 1.0 ml anhydrous dioxane, sulfone (0.20 mmol) and 10 µL DMSO were added (solid sulfones were added prior to putting the tube under vacuum). The solutions were stirred and heated at 80 °C for 16 h. After the reaction was cooled to room temperature, the crude mixture was filtered through a bed of Celite and washed with dichloromethane. Then, the solution was concentrated *in vacuo* and purified by column chromatography.



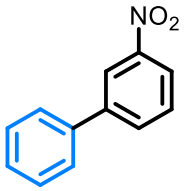
4-Methoxy-1,1'-biphenyl (1a)

Following the general procedure, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **1a** as a white solid (35 mg, 95%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 8.4 Hz, 4H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.86 (d, *J* = 0.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 140.8, 133.8, 128.7, 128.2, 126.8, 126.7, 114.2, 55.4. Spectral data are in agreement with the literature.[351]



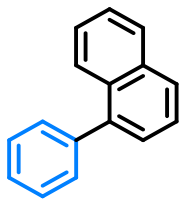
4-Trifluoromethane-1,1'-biphenyl (2a)

Following the general procedure, 4-(trifluoromethyl) phenylboronic acid (42 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **2a** as a white solid (33 mg, 75%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 9:1 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (s, 4H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.7, 139.8, 129.4 (q, 37.4 Hz) 129.0, 128.2, 127.6, 127.4, 127.3, 125.7 (q, 3.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4. Spectral data are in agreement with the literature.[352]



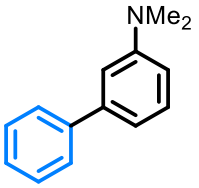
3-Nitro-1,1'-biphenyl (3a)

Following the general procedure, 3-nitrobenzeneboronic acid (50 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **3a** as a white solid (27 mg, 68%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.45 (t, *J* = 2.0 Hz, 1H), 8.22 – 8.17 (m, 1H), 7.92 (ddd, *J* = 7.7, 1.8, 1.0 Hz, 1H), 7.67 – 7.58 (m, 3H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.47 – 7.41 (m, 1H). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.12 (d, *J* = 9.2 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.54 (dd, *J* = 7.7, 2.6 Hz, 3H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.9, 143.0, 138.8, 133.2, 129.8, 129.3, 128.7, 127.3, 122.2, 122.1. Spectral data are in agreement with the literature.[353]



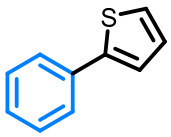
1-Phenylnaphthalene (4a)

Following the general procedure, 2-naphthylboronic acid (52 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **4a** as a white solid (40 mg, 98%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 9:1 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 3H), 7.62 – 7.39 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.8, 140.3, 133.9, 131.7, 130.1, 128.3(2C), 127.7, 127.3, 127.0, 126.1 (2C), 125.8, 125.4. Spectral data are in agreement with the literature.[354]



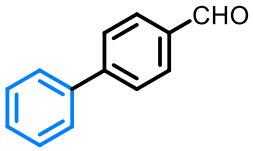
***N*,*N*-Dimethyl-[1,1'-biphenyl]-3-amine (5a)**

Following the general procedure, 3-(*N*,*N*- dimethylamino)phenylboronic acid (50 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **5a** as a white solid (26 mg, 68%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.1 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (dt, *J* = 10.6, 7.6 Hz, 2H), 7.00 – 6.93 (m, 2H), 6.78 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.03 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.0, 142.3, 142.3, 129.5, 128.6, 127.4, 127.1, 115.9, 111.7, 111.6, 40.8. Spectral data are in agreement with the literature.[355]



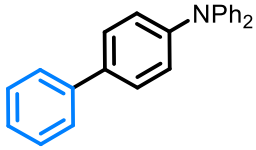
2-Phenylthiophene (6a)

Following the general procedure, 3-thienylboronic acid (38 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **6a** as a white solid (24 mg, 97%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.35 (m, 1H), 7.33 – 7.28 (m, 4H), 7.20 (t, *J* = 7.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4, 135.9, 128.8, 126.5, 126.4, 126.2, 126.1, 119.8. Spectral data are in agreement with the literature.[356]



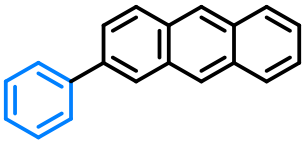
[1,1'-Biphenyl]-4-carbaldehyde (7a)

Following the general procedure, 4-formylphenylboronic acid (45 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **7a** as a white solid (10 mg, 28%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.0, 147.2, 139.7, 135.2, 130.3, 129.0, 128.5, 127.7, 127.4. Spectral data are in agreement with the literature.[357]



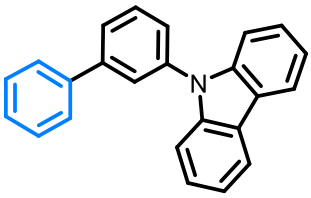
***N*,*N*-Diphenyl-[1,1'-biphenyl]-4-amine (8a)**

Following the general procedure, 4-(diphenylamino)phenylboronic acid (87 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **8a** as a white solid (63 mg, 98%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.16 (q, *J* = 8.3 Hz, 5H), 7.04 (d, *J* = 7.8 Hz, 6H), 6.93 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.8, 147.2, 140.7, 135.2, 129.3, 128.8, 127.8, 126.9, 126.7, 124.5, 124.0, 123.0. Spectral data are in agreement with the literature.[358]



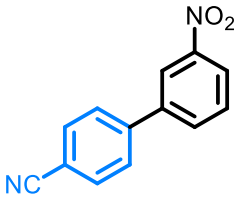
2-Phenylanthracene (9a)

Following the general procedure, 2-anthraceneboronic acid (67 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **9a** as a white solid (45 mg, 89%) after purification by automated flash column chromatography over silica (using petroleum ether and dichloromethane 9:1 as eluents). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 14.2 Hz, 2H), 8.21 (s, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 8.02 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.78 (t, *J* = 7.7 Hz, 3H), 7.56 – 7.44 (m, 4H), 7.42 (s, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 137.8, 132.1, 131.9, 131.8, 130.9, 128.9, 128.8, 128.2, 128.2, 127.4, 127.4, 126.6, 126.0, 125.7, 125.5, 125.5, 125.4. Spectral data are in agreement with the literature.[359]

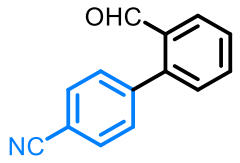


9-([1,1'-Biphenyl]-3-yl)-9*H*-carbazole (10a)

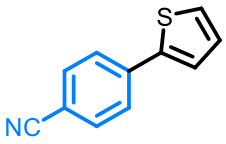
Following the general procedure, 3-(9H-carbazol-9-yl)phenylboronic acid (86 mg, 0.30 mmol) and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) afforded **10a** as a white solid (60 mg, 93%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.7 Hz, 2H), 7.83 (t, *J* = 1.7 Hz, 1H), 7.74 – 7.65 (m, 4H), 7.57 (dt, *J* = 7.4, 1.7 Hz, 1H), 7.52 – 7.41 (m, 7H), 7.32 (td, *J* = 7.5, 1.0 Hz, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2, 140.9, 140.2, 138.3, 130.3, 129.0, 127.9, 127.2, 126.2, 126.1, 125.9, 125.8, 123.5, 120.4, 120.0, 109.9. Spectral data are in agreement with the literature.[360]



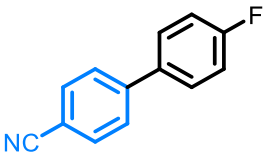
3'-Nitro-[1,1'-biphenyl]-4-carbonitrile (11a). Following the general procedure, 3-nitrobenzeneboronic acid (50 mg, 0.30 mmol) and 4-(trifluoromethyl)sulphonylbenzonitrile (47 mg, 0.20 mmol) afforded **11a** as a white solid (41 mg, 91%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 7:3 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (t, *J* = 1.8 Hz, 1H), 8.31 – 8.26 (m, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.84 – 7.77 (m, 2H), 7.77 – 7.72 (m, 2H), 7.68 (t, *J* = 8.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.8, 143.0, 140.8, 133.1, 133.0, 130.2, 127.9, 123.3, 122.1, 118.4, 112.4. Spectral data are in agreement with the literature. [361]



2'-Formyl-[1,1'-biphenyl]-4-carbonitrile (12a). Following the general procedure, 2-formylphenylboronic acid (45 mg, 0.30 mmol) and 4-(trifluoromethyl)sulphonylbenzonitrile (47 mg, 0.20 mmol) afforded **12a** as a white solid (10 mg, 26 %) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.2, 143.5, 142.8, 133.9, 133.6, 132.2, 130.7, 130.6, 128.9, 128.7, 118.4, 112.2. Spectral data are in agreement with the literature.[362]

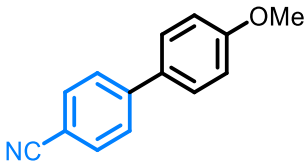


4-(Thiophen-2-yl)benzonitrile (13a). Following the general procedure, 3-thienylboronic acid (38 mg, 0.30 mmol) and 4-(trifluoromethyl)sulphonylbenzonitrile (47 mg, 0.20 mmol) afforded **13a** as a white solid (24 mg, 65 %) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (s, 4H), 7.59 – 7.56 (m, 1H), 7.44 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.40 (d, *J* = 5.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 140.0, 132.7, 127.2, 126.9, 125.9, 122.6, 119.0, 110.5. Spectral data are in agreement with the literature.[363]



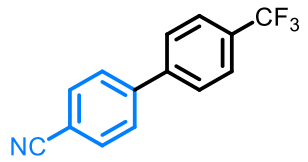
4'-Fluoro-[1,1'-biphenyl]-4-carbonitrile (14a)

Following the general procedure, 4-fluorophenylboronic acid (42 mg, 0.30 mmol) and 4-(trifluoromethyl)sulphonylbenzonitrile (47 mg, 0.20 mmol) afforded **14a** as a yellow solid (32 mg, 82 %) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.59 – 7.51 (m, 2H), 7.17 (t, *J* = 8.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.3 (d, *J* = 248.9 Hz), 144.7, 135.4 (d, *J* = 3.3 Hz), 132.8, 129.1 (d, *J* = 8.3 Hz), 127.7 (d, *J* = 0.7 Hz), 119.0, 116.2 (d, *J* = 21.7 Hz), 111.0. Spectral data are in agreement with the literature.[364]



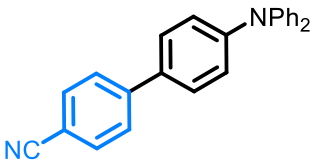
4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (15a)

Following the general procedure, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 4-(trifluoromethyl)sulphonylbenzonitrile (47 mg, 0.20 mmol) afforded **15a** as a yellow solid (35 mg, 84 %) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.60 (m, 4H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2, 145.2, 132.6, 131.5, 128.4, 127.1, 119.1, 114.6, 110.1, 55.4. Spectral data are in agreement with the literature.[365]



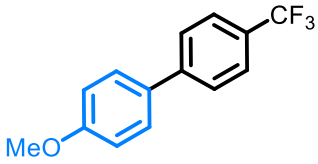
4'-(Trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile (16a)

Following the general procedure, 4- (trifluoromethyl) phenylboronic acid (42 mg, 0.3 mmol) and 4-(trifluoromethyl)sulphonylbenzonitrile (47 mg, 0.2 mmol) afforded **16a** as a white solid (30 mg, 68 %) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 – 7.63 (m, 8H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.1, 142.7, 132.8, 130.7 (q, *J* = 32.7 Hz), 127.9, 127.65, 126.10 (q, *J* = 3.7 Hz), 124.0 (d, *J* = 272.2 Hz), 118.6, 112.0. Spectral data are in agreement with the literature.[366]



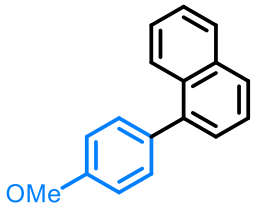
4'-Carbonitrile-*N*,*N*-diphenyl-[1,1'-biphenyl]-4-amine (17a)

Following the general procedure, 4-(diphenylamino)phenylboronic acid (87 mg, 0.30 mmol) and 4-(trifluoromethyl)sulphonylbenzonitrile (47 mg, 0.20 mmol) afforded **17a** as a yellow solid (52 mg, 75%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (q, *J* = 8.4 Hz, 4H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 4H), 7.18 (dd, *J* = 8.4, 2.2 Hz, 6H), 7.11 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.6, 147.3, 145.1, 132.6, 132.1, 129.5, 127.9, 127.0, 125.0, 123.6, 123.0, 119.2, 110.1. Spectral data are in agreement with the literature.[367]



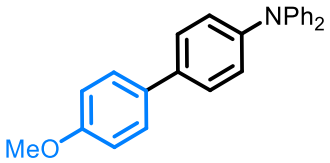
4-Methoxy-4'-(trifluoromethyl)-1,1'-biphenyl (18a)

Following the general procedure, 4- (trifluoromethyl) phenylboronic acid (42 mg, 0.30 mmol) and 1-methoxy-4-trifluoromethanesulfonyl-benzene (48 mg, 0.20 mmol) afforded **18a** as a yellow solid (28 mg, 56%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (s, 4H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 144.3, 132.2, 128.8, 128.4, 126.9, 125.8 (q, *J* = 3.5 Hz), 123.0, 114.4, 55.4. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.3. Spectral data are in agreement with the literature.[368]



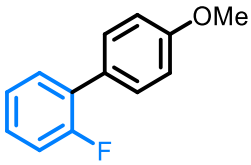
1-(4-Methoxyphenyl)naphthalene (19a)

Following the general procedure, 2-naphthylboronic acid (52 mg, 0.30 mmol) and 1-methoxy-4-trifluoromethanesulfonyl-benzene (48 mg, 0.20 mmol) afforded **19a** as a yellow solid (27 mg, 56%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.51 (q, *J* = 8.9, 8.1 Hz, 2H), 7.46 – 7.40 (m, 4H), 7.05 (d, *J* = 8.6 Hz, 2H), 3.91 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.1, 140.0, 134.0, 133.3, 132.0, 131.3, 128.4, 127.5, 127.0, 126.2, 126.1, 125.8, 125.5, 113.9, 55.5. Spectral data are in agreement with the literature.[369]



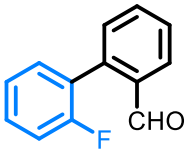
4'-Methoxy-*N*,*N*-diphenyl-[1,1'-biphenyl]-4-amine (20a)

Following the general procedure, 4-(diphenylamino)phenylboronic acid (87 mg 0.30 mmol) and 1-methoxy-4-trifluoromethanesulfonyl-benzene (48 mg, 0.20 mmol) afforded **20a** as a yellow solid (46 mg, 73%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). Spectral data are in agreement with the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.21 – 7.14 (m, 4H), 7.05 (d, *J* = 7.6 Hz, 6H), 6.94 (t, *J* = 7.3 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.76 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9, 147.9, 146.7, 135.1, 133.4, 129.4, 129.4, 127.8, 127.5, 124.4, 122.9, 114.3, 55.5. Spectral data are in agreement with the literature.[358]



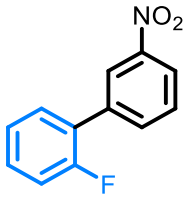
2-Fluoro-4'-methoxy-1,1'-biphenyl (21a)

Following the general procedure, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 1-fluoro-2-[(trifluoromethyl)sulfonyl]benzene (33 μL, 0.20 mmol) afforded **21a** as a white solid (34 mg, 84%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.45 (td, *J* = 7.8, 1.8 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.25 – 7.13 (m, 2H), 7.05 – 6.98 (m, 2H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0, 159.3, 158.6, 130.6 (d, *J* = 3.6 Hz), 130.2 (d, *J* = 3.3 Hz), 129.0 – 128.01 (m, 2C), 124.3 (d, *J* = 3.7 Hz), 116.2 (d, *J* = 22.8) 114.0, 55.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -118.23. Spectral data are in agreement with the literature.[370]



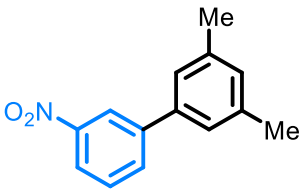
2'-Fluoro-[1,1'-biphenyl]-2-carbaldehyde (22a)

Following the general procedure, 2-formylphenylboronic acid (45 mg, 0.30 mmol) and 1-fluoro-2-[(trifluoromethyl)sulfonyl]benzene (33 μL, 0.20 mmol) afforded **22a** as a white solid (24 mg, 60%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.75 (d, *J* = 3.0 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.51 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.17 (td, *J* = 7.5, 1.8 Hz, 1H), 7.12 – 7.08 (m, 1H), 7.02 (t, *J* = 9.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.7 (d, *J* = 2.3 Hz), 159.6 (d, *J* = 246.7 Hz), 138.9, 133.9, 133.8, 132.0 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 0.9 Hz), 130.4 (d, *J* = 8.1 Hz), 128.5, 127.7, 125.5 (d, *J* = 15.7 Hz), 124.44 (d, *J* = 3.8 Hz), 115.8 (d, *J* = 22.2 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -115.6. Spectral data are in agreement with the literature.[371]



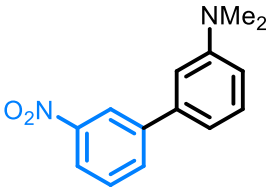
2-Fluoro-3'-nitro-1,1'-biphenyl (23a)

Following the general procedure, 3- nitrobenzeneboronic acid (50 mg, 0.30 mmol) and 1-fluoro-2-[(trifluoromethyl)sulfonyl]benzene (33 μL, 0.20 mmol) afforded **23a** as a yellow solid (34 mg, 78%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.39 (s, 1H), 8.24 – 8.15 (m, 1H), 7.90 – 7.83 (m, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.44 (td, *J* = 7.7, 1.7 Hz, 1H), 7.38 (tdd, *J* = 8.1, 5.1, 1.7 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.21 – 7.15 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.7, 158.7, 148.4, 137.4, 135.1 (d, *J* = 3.5 Hz), 130.5 (d, *J* = 2.8 Hz), 130.4 (d, *J* = 8.3 Hz), 129.4, 126.6 (d, *J* = 13.0 Hz), 124.4 (dd, *J* = 3.8 Hz), 122.6, 116.4 (d, *J* = 22.4 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -117.9. Spectral data are in agreement with the literature.[372]



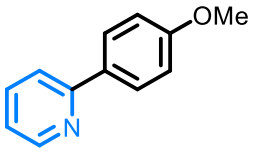
3',5'-Dimethyl-2-nitro-1,1'-biphenyl (24a)

Following the general procedure, 3,5-dimethylyphenylboronic acid (45 mg, 0.30 mmol) and 3-nitro-phenyl trifluoromethyl sulfone (51 mg, 0.20 mmol) afforded **24a** as a white solid (31 mg, 68%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.44 (t, *J* = 1.9 Hz, 1H), 8.18 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1H), 7.93 - 7.84 (m, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.24 (s, 2H), 7.08 (s, 1H), 2.41 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.6, 143.1, 138.8, 138.62, 133.1, 130.2, 129.6, 125.0, 121.95, 121.86, 21.4. Spectral data are in agreement with the literature.[373]



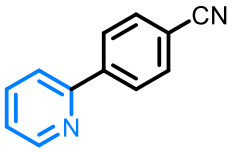
3-Nitro-3-(dimethylamino)-biphenyl (25a)

Following the general procedure, 3-(*N*,*N*- dimethylamino)phenylboronic acid (50 mg, 0.30 mmol) and 3-nitro-phenyl trifluoromethyl sulfone (51 mg, 0.20 mmol) afforded **25a** as a white solid (26 mg, 54%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 – 8.43 (m, 1H), 8.20 – 8.16 (m, 1H), 7.93 (s, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.38 – 7.33 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.91 – 6.88 (m, 1H), 6.80 (dd, *J* = 8.2, 2.3 Hz, 1H), 3.04 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.1, 148.6, 143.9, 139.7, 133.3, 129.8, 129.5, 122.1, 121.9, 115.5, 112.6, 111.0, 40.7. Spectral data are in agreement with the literature.[374]



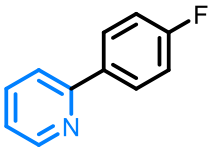
2-(4-Methoxyphenyl)pyridine (26a)

Following the general procedure, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 2-((trifluoromethyl)sulfonyl)pyridine (42 mg, 0.20 mmol) afforded **26a** as a white solid (30 mg, 81%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.98 -7.91 (m, 2H), 7.67 (s, 2H), 7.17 (ddd, *J* = 7.2, 4.8, 1.3 Hz, 1H), 7.02 - 6.97 (m, 2H), 3.86 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.4, 157.1, 149.5, 136.7, 132.0, 128.2, 121.4, 119.8, 114.1, 55.4. Spectral data are in agreement with the literature.[375]



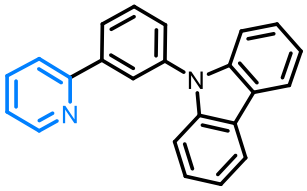
4-(Pyridin-2-yl)benzonitrile (27a)

Following the general procedure, 4-cyanobenzeneboronic acid (44 mg, 0.30 mmol) and 2-((trifluoromethyl)sulfonyl)pyridine (42 mg, 0.20 mmol) afforded **27a** as a white solid (27 mg, 75%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 3H), 7.35 – 7.28 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.2, 150.1, 143.5, 137.1, 132.6, 127.5, 123.4, 121.0, 118.8, 112.4. Spectral data are in agreement with the literature.[376]



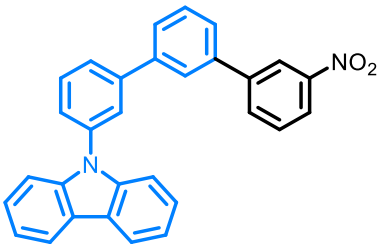
2-(4-Fluorophenyl)pyridine (28a)

Following the general procedure, 4-fluorophenylboronic acid (42 mg, 0.30 mmol) and 2-((trifluoromethyl)sulfonyl)pyridine (42 mg, 0.20 mmol) afforded **28a** as a white solid (25 mg, 72%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.67 (m, 1H), 8.00 - 7.96 (m, 2H), 7.75 (td, *J* = 7.9, 1.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.23 (ddd, *J* = 7.3, 4.8, 1.0 Hz, 1H), 7.19 - 7.13 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.5 (d, *J* = 248.4 Hz), 156.4, 149.7, 136.8, 135.5 (d, *J* = 3.1 Hz), 122.0, 128.7 120.2, 115.7 (*J* = 21.6 Hz). Spectral data are in agreement with the literature.[377]



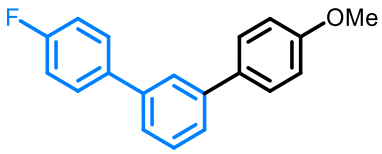
9-(3-(Pyridin-2-yl)phenyl)-9*H*-carbazole (29a)

Following the general procedure, 3-(9H-carbazol-9-yl)phenylboronic acid (86 mg, 0.30 mmol) and 2-((trifluoromethyl)sulfonyl)-pyridine (42 mg, 0.20 mmol) afforded **29a** as a white solid (45 mg, 70%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.67 (dt, *J* = 4.9, 1.4 Hz, 1H), 8.17 (t, *J* = 1.9 Hz, 1H), 8.12 (d, *J* = 7.7 Hz, 2H), 8.08 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.74-7.70 (m, 2H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.58 (ddd, *J* = 7.8, 1.9, 1.0 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.28-7.24 (m, 2H), 7.22 (ddd, *J* = 6.6, 5.2, 2.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.4, 149.9, 141.4, 140.9, 138.3, 137.0, 130.3, 127.6, 126.01, 125.98 125.7, 123.4, 122.7, 120.7, 120.3, 120.0, 109.9. Spectral data are in agreement with the literature.[378]



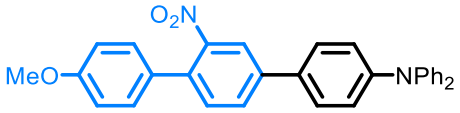
9-(3''-Nitro-[1,1':3',1''-terphenyl]-4-yl)-9*H*-carbazole (30a)

Following the general procedure, 3-(9H-carbazol-9-yl)phenylboronic acid (86 mg, 0.30 mmol) and sulfone **s4** (42 mg, 0.20 mmol) afforded **30a** as a colorless oil (30 mg, 81%) after purification by automated flash column chromatography over silica (using petroleum ether and dichloromethane as eluents, R_f 0.40 petroleum ether : dichloromethane 4:1). **HRMS (ESI):** calculated: 440.1525; found: 440.1519 (M+). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.54 - 8.50 (m, 1H), 8.25 - 8.17 (m, 3H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.90 -7.85 (m, 2H), 7.76 (s, 3H), 7.64 (s, 4H), 7.50 (s, 2H), 7.45 (d, *J* = 7.1 Hz, 2H), 7.32 (d, *J* = 7.0 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 142.6, 141.2, 140.9, 139.5, 138.4, 133.2, 130.5, 129.9, 127.4, 126.7, 126.3, 126.3, 126.1, 126.1, 125.9, 123.5, 122.3, 122.1, 120.4, 120.1, 109.8.



4-Fluoro-4''-methoxy-1,1':3',1''-terphenyl (31a)

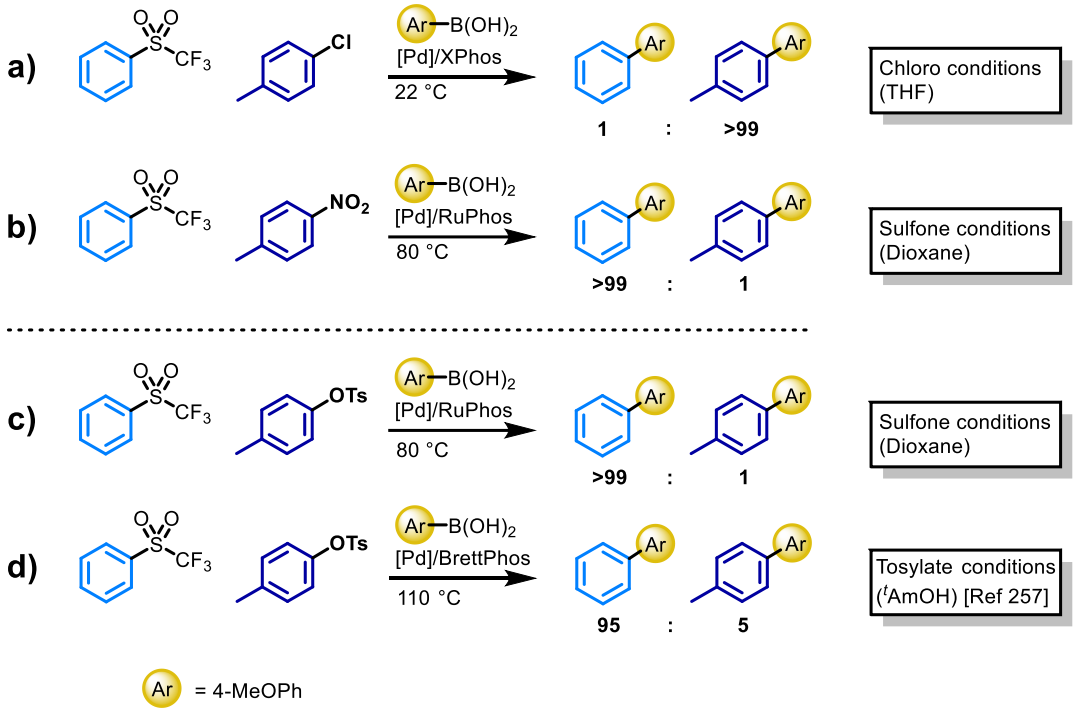
Following the general procedure, 4-methoxyphenylboronic acid (32 mg, 0.21 mmol) and 4'-fluoro-3-((trifluoromethyl)sulfonyl)-1,1'-biphenyl (43 mg, 0.14 mmol) afforded **31a** as a white solid (39 mg, 88 %) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 2.4, 1.1 Hz, 1H), 7.63 – 7.56 (m, 4H), 7.54 (ddd, *J* = 5.6, 3.6, 1.8 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.15 (t, *J* = 8.7 Hz, 2H), 7.03 – 6.98 (m, 2H), 3.87 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.5 (d, *J* = 246.4 Hz), 159.3, 141.5, 140.8, 137.4 (d, *J* = 3.2 Hz), 133.6, 129.2, 128.8 (d, *J* = 8.0 Hz), 128.3, 125.7, 125.6, 125.4, 115.7 (d, *J* = 21.4 Hz), 114.3, 55.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.7. Spectral data are in agreement with the literature.[379]



4,4''-Dimethoxy-2'-nitro-1,1':4',1''-terphenyl (32a)

Following the general procedure, 4-methoxyphenylboronic acid (23 mg 0.15 mmol) and 4'-methoxy-2-nitro-4-((trifluoromethyl)sulfonyl)-1,1'-biphenyl (35 mg, 0.10 mmol) afforded **32a** as a light yellow solid (25 mg, 73%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to dichloromethane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.8 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.02 (dd, *J* = 9.2, 2.3 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.0, 159.7, 149.7, 140.7, 133.7, 132.3, 130.8, 130.0, 129.3, 129.2, 128.2, 121.9, 114.6, 114.3, 55.4, 55.4. Spectral data are in agreement with the literature.[322]

Competition experiments



e) A microwave vial was charged with $Pd(OAc)_2$ (1.3 mg, 3 mol%.), XPhos (8.6 mg, 9 mol%), 4-methoxyphenylboronic acid (30 mg, 0.20 mmol) and K_3PO_4 (126 mg, 0.60 mmol). Then, the vial was evacuated and backfilled with nitrogen three times, followed by the addition of 1.0 ml anhydrous THF, phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol) and 4-chlorotoluene (24 µL, 0.20 mmol). The reaction mixture was stirred at 22 ˚C for 16 h, diluted in EtOAc and filtered through a plug of silica. The relative product ratios were determined by GC/MS.

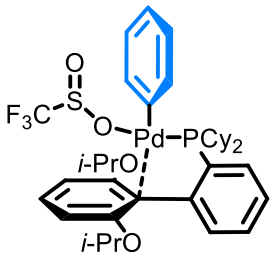
f) An analogous procedure to the one above was used, with $Pd(acac)_2$ (3.0 mg, 5 mol%) and RuPhos (18.6 mg, 20 mol%) as the catalyst, 4-nitrotoluene (27.4 mg, 0.20 mmol) as the competition substrate, anhydrous dioxane as solvent and 80 ˚C as the reaction temperature. The relative product ratios were determined by GC/MS.

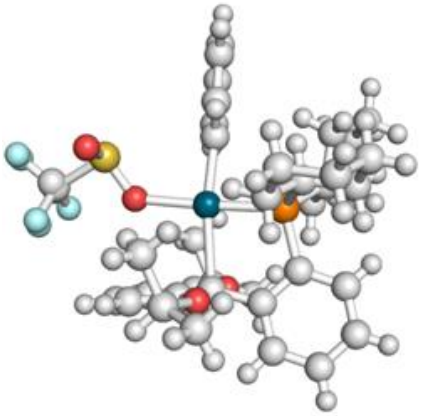
g) An analogous procedure to the one above (**b**) was used, using *p*-tolyl 4-methylbenzene-sulfonate (52.5 mg, 0.20 mmol) as the competition substrate. The relative product ratios were determined by GC/MS.

h) A microwave vial was charged with $Pd(OAc)_2$ (0.9 mg, 2 mol%.), BrettPhos (4.3 mg, 4 mol%), 4-methoxyphenylboronic acid (30 mg, 0.20 mmol), *p*-tolyl 4-methylbenzene-sulfonate (52.5 mg, 0.20 mmol) and K_3PO_4 (126 mg, 0.60 mmol). Then, the vial was evacuated and backfilled with nitrogen three times, followed

by the addition of 0.4 ml anhydrous *t*-amyl alcohol and phenyl trifluoromethyl sulfone (30 µL, 0.20 mmol). The reaction mixture was stirred at 22 ˚C for 16 h, diluted in EtOAc and filtered through a plug of silica. The relative product ratios were determined by GC/MS.

5.2.5. Isolation of palladium complex X1





Pd-complex X1

A 25 mL flask was charged with (cod)Pd(CH_2SiMe_3)$_2$ (90 mg, 0.23 mmol), RuPhos (97 mg, 0.21 mmol), phenyl trifluoromethyl sulfone (34 µL, 0.23 mmol) in dioxane (4 mL). The reaction mixture was stirred at 40 °C for 48 h inside the glovebox. The solvent was removed under reduced pressure and the residual brown solid was washed three times with 2.0 mL of hexane to remove unreacted ligand and phenyl trifluoromethyl sulfone. The residue was then dissolved in 4 mL $CHCl_3$ and was filtered through a bed of Celite. Removal of the $CHCl_3$ under reduced pressure gave the compound **X1** as a light brown solid. Recrystallization by slow diffusion of pentane into $CHCl_3$ in a 3:1 volume ratio at room temperature gave **X1** as light brown crystals (61 mg, 37%). **HRMS (ESI):** calculated: 649.2427; found: 649.2426 (M-SO_2CF_3). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 -7.54 (m, 2H), 7.47 -7.34 (m, 2H), 7.16 (d, *J* = 6.6 Hz, 2H), 7.00 - 6.79 (m, 4H), 6.66 (d, *J* = 8.6 Hz, 2H), 4.62 (hept, *J* = 6.0 Hz, 2H), 2.13 (q, *J* = 13.0, 11.4 Hz, 2H), 1.84 -1.54 (m, 12H), 1.41 (d, *J* = 6.0 Hz, 5H), 1.30 -1.06 (m, 7H), 1.04 (s, 6H), 0.84 - 0.70 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.8, 136.5, 136.5, 130.5, 127.9, 127.2, 126.5, 126.4, 125.0, 107.3, 70.8, 34.2, 34.0, 28.1, 27.9, 27.1, 27.0, 26.8, 26.7, 26.0, 22.2, 21.9, 21.8, 21.5.

Reaction of X1 with 4-methoxyphenylboronic acid in the presence of DMSO: In a nitrogen-filled glovebox, a vial was charged with **X1** (20 mg, 0.0255 mmol), 4-methoxyphenylboronic acid (7.0 mg, 0.038 mmol), K_3PO_4 (16mg, 0.077 mmol) and DMSO (1.0 μL) in dioxane (0.2 mL). The reaction mixture was stirred at 25 °C for 16h. Then, it was diluted with EtOAc, filtered through a plug of celite and purified by preparative TLC to afford compound **1** (4.3 mg, 92%).

Reaction of X1 with 4-methoxyphenylboronic acid without DMSO: An analogous procedure to the one described above (excluding DMSO) was used to afford compound **1** (4.5 mg, 97%).

Reaction of catalytic X1 with 4-methoxyphenylboronic acid with excess ligand and without DMSO: In a nitrogen-filled glovebox, a vial was charged with **X1** (7.8 mg, 5 mol%), 4-methoxyphenylboronic acid (45.6 mg, 0.30 mmol), K_3PO_4 (126mg, 0.60 mmol), RuPhos (14.0 mg, 15 mol%) and $PhSO_2CF_3$ (29.6 μL, 0.20 mmol) in dioxane (1.0 mL). The reaction mixture was stirred at 80 °C for 16h. Then, it was diluted with EtOAc, filtered through a plug of celite and purified by automated flash chromatography to afford compound **1** (35 mg, 95%).

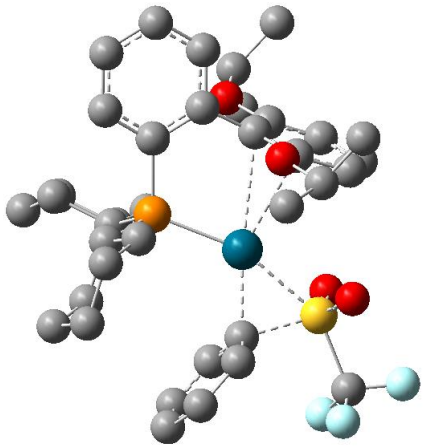
Reaction of catalytic X1 with 4-methoxyphenylboronic acid without excess ligand and DMSO: An analogous procedure to the one described above (excluding additional RuPhos) was used to afford compound **1** (23 mg, 62%).

5.2.6 DFT Calculations

Calculated Gibbs energies for the oxidative addition of the sulfone to Pd(0)-RuPhos (kcal/mol).

	CF3	Ph
Pd-dioxane	0	0
pi-complex	-25.50	-22.70
TS	-3.47	2.26
intermediate	-24.02	-29.12
XRD-intermediate	-26.07	-28.42

DFT calculations were performed using ORCA 4.0.1.2.[a] Gibbs energy corrections were determined using frequency analysis at the PBE/def2-SVP level. Structures were optimized using B3LYP/def2-TZVP[b] with the D3 correction for dispersion with Becke-Johnson damping.[c,d]The solvation energy was calculated using the SMD model for dioxane.[e]



The optimized structure of the transition state corresponding to the oxidative addition of Ph-SO_2CF_3 to Pd(0)-RuPhos. Hydrogen atoms are removed for clarity.

(a) Neese, F. The ORCA Program System. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2011**, *2* (1), 73–78.

(b) Schäfer, A.; Huber, C.; Ahlrichs, R. Fully Optimized Contracted Gaussian Basis Sets of Triple Zeta Valence Quality for Atoms Li to Kr. *J. Chem. Phys.* **1994**, *100* (8), 5829–5835.

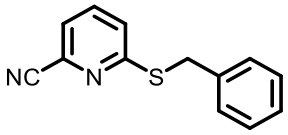
(c) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the Damping Function in Dispersion Corrected Density Functional Theory. *J. Comput. Chem.* **2011**, *32* (7), 1456–1465.

(d) Otero-de-la-Roza, A.; Johnson, E. R. Non-Covalent Interactions and Thermochemistry Using XDM-Corrected Hybrid and Range-Separated Hybrid Density Functionals. *J. Chem. Phys.* **2013**, *138* (20), 204109.

(e) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113* (18), 6378–6396.

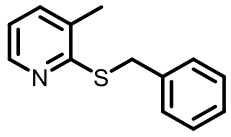
5.3 The coupling of sulfonyl fluorides

5.3.1 Synthesis of starting materials



6-(Benzylthio)picolinonitrile

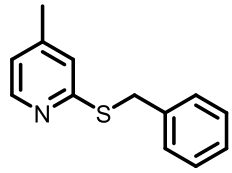
Prepared according to a modified literature procedure.[380] Benzyl thiol (1.34 g, 11 mmol) was added to a stirred suspension of sodium hydride in anhydrous THF (24 mL) at room temperature. After complete addition, a solution of 6-bromopicolinonitrile in THF (14 mL) was added and the solution was heated at 60 °C for 3 h. At the end of the reaction, volatiles were removed under reduced pressure and the resulting oily liquid was dissolved in ethyl acetate and washed with sat. sodium bicarbonate and brine. The resulting solution was dried over sodium sulfate and purified by column chromatography (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate) to yield the title compound as a colorless oil (1.52 g, 55%). **HRMS (ESI)**: calculated: 227.0643, found: 227.0670 (M+H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.37 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.29 – 7.22 (m, 1H), 4.43 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.6, 137.2, 136.25, 133.2, 129.2, 128.6, 127.4, 125.5, 124.3, 117.2, 34.4.



2-(Benzylthio)-3-methylpyridine

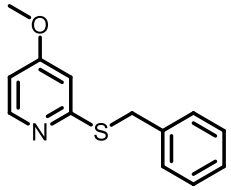
Prepared according to a modified literature procedure.[380] 2-chloro-3-methylpyridine (10.2 mmol) was added to a suspension of benzyl thiol (1.9 g, 15.3 mmol) and potassium carbonate (2.12 g, 15.3 mmol) in DSMO (10 mL) and the mixture was stirred at 150 °C for 16 h. After cooling to room temperature, 150 mL of water was added and was extracted twice with ethyl acetate. The organic phase was washed with

sat. $NaHCO_3$ and brine and then dried over sodium sulfate and purified by column chromatography (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate) to yield the title compound as a colorless oil (1.14 g, 89 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (ddd, *J* = 4.9, 1.7, 0.7 Hz, 1H), 7.66 – 7.38 (m, 2H), 7.37 – 7.27 (m, 3H), 7.26 – 7.10 (m, 1H), 6.94 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.50 (s, 2H), 2.24 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.8, 146.5, 138.3, 136.3, 130.6, 129.2, 128.5, 127.0, 119.3, 34.1, 18.5. Spectral data are consistent with the reported literature.[380]



2-(Benzylthio)-4-methylpyridine

Prepared according to a modified literature procedure.[380] 2-chloro-4-methylpyridine (1.5 mL, 13.4 mmol) was added to a suspension of benzyl thiol (2.2 mL, 18.8 mmol) and potassium carbonate (2.60 g, 18.8 mmol) in DSMO (13 mL) and the mixture was stirred at 150 °C for 5 h. After cooling to room temperature, 150 mL of water was added and was extracted twice with ethyl acetate. The organic phase was washed with sat. $NaHCO_3$ and brine and then dried over sodium sulfate and purified by column chromatography (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate) to yield the title compound as a colorless oil (1.75 g, 61 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 5.1 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.32 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.00 (s, 1H), 6.82 (ddd, *J* = 5.1, 1.5, 0.7 Hz, 1H), 4.44 (s, 2H), 2.26 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 149.1, 147.2, 138.1, 129.0, 128.5, 127.1, 122.6, 121.1, 34.4, 20.9. Spectral data are consistent with the reported literature.[380]



2-(Benzylthio)-4-methylpyridine

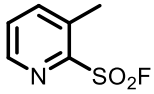
Prepared according to a modified literature procedure.[380] 2-chloro-4-methoxypyridine (1 mL, 8.91 mmol) was added to a suspension of benzyl thiol (0.87 mL, 7.4 mmol) and potassium carbonate (1.2 g, 8.9 mmol) in DSMO (9 mL) and the mixture was stirred at 150 °C for 3 h. After cooling to room temperature, 150 mL of water was added and was extracted twice with ethyl acetate. The organic phase was washed with sat. $NaHCO_3$ and brine and then dried over sodium sulfate and purified by column chromatography (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate) to yield the title compound as a colorless oil (193 mg, 11 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.8 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 6.69 – 6.67 (m, 1H), 6.57 (dd, *J* = 5.8, 2.4 Hz, 1H), 4.44 (s, 2H), 3.79 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.6, 160.3, 150.2, 138.0, 129.0, 128.5, 127.1, 107.7, 106.6, 55.1, 34.7. Spectral data are consistent with the reported literature.[380]

Representative procedure for the synthesis of sulfonyl fluorides:

Sulfonyl fluorides were prepared according to a modified literature procedure.[343] A round-bottom flask was charged with an aryl thiol or a benzylic thioether (6.25 mmol) and concentrated sulfuric acid (10 mL). Using a dropping funnel, 30 mL of 10-15% (m/m) (approx. 10 equiv) aqueous NaOCl solution was added dropwise over 4 h at 0 °C. The system was left open and care was taken to prevent exposure to chorine gas. After complete addition, the solution was extracted twice with ethyl acetate (25 mL), dried of sodium sulfate, and concentrated under reduced pressure to afford the crude sulfonyl chloride.

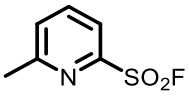
The sulfonyl chloride was dissolved in approx. 2 mL of acetonitrile and added to a solution of 2 g of KHF_2 in 6 mL H_2O and stirred for 2 h in an old deuterium oxide bottle (concentrated bifluoride solutions etch glassware). The reaction mixture was then diluted with 30 mL H_2O and washed once with 50 mL ethyl acetate. The organic

phase was washed with sat. sodium bicarbonate solution, brine, dried over sodium sulfate, concentrated, and purified by column chromatography.



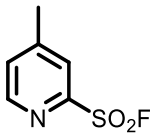
3-Methylpyridine-2-sulfonyl fluoride

Following the representative procedure, 2-(benzylthio)-4-methylpyridine (1.14 g, 5.29 mmol), 10-15% NaOCl solution (25 mL), sulfuric acid (8.4 mL) and potassium bifluoride (2 g) afforded 3-methylpyridine-2-sulfonyl fluoride as a brownish jelly (297 mg, 32%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.32 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 176.0182, found: 176.0177 (M+H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.76 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.52 (dd, *J* = 7.8, 4.6 Hz, 1H), 2.64 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.2 (dd, *J* = 29.4, 0.9 Hz), 147.4 (d, *J* = 2.1 Hz), 141.8 (dd, *J* = 1.2, 0.6 Hz), 135.0 (d, *J* = 1.0 Hz), 128.9 (d, *J* = 0.6 Hz), 18.9 (d, *J* = 1.4 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ 55.85.



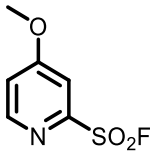
6-Methylpyridine-2-sulfonyl fluoride

Following the representative procedure, 6-methylpyridine-2-thiol (607 mg, 4.87 mmol), 10-15% NaOCl solution (25 mL), sulfuric acid (8 mL) and potassium bifluoride (2 g) afforded 6-methylpyridine-2-sulfonyl fluoride as a white solid (640 mg, 75%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.41 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 176.0182, found: 176.0176 (M+H). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.87 (m, 2H), 7.54 (dd, *J* = 7.3, 1.5 Hz, 1H), 2.70 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.3 (d, *J* = 1.1 Hz), 150.7 (d, *J* = 29.6 Hz), 138.5 (d, *J* = 0.6 Hz), 129.2, 121.2 (d, *J* = 2.3 Hz), 24.4. **^{19}F NMR** (471 MHz, $CDCl_3$) δ 55.07.



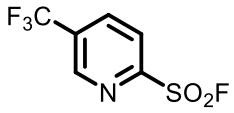
4-Methylpyridine-2-sulfonyl fluoride

Following the representative procedure, 2-(benzylthio)-4-methylpyridine (1.75 g, 8.13 mmol), 10-15% NaOCl solution (40 mL), sulfuric acid (13 mL) and potassium bifluoride (3.2 g) afforded 4-methylpyridine-2-sulfonyl fluoride as a yellow liquid (1.2 g, 84%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.38 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 176.0182, found: 176.0176 (M+H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.9 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.50 (d, *J* = 4.8 Hz, 1H), 2.53 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.2 (dd, *J* = 29.8, 2.6 Hz), 151.0 (dd, *J* = 2.8, 0.5 Hz), 150.7 (d, *J* = 1.3 Hz), 129.9 (d, *J* = 2.3 Hz), 124.9 (dd, *J* = 2.1, 0.5 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ 55.89.



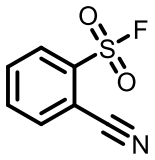
4-Methoxypyridine-2-sulfonyl fluoride

Following the representative procedure, 2-(benzylthio)-4-methoxypyridine (340 mg, 1.47 mmol), 10-15% NaOCl solution (7.5 mL), sulfuric acid (2.5 mL) and potassium bifluoride (0.6 g) afforded 4-methoxypyridine-2-sulfonyl fluoride as a yellowish oil (129 mg, 46%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.17 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 192.0131, found: 192.0122 (M+H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.6 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 5.6, 2.5 Hz, 1H), 3.98 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.31 (d, *J* = 1.3 Hz), 152.6 (d, *J* = 30.3 Hz), 152.1 (d, *J* = 1.5 Hz), 114.7, 110.8 (d, *J* = 2.2 Hz), 56.3. **^{19}F NMR** (471 MHz, $CDCl_3$) δ 55.43.



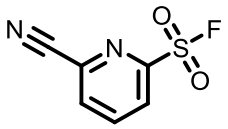
5-(Trifluoromethyl)pyridine-2-sulfonyl fluoride

Following the representative procedure, 5-(trifluoromethyl)pyridine-2-thiol (500 mg, 2.79 mmol), 10-15% NaOCl solution (13.4 mL), sulfuric acid (4.5 mL) and potassium bifluoride (0.6 g) afforded 5-(trifluoromethyl)pyridine-2-sulfonyl fluoride as a white solid (171 mg, 27%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.54 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 229.9899, found: 229.9894 (M+H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.10 (d, *J* = 2.1 Hz, 1H), 8.35 – 8.26 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.3 (qd, *J* = 32.5 Hz, 1.6 Hz), 148.2 (qd, *J* = 3.9, 1.4 Hz), 136.5 (q, *J* = 3.5 Hz), 131.9 (q, *J* = 34.3 Hz), 124.1 (d, *J* = 2.2 Hz), 122.2 (q, *J* = 273.8 Hz).**^{19}F NMR** (471 MHz, $CDCl_3$) δ 55.77 (1F), -62.82 (3F).



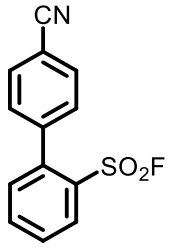
2-Cyanobenzenesulfonyl fluoride

Following the representative procedure, 2-cyanobenzenesulfonyl chloride (1.0 g, 5.40 mmol) and potassium bifluoride (2 g, 26 mmol) afforded 2-cyanobenzenesulfonyl fluoride as a white solid (894 mg, 97%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 7.4, 1.8 Hz, 1H), 8.01 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.97 – 7.87 (m, 2H). **^{13}C NMR** (126 MHz, CDCl3) δ δ 135.9 (d, *J* = 0.5 Hz), 135.6 (dd, *J* = 1.3, 0.5 Hz), 135.1 (dd, *J* = 26.9, 1.3 Hz), 133.5 (t, *J* = 0.9 Hz), 130.9 (d, *J* = 1.2 Hz), 114.1, 111.9 (t, *J* = 0.9 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ 64.53. Spectral data are consistent with the reported Literature.[381]



6-Cyanopyridine-2-sulfonyl fluoride

Following the representative procedure, 6-(benzylthio)picolinonitrile (1.52 g, 5.52 mmol), 10-15% NaOCl solution (30 mL), sulfuric acid (10 mL) and potassium bifluoride (2 g) afforded the title compound as a colorless oil (560 mg, 55%) after purification by automated flash column chromatography over silica using petroleum ether and dichloromethane as eluents, *Rf* 0.14 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 208.9791, found: 208.9788 (M+Na). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.28 (td, *J* = 7.9, 1.2 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.5 (d, *J* = 33.1 Hz), 140.6 (d, *J* = 0.6 Hz), 135.0 (d, *J* = 1.5 Hz), 133.2, 126.8 (d, *J* = 2.1 Hz), 115.0. **^{19}F NMR** (471 MHz, $CDCl_3$) δ 56.13.

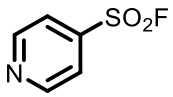


4'-Cyano-[1,1'-biphenyl]-2-sulfonyl fluoride

Prepared according to a modified literature procedure.[338] 2-bromobenzenesulfonylfluoride (227 mg, 0.87 mmol), 4-cyanophenylboronic acid (205 mg, 1.39 mmol), $Pd(OAc)_2$ (11.5 mg, 5 mol %.), triethylamine (400 µL, 2.87 mmol) were weighed into a round-bottom flask and the solvent (isopropanol/water 95:5, 11.5 mL) was added. The solution was stirred at room temperature for 3h in open air. After the reaction, the crude mixture was filtered through a bed of celite and washed with dichloromethane. Then, the solution was concentrated in vacuo and purified by column chromatography over silica using toluene as an eluent, *Rf* 0.42 (toluene), to afford the desired product as white crystals (187 mg, 73%). **HRMS (ESI)**: calculated: 284.0152, found: 284.0144 (M+Na). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.82 (td, *J* = 7.6, 1.3 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.68 (tt, *J* = 7.7, 1.4 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.44 (dd, *J* = 7.6, 1.3 Hz, 1H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 142.5, 140.9, 135.1, 132.4 (d, *J* = 1.1 Hz), 132.1, 131.9, 130.4 (d, *J* = 1.4 Hz), 129.8 (d, *J* = 1.7 Hz), 129.1 (d, *J* = 0.7 Hz), 118.4, 112.8. **^{19}F NMR** (471 MHz, $CDCl_3$) δ 68.23.

5.3.2 Unsuccessful substrates



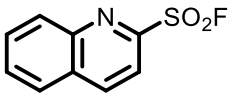
Pyridine-4-sulfonyl fluoride

Following the representative procedure, pyridine-4-thiol (1.00 g, 9.96 mmol), 10-15% NaOCl solution (48 mL), sulfuric acid (16 mL) and potassium bifluoride (3.2 g) afforded pyridine-4-sulfonyl fluoride as a colorless oil (381 mg, 26%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.01 (dt, *J* = 4.5, 1.2 Hz, 2H), 7.88 – 7.84 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.8, 141.3 (d, *J* = 27.3 Hz), 120.9 (d, *J* = 0.5 Hz). Spectral data are in agreement with the literature.[343]

Quinoline-8-sulfonyl fluoride

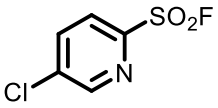
Following the representative procedure, quinoline-8-sulfonyl chloride (1.00 g, 4.39 mmol), and potassium bifluoride (1.5 g, 19.2 mmol) afforded quinoline-8-sulfonyl fluoride as a white solid (454 mg, 49%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.16 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 233.9995, found: 233.9989 (M+Na). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.53 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.32 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.24 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.72 (td, *J* = 7.8, 1.3 Hz, 1H), 7.64 (dd, *J* = 8.3, 4.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.7,

143.9, 136.5, 136.1, 133.1 (d, *J* = 2.0 Hz), 131.4, 129.1 (d, *J* = 1.2 Hz), 125.3 (d, *J* = 1.0 Hz), 123.0. **^{19}F NMR** (471 MHz, $CDCl_3$) δ 60.19.



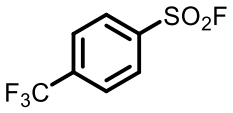
Quinoline-2-sulfonyl fluoride

Following the representative procedure, quinoline-2-thiol (500 mg, 3.10 mmol), 10-15% NaOCl solution (15 mL), sulfuric acid (5 mL) and potassium bifluoride (1 g) afforded quinoline-2-sulfonyl fluoride as a white solid (229 mg, 35%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.54 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 212.0176, found: 212.0170 (M+H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.7 Hz, 1H), 8.01 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.75 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.71 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 148.0, 137.5, 130.4, 128.4, 127.8, 126.4, 126.4, 117.2. **^{19}F NMR** (471 MHz, $CDCl_3$) δ 56.72.



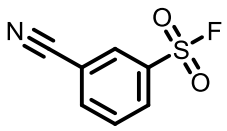
5-Chloropyridine-2-sulfonyl fluoride

Following the representative procedure, 5-chloropyridine-2-thiol (500 mg, 3.43 mmol), 10-15% NaOCl solution (20 mL), sulfuric acid (4 mL) and potassium bifluoride (1 g) afforded pyridine-4-sulfonyl fluoride as a white solid (370 mg, 55%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.80 – 8.76 (m, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 8.02 (ddd, *J* = 8.4, 2.3, 1.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.3 (d, *J* = 1.3 Hz), 149.1 (d, *J* = 32.0 Hz), 138.7, 138.34, 125.2 (d, *J* = 1.4 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ 56.80. Spectral data are in agreement with the literature.[343]



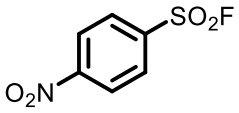
4-(Trifluoromethyl)benzenesulfonyl fluoride

Following the representative procedure, 4-(trifluoromethyl)benzenesulfonyl chloride (1.00 g, 4.09 mmol) and potassium bifluoride (1.3 g) afforded 4-(trifluoromethyl)benzenesulfonyl fluoride as a white solid (765 mg, 82%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3 (q, *J* = 33.5 Hz), 136.6 (dd, *J* = 26.2, 1.3 Hz), 129.3, 127.1 (q, *J* = 3.6 Hz), 122.9 (d, *J* = 273.4 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ 66.0 (1F), -63.5 (3F). Spectral data are in agreement with the reported literature.[343]



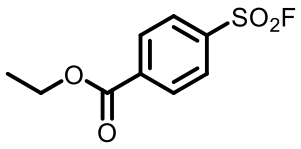
3-Cyanobenzenesulfonyl fluoride

Following the representative procedure, 3-cyanobenzenesulfonyl chloride (1.00 g, 5.40 mmol) and potassium bifluoride (2 g, 26 mmol) afforded 3-cyanobenzenesulfonyl fluoride as a white solid (730 mg, 80%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.32 (t, *J* = 1.8 Hz, 1H), 8.26 (dt, *J* = 8.1, 1.5 Hz, 1H), 8.07 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.83 (t, *J* = 7.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.6, 134.8 (d, *J* = 27.4 Hz), 132.2, 132.0, 130.9, 116.2, 114.7 (d, *J* = 0.7 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ 66.37. Spectral data are in agreement with the reported literature.[382]



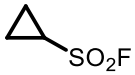
4-nitrobenzenesulfonyl fluoride

Following the representative procedure, 4-nitrobenzenesulfonyl chloride (1.10 g, 5.0 mmol) and potassium bifluoride (3.2 g) afforded 4-nitrobenzenesulfonyl fluoride as a white solid (960 mg, 94%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 – 8.45 (m, 2H), 8.29 – 8.21 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.8, 138.3 (d, *J* = 27.1 Hz), 130.0, 124.9. Spectral data are in agreement with the reported literature.[383]



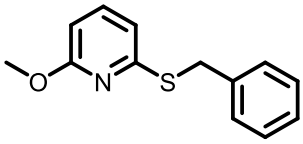
Ethyl 4-(fluorosulfonyl)benzoate

Following the representative procedure, 4-(chlorosulfonyl)benzoic acid (1.00 g, 4.90 mmol) and potassium bifluoride (1.0 g) afforded 4-(chlorosulfonyl)benzoic acid as a white solid which was used in the next step without purification. The crude product was added to a round-bottom flask with DCM (20 mL), oxalyl chloride (0.60 mL, 0.89 g, 7.00 mmol) and 3 drops of DMF. The solution was left to stir at room temperature under an argon atmosphere for 3 h, after which a 6:4 mixture of ethanol and pyridine (10 mL) was added. After 30 min, volatiles were evaporated under reduced pressure, diluted in ethyl acetate and washed once with H_2O and twice with a 1 M K_2CO_3 solution. Then, the product was purified by column chromatography (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate) to afford Ethyl 4-(fluorosulfonyl)benzoate as a white solid (1.0 g, 95% overall yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (dt, *J* = 8.0, 1.0 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5, 136.9, 136.6 (d, *J* = 25.3 Hz), 130.7, 128.5, 62.2, 14.3. Spectral data are in agreement with the reported literature.[383]



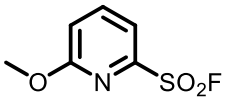
Cyclopropanesulfonyl fluoride

A solution of cyclopropanesulfonyl chloride (2.00 g, 14.2 mmol) in acetonitrile (4 mL) was added to a stirred solution of potassium bifluoride (2.0 g, 25.6 mmol) in water (4 mL). After 2 h, the reaction was extracted with diethyl ether and washed once with distilled water and twice with a saturated $NaHCO_3$ solution. Due to the volatile nature of the product, the solvent was carefully evaporated under reduced pressure (down to 100 mbar at 40 °C for 1 h) with no further purification. Cyclopropanesulfonyl fluoride was afforded as a colorless liquid (1.76 g, quant.) and NMR analysis displayed no significant impurities and was free of ether. **MS(EI):** calculated: 124, found: 124 (M+, low resolution). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.27 (tt, *J* = 7.8, 4.6 Hz, 1H), 1.63 – 1.56 (m, 2H), 1.35 (dddd, *J* = 8.8, 7.0, 5.5, 1.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 43.2, 9.2.



2-(benzylthio)-6-methoxypyridine

Prepared according to a modified literature procedure.[380] 2-chloro-6-methoxypyridine (1.15 g, 8 mmol) was added to a suspension of benzyl thiol (1.90 g, 15.3 mmol) and potassium carbonate (2.12 g, 15.3 mmol) in DSMO (10 mL) and the mixture was stirred at 150 °C for 3 h. After cooling to room temperature, 150 mL of water was added and was extracted twice with ethyl acetate. The organic phase was washed with sat. $NaHCO_3$ and brine and then dried over sodium sulfate and purified by column chromatography (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate) to yield the title compound a brownish oil (400 mg, 22 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 3H), 7.34 – 7.26 (m, 3H), 6.78 (dd, *J* = 7.5, 0.7 Hz, 1H), 6.44 (dd, *J* = 8.2, 0.6 Hz, 1H), 4.45 (s, 2H), 3.94 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 155.9, 138.7, 138.3, 128.8, 128.5, 127.1, 114.3, 106.0, 53.5, 34.4. Spectral data are consistent with the reported Literature.[380]



6-methoxypyridine-2-sulfonyl fluoride

Following the representative procedure, 2-(benzylthio)-6-methoxypyridine (400 mg, 1.76 mmol), 10-15% NaOCl solution (8.3 mL), sulfuric acid (2.75 mL) and potassium bifluoride (0.6 g) afforded 6-methoxypyridine-2-sulfonyl fluoride as a yellowish oil (188 mg, 56%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.57 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 189.9980, found: 189.9954 (M-H). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.70 (dt, *J* = 7.2, 0.8 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 4.04 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.5 (d, *J* = 0.9 Hz), 148.1 (d, *J* = 29.7 Hz), 139.9 (d, *J* = 0.8 Hz), 118.2, 117.4 (d, *J* = 2.6 Hz), 54.6. **^{19}F NMR** (471 MHz, $CDCl_3$) δ 53.69.

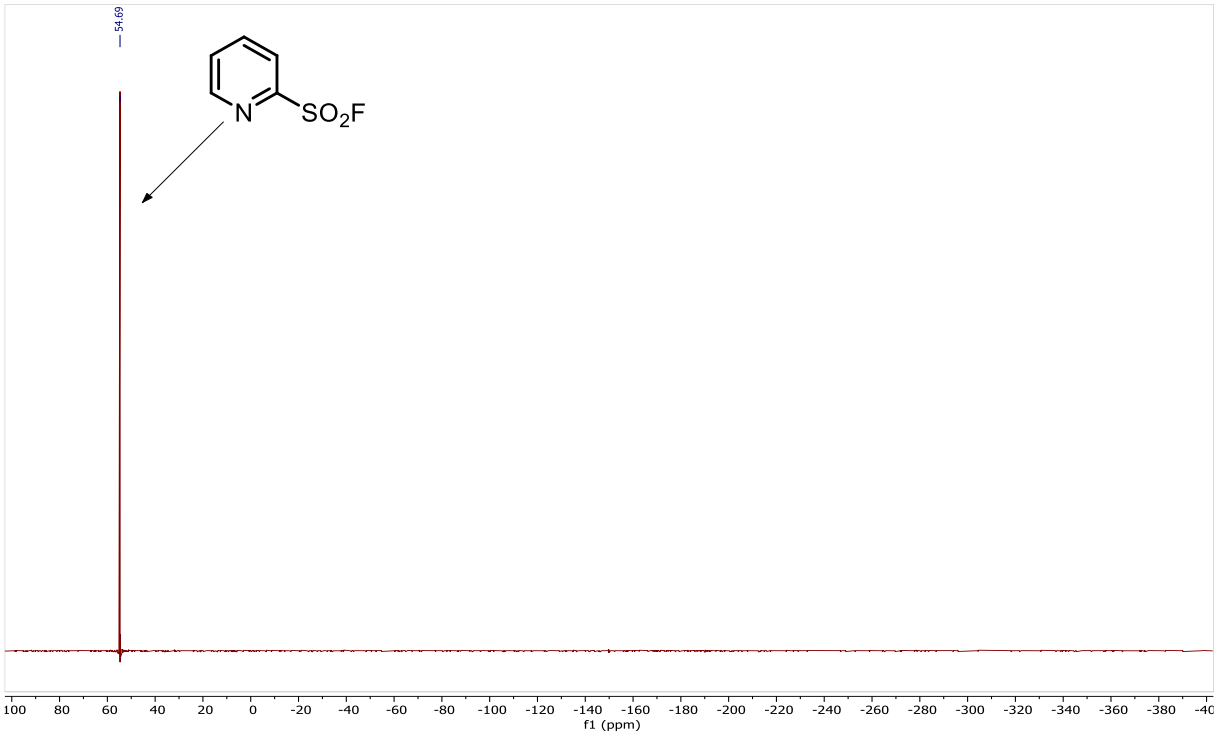
5.3.2 Mechanistic experiments

Stability of PyFluor with the Pd catalyst or Cu additive

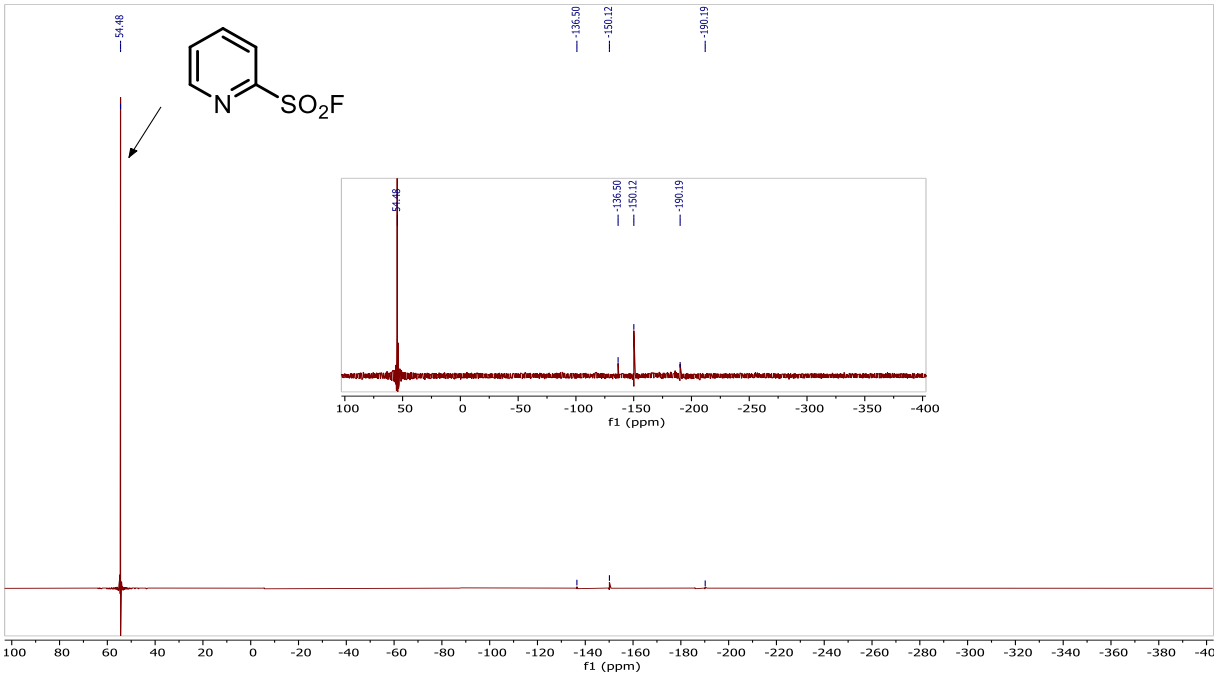
A: PyFluor (16.1 mg, 0.1 mmol) and PdG4-RuPhos (42.5 mg, 0.5 equiv) were charged into a microwave vial. The vial was sealed, evacuated, and backfilled with nitrogen three times. Then, 2.0 mL of anhydrous dioxane was added via syringe. The solution was stirred at 130 °C in an aluminum heating block. After 2 h and 8 h, a 100 µL aliquot was collected and diluted with 300 µL of deuterated toluene. The composition of the mixture was analyzed by ^{19}F NMR.

B: An analogous procedure to the one above was used, adding Cu(IPr)Cl (12.2 mg, 0.25 equiv).

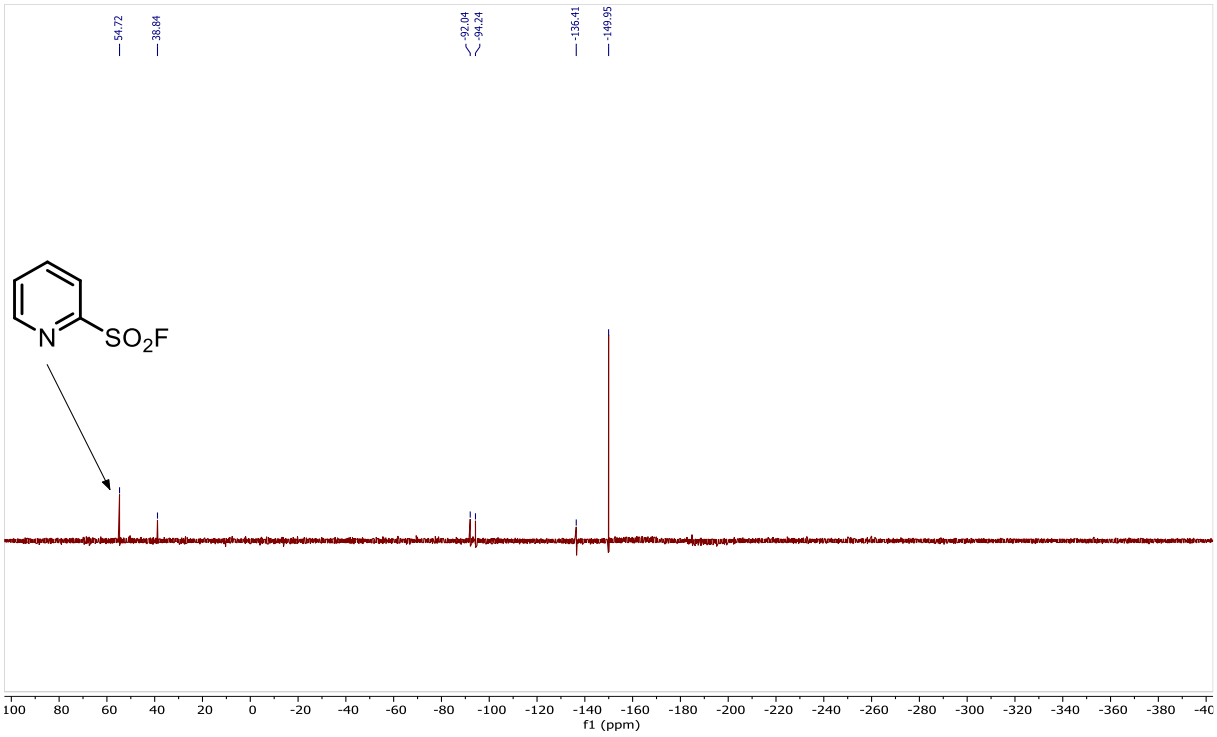
C: An analogous procedure to the one above was used, without any Pd (only Cu(IPr)Cl) and was only recorded after 2 h.



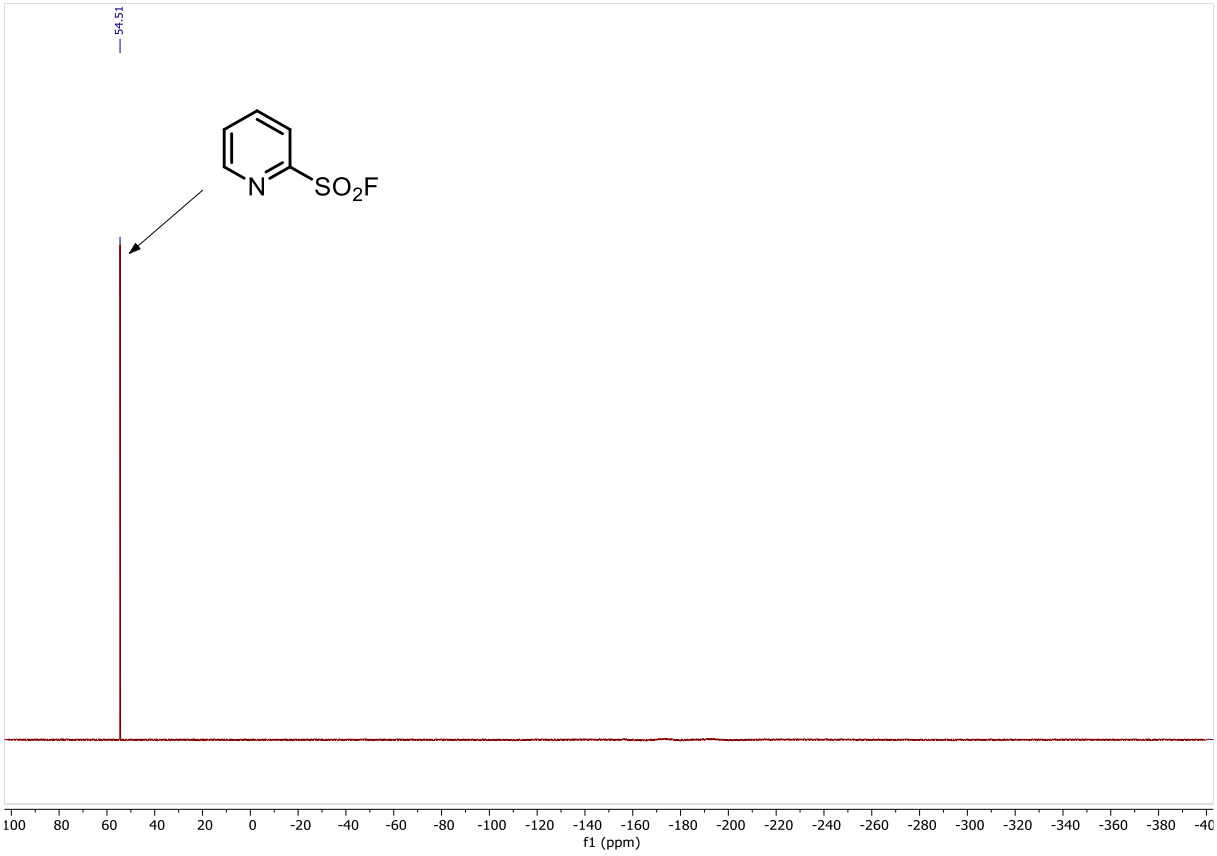
^{19}F NMR spectrum of reaction A after 2 h.



^{19}F NMR spectrum of reaction A after 8 h.

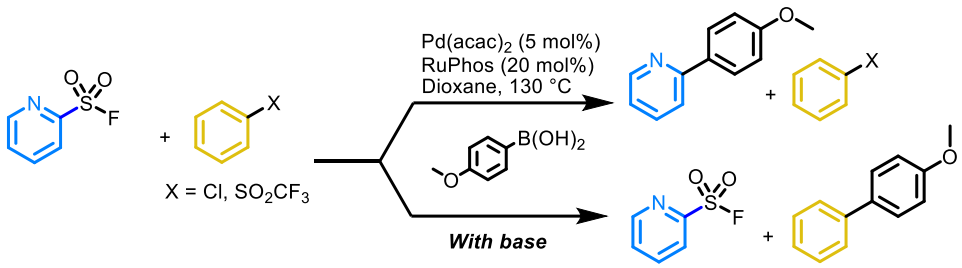


^{19}F NMR spectrum of reaction B after 2 h.



^{19}F NMR spectrum of reaction C after 2 h.

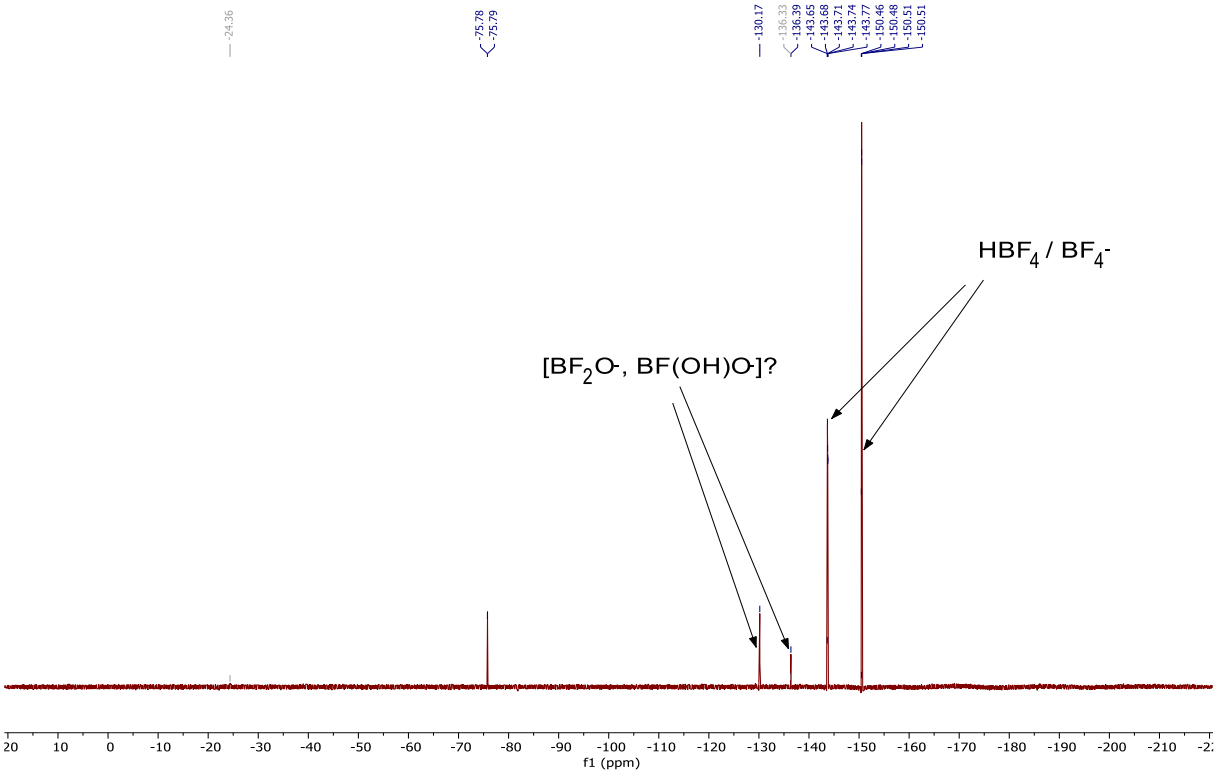
Orthogonal coupling



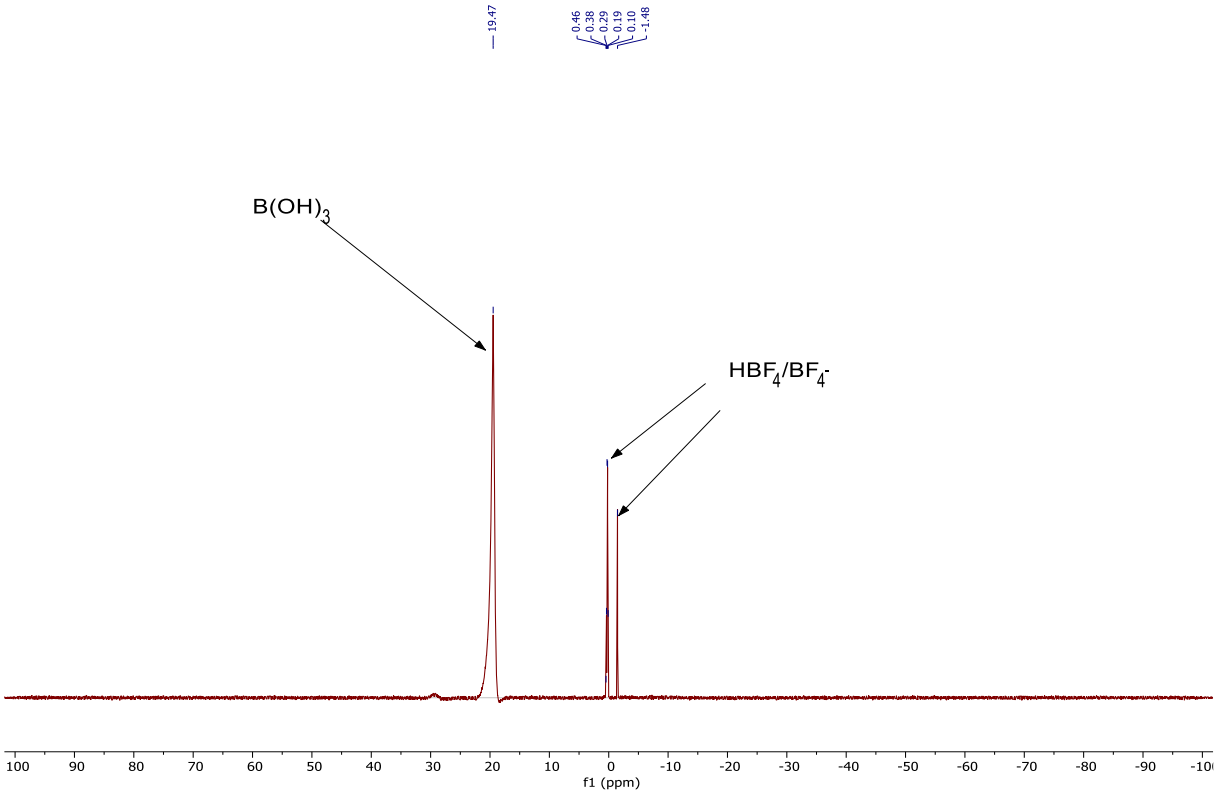
PyFluor (32mg, 0.20 mmol), boronic acid (0.20 mmol), $Pd(acac)_2$ (5 mol%) and RuPhos (20 mol%) were weighed into a microwave vial. The vial was sealed, evacuated, and backfilled with nitrogen 3 times. Then, 1.0 ml anhydrous dioxane was added via syringe (liquid sulfonyl fluorides were added during this step). The solutions were stirred and heated at 130 °C for 16 h in an aluminum heating block. After the reaction was cooled to room temperature, the crude mixture was diluted with ethyl acetate, filtered through a plug of silica, and analyzed by GC/MS. For the experiment with base, K_3PO_4 (126 mg, 0.60 mmol) was added.

Determination of the leaving group

PyFluor (32.2 mg, 0.20 mmol), 4-methoxyphenylboronic acid (45.6 mg, 0.30 mmol), $Pd(acac)_2$ (5 mol%) and RuPhos (20 mol%) were weighed into a microwave vial. The vial was sealed, evacuated, and backfilled with nitrogen 3 times. Then, 1.0 mL of anhydrous dioxane was added via syringe and the solution was stirred and heated to 130 °C for 16 h in an aluminum heating block. The crude mixture was then diluted with dichloromethane, filtered through a bed of Celite and washed with dichloromethane. Then, the solvent was evaporated under reduced pressure. The residue was dissolved in deuterated chloroform and extracted with D_2O. The D_2O phase was analyzed by ^{19}F NMR and ^{11}B NMR and compared to the spectra of a mixture of commercially available references, revealing the presence of BF_4^- and $B(OH)_3$. HRMS analysis confirmed the presence of these species along with several others ($B(OH)_2O^-$, $BF(OH)O^-$, BF_2O^-, BF_4^-), some of which constitute viable assignments for the thus unassigned peaks observed in ^{19}F NMR. **HRMS (ESI)**: [$B(OH)_2O^-$]: calculated: 61.0102, found: 61.0086; [$BF(OH)O^-$]: calculated: 63.0059, found: 63.0043; [BF_2O^-]: calculated: 65.0016, [BF_4^-]: found: 64.9999; calculated: 87.0035, found: 87.0019.



^{19}F NMR of the D_2O phase



^{11}B NMR of the D_2O phase

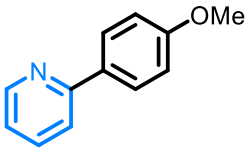
5.3.2 General procedures for cross-coupling reactions

Procedure A: Sulfonyl fluoride (0.20 mmol), 4-methoxyphenylboronic acid (31 mg, 0.20 mmol), $Pd(acac)_2$ (3 mg, 5 mol%) and RuPhos (18.6 mg, 20 mol%) were weighed into a microwave vial. The vial was sealed, evacuated, and backfilled with nitrogen 3 times. Then, 1.0 ml anhydrous dioxane and was added via syringe. The solution was stirred and heated at 130 °C for 16 h in an aluminum heating block. After the reaction was cooled to room temperature, the crude mixture was diluted with ethyl acetate, filtered through a bed of Celite and washed with ethyl acetate. Then, the solution was concentrated *in vacuo* and purified by column chromatography.

Procedure B: An analogous procedure to **procedure A** was used, using chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) [(iPr)CuCl] (2.5 mol%) and potassium bifluoride (50 mol%) as additives.

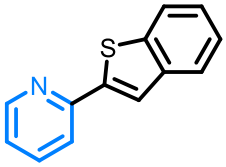
Procedure C: An analogous procedure to **procedure B** was used, using (2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]-palladium(II) methanesulfonate [RuPhos PdG3] (5 mol%) instead of $Pd(acac)_2$, 10 mol% RuPhos instead of 20 mol%. Additives: [(IPr)CuCl] (2.5 mol%) and potassium bifluoride (50 mol%).

5.3.3 Substrate scope



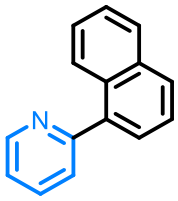
2-(4-Methoxyphenyl)pyridine (1b)

Following the general procedure A, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **1b** as a white solid (36 mg, 97%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, CDCl3) δ 8.65 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 8.02 – 7.90 (m, 2H), 7.73 – 7.63 (m, 2H), 7.16 (ddd, J = 7.2, 4.8, 1.4 Hz, 1H), 7.04 – 6.96 (m, 2H), 3.85 (s, 3H). **^{13}C NMR** (126 MHz, CDCl3) δ 160.5, 157.1, 149.6, 136.7, 132.1, 128.2, 121.4, 119.8, 114.1, 55.4. Spectral data are consistent with the reported literature.[5]



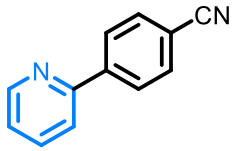
2-(Benzo[b]thiophen-2-yl)pyridine (2b)

Following the general **procedure A**, 4-cyanophenylboronic acid (35 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **2b** as a white solid (28 mg, 66%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.91 – 7.78 (m, 4H), 7.74 (td, *J* = 7.7, 1.8 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.22 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6, 149.8, 144.8, 140.7, 140.5, 136.6, 125.1, 124.5, 124.1, 122.62, 122.61, 121.1, 119.6. Spectral data are consistent with the reported literature.[384]



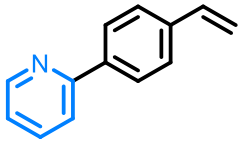
2-(Naphthalen-1-yl)pyridine (3b)

Following the general **procedure A**, naphthalen-1-ylboronic acid (52 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **3b** as a white solid (28 mg, 68 %) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, CDCl3) δ 8.81 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.14 – 8.06 (m, 1H), 7.98 – 7.88 (m, 2H), 7.82 (td, J = 7.7, 1.8 Hz, 1H), 7.64 – 7.53 (m, 3H), 7.50 (pd, J = 6.8, 1.6 Hz, 2H), 7.33 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl3) δ 159.3, 149.6, 138.5, 136.4, 134.0, 131.2, 128.9, 128.4, 127.5, 126.5, 125.9, 125.6, 125.3, 125.1, 122.1. Spectral data are consistent with the reported literature.[385]



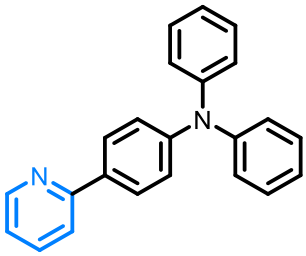
4-(Pyridin-2-yl)benzonitrile (4b)

Following the general **procedure A**, 4-cyanophenylboronic acid (44 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **4b** as a white solid (35 mg, 97%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.72 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 8.13 – 8.07 (m, 2H), 7.80 (td, *J* = 7.6, 1.8 Hz, 1H), 7.77 – 7.73 (m, 3H), 7.31 (ddd, *J* = 7.3, 4.8, 1.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.2, 150.1, 143.5, 137.1, 132.6, 127.5, 123.4, 121.0, 118.8, 112.4. Spectral data are consistent with the reported literature.[5]



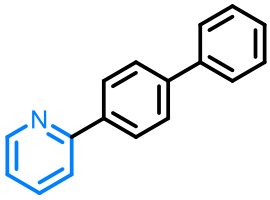
2-(4-Vinylphenyl)pyridine (5b)

Following the general **procedure A (6 h reaction time instead of 16 h)**, (4-vinylphenyl)boronic acid (44 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **5b** as a white solid (27 mg, 75%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, CDCl3) δ 8.69 (dt, J = 4.8, 1.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.24 – 7.19 (m, 1H), 6.77 (dd, J = 17.6, 10.8 Hz, 1H), 5.83 (dd, J = 17.6, 0.8 Hz, 1H), 5.31 (dd, J = 10.8, 0.9 Hz, 1H). **^{13}C NMR** (126 MHz, CDCl3) δ 157.1, 149.7, 138.8, 138.2, 136.6, 136.5, 127.0, 126.6, 122.0, 120.3, 114.4. Spectral data are consistent with the reported literature.[386]



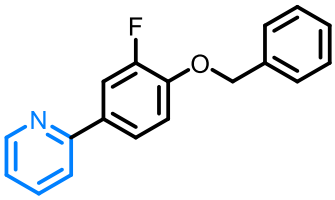
2-(4-Diphenyloamino)pyridine/N,N-diphenyl-4-(pyridin-2-yl)aniline (6b)

Following the general **procedure A**, 4-(diphenyloamino)phenylboronic acid (87 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **6b** as a light-yellow solid (31 mg, 48%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.74 – 7.64 (m, 2H), 7.30 – 7.25 (m, 4H), 7.19 – 7.12 (m, 7H), 7.08 – 7.03 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 149.7, 148.8, 147.6, 136.8, 133.2, 129.4, 127.8, 124.8, 123.33, 123.32, 121.6, 120.0. Spectral data are consistent with the reported literature.[192]



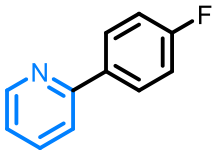
2-(4-Biphenyl)pyridine (7b)

Following the general **procedure A**, 4-biphenylboronic acid (59 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **7b** as a white solid (28 mg, 61%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (ddd, *J* = 4.8, 1.6, 1.1 Hz, 1H), 8.14 – 8.06 (m, 2H), 7.82 – 7.75 (m, 2H), 7.75 – 7.71 (m, 2H), 7.70 – 7.65 (m, 2H), 7.52 – 7.44 (m, 2H), 7.43 – 7.34 (m, 1H), 7.24 (ddd, *J* = 6.5, 4.8, 2.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1, 149.8, 141.8, 140.7, 138.4, 136.9, 128.9, 127.63, 127.57, 127.4, 127.2, 122.2, 120.6. Spectral data are consistent with the reported literature.[387]



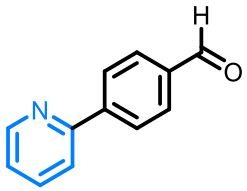
2-(4-Benzyloxy-3-fluorophenyl)pyridine (8b)

Following the general **procedure A**, 4-benzyloxy-3-fluorophenylboronic acid (74 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **8b** as a white solid (51 mg, 91%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.42 (EA:Pet. Ether 2:8). **HRMS (ESI):** calculated: 280.1132, found: 280.1124 (M+H). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.81 (dd, *J* = 12.6, 2.2 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.63 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.40 (tt, *J* = 6.4, 1.0 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.19 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H), 7.08 (t, *J* = 8.5 Hz, 1H), 5.20 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.8 (d, *J* = 2.3 Hz), 153.1 (d, *J* = 245.9 Hz), 149.7, 147.5 (d, *J* = 11.0 Hz), 136.8, 136.4, 133.2 (d, *J* = 6.3 Hz), 128.7, 128.2, 127.5, 122.650 (d, *J* = 3.4 Hz), 122.0, 119.9, 115.5 (d, *J* = 2.1 Hz), 114.9 (d, *J* = 19.9 Hz), 71.3. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -133.41 (dd, *J* = 12.7, 8.3 Hz).



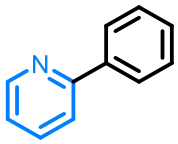
2-(4-Fluorophenyl)pyridine (9b)

Following the general **procedure A**, 4-fluorophenylboronic acid (42 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **9b** as a white solid (22 mg, 64%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.73 (tt, *J* = 5.1, 2.5 Hz, 1H), 7.67 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.22 (ddd, *J* = 7.3, 4.8, 1.2 Hz, 1H), 7.18 – 7.11 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.6, 162.7, 156.6 (d, *J* = 0.4 Hz), 149.8, 136.9, 135.7 (d, *J* = 3.2 Hz), 128.8 (d, *J* = 8.3 Hz), 121.3 (dd, *J* = 229.4, 0.6 Hz), 115.8 (d, *J* = 21.6 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -113.19. Spectral data are consistent with the reported literature.[5]



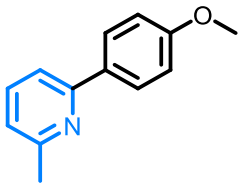
2-(4-Formylphenyl)pyridine (10b)

Following the general **procedure A**, 4-formylphenylboronic acid (45 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **10b** as a white solid (21 mg, 57%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.72 (dt, *J* = 4.8, 1.4 Hz, 1H), 8.19 – 8.11 (m, 2H), 8.00 – 7.93 (m, 2H), 7.82 – 7.74 (m, 2H), 7.33 – 7.24 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.1, 155.9, 150.0, 145.0, 137.1, 136.4, 130.2, 127.5, 123.2, 121.3. Spectral data are consistent with the reported literature.[388]



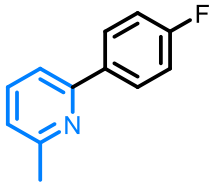
2-Phenylpyridine (11b)

Following the general **procedure A**, phenylboronic acid (36 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **11b** as a colorless oil (30 mg, 97%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (ddd, *J* = 4.8, 1.7, 1.1 Hz, 1H), 8.04 – 7.95 (m, 2H), 7.78 – 7.71 (m, 2H), 7.51 – 7.45 (m, 2H), 7.44 – 7.39 (m, 1H), 7.23 (ddd, *J* = 6.4, 4.8, 2.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 149.8, 139.5, 136.9, 129.1, 128.9, 127.0, 122.2, 120.7. Spectral data are consistent with the reported literature.[389]



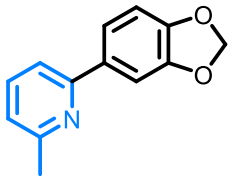
2-(4-Methoxyphenyl)-6-methylpyridine (12b)

Following the general **procedures B or C**, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 6-methylpyridine-2-sulfonyl fluoride (35 mg, 0.20 mmol) afforded **12b** as a yellow oil (39 mg, 98%, procedure B – 40 mg, quant., procedure C) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.45 (dt, *J* = 7.9, 0.8 Hz, 1H), 7.06 – 7.01 (m, 1H), 7.01 – 6.96 (m, 2H), 3.86 (s, 3H), 2.61 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.3, 158.2, 156.6, 136.8, 132.5, 128.2, 120.9, 116.9, 114.1, 55.4, 24.8. Spectral data are consistent with the reported literature.[390]



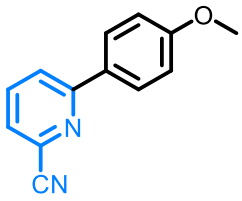
2-(4-Fluorophenyl)-6-methylpyridine (13b)

Following the general **procedure B**, 4-fluorophenylboronic acid (42 mg, 0.30 mmol) and 6-methylpyridine-2-sulfonyl fluoride (35 mg, 0.20 mmol) afforded **13b** as a yellow oil (30 mg, 80%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 3.7 Hz, 1H), 7.56 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.14 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.01 – 6.90 (m, 2H), 3.85 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.4 (d, *J* = 247.8 Hz), 158.4, 155.9 (d, *J* = 0.4 Hz), 137.0, 135.9 (d, *J* = 3.1 Hz), 128.8 (d, *J* = 8.3 Hz), 121.6 (d, *J* = 0.6 Hz), 117.3 (d, *J* = 0.7 Hz), 115.6 (d, *J* = 21.5 Hz), 24.7. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -113.61 (m). Spectral data are consistent with the reported literature.[390]



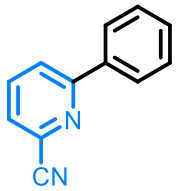
2-(Benzo[d][1,3]dioxol-5-yl)-6-methylpyridine (14b)

Following the general procedure 2, benzo[d][1,3]dioxol-5-ylboronic acid (50 mg, 0.30 mmol) and 6-methylpyridine-2-sulfonyl fluoride (35 mg, 0.20 mmol) afforded **14b** as a colorless oil (23 mg, 54%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.31 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 214.0868, found: 214.0862 (M+H). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (t, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.48 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.00 (s, 2H), 2.60 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 156.4, 148.2, 148.2, 136.9, 134.3, 121.2, 121.0, 117.0, 108.4, 107.5, 101.2, 24.8.



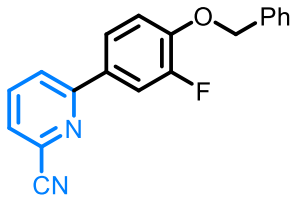
6-(4-Methoxyphenyl)picolinonitrile (15b)

Following the general **procedures B or C**, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 6-cyanopyridine-2-sulfonyl fluoride (37 mg, 0.20 mmol) afforded **15b** as a white solid (37 mg, 88 %, procedure B – 41 mg, 98 %, procedure C) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 2H), 7.87 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.82 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.54 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.02 – 6.96 (m, 2H), 3.87 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4, 158.6, 137.6, 133.6, 129.7, 128.5, 125.9, 122.7, 117.6, 114.4, 55.4. Spectral data are consistent with the reported literature.[391]



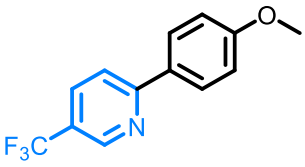
6-Phenylpicolinonitrile (16b)

Following the general **procedure B**, phenylboronic acid (37 mg, 0.30 mmol) and and 6-cyanopyridine-2-sulfonyl fluoride (37 mg, 0.20 mmol) afforded **16b** as a white solid (35 mg, 97%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 2H), 7.95 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.88 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.62 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.54 – 7.45 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.0, 137.8, 137.2, 133.8, 130.2, 129.0, 127.1, 126.6, 123.5, 117.5. Spectral data are consistent with the reported literature.[392]



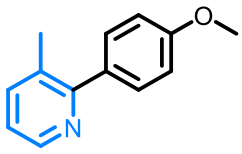
6-(4-(Benzyloxy)-3-fluorophenyl)picolinonitrile (17b)

Following the general **procedure B**, 4-benzyloxy-3-fluorophenylboronic acid (74 mg, 0.30 mmol) and and 6-cyanopyridine-2-sulfonyl fluoride (37 mg, 0.20 mmol) afforded **17b** as a white solid (57 mg, 94%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.27 (EA:Pet. Ether 2:8). **HRMS (ESI):** calculated: 327.0904, found: 327.0894 (M+Na). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 3H), 7.73 (ddd, *J* = 8.6, 2.3, 1.2 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.49 – 7.44 (m, 2H), 7.43 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 7.09 (t, *J* = 8.5 Hz, 1H), 5.22 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4 (d, *J* = 2.4 Hz), 153.0 (d, *J* = 246.9 Hz), 148.5 (d, *J* = 10.9 Hz), 137.8, 136.1, 133.8, 130.6 (d, *J* = 6.5 Hz), 128.7, 128.3, 127.4, 126.4, 123.0 (d, *J* = 3.4 Hz), 122.7, 117.4, 115.4 (d, *J* = 2.2 Hz), 115.0 (d, *J* = 20.2 Hz), 71.3. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -132.69 (dd, *J* = 12.3, 8.4 Hz).



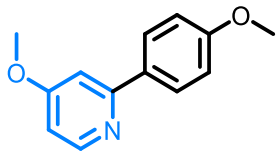
2-(4-Methoxyphenyl)-5-(trifluoromethyl)pyridine (18b)

Following the general **procedures B or C**, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 5-trifluoromethylypyridine-2-sulfonyl fluoride (37 mg, 0.20 mmol) afforded **18b** as a white solid (44mg, 87%, procedure B – 46 mg, 98 %, procedure C) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.89 (dt, *J* = 2.1, 1.0 Hz, 1H), 8.07 – 7.97 (m, 2H), 7.97 – 7.88 (m, 1H), 7.76 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.08 – 6.98 (m, 2H), 3.88 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.3, 160.3 (q, *J* = 1.5 Hz), 146.5 (q, *J* = 4.1 Hz), 133.8 (q, *J* = 3.5 Hz), 130.5 (d, *J* = 0.5 Hz), 125.0, 124.0 (q, *J* = 33.0 Hz), 123.9 (q, *J* = 272 Hz), 119.0, 114.3, 55.4. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.17. Spectral data are consistent with the reported literature.[393]



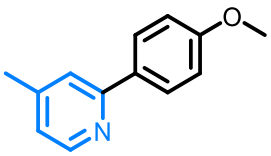
2-(4-Methoxyphenyl)-3-methylpyridine (19b)

Following the general **procedures B and C**, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 3-methylpyridine-2-sulfonyl fluoride (35 mg, 0.20 mmol) afforded **19b** as a yellow oil (22 mg, 55%, procedure B – 25 mg, 63 %, procedure C) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 3.7 Hz, 1H), 7.56 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.14 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.01 – 6.90 (m, 2H), 3.85 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.4, 158.3, 146.9, 138.6, 133.1, 130.7, 130.3, 121.7, 113.5, 55.3, 20.3. Spectral data are consistent with the reported literature.[394]



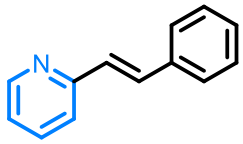
4-Methoxy-2-(4-methoxyphenyl)pyridine (20b)

Following the general **procedures B or C**, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 4-methoxypyridine-2-sulfonyl fluoride (38 mg, 0.20 mmol) afforded **20b** as a white solid (27mg, 63%, procedure B – 33 mg, 77 %, procedure C) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.7 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.71 (dd, *J* = 5.7, 2.4 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4, 160.5, 158.9, 150.8, 132.0, 128.2, 114.0, 107.6, 106.0, 55.4, 55.1. Spectral data are consistent with the reported literature.[395]



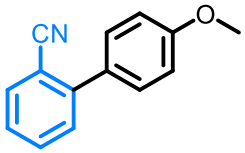
2-(4-Methoxyphenyl)-4-methylpyridine (21b)

Following the general **procedures B or C**, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 4-methylpyridine-2-sulfonyl fluoride (35 mg, 0.20 mmol) afforded **21b** as a white solid (32 mg, 80%, procedure B – 19 mg, 48 %, procedure C) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.48 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.02 – 6.95 (m, 3H), 3.85 (s, 3H), 2.39 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.4, 157.0, 149.3, 147.7, 132.1, 128.2, 122.5, 120.8, 114.1, 55.4, 21.3. Spectral data are consistent with the reported literature.[396]



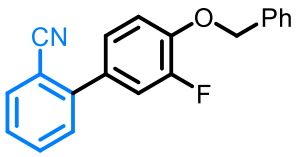
(E)-2-Styrylpyridine (22b)

Following the general **procedure A (6 h reaction time instead of 16 h)**, (E)-styrylboronic acid (44 mg, 0.30 mmol) and 2-(fluorosulfonyl)pyridine (32 mg, 0.20 mmol) afforded **22b** as a white solid (28 mg, 77%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 8:2 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (dt, *J* = 4.6, 1.5 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.63 – 7.55 (m, 3H), 7.38 (dd, *J* = 8.3, 6.7 Hz, 3H), 7.34 – 7.27 (m, 1H), 7.22 – 7.10 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 149.7, 136.7, 136.6, 132.7, 128.8, 128.4, 128.0, 127.1, 122.1, 122.1. Spectral data are consistent with the reported literature.[397]



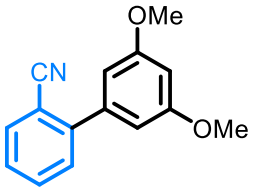
4'-Methoxy-[1,1'-biphenyl]-2-carbonitrile (23b)

Following the general **procedures B or C**, 4-methoxyphenylboronic acid (46 mg, 0.30 mmol) and 2-cyanobenzenesulfonyl fluoride (37 mg, 0.20 mmol) afforded **23b** as a white solid (31 mg, 74% procedure B – 26 mg, 62%, procedure C) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.61 (td, *J* = 7.7, 1.4 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.07 – 6.99 (m, 2H), 3.87 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.1, 145.2, 133.8, 132.8, 130.5, 130.0, 129.9, 127.1, 119.0, 114.2, 111.1, 55.4. Spectral data are consistent with the reported literature.[41]



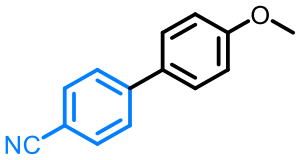
4'-(Benzyloxy)-3'-fluoro-[1,1'-biphenyl]-2-carbonitrile (24b)

Following the general **procedure C**, 4-benzyloxy-3-fluorophenylboronic acid (74 mg, 0.30 mmol) and 2-cyanobenzenesulfonyl fluoride (37 mg, 0.20 mmol) afforded **24b** as a white solid (31 mg, 55%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.40 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 326.0952, found: 326.0942 (M+Na). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H), 7.47 (ddd, *J* = 7.8, 4.2, 1.4 Hz, 3H), 7.41 (dd, *J* = 8.2, 6.6 Hz, 3H), 7.38 – 7.26 (m, 3H), 7.11 (t, *J* = 8.4 Hz, 1H), 5.21 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.6 (d, *J* = 247.6 Hz), 147.3 (d, *J* = 10.68 Hz), 144.0, 143.9, 136.3, 133.9, 132.9, 131.4 (d, *J* = 6.73 Hz), 128.7, 128.3, 127.6, 127.5, 124.8 (d, *J* = 3.63), 118.6, 116.8 (d, *J* = 19.62 Hz), 115.5 (d, *J* = 2.29 Hz), 111.1, 71.4. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -132.87 (dd, *J* = 11.6, 8.4 Hz).



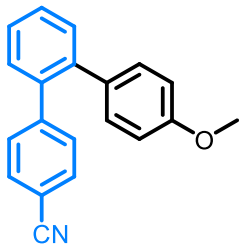
3',5'-Dimethoxy-[1,1'-biphenyl]-2-carbonitrile (25b)

Following the general **procedure C**, (3,5-dimethoxyphenyl)boronic acid (55 mg, 0.30 mmol) and 2-cyanobenzenesulfonyl fluoride (37 mg, 0.20 mmol) afforded **25b** as a white solid (22 mg, 46%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.41 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 240.1019, found: 240.1012 (M+H). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 2H), 6.54 (t, *J* = 2.3 Hz, 1H), 3.85 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.9, 145.4, 140.0, 133.8, 132.8, 129.9, 127.7, 118.6, 111.3, 107.0, 100.9, 55.5.



4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (26b)

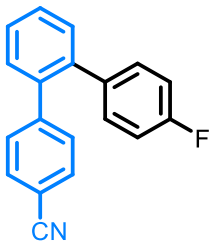
4-cyanobenzenesulfonyl fluoride (0.20 mmol), boronic acid (0.30 mmol), $Pd(acac)_2$ (5 mol%), RuPhos (20 mol%), $Co(acac)_3$ (2.5 mol%) and KHF_2 (50 mol%) were weighed into a microwave vial. The vial was sealed, evacuated, and backfilled with nitrogen 3 times. Then, 1.0 ml anhydrous dioxane was added via syringe. The solution was stirred and heated at 130 °C for 16 h. After the reaction was cooled to room temperature, the crude mixture was diluted with ethyl acetate, filtered through a bed of Celite and washed with ethyl acetate. Then, the solution was concentrated *in vacuo* and purified by column chromatography (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate) to afford **26b** as a white solid (28 mg, 68 % – 30 mg, 72 %, using 5 mol% PdG3RuPhos and 10 mol% RuPhos instead of 5 mol% $Pd(acac)_2$ and 20 mol% RuPhos). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (td, *J* = 7.7, 1.4 Hz, 1H), 7.55 – 7.46 (m, 3H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.04 – 7.00 (m, 2H), 3.86 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.1, 145.2, 133.8, 132.8, 130.5, 130.0, 129.9, 127.1, 114.2, 55.4. Spectral data are consistent with the reported literature.[398]



4''-Methoxy-[1,1':2',1''-terphenyl]-4-carbonitrile (27b)

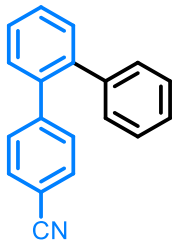
Following the general **procedure B**, 4-methoxyphenylboronic acid (49 mg, 0.30 mmol) and and 4'-cyano-[1,1'-biphenyl]-2-sulfonyl fluoride (52 mg, 0.20 mmol) afforded **27b** as a white solid (51 mg, 89%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.53 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 286.1226, found: 286.1217 (M+H). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.48 – 7.40 (m, 3H), 7.37

(dt, *J* = 6.6, 1.6 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.03 – 6.98 (m, 2H), 6.80 – 6.75 (m, 2H), 3.79 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 146.7, 140.3, 138.6, 132.9, 131.8, 130.9, 130.8, 130.6, 130.3, 128.6, 127.5, 119.0, 113.7, 110.2, 55.2.



4''-Fluoro-[1,1':2',1''-terphenyl]-4-carbonitrile (28b)

Following the general **procedure B**, 4-fluorophenylboronic acid (42 mg, 0.30 mmol) and and 4'-cyano-[1,1'-biphenyl]-2-sulfonyl fluoride (52 mg, 0.20 mmol) afforded **28b** as a white solid (23 mg, 42%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.61 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 296.0846, found: 296.0840 (M+Na). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.37 (m, 4H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.12 – 7.00 (m, 2H), 6.94 (t, *J* = 8.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 246.9 Hz), 146.3, 139.6, 138.7, 136.6 (d, *J* = 3.4 Hz), 131.9, 131.4 (d, *J* = 8.0 Hz), 130.8, 130.6, 130.4, 128.7, 128.0, 118.9, 115.2 (d, *J* = 21.4 Hz), 110.4. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -115.28.

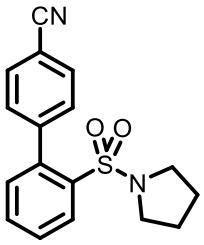


[1,1':2',1''-Terphenyl]-4-carbonitrile (29b)

Following the general **procedure B**, phenylboronic acid (37 mg, 0.30 mmol) and and 4'-cyano-[1,1'-biphenyl]-2-sulfonyl fluoride (52 mg, 0.20 mmol) afforded **29b** as a white solid (40 mg, 78%) after purification by automated flash column chromatography over silica (using a gradient from 10:0 to 9:1 of petroleum ether to ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 5H), 7.42 – 7.37 (m,

1H), 7.26 – 7.22 (m, 5H), 7.13 – 7.06 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5, 140.70, 140.65, 138.7, 131.7, 130.9, 130.6, 130.3, 129.8, 128.6, 128.2, 127.8, 127.0, 119.0, 110.3. Spectral data are consistent with the reported literature.[399]

5.3.5 Divergent Synthesis



2'-(Pyrrolidin-1-ylsulfonyl)-[1,1'-biphenyl]-4-carbonitrile (D1)

Prepared according to a modified literature procedure.[340] A vial was charged with 4'-cyano-[1,1'-biphenyl]-2-sulfonyl fluoride (65.3 mg, 0.25 mmol) and calcium bis(trifluoromethanesulfonimide) (165.1 mg, 0.275 mmol). Pyrrolidine (21.5 µL, 0.5 mmol) and *tert*-amyl alcohol (250 µL) were then added. The reaction was then heated to 90 °C for 4 h and afforded **D1** as white crystals (71 mg, 91%) after purification by automated flash column chromatography over silica using petroleum ether and ethyl acetate as eluents, R_f 0.20 (EA:Pet. Ether 2:8). **HRMS (ESI)**: calculated: 313.0995, found: 313.1005 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.32 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28 – 7.24 (m, 2H), 6.99 (dd, *J* = 7.6, 1.4 Hz, 1H), 2.63 – 2.55 (m, 4H), 1.44 – 1.37 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.7, 139.5, 138.0, 132.4, 132.2, 131.3, 130.3, 129.8, 128.6, 118.7, 111.6, 46.9, 25.6.

References

1. Miyaura, Norio. & Suzuki, Akira. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **95**, 2457–2483 (1995).
2. Suzuki, A. Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C□C Bonds (Nobel Lecture). *Angewandte Chemie International Edition* **50**, 6722–6737 (2011).
3. Miyaura, N. Cross-coupling reaction of organoboron compounds via base-assisted transmetalation to palladium(II) complexes. *Journal of Organometallic Chemistry* **653**, 54–57 (2002).
4. Yadav, M. R. *et al.* The Suzuki–Miyaura Coupling of Nitroarenes. *J. Am. Chem. Soc.* **139**, 9423–9426 (2017).
5. Chatelain, P., Sau, A., Rowley, C. N. & Moran, J. Suzuki–Miyaura Coupling of (Hetero)Aryl Sulfones: Complementary Reactivity Enables Iterative Polyaryl Synthesis. *Angewandte Chemie International Edition* **58**, 14959–14963 (2019).
6. Nambo, M., Keske, E. C., Rygus, J. P. G., Yim, J. C.-H. & Crudden, C. M. Development of Versatile Sulfone Electrophiles for Suzuki–Miyaura Cross-Coupling Reactions. *ACS Catal.* **7**, 1108–1112 (2017).
7. Clayden, J. & Julia, M. ortho-Substituted unsymmetrical biaryls from aryl tert-butyl sulfones. *J. Chem. Soc., Chem. Commun.* 1682–1683 (1993) doi:10.1039/C39930001682.
8. Nambo, M. & Crudden, C. M. Modular Synthesis of Triarylmethanes through Palladium-Catalyzed Sequential Arylation of Methyl Phenyl Sulfone. *Angewandte Chemie International Edition* **53**, 742–746 (2014).

9. Gong, L. *et al.* Ni-Catalyzed Suzuki–Miyaura Cross-Coupling of α-Oxo-vinylsulfones To Prepare C-Aryl Glycals and Acyclic Vinyl Ethers. *J. Am. Chem. Soc.* **141**, 7680–7686 (2019).

10. Ariki, Z. T., Maekawa, Y., Nambo, M. & Crudden, C. M. Preparation of Quaternary Centers via Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling of Tertiary Sulfones. *J. Am. Chem. Soc.* **140**, 78–81 (2018).

11. Hennessy, E. J. *et al.* Preparation of highly functionalized 1,5-disubstituted tetrazoles via palladium-catalyzed Suzuki coupling. *Tetrahedron Letters* **58**, 1709–1713 (2017).

12. Olah, G. A., Orlinkov, A., Oxyzoglou, A. B. & Prakash, G. K. S. Nitration of Strongly Deactivated Aromatics with Superacidic Mixed Nitric-Triflatoboric Acid (HNO3/2CF3SO3H-B(O3SCF3)3). *J. Org. Chem.* **60**, 7348–7350 (1995).

13. Sumii, Y., Taniguchi, M., Xu, X.-H., Tokunaga, E. & Shibata, N. Ortho-lithiation reaction of aryl triflones. *Tetrahedron* **74**, 5635–5641 (2018).

14. Okumura, S. & Nakao, Y. para-Selective Alkylation of Sulfonylarenes by Cooperative Nickel/Aluminum Catalysis. *Org. Lett.* **19**, 584–587 (2017).

15. Nambo, M. *et al.* Modular synthesis of α-fluorinated arylmethanes via desulfonylative cross-coupling. *Nature Communications* **10**, 4528 (2019).

16. Dong, J., Krasnova, L., Finn, M. G. & Sharpless, K. B. Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry. *Angewandte Chemie International Edition* **53**, 9430–9448 (2014).

17. Chinthakindi, P. K. & Arvidsson, P. I. Sulfonyl Fluorides (SFs): More Than Click Reagents? *European Journal of Organic Chemistry* **2018**, 3648–3666 (2018).

18. Varma, S. J., Muchowska, K. B., Chatelain, P. & Moran, J. Native iron reduces CO 2 to intermediates and end-products of the acetyl-CoA pathway. *Nature Ecology & Evolution* **2**, 1019–1024 (2018).

19. Fukuda, J., Nogi, K. & Yorimitsu, H. Cross-Coupling of Aryl Trifluoromethyl Sulfones with Arylboronates by Cooperative Palladium/Rhodium Catalysis. *Org. Lett.* **21**, 8987–8991 (2019).

20. Cheng, W., Zheng, Y., Feng, G., Grabow, J.-U. & Gou, Q. Conformation and bonding of 2-methoxypyridine and its monohydrate from rotational spectra. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **239**, 118434 (2020).

21. Fukuda, J., Nogi, K. & Yorimitsu, H. Cobalt-Catalyzed Reduction of Aryl Sulfones to Arenes by Means of Alkylmagnesium Reagents. *Asian Journal of Organic Chemistry* **7**, 2049–2052 (2018).

22. Wöhler, F. Ueber künstliche Bildung des Harnstoffs. *Annalen der Physik* **88**, 253–256 (1828).

23. Kolbe, H. Ueber Synthese der Salicylsäure. *Justus Liebigs Annalen der Chemie* **113**, 125–127 (1860).

24. Friedel, C. & Crafts, J. Sur une nouvelle méthode générale de synthèse d'hydrocarbures, d'acétones, etc. *C. R. Acad. Sci. Paris* **84**, 1392, 1450 (1877).

25. Wurtz, C.-A. Sur un aldéhyde-alcool. *Bull. Soc. Chim. Fr.* **17**, 436–442 (1872).

26. Borodin, A. V. von Richter, aus St. Petersburg am 17. October 1869. *Ber. Dtsch. Chem. Ges.* **2**, 552–553 (1869).

27. Grignard, V. Sur quelques nouvelles combinaisons organométaliques du magnésium et leur application à des synthèses d'alcools et d'hydrocabures. *C. R. Acad. Sci. Paris* **130**, 1322–25 (1900).

28. Fittig, R. Ueber einige Producte der trockenen Destillation essigsaurer Salze. *Justus Liebigs Annalen der Chemie* **110**, 17–23 (1859).

29. Mukaiyama, T. *et al.* Asymmetric Total Synthesis of Taxol\R. *Chemistry – A European Journal* **5**, 121–161 (1999).

30. Mukaiyama, T., Sato, T. & Hanna, J. Reductive coupling of carbonyl compounds to pinacols and olefins by using TiCl4 and Zn. *Chem. Lett.* **2**, 1041–1044 (1973).

31. McMurry, J. E. & Fleming, M. P. New method for the reductive coupling of carbonyls to olefins. Synthesis of .beta.-carotene. *J. Am. Chem. Soc.* **96**, 4708–4709 (1974).

32. McMurry, J. E. Carbonyl-coupling reactions using low-valent titanium. *Chem. Rev.* **89**, 1513–1524 (1989).

33. ter Wiel, M. K. J., van Delden, R. A., Meetsma, A. & Feringa, B. L. Increased Speed of Rotation for the Smallest Light-Driven Molecular Motor. *J. Am. Chem. Soc.* **125**, 15076–15086 (2003).

34. Glaser, C. Beiträge zur Kenntniss des Acetenylbenzols. *Berichte der deutschen chemischen Gesellschaft* **2**, 422–424 (1869).

35. Ullmann, F. & Bielecki, J. Ueber Synthesen in der Biphenylreihe. *Berichte der deutschen chemischen Gesellschaft* **34**, 2174–2185 (1901).

36. Chodkiewicz, W. & Codiot, P. Nouvelle synthèse de composé polyacétyléniques conjugués symmétriques et dissymétriques. *C. R. Acad. Sci. Paris* 1055 (1955).

37. Johansson Seechurn, C. C. C., Kitching, M. O., Colacot, T. J. & Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the

2010 Nobel Prize. *Angewandte Chemie International Edition* **51**, 5062–5085 (2012).

38. Kharasch, M. S. & Fields, E. K. Factors Determining the Course and Mechanisms of Grignard Reactions. IV. The Effect of Metallic Halides on the Reaction of Aryl Grignard Reagents and Organic Halides1. *J. Am. Chem. Soc.* **63**, 2316–2320 (1941).

39. Tamao, K., Sumitani, K. & Kumada, M. Selective carbon-carbon bond formation by cross-coupling of Grignard reagents with organic halides. Catalysis by nickel-phosphine complexes. *J. Am. Chem. Soc.* **94**, 4374–4376 (1972).

40. Corriu, R. J. P. & Masse, J. P. Activation of Grignard reagents by transition-metal complexes. A new and simple synthesis of trans-stilbenes and polyphenyls. *J. Chem. Soc., Chem. Commun.* 144a–144a (1972) doi:10.1039/C3972000144A.

41. Piller, F. M., Appukkuttan, P., Gavryushin, A., Helm, M. & Knochel, P. Convenient Preparation of Polyfunctional Aryl Magnesium Reagents by a Direct Magnesium Insertion in the Presence of LiCl. *Angewandte Chemie International Edition* **47**, 6802–6806 (2008).

42. Knappke, C. E. I. & Wangelin, A. J. von. 35 years of palladium-catalyzed cross-coupling with Grignard reagents: how far have we come? *Chem. Soc. Rev.* **40**, 4948–4962 (2011).

43. Adrio, J. & Carretero, J. C. Functionalized Grignard Reagents in Kumada Cross-Coupling Reactions. *ChemCatChem* **2**, 1384–1386 (2010).

44. Heravi, M. M., Zadsirjan, V., Hajiabbasi, P. & Hamidi, H. Advances in Kumada–Tamao–Corriu cross-coupling reaction: an update. *Monatsh Chem* **150**, 535–591 (2019).

45. Bhattacharjya, A., Klumphu, P. & Lipshutz, B. H. Kumada–Grignard-type biaryl couplings on water. *Nature Communications* **6**, 7401 (2015).

46. Beletskaya, I. P. & Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **100**, 3009–3066 (2000).

47. Mizoroki, T., Mori, K. & Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *BCSJ* **44**, 581–581 (1971).

48. Heck, R. F. & Nolley, J. P. Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.* **37**, 2320–2322 (1972).

49. Moritani, I. & Fujiwara, Y. Aromatic substitution of styrene-palladium chloride complex. *Tetrahedron Letters* **8**, 1119–1122 (1967).

50. Fujiwara, Y., Moritani, I., Danno, S., Asano, R. & Teranishi, S. Aromatic substitution of olefins. VI. Arylation of olefins with palladium(II) acetate. *J. Am. Chem. Soc.* **91**, 7166–7169 (1969).

51. Dounay, A. B. & Overman, L. E. The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* **103**, 2945–2964 (2003).

52. Dumrath, A., Lübbe, C. & Beller, M. Palladium-Catalyzed Cross-Coupling Reactions – Industrial Applications. *Palladium-Catalyzed Coupling Reactions* 445–489 (2013) doi:10.1002/9783527648283.ch12.

53. Torborg, C. & Beller, M. Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries. *Advanced Synthesis & Catalysis* **351**, 3027–3043 (2009).

54. Cassar, L. Synthesis of aryl- and vinyl-substituted acetylene derivatives by the use of nickel and palladium complexes. *Journal of Organometallic Chemistry* **93**, 253–257 (1975).

55. Dieck, H. A. & Heck, R. F. Palladium catalyzed synthesis of aryl, heterocyclic and vinylic acetylene derivatives. *Journal of Organometallic Chemistry* **93**, 259–263 (1975).

56. Sonogashira, K. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Letters* **16**, 4467–4470 (1975).

57. Chinchilla, R. & Nájera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **107**, 874–922 (2007).

58. Chinchilla, R. & Nájera, C. Recent advances in Sonogashira reactions. *Chem. Soc. Rev.* **40**, 5084–5121 (2011).

59. Thomas, A. M., Sujatha, A. & Anilkumar, G. Recent advances and perspectives in copper-catalyzed Sonogashira coupling reactions. *RSC Adv.* **4**, 21688–21698 (2014).

60. Negishi, E., King, A. O. & Okukado, N. Selective carbon-carbon bond formation via transition metal catalysis. 3. A highly selective synthesis of unsymmetrical biaryls and diarylmethanes by the nickel- or palladium-catalyzed reaction of aryl- and benzylzinc derivatives with aryl halides. *J. Org. Chem.* **42**, 1821–1823 (1977).

61. King, A. O., Okukado, N. & Negishi, E. Highly general stereo-, regio-, and chemo-selective synthesis of terminal and internal conjugated enynes by the Pd-catalysed reaction of alkynylzinc reagents with alkenyl halides. *J. Chem. Soc., Chem. Commun.* 683–684 (1977) doi:10.1039/C39770000683.

62. Zeng, F. & Negishi, E. A Novel, Selective, and Efficient Route to Carotenoids and Related Natural Products via Zr-Catalyzed Carboalumination and Pd- and Zn-Catalyzed Cross Coupling. *Org. Lett.* **3**, 719–722 (2001).

63. Nicolaou, K. C., Bulger, P. G. & Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angewandte Chemie International Edition* **44**, 4442–4489 (2005).

64. Heravi, M. M., Hashemi, E. & Nazari, N. Negishi coupling: an easy progress for C–C bond construction in total synthesis. *Mol Divers* **18**, 441–472 (2014).

65. Manley, P. W., Acemoglu, M., Marterer, W. & Pachinger, W. Large-Scale Negishi Coupling as Applied to the Synthesis of PDE472, an Inhibitor of Phosphodiesterase Type 4D. *Org. Process Res. Dev.* **7**, 436–445 (2003).

66. Negishi, E. Palladium- or nickel-catalyzed cross coupling. A new selective method for carbon-carbon bond formation. *Acc. Chem. Res.* **15**, 340–348 (1982).

67. Azarian, D., Dua, S. S., Eaborn, C. & Walton, D. R. M. Reactions of organic halides with R3 MMR3 compounds (M = Si, Ge, Sn) in the presence of tetrakis(triarylphosphine)palladium Davoud Azarian, Sujan S. Dua ,Colin Eaborn David R.M.Walton. *Journal of Organometallic Chemistry* **117**, C55–C57 (1976).

68. Kosugi, M., Shimizu, Y. & Migita, T. Alkylation, arylation, and vinylation of acyl chlorides by means of organotin compounds in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(o). *Chem. Lett.* **6**, 1423–1424 (1977).

69. Kosugi, M., Sasazawa, K., Shimizu, Y. & Migita, T. Reactions of allyltin compounds iii. allylation of aromatic halides with allyltributyltin in the presence of tetrakis(triphenylphosphine)palladium(o). *Chem. Lett.* **6**, 301–302 (1977).

70. Kosugi, M., Shimizu, Y. & Migita, T. Reaction of allyltin compounds : II. Facile preparation of allyl ketones via allyltins. *Journal of Organometallic Chemistry* **129**, C36–C38 (1977).

71. Milstein, D. & Stille, J. K. A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *J. Am. Chem. Soc.* **100**, 3636–3638 (1978).

72. Milstein, D. & Stille, J. K. Palladium-catalyzed coupling of tetraorganotin compounds with aryl and benzyl halides. Synthetic utility and mechanism. *J. Am. Chem. Soc.* **101**, 4992–4998 (1979).

73. Milstein, D. & Stille, J. K. Mild, selective, general method of ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *J. Org. Chem.* **44**, 1613–1618 (1979).

74. Cordovilla, C., Bartolomé, C., Martínez-Ilarduya, J. M. & Espinet, P. The Stille Reaction, 38 Years Later. *ACS Catal.* **5**, 3040–3053 (2015).

75. Heravi, M. M. & Mohammadkhani, L. Recent applications of Stille reaction in total synthesis of natural products: An update. *Journal of Organometallic Chemistry* **869**, 106–200 (2018).

76. Ragan, J. A. *et al.* Cross-Coupling Methods for the Large-Scale Preparation of an Imidazole−Thienopyridine: Synthesis of [2-(3-Methyl-3H-imidazol-4-yl)-thieno[3,2-b]pyridin-7-yl]-(2-methyl-1H-indol-5-yl)-amine. *Org. Process Res. Dev.* **7**, 676–683 (2003).

77. Miyaura, N., Yamada, K. & Suzuki, A. A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Letters* **20**, 3437–3440 (1979).

78. Miyaura, N. & Suzuki, A. Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst. *J. Chem. Soc., Chem. Commun.* 866–867 (1979) doi:10.1039/C39790000866.

79. Miyaura, N., Yano, T. & Suzuki, A. The palladium-catalyzed cross-coupling reaction of 1-alkenylboranes with allylic or benzylic bromides. Convenient syntheses of 1,4-alkadienes and allybenzenes from alkynes via hydroboration. *Tetrahedron Letters* **21**, 2865–2868 (1980).

80. Miyaura, N., Yanagi, T. & Suzuki, A. The Palladium-Catalyzed Cross-Coupling Reaction of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth. Commun.* **11**, 513–519 (1981).

81. Brown, D. G. & Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **59**, 4443–4458 (2016).

82. Lennox, A. J. J. & Lloyd-Jones, G. C. Selection of boron reagents for Suzuki–Miyaura coupling. *Chem. Soc. Rev.* **43**, 412–443 (2013).

83. Boronic Acids - Boronic Acids and Derivatives. *Sigma-Aldrich* https://www.sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16256939.

84. Miyaura, N. *et al.* Palladium-catalyzed inter- and intramolecular cross-coupling reactions of B-alkyl-9-borabicyclo[3.3.1]nonane derivatives with 1-halo-1-alkenes or haloarenes. Syntheses of functionalized alkenes, arenes, and cycloalkenes via a hydroboration-coupling sequence. *J. Am. Chem. Soc.* **111**, 314–321 (1989).

85. Chemler, S. R., Trauner, D. & Danishefsky, S. J. The B-Alkyl Suzuki–Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis. *Angewandte Chemie International Edition* **40**, 4544–4568 (2001).

86. Netherton, M. R., Dai, C., Neuschütz, K. & Fu, G. C. Room-Temperature Alkyl−Alkyl Suzuki Cross-Coupling of Alkyl Bromides that Possess β Hydrogens. *J. Am. Chem. Soc.* **123**, 10099–10100 (2001).

87. Martin, R. & Buchwald, S. L. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **41**, 1461–1473 (2008).

88. Conlon, D. A. *et al.* Process Development and Large-Scale Synthesis of a PDE4 Inhibitor. *Org. Process Res. Dev.* **10**, 36–45 (2006).

89. Ashworth, I. W. *et al.* Process Development of a Suzuki Reaction Used in the Manufacture of Lanabecestat. *Org. Process Res. Dev.* **22**, 1801–1808 (2018).

90. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **509**, 299–309 (2014).

91. Hu, X. Nickel-catalyzed cross coupling of non-activated alkyl halides: a mechanistic perspective. *Chem. Sci.* **2**, 1867–1886 (2011).

92. Han, F.-S. Transition-metal-catalyzed Suzuki–Miyaura cross-coupling reactions: a remarkable advance from palladium to nickel catalysts. *Chem. Soc. Rev.* **42**, 5270–5298 (2013).

93. Thapa, S., Shrestha, B., Gurung, S. K. & Giri, R. Copper-catalysed cross-coupling: an untapped potential. *Org. Biomol. Chem.* **13**, 4816–4827 (2015).

94. Ludwig, J. R., Simmons, E. M., Wisniewski, S. R. & Chirik, P. J. Cobalt-Catalyzed C(sp2)–C(sp3) Suzuki–Miyaura Cross Coupling. *Org. Lett.* (2020) doi:10.1021/acs.orglett.0c02934.

95. Neely, J. M., Bezdek, M. J. & Chirik, P. J. Insight into Transmetalation Enables Cobalt-Catalyzed Suzuki–Miyaura Cross Coupling. *ACS Cent. Sci.* **2**, 935–942 (2016).

96. Asghar, S., Tailor, S. B., Elorriaga, D. & Bedford, R. B. Cobalt-Catalyzed Suzuki Biaryl Coupling of Aryl Halides. *Angewandte Chemie International Edition* **56**, 16367–16370 (2017).

97. Crockett, M. P., Tyrol, C. C., Wong, A. S., Li, B. & Byers, J. A. Iron-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions between Alkyl Halides and Unactivated Arylboronic Esters. *Org. Lett.* **20**, 5233–5237 (2018).

98. Hatakeyama, T. *et al.* Iron-Catalyzed Suzuki−Miyaura Coupling of Alkyl Halides. *J. Am. Chem. Soc.* **132**, 10674–10676 (2010).

99. Wu, G. & Jacobi von Wangelin, A. Iron-catalysed Suzuki biaryl couplings. *Nature Catalysis* **1**, 377–378 (2018).

100. Cox, P. A. *et al.* Base-Catalyzed Aryl-B(OH)2 Protodeboronation Revisited: From Concerted Proton Transfer to Liberation of a Transient Aryl Anion. *J. Am. Chem. Soc.* **139**, 13156–13165 (2017).

101. Cox, P. A., Leach, A. G., Campbell, A. D. & Lloyd-Jones, G. C. Protodeboronation of Heteroaromatic, Vinyl, and Cyclopropyl Boronic Acids: pH–Rate Profiles, Autocatalysis, and Disproportionation. *J. Am. Chem. Soc.* **138**, 9145–9157 (2016).

102. Kuivila, H. G., Reuwer Jr., J. F. & Mangravite, J. A. Electrophilic displacement reactions: XV. Kinetics and mechanism of the base-catalyzed protodeboronation of areneboronic acids. *Canadian Journal of Chemistry* **41**, 3081–3090 (1963).

103. Thomas, A. A., Zahrt, A. F., Delaney, C. P. & Denmark, S. E. Elucidating the Role of the Boronic Esters in the Suzuki–Miyaura Reaction: Structural, Kinetic, and Computational Investigations. *Journal of the American Chemical Society* **140**, 4401–4416 (2018).

104. Suzuki, A. Recent advances in the cross-coupling reactions of organoboron derivatives with organic electrophiles, 1995–1998. *Journal of Organometallic Chemistry* **576**, 147–168 (1999).

105. Smith, G. B., Dezeny, G. C., Hughes, D. L., King, A. O. & Verhoeven, T. R. Mechanistic Studies of the Suzuki Cross-Coupling Reaction. *J. Org. Chem.* **59**, 8151–8156 (1994).

106. Braga, A. A. C., Morgon, N. H., Ujaque, G. & Maseras, F. Computational Characterization of the Role of the Base in the Suzuki−Miyaura Cross-Coupling Reaction. *J. Am. Chem. Soc.* **127**, 9298–9307 (2005).

107. Amatore, C., Le Duc, G. & Jutand, A. Mechanism of Palladium-Catalyzed Suzuki–Miyaura Reactions: Multiple and Antagonistic Roles of Anionic "Bases" and Their Countercations. *Chemistry – A European Journal* **19**, 10082–10093 (2013).

108. Busch, M., Wodrich, M. D. & Corminboeuf, C. A Generalized Picture of C–C Cross-Coupling. *ACS Catal.* **7**, 5643–5653 (2017).

109. Schmidt, A. F., Kurokhtina, A. A., Larina, E. V., Vidyaeva, E. V. & Lagoda, N. A. Is oxidative addition indeed the rate-determining step of the Suzuki–Miyaura reaction with less-reactive aryl chlorides under "ligand-free" conditions? *Journal of Organometallic Chemistry* **929**, 121571 (2020).

110. Christmann, U. & Vilar, R. Monoligated Palladium Species as Catalysts in Cross-Coupling Reactions. *Angewandte Chemie International Edition* **44**, 366–374 (2005).

111. Wei, C. S. *et al.* The Impact of Palladium(II) Reduction Pathways on the Structure and Activity of Palladium(0) Catalysts. *Angewandte Chemie International Edition* **52**, 5822–5826 (2013).

112. Amatore, C., Jutand, A. & Khalil, F. Neutral palladium(0) complexes from Pd(OAc)2 and tri-2-furylphosphine and their reactivity in oxidative addition of phenyl iodide. *Arkivoc* **2006**, 38–48 (2006).

113. Amatore, C., Jutand, A. & Suarez, A. Intimate mechanism of oxidative addition to zerovalent palladium complexes in the presence of halide ions and its relevance to the mechanism of palladium-catalyzed nucleophilic substitutions. *J. Am. Chem. Soc.* **115**, 9531–9541 (1993).

114. Johansson Seechurn, C. C. C., Sperger, T., Scrase, T. G., Schoenebeck, F. & Colacot, T. J. Understanding the Unusual Reduction Mechanism of Pd(II) to Pd(I): Uncovering Hidden Species and Implications in Catalytic Cross-Coupling Reactions. *J. Am. Chem. Soc.* **139**, 5194–5200 (2017).

115. Agrawal, D., Schröder, D. & Frech, C. M. Observation of Binuclear Palladium Clusters upon ESI-MS Monitoring of the Suzuki–Miyaura Cross-Coupling Catalyzed by a Dichloro-bis(aminophosphine) Complex of Palladium. *Organometallics* **30**, 3579–3587 (2011).

116. Amatore, C. & Pfluger, F. Mechanism of oxidative addition of palladium(0) with aromatic iodides in toluene, monitored at ultramicroelectrodes. *Organometallics* **9**, 2276–2282 (1990).

117. Barrios-Landeros, F. & Hartwig, J. F. Distinct Mechanisms for the Oxidative Addition of Chloro-, Bromo-, and Iodoarenes to a Bisphosphine Palladium(0) Complex with Hindered Ligands. *J. Am. Chem. Soc.* **127**, 6944–6945 (2005).

118. Gooßen, L. J., Koley, D., Hermann, H. & Thiel, W. The mechanism of the oxidative addition of aryl halides to Pd-catalysts: a DFT investigation. *Chem. Commun.* 2141–2143 (2004) doi:10.1039/B409144B.

119. Senn, H. M. & Ziegler, T. Oxidative Addition of Aryl Halides to Palladium(0) Complexes: A Density-Functional Study Including Solvation. *Organometallics* **23**, 2980–2988 (2004).

120. Kim, Y. M. & Yu, S. Palladium(0)-Catalyzed Amination, Stille Coupling, and Suzuki Coupling of Electron-Deficient Aryl Fluorides. *J. Am. Chem. Soc.* **125**, 1696–1697 (2003).

121. Proutiere, F., Aufiero, M. & Schoenebeck, F. Reactivity and Stability of Dinuclear Pd(I) Complexes: Studies on the Active Catalytic Species, Insights into Precatalyst Activation and Deactivation, and Application in Highly Selective Cross-Coupling Reactions. *J. Am. Chem. Soc.* **134**, 606–612 (2012).

122. García-Melchor, M., Braga, A. A. C., Lledós, A., Ujaque, G. & Maseras, F. Computational Perspective on Pd-Catalyzed C–C Cross-Coupling Reaction Mechanisms. *Acc. Chem. Res.* **46**, 2626–2634 (2013).

123. Proutiere, F. & Schoenebeck, F. Solvent Effect on Palladium-Catalyzed Cross-Coupling Reactions and Implications on the Active Catalytic Species. *Angewandte Chemie International Edition* **50**, 8192–8195 (2011).

124. Schoenebeck, F. & Houk, K. N. Ligand-Controlled Regioselectivity in Palladium-Catalyzed Cross Coupling Reactions. *J. Am. Chem. Soc.* **132**, 2496–2497 (2010).

125. Lyngvi, E. & Schoenebeck, F. Oxidative addition transition states of Pd(0) complexes in polar solvent—a DFT study involving implicit and explicit solvation. *Tetrahedron* **69**, 5715–5718 (2013).

126. Kozuch, S., Amatore, C., Jutand, A. & Shaik, S. What Makes for a Good Catalytic Cycle? A Theoretical Study of the Role of an Anionic Palladium(0)

Complex in the Cross-Coupling of an Aryl Halide with an Anionic Nucleophile. *Organometallics* **24**, 2319–2330 (2005).

127. Barder, T. E., Walker, S. D., Martinelli, J. R. & Buchwald, S. L. Catalysts for Suzuki−Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **127**, 4685–4696 (2005).

128. Mollar, C., Besora, M., Maseras, F., Asensio, G. & Medio-Simón, M. Competitive and Selective Csp3□Br versus Csp2□Br Bond Activation in Palladium-Catalysed Suzuki Cross-Coupling: An Experimental and Theoretical Study of the Role of Phosphine Ligands. *Chemistry – A European Journal* **16**, 13390–13397 (2010).

129. Littke, A. F., Dai, C. & Fu, G. C. Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *J. Am. Chem. Soc.* **122**, 4020–4028 (2000).

130. Perego, L. A., Payard, P.-A., Haddou, B., Ciofini, I. & Grimaud, L. Evidence for a Cooperative Mechanism Involving Two Palladium(0) Centers in the Oxidative Addition of Iodoarenes. *Chemistry – A European Journal* **24**, 2192–2199 (2018).

131. Bahmanyar, S., Borer, B. C., Kim, Y. M., Kurtz, D. M. & Yu, S. Proximity Effects in the Palladium-Catalyzed Substitution of Aryl Fluorides. *Org. Lett.* **7**, 1011–1014 (2005).

132. Braga, A. A. C., Morgon, N. H., Ujaque, G., Lledós, A. & Maseras, F. Computational study of the transmetalation process in the Suzuki–Miyaura cross-coupling of aryls. *Journal of Organometallic Chemistry* **691**, 4459–4466 (2006).

133. Carrow, B. P. & Hartwig, J. F. Distinguishing Between Pathways for Transmetalation in Suzuki−Miyaura Reactions. *J. Am. Chem. Soc.* **133**, 2116–2119 (2011).

134. Schmidt, A. F., Kurokhtina, A. A. & Larina, E. V. Role of a base in Suzuki-Miyaura reaction. *Russ J Gen Chem* **81**, 1573 (2011).

135. Amatore, C., Jutand, A. & Le Duc, G. Kinetic Data for the Transmetalation/Reductive Elimination in Palladium-Catalyzed Suzuki–Miyaura Reactions: Unexpected Triple Role of Hydroxide Ions Used as Base. *Chemistry – A European Journal* **17**, 2492–2503 (2011).

136. Amatore, C., Jutand, A. & Le Duc, G. Mechanistic Origin of Antagonist Effects of Usual Anionic Bases (OH−, CO32−) as Modulated by their Countercations (Na+, Cs+, K+) in Palladium-Catalyzed Suzuki–Miyaura Reactions. *Chemistry – A European Journal* **18**, 6616–6625 (2012).

137. Fuentes-Rivera, J. J., Zick, M. E., Düfert, M. A. & Milner, P. J. Overcoming Halide Inhibition of Suzuki–Miyaura Couplings with Biaryl Monophosphine-Based Catalysts. *Org. Process Res. Dev.* **23**, 1631–1637 (2019).

138. Molloy, J. J. *et al.* Interrogating Pd(II) Anion Metathesis Using a Bifunctional Chemical Probe: A Transmetalation Switch. *J. Am. Chem. Soc.* **140**, 126–130 (2018).

139. Grimaud, L. & Jutand, A. Role of Fluoride Ions in Palladium-Catalyzed Cross-Coupling Reactions-. *Synthesis* **49**, 1182–1189 (2017).

140. Düfert, M. A., Billingsley, K. L. & Buchwald, S. L. Suzuki-Miyaura Cross-Coupling of Unprotected, Nitrogen-Rich Heterocycles: Substrate Scope and Mechanistic Investigation. *J. Am. Chem. Soc.* **135**, 12877–12885 (2013).

141. Uenishi, J., Beau, J. M., Armstrong, R. W. & Kishi, Y. Dramatic rate enhancement of Suzuki diene synthesis. Its application to palytoxin synthesis. *J. Am. Chem. Soc.* **109**, 4756–4758 (1987).

142. Thomas, A. A. & Denmark, S. E. Pre-transmetalation intermediates in the Suzuki-Miyaura reaction revealed: The missing link. *Science* **352**, 329–332 (2016).

143. Thomas, A. A., Wang, H., Zahrt, A. F. & Denmark, S. E. Structural, Kinetic, and Computational Characterization of the Elusive Arylpalladium(II)boronate Complexes in the Suzuki–Miyaura Reaction. *J. Am. Chem. Soc.* **139**, 3805–3821 (2017).

144. Ortuño, M. A., Lledós, A., Maseras, F. & Ujaque, G. The Transmetalation Process in Suzuki–Miyaura Reactions: Calculations Indicate Lower Barrier via Boronate Intermediate. *ChemCatChem* **6**, 3132–3138 (2014).

145. Yunker, L. P. E. *et al.* Real-Time Mass Spectrometric Investigations into the Mechanism of the Suzuki–Miyaura Reaction. *Organometallics* **37**, 4297–4308 (2018).

146. Darses, S., Genêt, J.-P., Brayer, J.-L. & Demoute, J.-P. Cross-coupling reactions of arenediazonium tetrafluoroborates with potassium aryl- or alkenyltrifluoroborates catalyzed by palladium. *Tetrahedron Letters* **38**, 4393–4396 (1997).

147. Darses, S., Jeffery, T., Genet, J.-P., Brayer, J.-L. & Demoute, J.-P. Cross-coupling of arenediazonium tetrafluoroborates with arylboronic acids catalysed by palladium. *Tetrahedron Letters* **37**, 3857–3860 (1996).

148. Chen, L., Sanchez, D. R., Zhang, B. & Carrow, B. P. "Cationic" Suzuki–Miyaura Coupling with Acutely Base-Sensitive Boronic Acids. *J. Am. Chem. Soc.* **139**, 12418–12421 (2017).

149. Bonin, H., Fouquet, E. & Felpin, F.-X. Aryl Diazonium versus Iodonium Salts: Preparation, Applications and Mechanisms for the Suzuki–Miyaura Cross-Coupling Reaction. *Advanced Synthesis & Catalysis* **353**, 3063–3084 (2011).

150. Kang, S.-K., Lee, H.-W., Jang, S.-B. & Ho, P.-S. Palladium-Catalyzed Cross-Coupling of Organoboron Compounds with Iodonium Salts and Iodanes. *J. Org. Chem.* **61**, 4720–4724 (1996).

151. Kang, S.-K., Yamaguchi, T., Kim, T.-H. & Ho, P.-S. Copper-Catalyzed Cross-Coupling and Carbonylative Cross-Coupling of Organostannanes and Organoboranes with Hypervalent Iodine Compounds. *J. Org. Chem.* **61**, 9082–9083 (1996).

152. Xia, M. & Chen, Z.-C. Hypervalent Iodine in Synthesis XXXIII: Palladium-Catalyzed Cross-Coupling Reaction of Potassium Aryltrifluoroborates with Diaryliodonium Salts and Hydroxy(tosyloxy)iodobenzene. *Synthetic Communications* **29**, 2457–2465 (1999).

153. Yan, J., Hu, W. & Rao, G. A Novel and Efficient Coupling Reaction of Sodium Tetraphenylborate with Hypervalent Iodonium Salts. *Synthesis* **2006**, 943–945 (2006).

154. Yan, J., Zhu, M. & Zhou, Z. Rapid Microwave-Promoted Catalyst- and Base-Free Suzuki-Type Coupling Reaction in Water. *European Journal of Organic Chemistry* **2006**, 2060–2062 (2006).

155. Gomberg, M. & Bachmann, W. E. The synthesis of biaryl compounds by means of the diazo reaction. *J. Am. Chem. Soc.* **46**, 2339–2343 (1924).

156. Felpin, F.-X. & Sengupta, S. Biaryl synthesis with arenediazonium salts: cross-coupling, CH-arylation and annulation reactions. *Chem. Soc. Rev.* **48**, 1150–1193 (2019).

157. Yan, J., Zhou, Z. & Zhu, M. Rapid Microwave-Promoted Base-Free Suzuki Coupling Reaction of Sodium Tetraphenylborate with Hypervalent Iodonium Compounds in Water. *Synthetic Communications* **36**, 1495–1502 (2006).

158. Zhang, C. *et al.* Base-free Suzuki-Miyaura Coupling of (Z)-Trifluoromethyl Alkenyltriflates: An Efficient Approach to α-Trifluoromethyl Arylenes. *ChemistrySelect* **5**, 13099–13102 (2020).

159. Ohashi, M., Saijo, H., Shibata, M. & Ogoshi, S. Palladium-Catalyzed Base-Free Suzuki–Miyaura Coupling Reactions of Fluorinated Alkenes and Arenes via a Palladium Fluoride Key Intermediate. *European Journal of Organic Chemistry* **2013**, 443–447 (2013).

160. Malapit, C. A., Bour, J. R., Brigham, C. E. & Sanford, M. S. Base-free nickel-catalysed decarbonylative Suzuki–Miyaura coupling of acid fluorides. *Nature* **563**, 100–104 (2018).

161. Zhang, C. *et al.* Density Functional Theory Mechanistic Insight into the Base-Free Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling of Acid Fluoride: Concerted versus Stepwise Transmetalation. *J. Org. Chem.* **84**, 13983–13991 (2019).

162. Lu, X.-Y. *et al.* Base-free Ni-catalyzed Suzuki-type cross-coupling reactions of epoxides with boronic acids. *Chem. Commun.* **56**, 109–112 (2019).

163. Reina, A. *et al.* Development and Mechanistic Investigations of a Base-Free Suzuki–Miyaura Cross-Coupling of α,α-Difluoroacetamides via C–N Bond Cleavage. *ACS Catal.* **10**, 2189–2197 (2020).

164. Yasuike, S., Qin, W., Sugawara, Y. & Kurita, J. Suzuki-type cross-coupling reaction of pentavalent triarylantimony diacetates with arylboronic acids without a base. *Tetrahedron Letters* **48**, 721–724 (2007).

165. Qin, W. *et al.* Triarylantimony dicarboxylates as pseudo-halides for palladium-catalyzed cross-coupling reaction with arylboronic acids and triarylbismuthanes without any base. *Journal of Organometallic Chemistry* **693**, 109–116 (2008).

166. Emmanuvel, L. & Sudalai, A. Phosphine ligand and base-free, Pd- catalyzed oxidative cross-coupling reaction of arylboronic acids with arylmercuric acetates. *Arkivoc* **2007**, 126–133 (2007).

167. Legros, J.-Y. & Fiaud, J.-C. Palladium-catalyzed phenylation of allylic acetates by tetraphenylborate anion. *Tetrahedron Letters* **31**, 7453–7456 (1990).

168. Ciattini, P. G., Morera, E. & Ortar, G. Palladium-catalyzed cross-coupling reactions of vinyl and aryl triflates with tetraarylborates. *Tetrahedron Letters* **33**, 4815–4818 (1992).

169. Vasu, D., Yorimitsu, H. & Osuka, A. Base-Free Palladium-Catalyzed Cross-Coupling of Arylsulfonium Salts with Sodium Tetraarylborates. *Synthesis* **47**, 3286–3291 (2015).

170. Ostrowska, S., Lorkowski, J., Kubicki, M. & Pietraszuk, C. [Pd(μ-OH)Cl(IPr)2]—A Highly Efficient Precatalyst for Suzuki–Miyaura Coupling also Able To Act under Base-Free Conditions. *ChemCatChem* **8**, 3580–3583 (2016).

171. Hartwig, J. F. *Organotransition metal chemistry: from bonding to catalysis*. (2010).

172. Hartwig, J. F. Electronic Effects on Reductive Elimination To Form Carbon−Carbon and Carbon−Heteroatom Bonds from Palladium(II) Complexes. *Inorg. Chem.* **46**, 1936–1947 (2007).

173. Pérez-Rodríguez, M. *et al.* C−C Reductive Elimination in Palladium Complexes, and the Role of Coupling Additives. A DFT Study Supported by Experiment. *J. Am. Chem. Soc.* **131**, 3650–3657 (2009).

174. Lanci, M. P., Remy, M. S., Kaminsky, W., Mayer, J. M. & Sanford, M. S. Oxidatively Induced Reductive Elimination from (tBu2bpy)Pd(Me)2:

Palladium(IV) Intermediates in a One-Electron Oxidation Reaction. *J. Am. Chem. Soc.* **131**, 15618–15620 (2009).

175. Rudenko, A. E. *et al.* Ligand-Induced Reductive Elimination of Ethane from Azopyridine Palladium Dimethyl Complexes. *J. Am. Chem. Soc.* **140**, 11408–11415 (2018).

176. Gensch, T., Thoran, R., Richter, N. & Knölker, H.-J. Reductive Eliminations from Diarylpalladium(II) Complexes: A Combined Experimental and Computational Investigation. *Chemistry – A European Journal* **23**, 15116–15123 (2017).

177. Roy, D. & Uozumi, Y. Recent Advances in Palladium-Catalyzed Cross-Coupling Reactions at ppm to ppb Molar Catalyst Loadings. *Advanced Synthesis & Catalysis* **360**, 602–625 (2018).

178. Franzén, R. The Suzuki, the Heck, and the Stille reaction - three versatile methods for the introduction of new C-C bonds on solid support. *Canadian Journal of Chemistry* (2011) doi:10.1139/v00-089.

179. Hussain, I., Capricho, J. & Yawer, M. A. Synthesis of Biaryls via Ligand-Free Suzuki–Miyaura Cross-Coupling Reactions: A Review of Homogeneous and Heterogeneous Catalytic Developments. *Advanced Synthesis & Catalysis* **358**, 3320–3349 (2016).

180. Homogeneous Pd Catalysts - Palladium Catalysts. *Sigma-Aldrich* https://www.sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16248018.

181. Amatore, C. *et al.* Kinetic Data on the Synergetic Role of Amines and Water in the Reduction of Phosphine-Ligated Palladium(II) to Palladium(0). *European Journal of Organic Chemistry* **2014**, 4709–4713 (2014).

182. Wagschal, S. *et al.* Formation of XPhos-Ligated Palladium(0) Complexes and Reactivity in Oxidative Additions. *Chemistry – A European Journal* **25**, 6980–6987 (2019).

183. Kinzel, T., Zhang, Y. & Buchwald, S. L. A New Palladium Precatalyst Allows for the Fast Suzuki−Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids. *J. Am. Chem. Soc.* **132**, 14073–14075 (2010).

184. Bruno, N. C., Tudge, M. T. & Buchwald, S. L. Design and preparation of new palladium precatalysts for C–C and C–N cross-coupling reactions. *Chem. Sci.* **4**, 916–920 (2013).

185. Ingoglia, B. T. & Buchwald, S. L. Oxidative Addition Complexes as Precatalysts for Cross-Coupling Reactions Requiring Extremely Bulky Biarylphosphine Ligands. *Org. Lett.* **19**, 2853–2856 (2017).

186. G3 and G4 Buchwald Precatalysts. *Sigma-Aldrich* https://www.sigmaaldrich.com/technical-documents/articles/technology-spotlights/g3-and-g4-buchwald-precatalysts.html.

187. Adrio, L. A., Nguyen, B. N., Guilera, G., Livingston, A. G. & Hii, K. K. (Mimi). Speciation of Pd(OAc)2 in ligandless Suzuki–Miyaura reactions. *Catal. Sci. Technol.* **2**, 316–323 (2012).

188. Liu, C., Zhang, Y., Liu, N. & Qiu, J. A simple and efficient approach for the palladium-catalyzed ligand-free Suzuki reaction in water. *Green Chem.* **14**, 2999–3003 (2012).

189. Li, Z. *et al.* Palladium-Catalyzed Suzuki Reactions in Water with No Added Ligand: Effects of Reaction Scale, Temperature, pH of Aqueous Phase, and Substrate Structure. *Org. Process Res. Dev.* **20**, 1489–1499 (2016).

190. Liang, Q. *et al.* Palladium-Catalyzed, Ligand-Free Suzuki Reaction in Water Using Aryl Fluorosulfates. *Org. Lett.* **17**, 1942–1945 (2015).

191. Hirakawa, T. *et al.* First-Principles Molecular Dynamics Analysis of Ligand-Free Suzuki–Miyaura Cross-Coupling in Water: Transmetalation and Reductive Elimination. *J. Phys. Chem. C* **121**, 19904–19914 (2017).

192. Liu, C., Rao, X., Song, X., Qiu, J. & Jin, Z. Palladium-catalyzed ligand-free and aqueous Suzuki reaction for the construction of (hetero)aryl-substituted triphenylamine derivatives. *RSC Adv.* **3**, 526–531 (2012).

193. Liu, C. & Li, X. Oxygen-Promoted Suzuki–Miyaura Reaction for Efficient Construction of Biaryls. *The Chemical Record* **16**, 84–97 (2016).

194. Bedford, R. B. *et al.* Facile Hydrolysis and Alcoholysis of Palladium Acetate. *Angewandte Chemie* **127**, 6691–6694 (2015).

195. Leyva-Pérez, A., Oliver-Meseguer, J., Rubio-Marqués, P. & Corma, A. Water-Stabilized Three- and Four-Atom Palladium Clusters as Highly Active Catalytic Species in Ligand-Free C□C Cross-Coupling Reactions. *Angewandte Chemie International Edition* **52**, 11554–11559 (2013).

196. Reddy, K. S. S. V. P. & Deshpande, P. A. On the ligand-free palladium cluster catalysed Suzuki–Miyaura reaction. *Phys. Chem. Chem. Phys.* **22**, 25021–25031 (2020).

197. Walker, S. D., Barder, T. E., Martinelli, J. R. & Buchwald, S. L. A Rationally Designed Universal Catalyst for Suzuki–Miyaura Coupling Processes. *Angewandte Chemie International Edition* **43**, 1871–1876 (2004).

198. Montgomery, M. *et al.* The surprisingly facile formation of Pd(I)–phosphido complexes from ortho-biphenylphosphines and palladium acetate. *Dalton Trans.* **48**, 3539–3542 (2019).

199. Crabtree, R. H. NHC ligands versus cyclopentadienyls and phosphines as spectator ligands in organometallic catalysis. *Journal of Organometallic Chemistry* **690**, 5451–5457 (2005).

200. Crabtree, R. H. Carbonyls, Phosphine Complexes, and Ligand Substitution Reactions. in *The Organometallic Chemistry of the Transition Metals* 87–124 (John Wiley & Sons, Ltd, 2005). doi:10.1002/0471718769.ch4.

201. Tolman, C. A. Steric effects of phosphorus ligands in organometallic chemistry and homogeneous catalysis. *Chem. Rev.* **77**, 313–348 (1977).

202. Kong, K. C. & Cheng, C. H. Facile aryl-aryl exchange between the palladium center and phosphine ligands in palladium(II) complexes. *J. Am. Chem. Soc.* **113**, 6313–6315 (1991).

203. Walan, P., Davidsson, S., Johansson, S. & Höök, M. Phosphate rock production and depletion : Regional disaggregated modeling and global implications. *Resources, Conservation and Recycling* **93**, 178–187 (2014).

204. von Horn, J. & Sartorius, C. *Impact of supply and demand on the price development of phosphate (fertilizer)*. (2009).

205. Mew, M. C. Phosphate rock costs, prices and resources interaction. *Science of The Total Environment* **542**, 1008–1012 (2016).

206. Würtz, S. & Glorius, F. Surveying Sterically Demanding N-Heterocyclic Carbene Ligands with Restricted Flexibility for Palladium-catalyzed Cross-Coupling Reactions. *Acc. Chem. Res.* **41**, 1523–1533 (2008).

207. Herrmann, W. A., Öfele, K., Elison, M., Kühn, F. E. & Roesky, P. W. Nucleophilic cyclocarbenes as ligands in metal halides and metal oxides. *Journal of Organometallic Chemistry* **480**, c7–c9 (1994).

208. Konnick, M. M., Guzei, I. A. & Stahl, S. S. Characterization of Peroxo and Hydroperoxo Intermediates in the Aerobic Oxidation of N-Heterocyclic-Carbene-Coordinated Palladium(0). *J. Am. Chem. Soc.* **126**, 10212–10213 (2004).

209. Navarro, O., Kelly, R. A. & Nolan, S. P. A General Method for the Suzuki−Miyaura Cross-Coupling of Sterically Hindered Aryl Chlorides: Synthesis of Di- and Tri-ortho-substituted Biaryls in 2-Propanol at Room Temperature. *J. Am. Chem. Soc.* **125**, 16194–16195 (2003).

210. Gstöttmayr, C. W. K., Böhm, V. P. W., Herdtweck, E., Grosche, M. & Herrmann, W. A. A Defined N-Heterocyclic Carbene Complex for the Palladium-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides at Ambient Temperatures. *Angewandte Chemie International Edition* **41**, 1363–1365 (2002).

211. Wu, L. *et al.* Room-Temperature Synthesis of Tetra-ortho-Substituted Biaryls by NHC-Catalyzed Suzuki–Miyaura Couplings. *Chemistry – A European Journal* **17**, 12886–12890 (2011).

212. Chartoire, A. *et al.* [Pd(IPr*)(cinnamyl)Cl]: An Efficient Pre-catalyst for the Preparation of Tetra-ortho-substituted Biaryls by Suzuki–Miyaura Cross-Coupling. *Chemistry – A European Journal* **18**, 4517–4521 (2012).

213. Vanden Broeck, S. M. P., Nahra, F. & Cazin, C. S. J. Bulky-Yet-Flexible Carbene Ligands and Their Use in Palladium Cross-Coupling. *Inorganics* **7**, 78 (2019).

214. Burstein, C., Lehmann, C. W. & Glorius, F. Imidazo[1,5-a]pyridine-3-ylidenes—pyridine derived N-heterocyclic carbene ligands. *Tetrahedron* **61**, 6207–6217 (2005).

215. Yin, J., Rainka, M. P., Zhang, X.-X. & Buchwald, S. L. A Highly Active Suzuki Catalyst for the Synthesis of Sterically Hindered Biaryls: Novel Ligand Coordination. *J. Am. Chem. Soc.* **124**, 1162–1163 (2002).

216. Kashihara, M., Zhong, R.-L., Semba, K., Sakaki, S. & Nakao, Y. Pd/NHC-catalyzed cross-coupling reactions of nitroarenes. *Chem. Commun.* **55**, 9291–9294 (2019).

217. Chen, K. *et al.* Sterically hindered N-heterocyclic carbene/palladium(II) catalyzed Suzuki–Miyaura coupling of nitrobenzenes. *Chem. Commun.* **55**, 9287–9290 (2019).

218. Yi, X., Chen, K., Guo, J., Chen, W. & Chen, W. Nickel(II)/N-Heterocyclic Carbene Catalyzed Desulfinylative Arylation by C−S Cleavage of Aryl Sulfoxides with Phenylboronic Acids. *Advanced Synthesis & Catalysis* **362**, 4373–4377 (2020).

219. McMillen, D. F. & Golden, D. M. Hydrocarbon Bond Dissociation Energies. *Annu. Rev. Phys. Chem.* **33**, 493–532 (1982).

220. Kawada, K. *et al.* Total Synthesis of Terprenin, a Highly Potent and Novel Immunoglobulin E Antibody Suppressant. *Angewandte Chemie International Edition* **37**, 973–975 (1998).

221. Gray, G. W., Hird, M., Lacey, D. & Toyne, K. J. The synthesis and transition temperatures of some 4,4″-dialkyl- and 4,4″-alkoxyalkyl-1,1′:4′,1″-terphenyls with 2,3- or 2′,3′-difluoro substituents and of their biphenyl analogues. *J. Chem. Soc., Perkin Trans. 2* 2041–2053 (1989) doi:10.1039/P29890002041.

222. Grushin, V. V. & Alper, H. Transformations of Chloroarenes, Catalyzed by Transition-Metal Complexes. *Chem. Rev.* **94**, 1047–1062 (1994).

223. Fu, J. -m & Snieckus, V. Connections to the directed ortho metalation strategy. Pd(0)-catalyzed cross coupling of aryl boronic acids with aryl triflates. *Tetrahedron Letters* **31**, 1665–1668 (1990).

224. Oh-e, T., Miyaura, N. & Suzuki, A. Palladium-Catalyzed Cross-Coupling Reaction of Aryl or Vinylic Triflates with Organoboron Compounds. *Synlett* **1990**, 221–223 (1990).

225. Huth, A., Beetz, I. & Schumann, I. Synthesis of diarylic compounds by palladium catalyzed reaction of aromatic triflates with boronic acids. *Tetrahedron* **45**, 6679–6682 (1989).

226. Jutand, A. & Mosleh, A. Rate and Mechanism of Oxidative Addition of Aryl Triflates to Zerovalent Palladium Complexes. Evidence for the Formation of Cationic (.sigma.-Aryl)palladium Complexes. *Organometallics* **14**, 1810–1817 (1995).

227. Alami, M., Ferri, F. & Linstrumelle, G. An Efficient palladium-catalysed reaction of vinyl and aryl halides or triflates with terminal alkynes. *Tetrahedron Letters* **34**, 6403–6406 (1993).

228. Espino, G., Kurbangalieva, A. & Brown, J. M. Aryl bromide/triflate selectivities reveal mechanistic divergence in palladium-catalysed couplings; the Suzuki–Miyaura anomaly. *Chem. Commun.* 1742–1744 (2007) doi:10.1039/B701517H.

229. Tobisu, M., Xu, T., Shimasaki, T. & Chatani, N. Nickel-Catalyzed Suzuki–Miyaura Reaction of Aryl Fluorides. *J. Am. Chem. Soc.* **133**, 19505–19511 (2011).

230. Colleville, A. P., Horan, R. A. J. & Tomkinson, N. C. O. Aryldiazonium Tetrafluoroborate Salts as Green and Efficient Coupling Partners for the Suzuki–

Miyaura Reaction: From Optimisation to Mole Scale. *Org. Process Res. Dev.* **18**, 1128–1136 (2014).

231. Baumeister, P., Meyer, W., Oertle, K., Seifert, G. & Steiner, H. Invention and Development of a Novel Catalytic Process for the Production of a Benzenesulfonic Acid-Building Block. *CHIMIA International Journal for Chemistry* **51**, 144–144 (1997).

232. Andrus, M. B. & Song, C. Palladium−Imidazolium Carbene Catalyzed Aryl, Vinyl, and Alkyl Suzuki−Miyaura Cross Coupling. *Org. Lett.* **3**, 3761–3764 (2001).

233. Trusova, M. E. *et al.* Ultra-fast Suzuki and Heck reactions for the synthesis of styrenes and stilbenes using arenediazonium salts as super-electrophiles. *Org. Chem. Front.* **5**, 41–45 (2017).

234. Sengupta, S. & Sadhukhan, S. K. Iodoarenediazonium salts: A new class of aromatic substrates for differential palladium catalyzed reactions. *Tetrahedron Letters* **39**, 715–718 (1998).

235. Taylor, R. H. & Felpin, F.-X. Suzuki−Miyaura Reactions of Arenediazonium Salts Catalyzed by Pd(0)/C. One-Pot Chemoselective Double Cross-Coupling Reactions. *Org. Lett.* **9**, 2911–2914 (2007).

236. Felpin, F.-X. & Fouquet, E. Efficient and Practical Cross-Coupling of Arenediazonium Tetrafluoroborate Salts with Boronic Acids Catalyzed by Palladium(0)/Barium Carbonate. *Advanced Synthesis & Catalysis* **350**, 863–868 (2008).

237. Bonin, H., Delbrayelle, D., Demonchaux, P. & Gras, E. Base free aryl coupling of diazonium compounds and boronic esters: self-activation allowing an overall highly practical process. *Chem. Commun.* **46**, 2677–2679 (2010).

238. Schmidt, B., Elizarov, N., Schilde, U. & Kelling, A. Dual Role of Acetanilides: Traceless Removal of a Directing Group through Deacetylation/Diazotation and Palladium-Catalyzed C–C-Coupling Reactions. *J. Org. Chem.* **80**, 4223–4234 (2015).

239. Mo, F., Qiu, D., Jiang, Y., Zhang, Y. & Wang, J. A base-free, one-pot diazotization/cross-coupling of anilines with arylboronic acids. *Tetrahedron Letters* **52**, 518–522 (2011).

240. Joncour, R. *et al.* Chelation-Assisted Cross-Coupling of Anilines through In Situ Activation as Diazonium Salts with Boronic Acids under Ligand-, Base-, and Salt-Free Conditions. *Chemistry – A European Journal* **19**, 9291–9296 (2013).

241. Oger, N., Le Grognec, E. & Felpin, F.-X. Palladium Nanoparticles Supported on Sulfonic Acid Functionalized Silica as Trifunctional Heterogeneous Catalysts for Heck and Suzuki Reactions. *ChemCatChem* **7**, 2085–2094 (2015).

242. Saeki, T., Son, E.-C. & Tamao, K. Boron Trifluoride Induced Palladium-Catalyzed Cross-Coupling Reaction of 1-Aryltriazenes with Areneboronic Acids. *Org. Lett.* **6**, 617–619 (2004).

243. Liu, C.-Y., Gavryushin, A. & Knochel, P. Synthesis of Functionalized o-, m-, and p-Terphenyl Derivatives by Consecutive Cross-Coupling Reactions of Triazene-Substituted Arylboronic Esters. *Chemistry – An Asian Journal* **2**, 1020–1030 (2007).

244. Nan, G., Ren, F. & Luo, M. Suzuki–Miyaura cross-coupling reaction of 1-aryltriazenes with arylboronic acids catalyzed by a recyclable polymer-supported N-heterocyclic carbene–palladium complex catalyst. *Beilstein J. Org. Chem.* **6**, 0–0 (2010).

245. Zhou, T. & Szostak, M. Palladium-catalyzed cross-couplings by C–O bond activation. *Catal. Sci. Technol.* **10**, 5702–5739 (2020).

246. Subramanian, L. R. *et al.* Nonafluorobutanesulfonyl Fluoride. *Encyclopedia of Reagents for Organic Synthesis* 1–14 (2018) doi:10.1002/047084289X.rn061.pub2.

247. Högermeier, J. & Reissig, H.-U. Nine Times Fluoride can be Good for your Syntheses. Not just Cheaper: Nonafluorobutanesulfonates as Intermediates for Transition Metal-Catalyzed Reactions. *Advanced Synthesis & Catalysis* **351**, 2747–2763 (2009).

248. Rottländer, M. & Knochel, P. Palladium-Catalyzed Cross-Coupling Reactions with Aryl Nonaflates: A Practical Alternative to Aryl Triflates. *J. Org. Chem.* **63**, 203–208 (1998).

249. Joy, M. N. & Bakulev, V. A. Is nonaflate a better leaving group than corresponding triflate? A case study in the palladium catalyzed cross-coupling reaction of 7-substituted coumarins. *AIP Conference Proceedings* **2063**, 030015 (2019).

250. Roth, G. P. & Fuller, C. E. Palladium cross-coupling reactions of aryl fluorosulfonates: an alternative to triflate chemistry. *J. Org. Chem.* **56**, 3493–3496 (1991).

251. Hanley, P. S., Ober, M. S., Krasovskiy, A. L., Whiteker, G. T. & Kruper, W. J. Nickel- and Palladium-Catalyzed Coupling of Aryl Fluorosulfonates with Aryl Boronic Acids Enabled by Sulfuryl Fluoride. *ACS Catal.* **5**, 5041–5046 (2015).

252. Zhang, E. *et al.* Chemoselective Synthesis of Polysubstituted Pyridines from Heteroaryl Fluorosulfates. *Chemistry – A European Journal* **22**, 5692–5697 (2016).

253. Mendel, M., Kalvet, I., Hupperich, D., Magnin, G. & Schoenebeck, F. Site-Selective, Modular Diversification of Polyhalogenated Aryl Fluorosulfates (ArOSO2F) Enabled by an Air-Stable PdI Dimer. *Angewandte Chemie International Edition* **59**, 2115–2119 (2020).

254. Percec, V., Bae, J.-Y. & Hill, D. H. Aryl Mesylates in Metal Catalyzed Homocoupling and Cross-Coupling Reactions. 2. Suzuki-Type Nickel-Catalyzed Cross-Coupling of Aryl Arenesulfonates and Aryl Mesylates with Arylboronic Acids. *J. Org. Chem.* **60**, 1060–1065 (1995).

255. Nguyen, H. N., Huang, X. & Buchwald, S. L. The First General Palladium Catalyst for the Suzuki−Miyaura and Carbonyl Enolate Coupling of Aryl Arenesulfonates. *J. Am. Chem. Soc.* **125**, 11818–11819 (2003).

256. So, C. M., Lau, C. P. & Kwong, F. Y. A General Palladium-Catalyzed Suzuki–Miyaura Coupling of Aryl Mesylates. *Angewandte Chemie International Edition* **47**, 8059–8063 (2008).

257. Bhayana, B., Fors, B. P. & Buchwald, S. L. A Versatile Catalyst System for Suzuki−Miyaura Cross-Coupling Reactions of C(sp2)-Tosylates and Mesylates. *Org. Lett.* **11**, 3954–3957 (2009).

258. Dikova, A., Cheval, N. P., Blanc, A., Weibel, J.-M. & Pale, P. Aryl and heteroaryl nosylates as stable and cheap partners for Suzuki–Miyaura cross-coupling reactions. *Tetrahedron* **72**, 1960–1968 (2016).

259. Albaneze-Walker, J. *et al.* Imidazolylsulfonates: Electrophilic Partners in Cross-Coupling Reactions. *Org. Lett.* **11**, 1463–1466 (2009).

260. Joseph, J. T. *et al.* Aryl/heteroaryl pentafluorobenzenesulfonates (ArOPFBs): new electrophilic coupling partners for room temperature Suzuki–Miyaura cross-coupling reactions. *Tetrahedron Letters* **56**, 5106–5111 (2015).

261. Quasdorf, K. W., Riener, M., Petrova, K. V. & Garg, N. K. Suzuki−Miyaura Coupling of Aryl Carbamates, Carbonates, and Sulfamates. *J. Am. Chem. Soc.* **131**, 17748–17749 (2009).

262. Melvin, P. R., Hazari, N., Beromi, M. M., Shah, H. P. & Williams, M. J. Pd-Catalyzed Suzuki–Miyaura and Hiyama–Denmark Couplings of Aryl Sulfamates. *Org. Lett.* **18**, 5784–5787 (2016).

263. Wang, Z.-Y., Ma, Q.-N., Li, R.-H. & Shao, L.-X. Palladium-catalyzed Suzuki–Miyaura coupling of aryl sulfamates with arylboronic acids. *Org. Biomol. Chem.* **11**, 7899–7906 (2013).

264. Huffman, M. A. & Yasuda, N. Alternatives to Vinyl Triflates for Cross-Coupling with Arylboronic Acids. *Synlett* **1999**, 471–473 (1999).

265. Sasaki, M., Fuwa, H., Ishikawa, M. & Tachibana, K. A General Method for Convergent Synthesis of Polycyclic Ethers Based on Suzuki Cross-Coupling: Concise Synthesis of the ABCD Ring System of Ciguatoxin. *Org. Lett.* **1**, 1075–1077 (1999).

266. Lepifre, F., Buon, C., Rabot, R., Bouyssou, P. & Coudert, G. Palladium-catalysed coupling of vinyl phosphates with aryl or heteroaryl boronic acids. Application to the synthesis of substituted nitrogen containing heterocycles. *Tetrahedron Letters* **40**, 6373–6376 (1999).

267. Kang, F.-A., Sui, Z. & Murray, W. V. Pd-Catalyzed Direct Arylation of Tautomerizable Heterocycles with Aryl Boronic Acids via C−OH Bond Activation Using Phosphonium Salts. *J. Am. Chem. Soc.* **130**, 11300–11302 (2008).

268. Guo, J., Harling, J. D., Steel, P. G. & Woods, T. M. Phosphinates as new electrophilic partners for cross-coupling reactions. *Org. Biomol. Chem.* **6**, 4053–4058 (2008).

269. Chen, H. *et al.* Nickel-Catalyzed Cross-Coupling of Aryl Phosphates with Arylboronic Acids. *J. Org. Chem.* **76**, 2338–2344 (2011).

270. Liu, C., Ji, C.-L., Qin, Z.-X., Hong, X. & Szostak, M. Synthesis of Biaryls via Decarbonylative Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling of Carboxylic Acids. *iScience* **19**, 749–759 (2019).

271. Bouyssi, D., Gerusz, V. & Balme, G. A Novel Palladium Catalyst for Cross-Coupling of Allyl Acetates with Arylboronic Acids. *European Journal of Organic Chemistry* **2002**, 2445–2448 (2002).

272. Mondal, M., Begum, T. & Bora, U. Chemoselective acyl C–O bond activation in esters for Suzuki–Miyaura coupling. *Org. Chem. Front.* **4**, 1430–1434 (2017).

273. Lei, P. *et al.* Suzuki–Miyaura cross-coupling of amides and esters at room temperature: correlation with barriers to rotation around C–N and C–O bonds. *Chem. Sci.* **8**, 6525–6530 (2017).

274. Ben Halima, T. *et al.* Palladium-Catalyzed Suzuki–Miyaura Coupling of Aryl Esters. *J. Am. Chem. Soc.* **139**, 1311–1318 (2017).

275. Takise, R., Muto, K. & Yamaguchi, J. Cross-coupling of aromatic esters and amides. *Chem. Soc. Rev.* **46**, 5864–5888 (2017).

276. Ogiwara, Y., Sakino, D., Sakurai, Y. & Sakai, N. Acid Fluorides as Acyl Electrophiles in Suzuki–Miyaura Coupling. *European Journal of Organic Chemistry* **2017**, 4324–4327 (2017).

277. Guan, B.-T., Wang, Y., Li, B.-J., Yu, D.-G. & Shi, Z.-J. Biaryl Construction via Ni-Catalyzed C−O Activation of Phenolic Carboxylates. *J. Am. Chem. Soc.* **130**, 14468–14470 (2008).

278. Muto, K., Yamaguchi, J., Musaev, D. G. & Itami, K. Decarbonylative organoboron cross-coupling of esters by nickel catalysis. *Nature Communications* **6**, 7508 (2015).

279. LaBerge, N. A. & Love, J. A. Nickel-Catalyzed Decarbonylative Cou-pling of Aryl Esters and Arylboronic Acids. *European Journal of Organic Chemistry* **2015**, 5546–5553 (2015).

280. Kuwano, R. & Yokogi, M. Suzuki−Miyaura Cross-Coupling of Benzylic Carbonates with Arylboronic Acids. *Org. Lett.* **7**, 945–947 (2005).

281. Yu, J.-Y. & Kuwano, R. Suzuki-Miyaura Coupling of Diarylmethyl Carbonates with Arylboronic Acids: A New Access to Triarylmethanes. *Org. Lett.* **10**, 973–976 (2008).

282. Sirois, L. E. *et al.* Process Development for a Locally Acting SGLT1 Inhibitor, LX2761, Utilizing sp3–sp2 Suzuki Coupling of a Benzyl Carbonate. *Org. Process Res. Dev.* **23**, 45–61 (2019).

283. Tobisu, M., Shimasaki, T. & Chatani, N. Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters. *Angewandte Chemie International Edition* **47**, 4866–4869 (2008).

284. Meng, G., Shi, S. & Szostak, M. Cross-Coupling of Amides by N–C Bond Activation. *Synlett* **27**, 2530–2540 (2016).

285. Shi, S., Meng, G. & Szostak, M. Synthesis of Biaryls through Nickel-Catalyzed Suzuki–Miyaura Coupling of Amides by Carbon–Nitrogen Bond Cleavage. *Angewandte Chemie International Edition* **55**, 6959–6963 (2016).

286. Liu, C. *et al.* Acyl and Decarbonylative Suzuki Coupling of N-Acetyl Amides: Electronic Tuning of Twisted, Acyclic Amides in Catalytic Carbon–Nitrogen Bond Cleavage. *ACS Catal.* **8**, 9131–9139 (2018).

287. Luo, Z. *et al.* Palladium-Catalyzed Decarbonylative Suzuki–Miyaura Coupling of Amides To Achieve Biaryls via C–N Bond Cleavage. *J. Org. Chem.* **84**, 10559–10568 (2019).

288. Blakey, S. B. & MacMillan, D. W. C. The First Suzuki Cross-Couplings of Aryltrimethylammonium Salts. *J. Am. Chem. Soc.* **125**, 6046–6047 (2003).

289. Wang, T. *et al.* Palladium catalyzed Suzuki cross-coupling of benzyltrimethylammonium salts via C–N bond cleavage. *RSC Adv.* **7**, 15805–15808 (2017).

290. Peng, Z. *et al.* Palladium-Catalyzed Suzuki Cross-Coupling of Arylhydrazines via C–N Bond Cleavage. *J. Org. Chem.* **79**, 2733–2738 (2014).

291. Li, Y., Liu, W., Tian, Q., Yang, Q. & Kuang, C. Palladium-Catalyzed Suzuki Cross-Coupling of Phenylhydrazine or (Phenylsulfonyl)hydrazine. *European Journal of Organic Chemistry* **2014**, 3307–3312 (2014).

292. Tiemann, Ferd. Ueber eine Darstellung von o-Chloranisaldehyd aus p-Nitrotoluol. *Berichte der deutschen chemischen Gesellschaft* **24**, 699–713 (1891).

293. Beck, J. R. Nucleophilic displacement of aromatic nitro groups. *Tetrahedron* **34**, 2057–2068 (1978).

294. Cheng, H.-G., Chen, H., Liu, Y. & Zhou, Q. The Liebeskind–Srogl Cross-Coupling Reaction and its Synthetic Applications. *Asian Journal of Organic Chemistry* **7**, 490–508 (2018).

295. Prokopcová, H. & Kappe, C. O. The Liebeskind–Srogl C–C Cross-Coupling Reaction. *Angewandte Chemie International Edition* **48**, 2276–2286 (2009).

296. Mai, S., Li, W., Li, X., Zhao, Y. & Song, Q. Palladium-catalyzed Suzuki-Miyaura coupling of thioureas or thioamides. *Nature Communications* **10**, 5709 (2019).

297. Lou, J. *et al.* Transition-metal mediated carbon–sulfur bond activation and transformations: an update. *Chem. Soc. Rev.* **49**, 4307–4359 (2020).

298. Pan, F., Wang, H., Shen, P.-X., Zhao, J. & Shi, Z.-J. Cross coupling of thioethers with aryl boroxines to construct biaryls via Rh catalyzed C–S activation. *Chem. Sci.* **4**, 1573–1577 (2013).

299. Hooper, J. F., Young, R. D., Pernik, I., Weller, A. S. & Willis, M. C. Carbon–carbon bond construction using boronic acids and aryl methyl sulfides: orthogonal reactivity in Suzuki-type couplings. *Chem. Sci.* **4**, 1568–1572 (2013).

300. Creech, G. S. & Kwon, O. Synthesis of nitrodienes, nitrostyrenes, and nitrobiaryls through palladium-catalyzed couplings of β-nitrovinyl and o-nitroaryl thioethers. *Chem. Sci.* **4**, 2670–2674 (2013).

301. Srogl, J., Allred, G. D. & Liebeskind, L. S. Sulfonium Salts. Participants par Excellence in Metal-Catalyzed Carbon−Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **119**, 12376–12377 (1997).

302. Cowper, P., Jin, Y., Turton, M. D., Kociok-Köhn, G. & Lewis, S. E. Azulenesulfonium Salts: Accessible, Stable, and Versatile Reagents for Cross-Coupling. *Angewandte Chemie International Edition* **55**, 2564–2568 (2016).

303. Berger, F. *et al.* Site-selective and versatile aromatic C−H functionalization by thianthrenation. *Nature* **567**, 223–228 (2019).

304. Chen, Q. *et al.* Suzuki–Miyaura Cross-Coupling of Sulfoxides. *ACS Catal.* **10**, 8168–8176 (2020).

305. Dubbaka, S. R. & Vogel, P. Palladium-Catalyzed Suzuki−Miyaura Cross-Couplings of Sulfonyl Chlorides and Boronic Acids. *Organic Letters* **6**, 95–98 (2004).

306. Wei, Z., Xue, D., Zhang, H. & Guan, J. Desulfonative pd-catalyzed coupling of aryl trifluoroborates with arylsulfonyl chlorides. *Applied Organometallic Chemistry* **30**, 767–771 (2016).

307. Cherepakha, A. Y. *et al.* Hetaryl Bromides Bearing the SO2F Group – Versatile Substrates for Palladium-Catalyzed C–C Coupling Reactions. *European Journal of Organic Chemistry* **2018**, 6682–6692 (2018).

308. Cella, R. *et al.* Suzuki−Miyaura Cross-Coupling Reactions of Aryl Tellurides with Potassium Aryltrifluoroborate Salts. *J. Org. Chem.* **71**, 244–250 (2006).

309. Cella, R. & Stefani, H. A. Ultrasound-assisted synthesis of Z and E stilbenes by Suzuki cross-coupling reactions of organotellurides with potassium organotrifluoroborate salts. *Tetrahedron* **62**, 5656–5662 (2006).

310. Stefani, H. A. *et al.* Synthesis of 1,3-enynes via Suzuki-type reaction of vinylic tellurides and potassium alkynyltrifluoroborate salts. *Tetrahedron Letters* **46**, 563–567 (2005).

311. Kang, S.-K., Hong, Y.-T., Kim, D.-H. & Lee, S.-H. Palladium-Catalysed Cross-Coupling of Organotellurium Compounds with Organoboronic Acids. *Journal of Chemical Research* **2001**, 283–285 (2001).

312. Stein, A. L., Bilheri, F. N. & Zeni, G. Application of organoselenides in the Suzuki, Negishi, Sonogashira and Kumada cross-coupling reactions. *Chem. Commun.* **51**, 15522–15525 (2015).

313. Xia, Y., Wang, J. & Dong, G. Suzuki–Miyaura Coupling of Simple Ketones via Activation of Unstrained Carbon–Carbon Bonds. *J. Am. Chem. Soc.* **140**, 5347–5351 (2018).

314. Yadav, M. R. *et al.* The Suzuki–Miyaura Coupling of Nitroarenes. *Journal of the American Chemical Society* **139**, 9423–9426 (2017).

315. Schroeter, F., Soellner, J. & Strassner, T. Cross-Coupling Catalysis by an Anionic Palladium Complex. *ACS Catal.* **7**, 3004–3009 (2017).

316. Clayden, J. & Julia, M. ortho-Substituted unsymmetrical biaryls from aryl tert-butyl sulfones. *Journal of the Chemical Society, Chemical Communications* 1682 (1993) doi:10.1039/c39930001682.

317. Cook, J. L., Hunter, C. A., Low, C. M. R., Perez-Velasco, A. & Vinter, J. G. Preferential Solvation and Hydrogen Bonding in Mixed Solvents. *Angewandte Chemie International Edition* **47**, 6275–6277 (2008).

318. Chatelain, Paul, Sau, Abhijit, Rowley, Christopher N. & Moran, Joseph. CCDC 1948443: Experimental Crystal Structure Determination. doi:10.5517/CCDC.CSD.CC23DJ02.

319. de Gombert, A., McKay, A. I., Davis, C. J., Wheelhouse, K. M. & Willis, M. C. Mechanistic Studies of the Palladium-Catalyzed Desulfinative Cross-Coupling of Aryl Bromides and (Hetero)Aryl Sulfinate Salts. *J. Am. Chem. Soc.* **142**, 3564–3576 (2020).

320. Fors, B. P. & Buchwald, S. L. Pd-Catalyzed Conversion of Aryl Chlorides, Triflates, and Nonaflates to Nitroaromatics. *J. Am. Chem. Soc.* **131**, 12898–12899 (2009).

321. Roberti, M. *et al.* Identification of a Terphenyl Derivative that Blocks the Cell Cycle in the G0−G1 Phase and Induces Differentiation in Leukemia Cells. *J. Med. Chem.* **49**, 3012–3018 (2006).

322. Kazi, S. A., Campi, E. M. & Hearn, M. T. W. A convenient and efficient one pot synthesis of unsymmetrically substituted p -terphenyls via a phosphine-free double Suzuki cross-coupling protocol using 1,4-dibromo-2-nitrobenzene as the substrate. *Tetrahedron* **74**, 1731–1741 (2018).

323. Steinkopf, W. Über Aromatische Sulfofluoride. *Journal für Praktische Chemie* **117**, 1–82 (1927).

324. Qin, H.-L., Zheng, Q., Bare, G. A. L., Wu, P. & Sharpless, K. B. A Heck–Matsuda Process for the Synthesis of β-Arylethenesulfonyl Fluorides: Selectively Addressable Bis-electrophiles for SuFEx Click Chemistry. *Angewandte Chemie International Edition* **55**, 14155–14158 (2016).

325. Zha, G.-F. *et al.* Palladium-Catalyzed Fluorosulfonylvinylation of Organic Iodides. *Angewandte Chemie International Edition* **56**, 4849–4852 (2017).

326. Chinthakindi, P. K. *et al.* A Synthesis of "Dual Warhead" β-Aryl Ethenesulfonyl Fluorides and One-Pot Reaction to β-Sultams. *Org. Lett.* **19**, 480–483 (2017).

327. Moku, B., Fang, W.-Y., Leng, J., Kantchev, E. A. B. & Qin, H.-L. Rh(I)–Diene-Catalyzed Addition of (Hetero)aryl Functionality to 1,3-Dienylsulfonyl Fluorides Achieving Exclusive Regioselectivity and High Enantioselectivity: Generality and Mechanism. *ACS Catal.* **9**, 10477–10488 (2019).

328. Li, C. & Qin, H.-L. Rh-Catalyzed Annulative Insertion of Terminal Olefin onto Pyridines via a C–H Activation Strategy Using Ethenesulfonyl Fluoride as Ethylene Provider. *Org. Lett.* **21**, 4495–4499 (2019).

329. Chen, X.-Y., Wu, Y., Zhou, J., Wang, P. & Yu, J.-Q. Synthesis of β-Arylethenesulfonyl Fluoride via Pd-Catalyzed Nondirected C–H Alkenylation. *Org. Lett.* **21**, 1426–1429 (2019).

330. Ncube, G. & Huestis, M. P. Directed Cp*RhIII-Catalyzed Fluorosulfonylvinylation of Arenes. *Organometallics* **38**, 76–80 (2019).

331. Li, C., Wang, S.-M. & Qin, H.-L. A Rh-Catalyzed Air and Moisture Tolerable Aldehyde (Ketone)-Directed Fluorosulfonylvinylation of Aryl C(sp2)–H Bonds. *Org. Lett.* **20**, 4699–4703 (2018).

332. Lou, T. S.-B., Bagley, S. W. & Willis, M. C. Cyclic Alkenylsulfonyl Fluorides: Palladium-Catalyzed Synthesis and Functionalization of Compact Multifunctional Reagents. *Angewandte Chemie* **131**, 19035–19039 (2019).

333. Moku, B. *et al.* Rh-Catalyzed Highly Enantioselective Synthesis of Aliphatic Sulfonyl Fluorides. *iScience* **21**, 695–705 (2019).

334. Leng, J., Alharbi, N. S. & Qin, H.-L. Construction of α-(Hetero)aryl Ethenesulfonyl Fluorides for SuFEx Click Chemistry. *European Journal of Organic Chemistry* **2019**, 6101–6105 (2019).

335. Wang, S.-M., Moku, B., Leng, J. & Qin, H.-L. Rh-Catalyzed Carboxylates Directed C–H Activation for the Synthesis of ortho-Carboxylic 2-Arylethenesulfonyl Fluorides: Access to Unique Electrophiles for SuFEx Click Chemistry. *European Journal of Organic Chemistry* **2018**, 4407–4410 (2018).

336. Zha, G.-F. *et al.* Gram-Scale Synthesis of β-(Hetero)arylethenesulfonyl Fluorides via a Pd(OAc)2 Catalyzed Oxidative Heck Process with DDQ or AgNO3 as an Oxidant. *Advanced Synthesis & Catalysis* **359**, 3237–3242 (2017).

337. Lou, T. S.-B. & Willis, M. C. Arylsulfonyl fluoride boronic acids: Preparation and coupling reactivity. *Tetrahedron* **76**, 130782 (2020).

338. Chinthakindi, P. K., Kruger, H. G., Govender, T., Naicker, T. & Arvidsson, P. I. On-Water Synthesis of Biaryl Sulfonyl Fluorides. *J. Org. Chem.* **81**, 2618–2623 (2016).

339. Mukherjee, P. *et al.* Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides. *Org. Lett.* **20**, 3943–3947 (2018).

340. Mahapatra, S. *et al.* SuFEx Activation with Ca(NTf2)2: A Unified Strategy to Access Sulfamides, Sulfamates, and Sulfonamides from S(VI) Fluorides. *Org. Lett.* **22**, 4389–4394 (2020).

341. Smedley, C. J. *et al.* Bifluoride Ion Mediated SuFEx Trifluoromethylation of Sulfonyl Fluorides and Iminosulfur Oxydifluorides. *Angewandte Chemie* **131**, 4600–4604 (2019).

342. Molander, G. A., Cavalcanti, L. N. & García-García, C. Nickel-Catalyzed Borylation of Halides and Pseudohalides with Tetrahydroxydiboron [B2(OH)4]. *J. Org. Chem.* **78**, 6427–6439 (2013).

343. Nielsen, M. K., Ugaz, C. R., Li, W. & Doyle, A. G. PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent. *J. Am. Chem. Soc.* **137**, 9571–9574 (2015).

344. Jiang, Y., Fang, W.-Y., Rakesh, K. P. & Qin, H.-L. Copper-catalyzed mild desulfonylation of vinyl sulfonyl molecules. *Org. Chem. Front.* **7**, 1696–1702 (2020).

345. Sharninghausen, L. S. *et al.* NHC-Copper Mediated Ligand-Directed Radiofluorination of Aryl Halides. *J. Am. Chem. Soc.* **142**, 7362–7367 (2020).

346. Mossine, A. V. *et al.* One-pot synthesis of high molar activity 6-[18F]fluoro-L-DOPA by Cu-mediated fluorination of a BPin precursor. *Org. Biomol. Chem.* **17**, 8701–8705 (2019).

347. Gregory Landelle & Armen Panossian and Frederic R. Leroux. Trifluoromethyl Ethers and –Thioethers as Tools for Medicinal Chemistry and Drug Discovery. *Current Topics in Medicinal Chemistry* **14**, 941–951 (2014).

348. Lin, X. *et al.* Copper-catalyzed trifluoromethylation of arylsulfinate salts using an electrophilic trifluoromethylation reagent. *Tetrahedron* **69**, 2628–2632 (2013).

349. Smedley, C. J. *et al.* Bifluoride Ion Mediated SuFEx Trifluoromethylation of Sulfonyl Fluorides and Iminosulfur Oxydifluorides. *Angewandte Chemie International Edition* **58**, 4552–4556 (2019).

350. Chen, L. *et al.* A convenient synthesis of sulfones via light promoted couplings of sodium sulfinates and aryl halides. *Adv. Synth. Catal.* adsc.201801390 (2018) doi:10.1002/adsc.201801390.

351. Zhang, Z. & Wang, Z. Diatomite-Supported Pd Nanoparticles: An Efficient Catalyst for Heck and Suzuki Reactions. *The Journal of Organic Chemistry* **71**, 7485–7487 (2006).

352. Liu, C. *et al.* Acyl and Decarbonylative Suzuki Coupling of *N* -Acetyl Amides: Electronic Tuning of Twisted, Acyclic Amides in Catalytic Carbon–Nitrogen Bond Cleavage. *ACS Catalysis* **8**, 9131–9139 (2018).

353. Pourbaix, C., Carreaux, F. & Carboni, B. Metal-Catalyzed Release of Supported Boronic Acids for C−C Bond Formation. *Organic Letters* **3**, 803–805 (2001).

354. Dewanji, A., Murarka, S., Curran, D. P. & Studer, A. Phenyl Hydrazine as Initiator for Direct Arene C–H Arylation via Base Promoted Homolytic Aromatic Substitution. *Organic Letters* **15**, 6102–6105 (2013).

355. Martinez-Solorio, D. *et al.* Design, Synthesis, and Validation of an Effective, Reusable Silicon-Based Transfer Agent for Room-Temperature Pd-Catalyzed Cross-Coupling Reactions of Aryl and Heteroaryl Chlorides with Readily Available Aryl Lithium Reagents. *Journal of the American Chemical Society* **138**, 1836–1839 (2016).

356. Guerra, R. R. G. *et al.* Factorial design evaluation of the Suzuki cross-coupling reaction using a magnetically recoverable palladium catalyst. *Tetrahedron Letters* **58**, 903–908 (2017).

357. Mäsing, F., Nüsse, H., Klingauf, J. & Studer, A. Visible-Light-Enabled Preparation of Palladium Nanoparticles and Application as Catalysts for Suzuki–Miyaura Coupling. *Organic Letters* **20**, 752–755 (2018).

358. Simpson, Q., Sinclair, M. J. G., Lupton, D. W., Chaplin, A. B. & Hooper, J. F. Oxidative Cross-Coupling of Boron and Antimony Nucleophiles via Palladium(I). *Organic Letters* **20**, 5537–5540 (2018).

359. Rafiq, S. & Mohanakrishnan, A. Synthesis of Annulated Arenes and Heteroarenes by Hydriodic Acid and Red Phosphorus Mediated Reductive Cyclization of 2-(Hetero)aroylbenzoic Acids or 3-(Hetero)arylphthalides. *Synlett* **28**, 362–370 (2016).

360. Tao, S., Liu, N. & Dai, B. One-pot two-step synthesis of N-arylcarbazole-based skeleton. *RSC Advances* **6**, 43250–43260 (2016).

361. Tang, J., Biafora, A. & Goossen, L. J. Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating ortho Substituents. *Angewandte Chemie International Edition* **54**, 13130–13133 (2015).

362. Shen, Z.-L., Sommer, K. & Knochel, P. Expedient Preparation of Aryllithium and Arylzinc Reagents from Aryl Chlorides Using Lithium 4,4′-Di-tert-Butylbiphenylide and Zinc(II) Chloride. *Synthesis* **47**, 2617–2630 (2015).

363. Chen, X., Zhou, L., Li, Y., Xie, T. & Zhou, S. Synthesis of Heteroaryl Compounds through Cross-Coupling Reaction of Aryl Bromides or Benzyl Halides with Thienyl and Pyridyl Aluminum Reagents. *The Journal of Organic Chemistry* **79**, 230–239 (2014).

364. Ghaleshahi, H. G., Antonacci, G. & Madsen, R. Manganese-Catalyzed Aerobic Heterocoupling of Aryl Grignard Reagents: Manganese-Catalyzed Aerobic Heterocoupling of Aryl Grignard Reagents. *European Journal of Organic Chemistry* **2017**, 1331–1336 (2017).

365. Bernhardt, S., Manolikakes, G., Kunz, T. & Knochel, P. Preparation of Solid Salt-Stabilized Functionalized Organozinc Compounds and their Application to Cross-Coupling and Carbonyl Addition Reactions. *Angewandte Chemie International Edition* **50**, 9205–9209 (2011).

366. Hua, X., Masson-Makdissi, J., Sullivan, R. J. & Newman, S. G. Inherent vs Apparent Chemoselectivity in the Kumada–Corriu Cross-Coupling Reaction. *Organic Letters* **18**, 5312–5315 (2016).

367. Liu, C., Ni, Q. & Qiu, J. Very Fast, Ligand-Free and Aerobic Protocol for the Synthesis of 4-Aryl-Substituted Triphenylamine Derivatives. *European Journal of Organic Chemistry* **2011**, 3009–3015 (2011).

368. Ackermann, L. & Althammer, A. Air-Stable PinP(O)H as Preligand for Palladium-Catalyzed Kumada Couplings of Unactivated Tosylates. *Organic Letters* **8**, 3457–3460 (2006).

369. Malapit, C. A., Ichiishi, N. & Sanford, M. S. Pd-Catalyzed Decarbonylative Cross-Couplings of Aroyl Chlorides. *Organic Letters* **19**, 4142–4145 (2017).

370. Erb, W., Albini, M., Rouden, J. & Blanchet, J. Sequential One-Pot Access to Molecular Diversity through Aniline Aqueous Borylation. *The Journal of Organic Chemistry* **79**, 10568–10580 (2014).

371. Kristensen, J., Lysén, M., Vedsø, P. & Begtrup, M. Synthesis of Ortho Substituted Arylboronic Esters by in Situ Trapping of Unstable Lithio Intermediates. 3.

372. Tang, J., Biafora, A. & Goossen, L. J. Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating ortho Substituents. *Angewandte Chemie International Edition* **54**, 13130–13133 (2015).

373. Gooßen, L. J., Rodríguez, N., Lange, P. P. & Linder, C. Decarboxylative Cross-Coupling of Aryl Tosylates with Aromatic Carboxylate Salts. *Angewandte Chemie International Edition* **49**, 1111–1114 (2010).

374. Roy, P.-P., D'Souza, K., Cuperlovic-Culf, M., Kienesberger, P. C. & Touaibia, M. New Atglistatin closely related analogues: Synthesis and structure-activity relationship towards adipose triglyceride lipase inhibition. *European Journal of Medicinal Chemistry* **118**, 290–298 (2016).

375. Parmentier, M., Gros, P. & Fort, Y. Pyridino-directed lithiation of anisylpyridines: new access to functional pyridylphenols. *Tetrahedron* **61**, 3261–3269 (2005).

376. Fang, W.-Y. & Qin, H.-L. Cascade Process for Direct Transformation of Aldehydes (RCHO) to Nitriles (RCN) Using Inorganic Reagents $NH_2OH/Na_2CO_3/SO_2F_2$ in DMSO. *The Journal of Organic Chemistry* acs.joc.8b03164 (2019) doi:10.1021/acs.joc.8b03164.

377. Luzung, M. R., Patel, J. S. & Yin, J. A Mild Negishi Cross-Coupling of 2-Heterocyclic Organozinc Reagents and Aryl Chlorides. *The Journal of Organic Chemistry* **75**, 8330–8332 (2010).

378. Tang, M. *et al.* Synthesis, characterization and optical properties of novel Ir(III) complexes bearing N-heterocycle substituents. *Journal of Organometallic Chemistry* **880**, 363–367 (2019).

379. Daniels, D., Brown, J., Gayral, M., Xu, Y. & Stewart, M. Disubstituted Benzenes from Acyclic Precursors by a [5+1] Annulation. *Synlett* **2009**, 1387–1390 (2009).

380. Nishida, H. *et al.* Exploration of pyrrole derivatives to find an effective potassium-competitive acid blocker with moderately long-lasting suppression of gastric acid secretion. *Bioorganic & Medicinal Chemistry* **25**, 3447–3460 (2017).

381. Kwon, J. & Kim, B. M. Synthesis of Arenesulfonyl Fluorides via Sulfuryl Fluoride Incorporation from Arynes. *Org. Lett.* **21**, 428–433 (2019).

382. Liu, S., Huang, Y., Xu, X.-H. & Qing, F.-L. Fluorosulfonylation of arenediazonium tetrafluoroborates with Na2S2O5 and N-fluorobenzenesulfonimide. *Journal of Fluorine Chemistry* **240**, 109653 (2020).

383. Liu, Y. *et al.* Arenesulfonyl Fluoride Synthesis via Copper-Catalyzed Fluorosulfonylation of Arenediazonium Salts. *Org. Lett.* **22**, 2281–2286 (2020).

384. Amarne, H., Baik, C., Murphy, S. K. & Wang, S. Steric and Electronic Influence on Photochromic Switching of N,C-Chelate Four-Coordinate Organoboron Compounds. *Chemistry – A European Journal* **16**, 4750–4761 (2010).

385. Kim, K. D. & Lee, J. H. Visible-Light Photocatalyzed Deoxygenation of N-Heterocyclic N-Oxides. *Org. Lett.* **20**, 7712–7716 (2018).

386. Mizuno, H., Takaya, J. & Iwasawa, N. Rhodium(I)-Catalyzed Direct Carboxylation of Arenes with CO2 via Chelation-Assisted C−H Bond Activation. *J. Am. Chem. Soc.* **133**, 1251–1253 (2011).

387. Deng, J. Z. *et al.* Copper-Facilitated Suzuki Reactions: Application to 2-Heterocyclic Boronates. *Org. Lett.* **11**, 345–347 (2009).

388. Vandromme, L., Reißig, H.-U., Gröper, S. & Rabe, J. P. Practical Routes to 2,6-Disubstituted Pyridine Derivatives. *European Journal of Organic Chemistry* **2008**, 2049–2055 (2008).

389. Hao, W., Xi, Z. & Cai, M. A Practical Synthesis of Biaryls and Aromatic Acetylenes by Stille Coupling in Room-Temperature Ionic Liquids. *Synthetic Communications* **42**, 2396–2406 (2012).

390. Yao, X. *et al.* Palladium-Catalyzed Cascade Reactions of δ-Ketonitriles with Arylboronic Acids: Synthesis of Pyridines. *ACS Comb. Sci.* **22**, 114–119 (2020).

391. Requet, A., Yalgin, H. & Prim, D. Convenient and rapid strategies towards 6-(hetero)aryl pyridylmethylamines: first catalytic issues. *Tetrahedron Letters* **56**, 1378–1382 (2015).

392. Elbert, B. L. *et al.* C−H Cyanation of 6-Ring N-Containing Heteroaromatics. *Chemistry – A European Journal* **23**, 14733–14737 (2017).

393. Metzger, A., Melzig, L., Despotopoulou, C. & Knochel, P. Pd-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles. *Org. Lett.* **11**, 4228–4231 (2009).

394. Yang, Q.-L. *et al.* Palladium-Catalyzed Electrochemical C–H Alkylation of Arenes. *Organometallics* **38**, 1208–1212 (2019).

395. Bartolomeu, A. de A., Silva, R. C., Brocksom, T. J., Noël, T. & de Oliveira, K. T. Photoarylation of Pyridines Using Aryldiazonium Salts and Visible Light: An EDA Approach. *J. Org. Chem.* **84**, 10459–10471 (2019).

396. Markovic, T., Rocke, B. N., Blakemore, D. C., Mascitti, V. & Willis, M. C. Catalyst Selection Facilitates the Use of Heterocyclic Sulfinates as General Nucleophilic Coupling Partners in Palladium-Catalyzed Coupling Reactions. *Org. Lett.* **19**, 6033–6035 (2017).

397. Chen, H.-J., Chiu, C.-C., Wang, T., Lee, D.-S. & Lu, T.-J. Bis-NHC–Ag/Pd(OAc)2 Catalytic System Catalyzed Transfer Hydrogenation Reaction. *Catalysts* **11**, 8 (2021).

398. Suzuki–Miyaura Cross-Coupling of Sulfoxides | ACS Catalysis. https://pubs-acs-org.scd-rproxy.u-strasbg.fr/doi/10.1021/acscatal.0c01462.

399. Yoshida, H., Okada, K., Kawashima, S., Tanino, K. & Ohshita, J. Platinum-catalysed diborylation of arynes: synthesis and reaction of 1,2-diborylarenes. *Chem. Commun.* **46**, 1763–1765 (2010).

Appendix

A. Prebiotic project

In parallel to the work on the Suzuki coupling, I applied my knowledge in transition-metal catalyzed C–C bond formation to a prebiotic project examining the emergence of ancient metabolic networks on the early earth. The Acetyl-CoA pathway, an ancient carbon-fixation pathway, was found to be feasible without any enzymes, using Fe(0) under pressure of CO_2 in water, with the addition of KCl. The formation of acetate, end-product of this pathway, was observed, which is a rare example of the formation of a C–C bond in water using relatively inert starting materials. Pyruvate, a C_3 compound was also formed, which corresponds to the first step of another ancient anabolic metabolic pathway: the reverse Krebs cycle or reverse tricarboxylic acid cycle.

These results were published in *Nature ecology and evolution* (vide infra).

To elucidate the mechanism, I carried out further experimental work to trap the postulated reactive Me-Fe species. Under the same reaction conditions, but with the addition of a nitrate salt, methylamine was observed, which confirms the Fe-Me mediated mechanism postulated in the aforementioned paper.

Other work was also carried out to find alternative conditions to form pyruvate form acetyl compounds via reductive carboxylation, under conditions analogous to the rTCA.

This work was not included in the present thesis due it its contrast with the chemistry exposed herein.

Paper on prebiotic carbon fixation project

See: Varma, S. J., Muchowska, K. B., Chatelain, P. & Moran, J. Native iron reduces CO 2 to intermediates and end-products of the acetyl-CoA pathway. *Nature Ecology & Evolution* **2**, 1019–1024 (2018).

B. Paper on the Suzuki coupling of aryl sulfones

See: Chatelain, P., Sau, A., Rowley, C. N. & Moran, J. Suzuki–Miyaura Coupling of (Hetero)Aryl Sulfones: Complementary Reactivity Enables Iterative Polyaryl Synthesis. *Angewandte Chemie International Edition* **58**, 14959–14963 (2019).

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The Suzuki Cross-Coupling of Aryl Sulfones and Sulfonyl Fluorides

Résumé

La réaction de Suzuki est une des méthodes les plus répandues pour former des liaisons carbone-carbone. Depuis sa découverte en 1979, de nombreuses méthodes ont été développées pour étendre cette méthode à d'autres électrophiles. Cette thèse décrit le couplage de Suzuki en utilisant des électrophiles soufrés robustes : les sulfones et les fluorures de sulfonyle. Ces deux groupements possèdent des propriétés uniques dans leur réactivité qui leur permettent d'être complémentaires aux électrophiles existants. Les sulfones peuvent être utilisés comme groupement directeur pour des fonctionnalisations *ortho*- *méta*- et *para*- sélectives et ont une réactivité intermédiaire qui permet la synthèse de terphényles à partir de sulfones d'aryles poly-fonctionnalisées. Les fluorures de sulfonyle ont l'avantage d'être réactifs en absence de base qui est normalement requise pour cette réaction. Ils sont principalement utilisés dans des réactions très efficaces et sélectives pour former des liaisons S–N, S–O ou S–C. La méthode développée ici permet la synthèse divergente de liaisons C–C à partir de ces substrats.

Mots-clés : Suzuki, couplage, palladium, sulfone, fluorure de sulfonyle, catalyse par métaux de transition, sans base, terphényles

Abstract

The Suzuki coupling is one of the preferred methods for the formation of carbon-carbon bonds. Since its discovery in 1979, much effort has been made to extend its scope to new, alternative electrophiles. This thesis describes the coupling of robust sulfur-based electrophiles: sulfones and sulfonyl fluorides. These functional groups present favorable properties that are not seen in electrophiles previously used in this reaction. Sulfones can be used as a directing group on arenes for selective *ortho*- *meta*- and *para*-functionalization and have a reactivity complementary to existing electrophiles, permitting the straightforward synthesis of terphenyls from polysubstituted arenes. Sulfonyl fluorides are mainly used in SuFEx chemistry, a branch of click chemistry used to form S–N, S–O and S–C bonds. The present method forms C–C bonds from sulfonyl fluorides, turning this functional group into a branching point for divergent synthetic schemes.

Keywords: Suzuki, coupling, palladium, sulfone, sulfonyl fluoride, transition-metal catalysis, base-free, terphenyls