BORON-MEDIATED THERMODYNAMIC RESOLUTION OF AXIALLY CHIRAL PYRIDINES AND ITS APPLICATION IN THE ASYMMETRIC TOTAL SYNTHESIS OF STREPTONIGRIN

The University Of Sheffield.

Department of Chemistry

A thesis submitted in partial fulfilment of the degree of Doctor of Philosophy

Luis Fernando Valdez Pérez

Supervisor: Prof. Joseph P. A. Harrity

September 2022

This thesis is dedicated to my mom, Alejandra, and to my brother Carlos.

Esta tésis está dedicada para mi mamá, Alejandra, y para mi hermano, Carlos.

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Abstract

Atropisomers represent an important class of chiral molecules and there are many prominent natural products and pharmaceuticals that exhibit atropisomerism, however general stereoselective synthetic routes to these compounds are relatively rare. In this work, we developed a novel thermodynamic resolution process that allows access to these compounds in enantioenriched form. This approach takes advantage of several features of organoboron chemistry:

- a mild boron-directed regioselective cycloaddition for the construction of highly functionalised pyridines;
- boron ligand substitution for the synthesis of chiral organoboronic esters;
- control of atroposelectivity through a dynamic resolution process that exploits the Lewis acidity of trivalent boron chemistry
- stereoretentive synthesis of atropisomeric products by virtue of the versatile organoboronic ester functional group;
- recycle of the minor diastereomer is possible thanks to the thermodynamic nature of the resolution.

Furthermore, the strategy is the first reported thermodynamic strategy for the resolution of atropisomers. The applicability of this method is further highlighted by the first highly enantioselective synthesis of streptonigrin. Even though this molecule has been deeply studied since its discovery in 1959 and is a very well-known example of atropoisomeric natural products, a synthetic method that allows access to this compound with high levels of enantiocontrol has been lacking until now.

Acknowledgements

First, I would like to thank Joe Harrity for giving me the opportunity to work in his research group. Joe, you have been the best supervisor I could have asked for. Thanks for all your support, time and mentorship. Being in your research group has allowed me to learn so much and how to think as a scientist. It was always a shot of energy to share the excitement of sharing new findings and the excitement when a problem was solved. I hope life keeps us in touch in the future and I am sure more exciting ideas and projects will come for you. Thanks for your trust, it was not an easy road, but we have made it :)

Thanks as well to all the Harrity group members that I have met during my PhD, I've learned something different from everyone, and even though it was though, the group helped me to shape the chemist I am today.

Chris, I learned a lot from you, and you were very supportive when I needed it, thanks for giving me a hand.

Dan, thanks for those talks about videogames and those science discussions. Keep being cool.

Jiaxin & Wenzheng, you guys are doing great. I admire you guys for being so hard-working, keep up the nice work!

Gianna, even though you were just in the group for 6 months, that time was enough to forge a very nice friendship. I visited more places in Sheffield when you were around than what I did in 3 years. I'm sure this friendship will be long lasting.

Lorena, no puedo creer lo afortunado que fui de que fueras mi terapeuta. Gracias a ti, me di cuenta lo que de verdad es vivir el presente, el *estar ahí*. Eres de las personas más chidas e inteligentes que he conocido, te admiro como no tienes una idea. Todo lo que aprendí de ti se quedará conmigo para toda la vida. Muchas gracias por todo.

Next, I would like to thank the most special person in my life, my mom. Gracias por todo tu amor y tu apoyo siempre, y este logró también es tuyo, por que has estado apoyándome en los éxitos, pero también en los momentos más duros. Siempre le agradeceré a la vida que me haya permitido ser tu hijo.

Paty, obesa del mal. Gracias a ti por estar para escuchar mis crisis y estar siempre ahí.

A mis amigos, Romina, Carlos, Felipin, Dulce. Me dolió mucho haber tenido que separarme de ustedes, pero a pesar de ello seguirán siendo mis amigos. Los admiro porque lo que han logrado y por lo que les falta por lograr. Muchas gracias por estar ahí amigos.

Sam! Eres de las personas más chidas y alivianadas que conozco, y también de las más me han echado la mano. Gracias por tantas pláticas, por ser una excelente compañía y por hacerme reír tanto.

Finalmente, quisiera darte las gracias, Víctor. Gracias por todo el amor y el apoyo que me disté desde que te conocí. Estuviste ahí para mí en las buenas y en las malas y siempre te lo agradeceré. Jamás olvidaré todo lo que vivimos juntos, y siempre te desearé nada más que lo mejor. De verdad espero que te vaya muy bien en la vida y que, cualquiera que sea el camino que tomes, siempre lo hagas por tu felicidad y bienestar. Te quiero mucho ratón, de verdad, gracias por todo.

And the rest of people, friends, family, and colleagues, who were alongside me during this journey, just for a moment or all of it, thanks for your support and time.

Gracias al Consejo Nacional de Ciencia y Tecnología (CONACYT) de México por la beca de doctorado otorgada para el desarrollo de este proyecto (CVU 903768).

Abbreviations

Ac	Acetyl
aq.	Aqueous
Ar	Aryl
au	Arbitrary Units
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BINOL	1,1’-bi-2,2’-Naphthol
br	Broad
BTC	Triphosgene
^{n}Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
Bz	Benzoyl
ca.	Circa (Approximately)
CAN	Ceric Ammonium Nitrate
cat.	Catalytic
Cy	Cyclohexyl
d.r.	Diastereomeric ratio
DCE	Dichloroethane
DCM	Dichloromethane
DHP	*O*-(2,4-Dinitrophenyl)hydroxylamine
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium Hydride
DIPEA	Diisopropylethylamine
DMAP	*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
EDCI	*N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride
e.e.	Enantiomeric excess

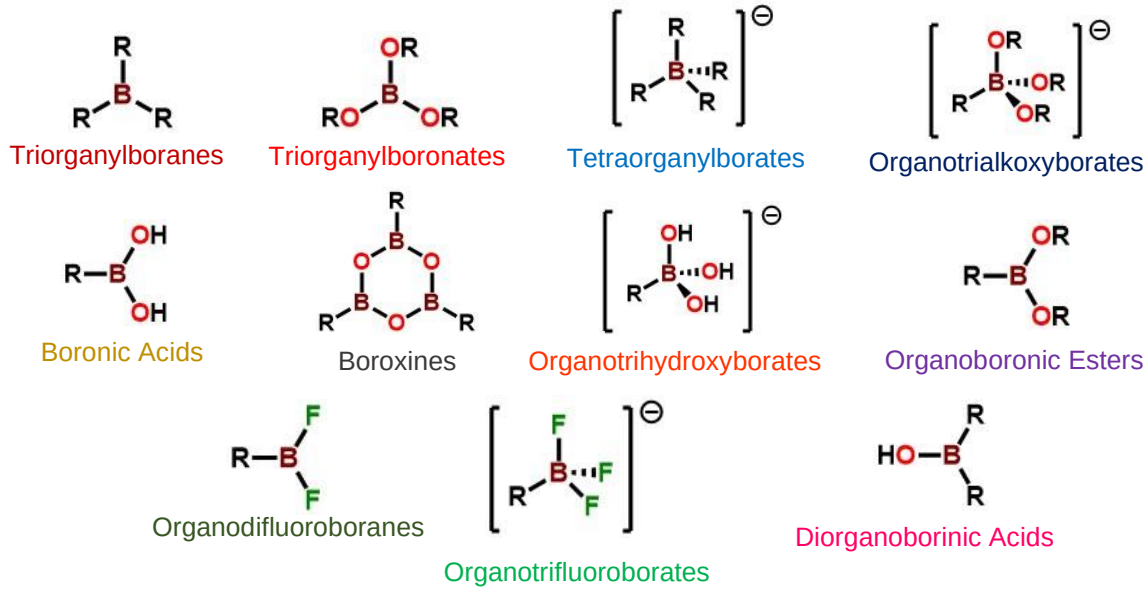
e.r.	Enantiomeric ratio
ESI	Electrospray Ionization
equiv.	Equivalent
Et	Ethyl
FTIR	Fourier-Transform Infrarred
GC	Gas Chromatography
HAS	Hydroxylamine-*O*-sulfonic Acid
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
IBX	*o*-Iodoxybenzoic Acid
Im	Imidazole
LC	Liquid Chromatography
LCMS	Liquid Chromatography-Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
***m*CPBA**	*meta*-Chloroperbenzoic Acid
Me	Methyl
min	Minute
M.P.	Melting Point
MS	Mass Spectrometry
Ms	Mesyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMM	*N*-Methyl Morpholine
NMP	1-Methyl-2-pyrrolidine
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
Ph	Phenyl
phen	1,10-Phenanthroline
PIDA	(Diacetoxy)iodo benzene

Pin	Pinacolato
^{i}Pr	*Iso*propyl
Prd	Product
Py	Pyridine
r.t.	Room temperature
SAM	*S*-Adenosyl methionine
SM	Starting Material
S_EA	Electrophilic Aromatic Substitution
S_N2	Bimolecular Nucleophillic Substitution
S_NAr	Nucleophilic Aromatic Substitution
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBA	Tetrabutylammonium
TC	Thiophene-2-carboxylate
Tf	Trifyl
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

Chapter 1. Introduction

1.1 Organoboron Compounds in Synthetic Organic Chemistry

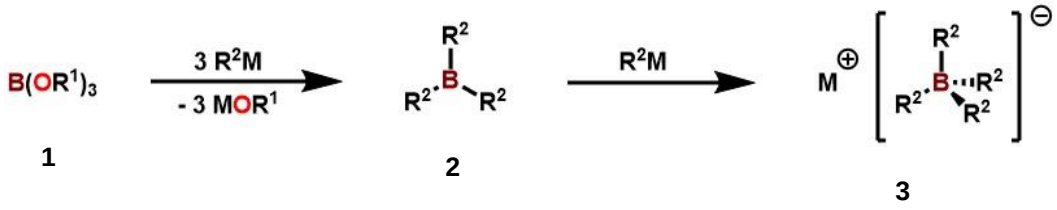
Organoboron compounds are important materials for a wide range of synthetic applications. The Lewis acidity of the boron atom provides remarkable properties to this class of compounds.[1] Such is the versatility of boron-containing compounds that the term "metallomimetic" has emerged to account for the similarities between some boron mediated processes and transition metal chemistry.[2]



Scheme 1. Common organoboron species found in organic chemistry.

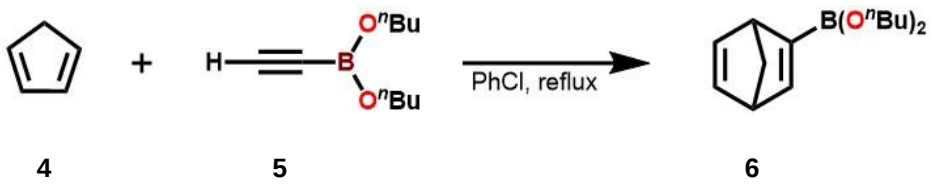
One of the most important applications of organoboron compounds are as starting materials for the Suzuki-Miyaura cross-coupling reaction. In this sense, the synthesis of boron-substituted aryls and heteroaryls is of relevance to modern synthetic chemistry. Common methods for their synthesis often require the use of stoichiometric amounts of main-group organometallics, such as organolithium or Grignard reagents.[3] The drawback here is that these reactions show limited functional group tolerance. Also, care must be taken when using

strongly nucleophilic organometallics for the synthesis of organoboron compounds **2**, as an excess of these reagents often leads to the formation of the corresponding borate species **3** (Scheme 2).



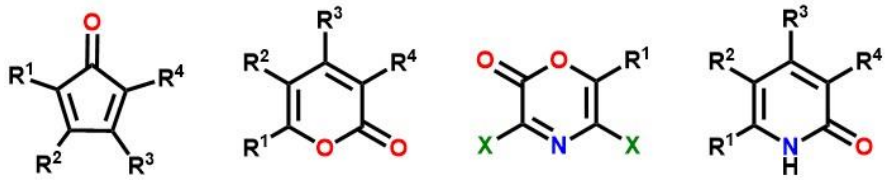
Scheme 2. Formation of organoboron compounds 2 and borate species 3 with main-group organometallics (M = Li, Mg) starting from a trialkyl borate 1.

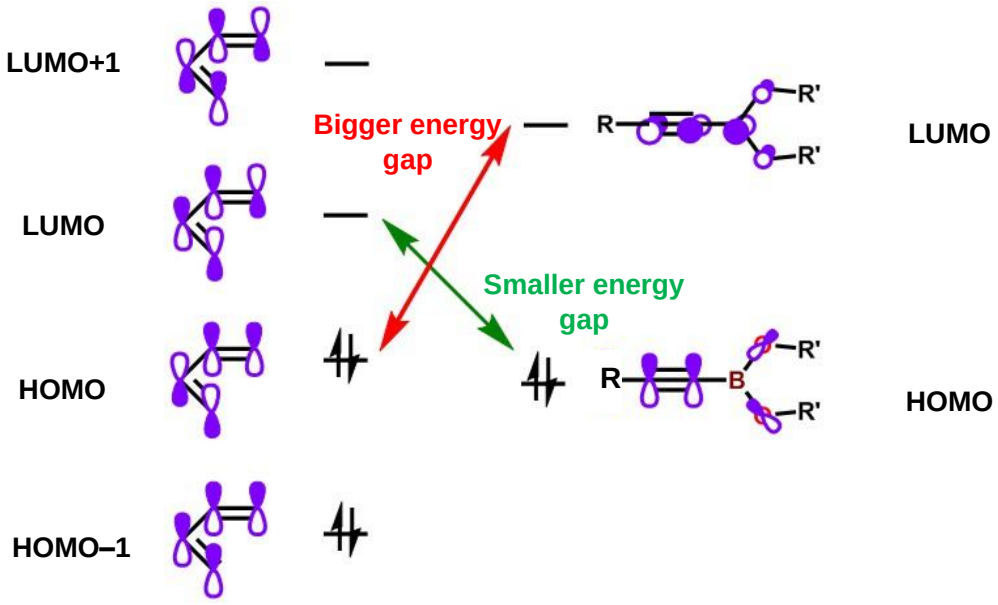
The use of organoaluminium compounds does not impose this problem, however, these reactants are usually pyrophoric and represent a practical danger.[4] Milder conditions for the synthesis of organoboron compounds using transition-metal catalysis have emerged as alternatives for the synthesis of boron-containing aromatics and heteroaromatic analogues.[5] Complementary to these approaches is a cycloaddition strategy which consists of the construction of the ring and integration of the boron functionality in the same step. A common example of this approach is the [4 + 2] cycloaddition reaction using alkynylboronates as dienophiles.[6,7] Early examples of this methodology focused on the reaction of cyclopentadiene **4** with dibutyl ethynylboronate **5,** giving a norbornadieneboronate **6** (Scheme 3).[8]



Scheme 3. [4 + 2] Cycloaddition of 5 with cyclopentadiene.

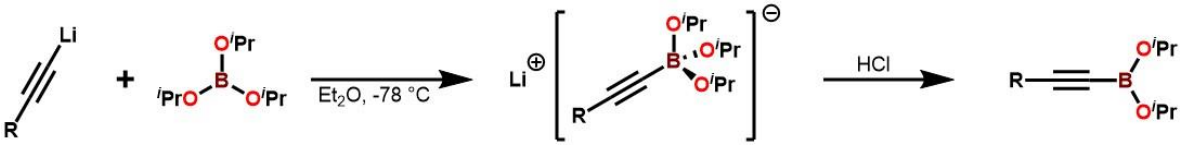
Alkynylboronates act as electron-rich dienenophiles in [4 + 2] cycloadditions and react with electron-deficient dienes in an inverse-electron demand cycloaddition event. This observed reactivity is due to the π-backdonation of electron density from the oxygen atoms' lone pairs to the vacant *p* orbital on boron, making the LUMO too high in energy to react with the HOMO of an electron-rich diene. Correspondingly, the HOMO of alkynylboronates is increased in energy, thus it interacts with the diene's LUMO (**Scheme 4**).[6] These Diels-Alder reactions proceed with cyclopentadienones **7**, pyrones **8**, 3,5-dihalo-2*H*-1,4-oxazin-2-ones **9**, and 2[1*H*]-pyrazinones **10**.[9]





Scheme 4. Sketch of frontier molecular orbitals of a diene and an alkynylboronate, respectively.

Alkynylboronates can be prepared from the reaction of alkynyllithium reagents **11** with tri(*iso*propyl) borate **12**. The reaction initially gives lithium (alkynyl(triisopropoxy))borates **13**, which, upon treatment with anhydrous HCl, produce alkynylboronates **14** (**Scheme 5**).[10] Different esters can be prepared by transesterification of the alkynylboronates **14**, or by using a different borate from the start.

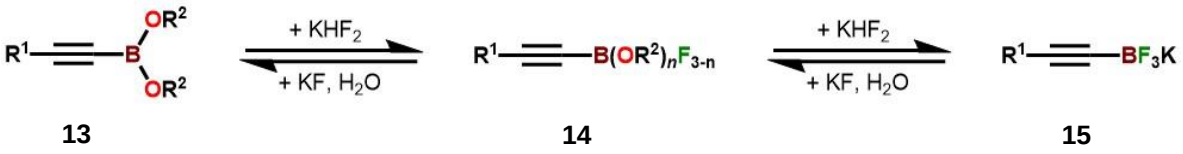


11 **12** **13** **14**

Scheme 5. Synthesis of diisopropyl alkynylboronates.

Other pathways involve transition-metal,[11] or lanthanide,[12] catalysed dehydrogenative coupling of terminal alkynes with hydroboranes.

Organoboronic esters are prone to hydrolysis and organoboronic acids can be susceptible of oxidation if stored under ambient conditions, thus bringing a practical problem to their use, purification and storing. Also, extremely dry conditions can also be harmful, particularly to organoboronic acids, as they may form unreactive boroxines that affect their reactivity and are difficult to characterize.[13] As an alternative, organotrifluoroborates have emerged as superior boron species in comparison.[14] Such species form stable potassium salts that are often monomeric, crystalline solids, which are highly air and moisture stable with indefinite shelf lives. Potassium alkynyltrifluoroborates **15** can be prepared from the respective boronic acids or boronic esters **13** by their treatment with inexpensive KHF_2 (**Scheme 6**).[15]

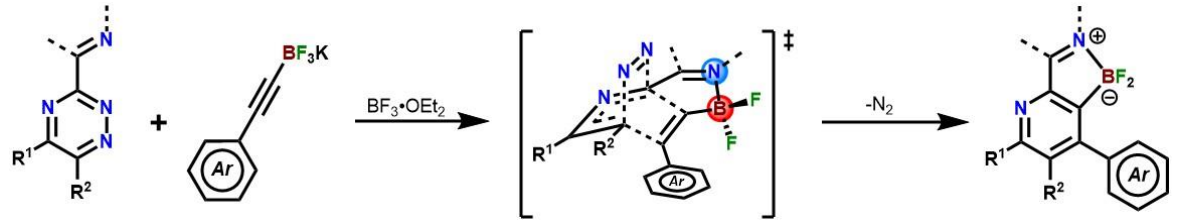


13 14 15

Scheme 6. Synthesis of potassium alkynyltrifluoroborate salts.

1.2 The Boron-Directed Cycloaddition Strategy

Although alkynylboron compounds are suitable components in [4 + 2] cycloadditions, yields tend to be good at best, with harsh conditions and long reaction times often required.[16] Another problem that can arise is the regioselectivity of the cycloaddition. While steric hindrance can serve to direct the outcome of the reaction, most of the times a lack of control is observed. As a solution, the idea of taking advantage of the Lewis acidic properties of boron, originated within the research group. This idea consists of the integration of a Lewis basic group to the diene fragment. So, as the reaction proceeds, the formation of a Lewis acid-base complex will control the outcome of the cycloaddition reaction (**Scheme 7**).[17]



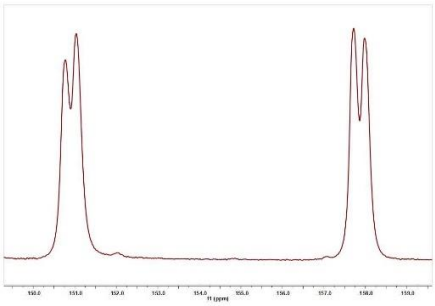
16 17 TS1 18

Scheme 7. Boron directed [4 + 2] cycloaddition of 1,2,4-triazines and potassium alkynyltrifluoroborate salts in the presence of BF_3.

The use of Lewis acid-base directed cycloadditions is of huge relevance to this project. Specifically, we aimed to use this methodology for the preparation of biaryl products **18** by the reaction of potassium (aryl)alkynyltrifluoroborate salts **17** with 1,2,4-triazines **16**. In this

sense, 1,2,4-triazines, equipped with a Lewis basic group, undergo [4 + 2] cycloaddition reactions with the trifluoroborate salt *via* an inverse electron-demand *aza*-Diels-Alder reaction. This process ultimately gives rise to highly substituted pyridines with a boron-functional group (incorporated as a BF_2 moiety), coupled to an aryl ring. Upon the addition of a fluorophilic Lewis acid, such as BF_3, the trifluoroborate is converted to a highly Lewis acidic difluoroborane (RBF_2). This promotes coordination between the boron atom and the Lewis basic group, allowing the regioselectivity of the reaction to be controlled.

The reaction initially proceeds to form a bridged bicyclic transition state **TS1**, which expels a molecule of N_2, giving the desired pyridine. The formation of the Lewis acid-base complex allows the reaction to proceed regioselectively under mild conditions and short reaction times. In principle, other aromatic cyclic scaffolds can be prepared, by varying the benzenoid diene employed. An unexpected observation from this chemistry was that ^{19}F NMR spectra of organodifluoroborane products **18**, such as **19**, with unsymmetrical southern aryl rings showed an AB doublet spin system rather than an expected singlet.



19

Scheme 8. ^{19}F NMR (377 MHz, $CDCl_3$) spectrum of compound 19. δ –150.9 (d, *J* = 95.9 Hz), –157.9 (d, *J* = 96.7 Hz).

After further analysis it was realized that the reason behind this observation is that such F atoms are diastereotopic. This phenomenon arises because of the restricted rotation around

the newly formed biaryl single bond giving place to a racemic mixture of axially chiral (*vide infra*) biaryl pyridines and thus to the observed ^{19}F NMR spectra.

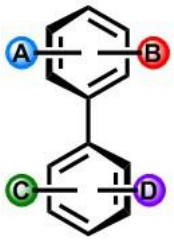
1.3.1 Atropisomerism

The isomerization caused by the restricted rotation around a single bond receives the name of ***atropisomerism***. It was first reported by Christie and Kenner back in 1922 when they were investigating biaryl 6,6'dinitro-2,2'-diphenic acid.[18] The term atropisomerism comes from the Greek "***a***", which means "not" or "without" and "***tropos***", which means "turn". Interestingly, these isomers lack stereogenic centres, yet they exist as enantiomers. Later, it was proposed that atropisomers should be separable if they possess a half-life of at least 1000 s (16.7 min).[19] With a progressive demand for this type of compounds, the term "***atroposelective***" was coined to qualify those reactions featuring the synthesis of atropoisomeric compounds, mainly biaryl systems, with good stereocontrol.[20]

Let us consider a biaryl system of the type of **20**.

There may be 3 possible situations:

1) **A** ≠ **C** and **B** ≠ **D**
2) **A** = **C** and **B** = **D**
3) **A** = **C** = **B** = **D**



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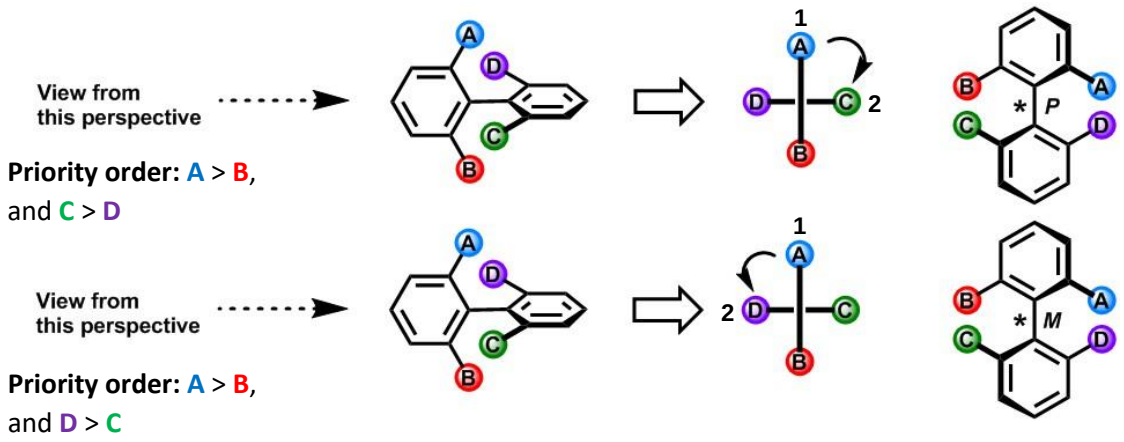
In the first case, the molecule will be clearly atropisomeric as long as the rotation of the biaryl axis is constrained enough. If **A** = **C** and **B** = **D**, as in the second case, the molecule is C_2-symmetric but still chiral (again, assuming restricted rotation about the biaryl bond). Even for the third case, the molecule may be chiral if the substituents are joined by a bridge.[21]

These D_2-symmetric species lack reflection planes, failing to possess an S_n axis and thus they show chirality.

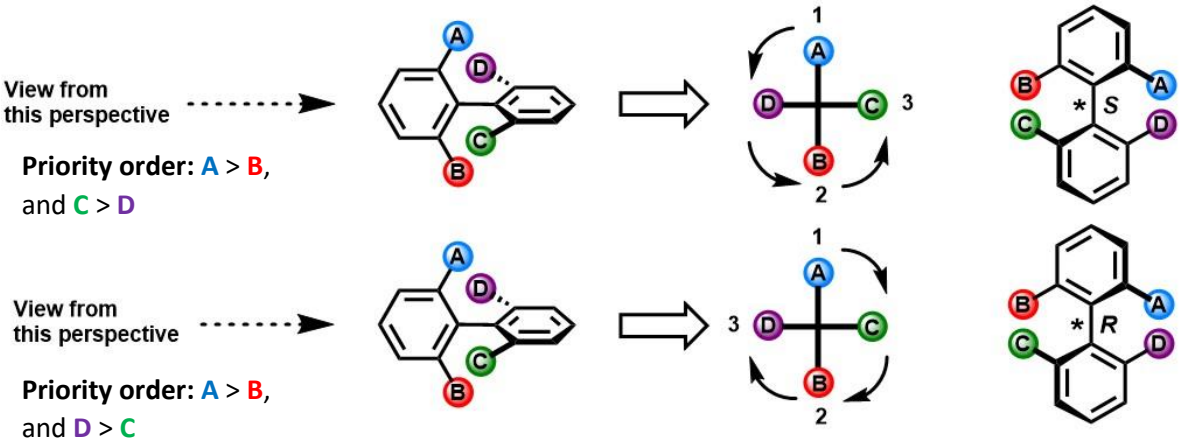
To assign the absolute configuration of these systems, one must draw a Newman projection along the biaryl bond. This will show a proximal and a distal ring, respectively. The proximal ring is set such that the higher-priority *ortho*-group, according to the Cahn-Ingold-Prelog rules, is up and the lower-priority *ortho*-group is down. In this projection, the rings are set such that they form a 90º angle. Then the shortest path from the higher priority group from the proximal ring to the higher priority one in the distal ring is drawn. If the path drawn is counterclockwise, then the configuration is *M* (minus); if it is clockwise, then the configuration is *P* (plus) (**Scheme 9**). The assignment of configuration is similar in prochiral systems, in which the descriptors used are pro-*M* and pro-*P*.



Scheme 9. Assignment of absolute configuration in atropisomeric biaryl compounds with helicity rules.

It is also possible to assign the absolute configuration using the classical *R* and *S* stereochemical descriptors as in compounds with central chirality. The procedure is similar as in the assignment of *M* and *P* descriptors, the difference relays in the priority group order assignment. In this system, the two *ortho* groups on the proximal ring are assigned a priority according to the Cahn-Ingold-Prelog rules, these will become one and two, respectively. The

third group in overall priority is the one with major priority on the distal ring. Once priority of groups has been assigned, the direction of the path from one to two to three gives the stereochemical descriptor; if it is clockwise then stereochemistry is *R*, if it is counterclockwise then it is *S*.



Scheme 10. Assignment of absolute configuration in atropisomeric biaryl compounds with *R* and *S* stereodescriptors.

Although more familiar, this system has become less popular due to confusions and misassignments of the stereochemistry. A common mistake made while assigning the priority of groups is doing it regardless of the location of the groups with respect to the ring systems, leading to the wrong descriptor being assigned. The most important thing to remember is that only the groups in the proximal rings can have priority one and two, respectively, and only the groups in the distal rings can have priority three and four, respectively.

The key condition for atropisomeric compounds to exist as isomers is the rotational stability of the bond connecting the two rings. In contrast to conformationally fixed stereogenic centres, which racemize *via* bond breaking/bond forming processes, racemization in atropoisomeric compounds involves a dynamic intramolecular process where only bond rotation is needed to undergo racemization. In this sense, temperature plays an important role.

If the temperature is sufficiently low, even ring systems with low sterically demanding groups may exhibit atropisomerism.[20] On the other hand, heating biaryl compounds may cause atropisomerisation, resulting in a thermodynamic equilibration that causes complete loss of the stereochemical information.[22]

Consequently, a brief discussion of the factors that affect the configurational stability of axially chiral biaryl systems is relevant; these factors are:

- The steric demand of the substituents near the axis
- The presence of bridges and their rigidity
- The mechanisms involved in atropisomerisation

Regarding the third factor, the physical mechanism of atropisomerisation refers to the actual rotation along the C–C bond connecting both ring systems. Quantum-chemical calculations have shown that the isomerization occurs by distortion of the bonds to the *ortho*-substituents and the aryl rings, such that the substituents can pass each other.[23] Other mechanisms involve chemical or photochemical promotion of the isomerization process (*vide infra*).

1.3.2 Atropisomerism. Effect of Substituents

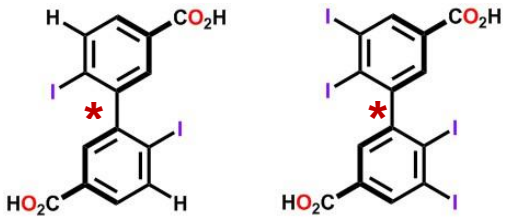
The substitution pattern on the rings around a chiral axis may have a profound influence on the rotational barrier of biaryl compounds. In the first place, *ortho* substituents must be considered, which increase the rotation barrier by their steric repulsion. Generally speaking, the bigger their van der Waals radii,[24] the larger the effect they exert and thus the more

rotational stability they can provide. In this sense, common substituents can be arranged according to this parameter as follows:

$$I > Br > Me > Cl > NO_2 > CO_2H > OMe > F > H$$

The number of *ortho*-substituents in the biaryl compound is also important to consider. Mono-*ortho*-substituted biaryl compounds do not form stable atropisomers at room temperature. Di-*ortho*-substituted analogues can form stable atropisomers at room temperature only if their substituents are large enough, while tri-*ortho*-substituted biaryl compounds are normally able to form stable atropisomers.[25,26] This is because, in the transition state, two non-hydrogen substituents must pass each other regardless of direction of rotation. Nevertheless, if the substituents are not big enough, then slow rotation of the axis is permitted, and the stability of rotation diminishes. Atropisomerism is nearly always obtained with *tetra*-substituted compounds even with low demanding substituents.[27] The rotational barriers in these compounds can get so high that the atropisomerization temperature cannot be reached and decomposition of the biaryl compound occurs first.[20]

Furthermore, *meta*-substituents can also influence atropisomerism. These substituents can increase rotational stability by "pushing" the *ortho*-substituents closer to the axis. This pushing effect can prevent the *ortho* substituents from bending out of the way in the transition state (**Scheme 10**).[24]

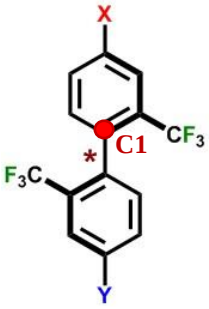


21 **22**

$\Delta G^{\ddagger}_{298\,K}$ = 98 kJ·mol^{-1} $\Delta G^{\ddagger}_{298\,K}$ = 126 kJ·mol^{-1}

Scheme 10. Effect of *meta*-iodo atoms in the rotational barrier of 2,2'-diiodo-diphenyl-5,5'-dicarboxylic acid.

Finally, *para*-substituents may have an impact the rotational barrier as well, albeit this is typically an electronic effect. Electron donation from these substituents increases the sp^3 character at C1, thus changing the geometry at that carbon and facilitating the ability of the *ortho*-substituents to bend out of the plane in the transition state. The change of hybridization implies a lengthening of the bond, which will decrease the steric repulsion of the substituents.[20] Following the same logic, electron-withdrawing groups increase the rotational barrier as they decrease the electron density on C1 and make it more difficult to bend the *ortho*-substituents out of the plane (**Scheme 11**).



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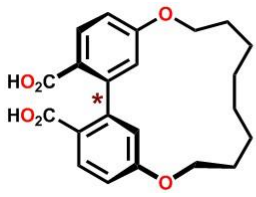
X	Y	$\Delta G^{\ddagger}_{298\,K}$/kJ·mol^{-1}
H	H	107
NH_2	NH_2	100
OMe	OMe	102
NH_2	H	102
OMe	H	104
NO_2	H	108
NO_2	NO_2	110

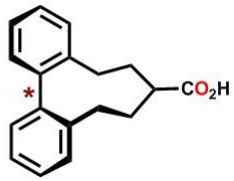
Scheme 11. Effect of *para*-substituents in the rotational barriers of 2,2'-bis(trifluoromethyl)-4,-4'-di-substituted biphenyls 23.

1.3.3 Atropisomerism. Bridges in Biaryl Systems

The presence of a bridge between the two ring systems may, or may not, affect the isomerization barrier; the determining factor here lies on the size of the ring. For example, connecting two *ortho*-carbon atoms with a single atom to generate a five-membered ring results in free rotation at room temperature.[28] Changing to a six-membered ring bridge makes rotation less accessible. The presence of stereogenic centres in the bridges can also influence atropisomerisation. This occurs because exocyclic substituents adopt their thermodynamically most favourable conformation, favouring one atropisomer in the process.[20] Larger bridges may cause atropisomerisation by geometrical constraints of the ring. Compounds **24** and **25** are examples of this situation.[29,30] Even with small steric hindrance, large bridges may be capable of inducing atropisomerism.



24

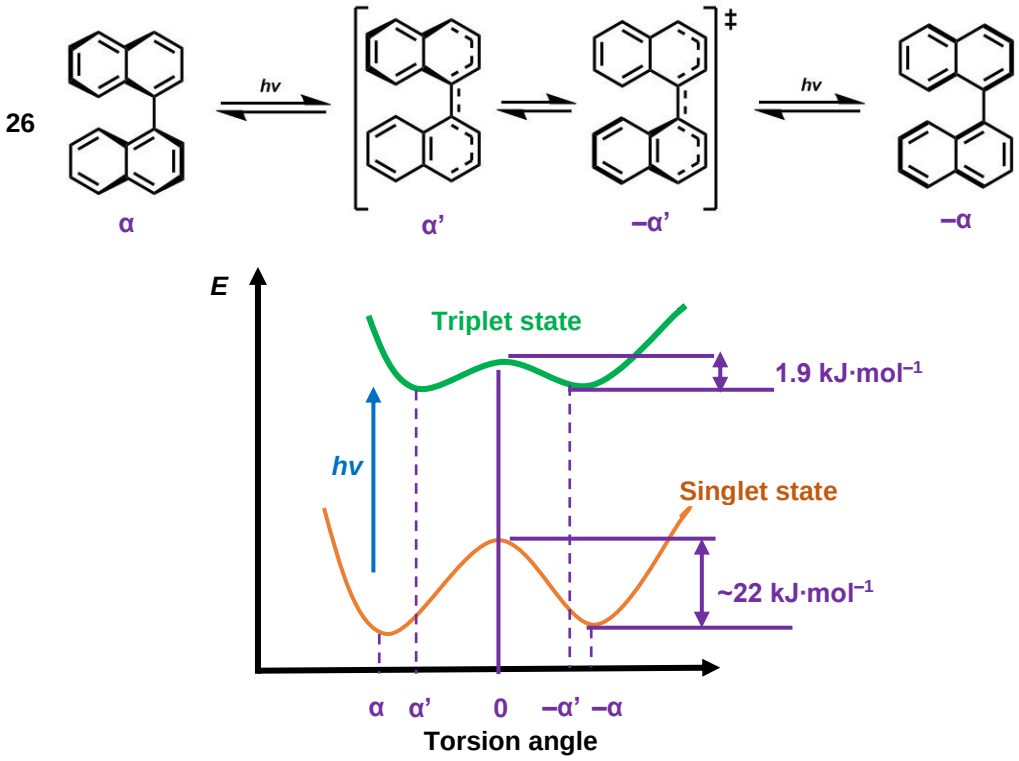


25

1.3.4 Atropisomerism. Alternative Atropisomeriztion Mechanisms

Previously, it was stated that there are mechanisms different from the physical restriction of rotation that can influence atropisomerization equilibria. One of such mechanisms is photoinduction. It has been observed that, upon irradiation with light, enantioenriched mixtures of biaryl compounds can undergo racemization. The mechanisms suggested for this vary according to the molecular structure of the compounds.[31,32] In the case of 1,1'-

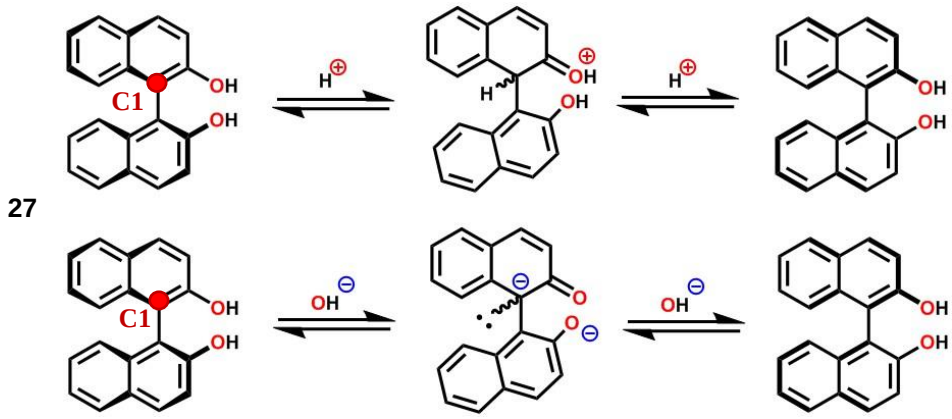
binaphthyl **26**, it has been proposed that irradiation with light induces racemization *via* excitation to the triplet state. The diradical character causes the aryl-aryl bond order to increase, thus the structure flattens and the rotational barrier decreases (**Scheme 12**).[31]



Scheme 12. Photoracemization of 1,1'-binaphtyl 26.

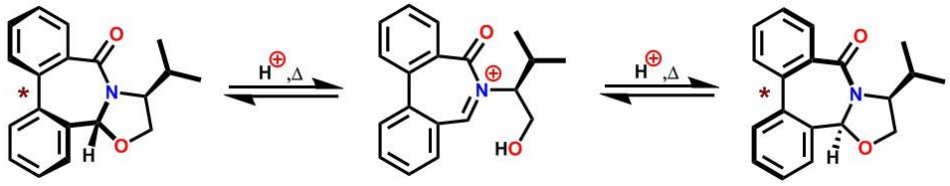
Other mechanisms may involve racemization in the presence of a chemical stimuli, such as the presence of acid.[22] BINOL **27** is rotationally stable even upon heating at 100 °C for 24 h under neutral conditions. In acidic media however, **27** racemizes within 24 h at 100 °C. Once protonation occurs, there is a change in the hybridization of C1, which facilitates the bending of the substituents. This geometrical change favours racemization. In a similar way, subjecting **27** to basic conditions also causes racemization, presumably by formation of a

bisphenolate dianion that increases the electron density at C1, generating a sp^3-hybridized carbanion that lowers the rotational barrier (**Scheme 13**).



Scheme 13. Acid and base induced racemization of BINOL.

Cyclic lactam **28** offers another example to illustrate this mechanism. Addition of acid makes **28** undergo racemization in 3 days with addition of a catalytic amount of *p*-toluenesulfonic acid (**Scheme 14**). In this case, not only there is a change of hybridization that alters the integrity of the biaryl axis configuration, but also the cleavage of the fused oxazolidine ring also favours loss of structural integrity, further facilitating atropisomerization.[33]

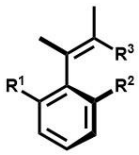


Scheme 14. Acid-catalysed atropisomerization of bridged biaryl lactam 28.

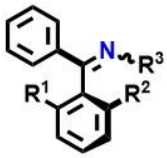
1.3.5 Atropisomerism. Non-Biaryl and Heterobiaryl Systems

Although not relevant for this work, it should be noted that atropisomers are not only limited to biaryl systems. Other functionalised aryl rings can present atropisomerism under appropriate circumstances.[34] There is a growing library of compounds with C_{sp2}–X (X = C, N, P, O, S) rotationally hindered bonds which includes, but is not limited to:

C-C bonds

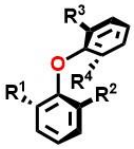


Styrenes



Imines

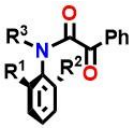
C-O bonds



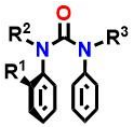
Diaryl ethers

C-N bonds

Anilides

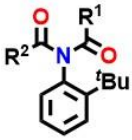


Oxoamides

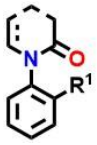


Ureas

Carbamates

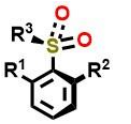


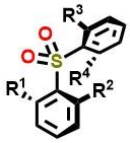
Acyclic imides



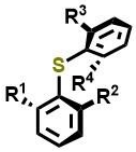
Lactams

C-S bonds

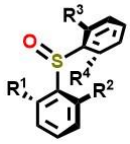




Sulfones



Sulfides

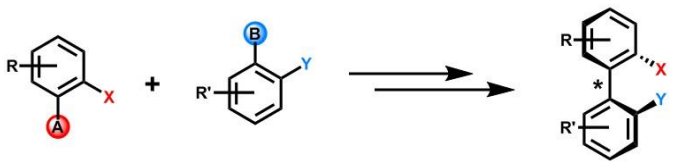


Sulfoxides

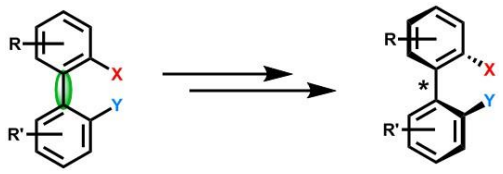
1.4 General Strategies for the Atroposelective Synthesis of Axially Chiral Biaryl Compounds

There are three general strategies towards the atroposelective synthesis of biaryl compounds:

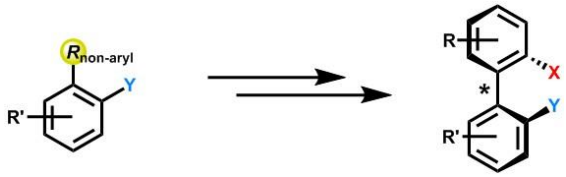
1) Direct-Atroposelective Biaryl Coupling Strategies



2) Resolution or Desymmetrization Strategies

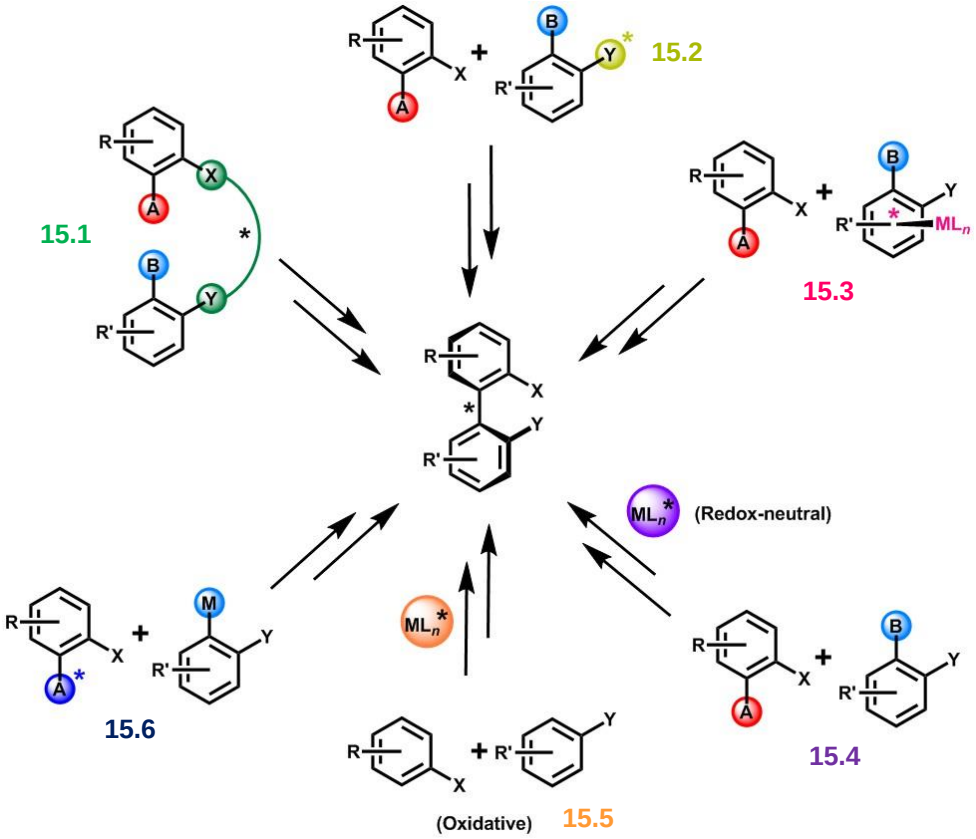


3) Cyclization Strategies



1.5 Direct Atroposelective Biaryl Coupling Strategies

Cross-coupling strategies involve the construction of the biaryl system by direct atroposelective formation of the biaryl bond. Atroposelectivity is achieved by several different approaches (**Scheme 15**). The first one, involves the presence of a chiral bridge that joins the rings and introduces the stereochemical information; once the coupling has been performed, the bridge can be detached (**15.1**). A second approach involves the presence of a chiral *ortho* substituent (**15.2**). Thirdly, a traceless removable chiral element can be used; this has been done by using planar η^6–chromium complexes (**15.3**) or, in a different approach, with the presence of a chiral leaving group in one of the rings (**15.6**). Other strategies involve the redox-neutral (**15.4**) or oxidative coupling (**15.5**) of the ring systems with chiral organometallic complexes to provide stereochemical information. The construction of biaryl systems quite often requires harsh conditions that can affect the atropisomeric ratio of the products, so a balance must be found such that the coupling takes place with integrity of the stereochemical selectivity. A summary of the advantages and disadvantages of these strategies is presented in **Table 1**.

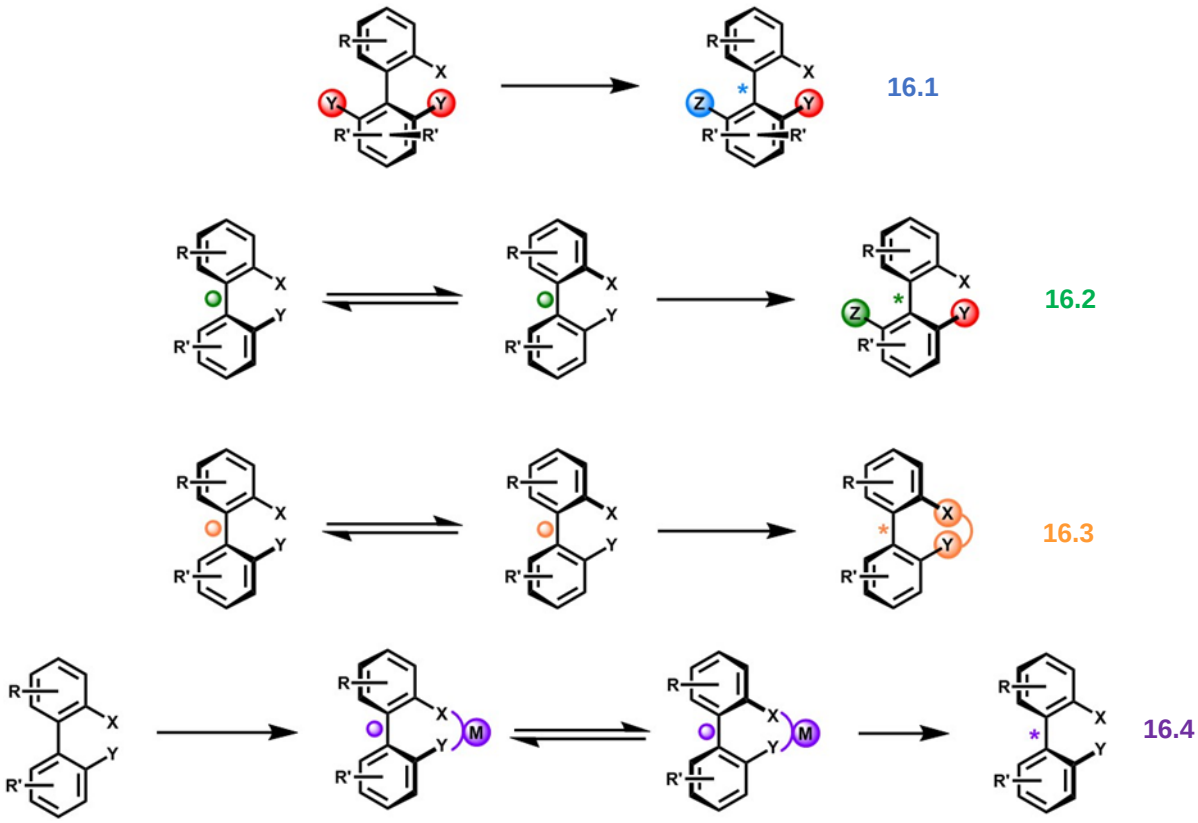


Scheme 15. Direct atroposelective biaryl coupling methodologies.

Table 1. Summary of direct atroposelective biaryl coupling strategies			
Strategy	**Functional Group Requirement**	**Pros**	**Cons**
Direct Intramolecular Diastereoselective Biaryl Coupling with Chiral Bridges[35–39]	Common bridges require carboxylic acid, phenol, and aldehyde functionalities.	Large bridges (7-membered and higher-membered rings) can induce atroposelectivity even with low steric demanding substituents *ortho* to the biaryl bond.	Both ring fragments require carboxylic acid, phenol, and aldehyde functionalities *ortho* to the position where the biaryl bond is going to be formed.
			Bridge-forming and bridge detaching steps must be included in the synthetic sequence.
Intermolecular Coupling with Chiral *ortho* Substituents[40–44]	A chiral auxiliary *ortho* to the biaryl bond.	Only one ring fragment equipped with the chiral auxiliary is needed.	So far, only chiral oxazolines have been deeply investigated.
			A chiral detachment step is usually needed.
Intermolecular Coupling with an Element of Planar Chirality[45–48]	$Cr(CO)_3$ fragment has to be installed in the aryl halide ring.	The presence of $Cr(CO)_3$ accelerates oxidative addition of the aryl halide.	The metallation step of the $Cr(CO)_3$ fragment is not always efficient.
		Detachment of the Cr fragment is traceless.	The use of toxic Cr opposes to the principles of green chemistry.
Redox-Neutral Cross-Coupling Catalysed by Chiral Metal Complexes[49–52]	Only an halide (typically Br or I) and an aryl boronic acid.	Chiral induction is achieved with chiral ligands, so no strict functionalities are required in any of the ring fragments other than the needed for the cross-coupling.	Often, long reaction times and high temperatures are needed, which can affect the stereochemical outcome.
		No extra synthetic steps need to be considered.	Hydrodehalogenation and proto-deboronation side reactions are common.
			The Suzuki-Miyaura cross coupling is usually susceptible to steric hindrance near the coupling site.
Oxidative Coupling in the Presence of Chiral Additives[53–55]	Usually only hydroxy groups *ortho* to the coupling site are needed.	Symmetrical fragments can be easily prepared.	Only symmetrical fragments have been fully exploited.
Intermolecular Coupling with Chiral Leaving Groups[56–59]	A chiral leaving group at the coupling site.	Biaryl bond formation and detachment of the chiral auxiliary are made in the same step.	A chelating substituent ortho to the chiral leaving group is needed.
			The ring fragment bearing the chiral auxiliary must be suitable for a S_NAr reaction.

1.6 Desymmetrization and Resolution Techniques

An alternative strategy to target atroposelectivity is through desymmetrization or resolution (**Scheme 16**); in these cases, there must be a pre-formed axis that can be achiral, but rotationally hindered, or asymmetric but rotationally unstable. For the first situation to be met, one of the ring systems must be symmetric. In this sense, a transformation of one of its substituents will break the symmetry and produce a chiral biaryl product. Biaryl products meeting this situation are candidates to undergo a desymmetrization process (**16.1**).[60–62] Regarding the second criterion, one may start from a mixture of atropisomers that interconvert rapidly due to a low rotational barrier. The atropodifferentiation can be made by a dynamic kinetic resolution process. Within this methodology, there are different strategies towards the resolution process. The first strategy is the selective transformation/addition of one *ortho*-substituent in just one atropisomer, locking its configuration in the process (**16.2**).[63–65] The second strategy is to promote a dynamic kinetic resolution *via* formation of a bridge (**16.3**). Again, the bridge-forming reaction must be selective towards just one atropisiomer, or provide chiral information, so that only one isomer is favoured. This approach also requires the bridge to provide enough stability such that the ring systems do not easily rotate.[33,66,67] As discussed previously, short bridges tend not to be rigid enough and fail to provide the configurational stability required. For these situations, a dynamic kinetic resolution by cleavage of a bridge can be employed.[20,68–70] Finally, configurationally stable atropisomers may undergo formation of a transient bridge (*via* a chelation process) and a subsequent dynamic resolution that result in bridge cleavage leads to the resolution of racemic mixtures (**16.4**).[71–73]

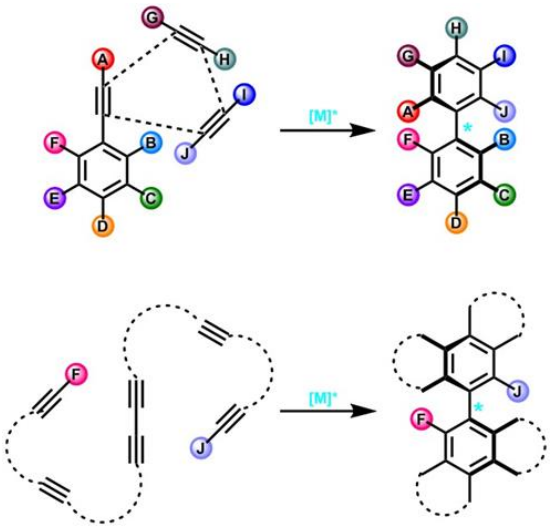


Scheme 16. Desymmetrization and resolution strategies for atropodifferentiation.

1.7 Cyclization Strategies

Of all the strategies available, the cyclization one is the least exploited to date. Basically, the concept relies on the construction of the aryl systems from preformed C–C bonds. Therefore, these previously linked carbon fragments must be able to undergo benzannulation reactions. The most explored methods so far are based on [2 + 2 + 2] cycloaddition reactions. The method is quite versatile in the sense that the rings to be made do not require any strict substitution pattern. Alternatively, one can start from a prebuilt C_{aryl}-C_{alkyne} unit, in which the aryl may possess any substitution pattern, or from hexynes constructed stepwise *via* Sonogashira coupling reactions (**Scheme 17**). Although transition-metal-catalysed [2 + 2 + 2]

cycloadditions have been reported before, only recently atroposelective examples have appeared in the literature.[74]



Scheme 17. Approaches towards the cyclization strategy.

Currently available catalysts for this chemistry include chiral Co^{I} cyclopentadiene complexes, neutral Ir^{I} and cationic Rh^{I} complexes. In the cases of Rh and Ir catalysts, chirality induction is made by using commercially available axially chiral bisphosphine ligands. In particular, cobalt complexes have been employed for the construction of axially chiral aryl-pyridines and biaryl phosphorus compounds.[75,76] Iridium complexes have been found to be suitable for the [2 + 2 + 2] cycloadditions of diynes, tetraynes, and hexaynes with aryl groups at the termini. The bigger size of Ir makes its compounds more suitable for these type of transformations.[77,78] On the other hand, rhodium complexes are useful for the atroposelective [2 + 2 + 2] cycloadditions of electron-rich alkynes and electron-deficient unsaturated compounds, such as electron-poor alkynes, nitriles, and isocyanates.[79,80]

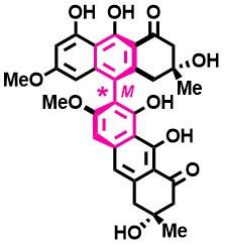
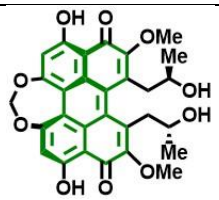
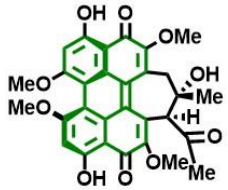
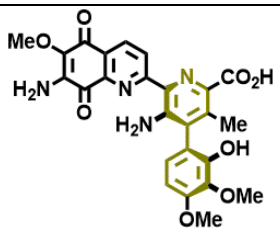
Although the synthetic toolbox for the atroposelective synthesis of biaryl compounds contains several interesting methodologies, not all of them are suitable for every situation.

To date, there is still not a general strategy for the *atropo*selective synthesis of biaryl systems and each situation must be studied individually to stablish the best synthetic approach.

1.8 Atropisomerism in Natural Products

The discovery and synthesis of natural products that contain axially chiral elements have attracted the attention of synthetic organic chemists not only because of their promising pharmaceutical activities, but also because of the intellectual and practical challenges that their syntheses represent. The most difficult challenge is achieving the synthesis with satisfactory atropo-stereoselectivity. The synthesis must be cleverly designed, so that no undesired atropisomerizaton takes place during the synthesis. Once the chiral axis has been installed, subjecting synthetic intermediates to harsh conditions such as high temperatures, light, acids, or bases, may erode *atropo*-stereointegrity of the following intermediates, or even, the final product. Also, isolation protocols must be carefully undertaken and must be a concern when carrying out practical work.

In terms of naturally occurring axially chiral biaryl molecules, these can be divided into two big groups: non-bridged and bridged axially chiral biaryl natural products. This division makes sense considering that bridges can provide bond-rotation stability to biaryl systems even when the steric demand of the *ortho* substituents is not high. Non-bridged axially chiral biaryl products can be further classified into four different subdivisions: Axially Chiral Biaryl Natural Products, Axially Chiral Biaryls with Fused Heterocycles, Axially Chiral Multiply Coupled Biaryls, and Axially Chiral Heterobiaryls (**Table 2**).

Table 2. Non-Bridged Axially Chiral Natural Products		
Subclass	**Moiety**	**Selected Examples**
Axially Chiral Biaryls Natural Products		 **(*P*)–Mastigophorene**  **(*M*)–Gossypol**  **(*M*)–Phlegmacin B_1**
Axially Chiral Biaryls with Fused Heterocycles		 **(+)–(*P*)–Kotanin**  **(*M*)–Desertorin A**  **(–)–(*M*)–Nigerone**
Axially Chiral Multiply Coupled Biaryls		 **(*M*)–Cercosporin**  **(*M*)–Shiraiachrome A**
Axially Chiral Heterobiaryls		 **(*M*)–Streptonigrin**

The first category includes natural products with a typical chiral biaryl moiety. In general, these molecules are constituted by coupled biphenyls (*e.g.* (*P*)–mastigophorene)),[81–83] binaphtalenes (*e.g.* (*M*)-gossypol),[84–86] bianthracenes (*e.g.* (*M*)-phlegmicin B_1),[87,88] and cross-coupled biaryl molecules.[89] Biphenyls are the simplest naturally occurring biaryl products, nevertheless the presence of these in nature is quite scarce because of their low

atropisomerization barrier.[90] The second subclass includes all biaryl compounds in which one, or both aryl rings are fused with a heterocycle. This subdivision is important because of the wide structural diversity that these molecules present. Naturally occurring bioflavonoids,[91] bicoumarins,[92] binaphthopyrones (*e.g.* (–)–(*M*)–nigerone[93] and isonigerone[94]), and biscarbazole alkaloids are just a few examples of families of these products.[95,96] It is also worth noting that some of these compounds present fused saturated heterocycles with stereogenic centres, which may have an important influence on the configuration of the biaryl bond.

Axially chiral multiply coupled biaryls are characterized by a second or even a third biaryl bond. Perylenequinones constitute the biggest group of these naturally occurring compounds;[97] they are coloured and photochemically active molecules and are mostly isolated from moulds.[98] Even though more biaryl bonds leads to structure flattening, atropisomerism is still possible although it requires certain structural conditions such as the presence of side chains *ortho* to the biaryl link (*e.g.* (*M*)–cercosporin),[99] or a ring connecting the biaryl system (*e.g.* (*M*)–shiraiachrome A).[100] These structural features allow the biaryl system to be hindered enough for atropisomerism to occur and are common in isolated perylenequinones. Finally, there are axially chiral heterobiaryls whose presence in nature is quite scarce. The most representative example of this class is the antitumor compound streptonigrin,[101,102] although recently, more examples have started to appear in the literature, for example, reported ancistrocladinium A and B feature an unprecedented C–N biaryl bond.[103,104]

The bridged axially chiral biaryl natural products division can be further subdivided into five different subdivisions: bridged biaryl lignans,[105] biaryl lactones (*e.g.* ellagitannins), biaryl

cyclopeptides (*e.g*. vancomycin and teicoplanin), all-carbon bridged biaryls, and multicyclic bridged biaryls.

1.9 Atropisomerism in Medicinal Chemistry

Chirality plays a pivotal role in the development of drugs as stereoisomers may have completely different properties in terms of pharmacodynamics, pharmacokinetics, and toxicity.[106] However, obtaining enantiopure drugs can be challenging when atropisomerism is present, as racemization only requires bond rotation. The racemization times for atropisomers may vary from milliseconds to thousands of years depending on the factors mentioned in previous sections. For this reason, atropisomerism can change the development program of a new drug from promising to infeasible due to the necessity for stable drugs to prevent tragedies such as the one occurred by thalidomide.[107] Atropisomerism is often overlooked, and it rather tends to surge during the lead discovery processes where controlling conformation is key. As is the case for drugs with point chirality, atropisomers may not only have completely different properties, such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, but also crystallization properties and *in vivo* racemization rates may differ significantly compared to *in vitro* or *ex vivo* rates.[108]

In medicinal chemistry, atropisomers are divided in three classes: class 1 comprises those atropisomers with rotation rates in the order of seconds; class 2 considers those with rotation rates from hours to days; finally, class 3 includes those which rotation rates are in the order of years.[106] Drug development is then done with these classes in mind and considering the recommendations of regulatory agencies such as the U.S. Food & Drug Administration. Regulatory agencies recommend that drugs with chiral elements may be produced either as

racemates or as single stereoisomers depending on their pharmacological profiles. Drug candidates may be developed as racemates if pharmacokinetic and toxicological evaluations for both isomers are available, or, if the candidate drug racemizes under physiological conditions. Also, if separation of such compounds proves to be impractical, the pharmacological evaluation of the racemate must show a benign toxicological profile to support that the use of the racemate is safe. On the other hand, drugs may be developed as single enantiomers, or diastereoisomers. Thanks to the combined advances achieved in analytical and separation techniques, and the development of stereoselective asymmetric methodologies, it has become easier to obtain stereochemically pure drugs.

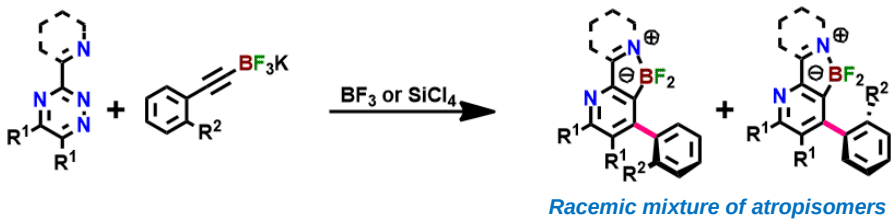
Having in mind these recommendations for the development of drugs with point chirality, atropisomers may also be developed either as racemates or as single stereoisomers. To this end, ideal atropoisomeric drugs should fall either in class 1 for racemates, or in class 3 for pure enantiomers for their development. Atropisomers considered in class 2 must be avoided as they impose a practical problem. The time frame for isomerization in such cases is too difficult to work with, as the candidate drug may isomerize during the isolation, pharmacological evaluation, or storage periods. To avoid failures in the discovery process, atropisomer-related situations should be addressed as early as possible.

When atropisomers appear during lead optimization, it is then time to choose the best approach to tackle the problem. Generally speaking, there are three approaches to consider: the first one is to decrease the rotational barrier and work the drug as a racemate; the second one is to increase the rotational stability by increasing the steric hindrance and work with a single atropisomer; and the third one is to symmetrize the molecule and get rid of the axial chirality altogether.[106]

Chapter 2. Boron-Mediated Thermodynamic Dynamic Resolution of Axially Chiral Pyridines

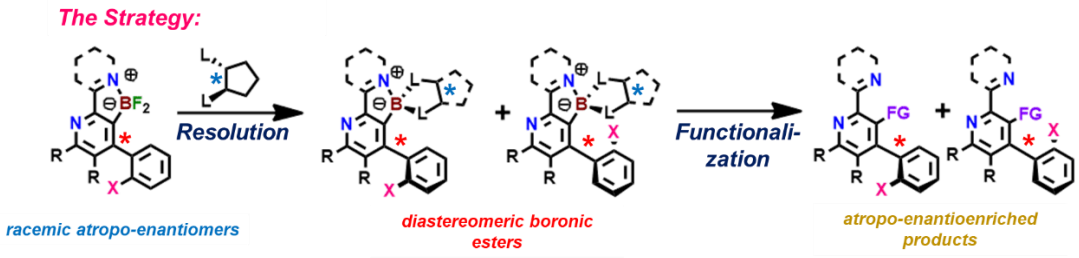
2.1 Pyridines in Synthetic Organic Chemistry

As described in the previous chapter, 1,2,4-triazines equipped with a Lewis basic group undergo cycloaddition reactions with (aryl)alkynyltrifluoroborates in the presence of fluorophilic Lewis acids to afford highly substituted pyridine organodifluoroboranes (**Scheme 18**). The regiochemistry of the reaction is controlled by the formation of a Lewis adduct between the boron atom and the Lewis basic group of the triazine at C3.



Scheme 18. General boron-directed cycloaddition reaction of a triazine and an unsymmetrical potassium (aryl)alkynyltrifluoroborate.

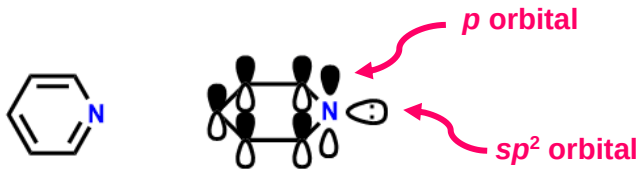
This methodology originated from our group and has been deeply explored in our laboratory.[16,17,109] When the aryl ring of the alkynyltrifluoroborate component is unsymmetrical, the outcome is a racemic mixture of biaryl atropisomers. The central objective of this work was then to develop a strategy for the resolution of this racemic mixture taking advantage of the versatility of the boron atom.



Scheme 19. Proposed strategy for the resolution of atroporacemic pyridine organodifluoroboranes.

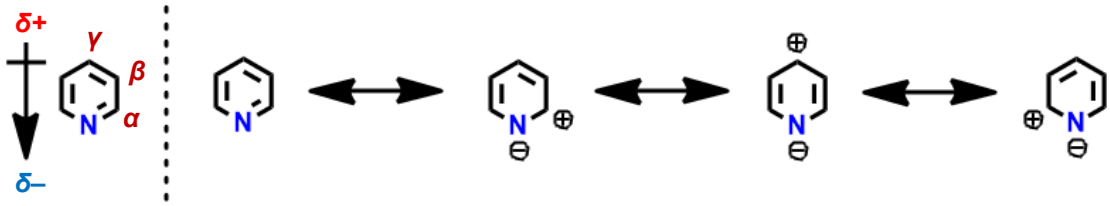
We hypothesized that the fluorine atoms of the pyridine organodifluoroborane could be substituted by a chiral auxiliary, for example, a chiral diol. This process would yield two diastereomers which could be separated, *i.e.* by column chromatography, and finally the organoboronic ester functional group could be exchanged by virtually any other functional group thanks to the synthetic versatility of organoboron compounds to give functionalized atropoenantioenriched pyridines (**Scheme 19**).[110] With this hypothesis in mind, we decided to prepare a scope of different pyridine organodifluoroboranes to confirm that indeed the formation of atropisomers is a general outcome, and second, to evaluate how the substitution pattern of the system could affect the outcome of the resolution. Pyridines were chosen as starting points for this project as they are one of the most relevant classes of heteroaromatics in several fields such as agrochemicals, pharmaceuticals, and chemical biology.[111]

Pyridines are six-membered heterocycles analogous to benzene, where a CH is formally replaced with a N atom. Just as benzenes, pyridines are planar and aromatic. In pyridines, the N atom possesses sp^2 hybridization, where two of the sp^2 orbitals are part of the pyridine's σ-framework, and the third one allocates a lone pair of electrons which are perpendicular to the π-electron cloud and is not involve in the aromatic system. The unhybridized p orbital is parallel to and is part of the aromatic π-electron system.[112]



Scheme 20. Orbital description of pyridine.

The presence of a nitrogen atom has profound inductive and mesomeric effects in the electron distribution of pyridine, and hence in its chemistry, resulting in a permanent dipole towards the nitrogen atom and fractional positive charges on the carbons of the ring, mainly on the α and γ positions (**Scheme 21**).



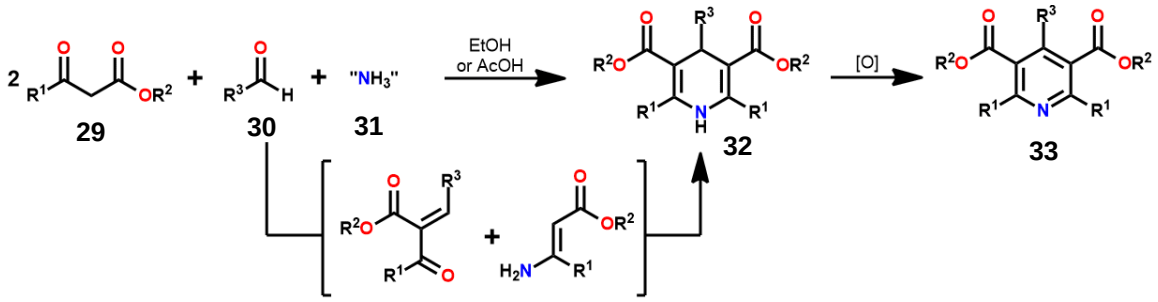
Scheme 21. Polarization and mesomeric effects of the nitrogen atom in pyridines.

The consequence of these effects is a decreased susceptibility towards electrophilic attack, and an increased reactivity for nucleophilic attack. Electrophilic aromatic substitution (S_EAr) is rather difficult in pyridines. Upon exposure to an electrophile, pyridines first react with the sp^2 lone pair of electrons located at the nitrogen atom, yielding a pyridinium cation, which is even less reactive towards electrophiles. On the other hand, the partial positive charges of the carbon atoms favour nucleophilic aromatic substitution (S_NAr) reactivity. Attack of a nucleophile into an unsubstituted pyridine ring would formally require loss of a hydride. As this is an unfavourable process, usually the product will be a dihydropyridine, which will require an extra oxidation step to get the aromatized pyridine product. In some cases, this

oxidation can readily occur even under air exposure. However, the presence of leaving groups (such as halides) further increases the susceptibility of pyridines to undergo these reactions, both by increasing the electropositivity of the target C atom and by allocating the incoming negative charge from the nucleophile. Because of their huge relevance, several synthetic methodologies have been developed to access pyridines, some of which will be briefly described (*vide infra*).

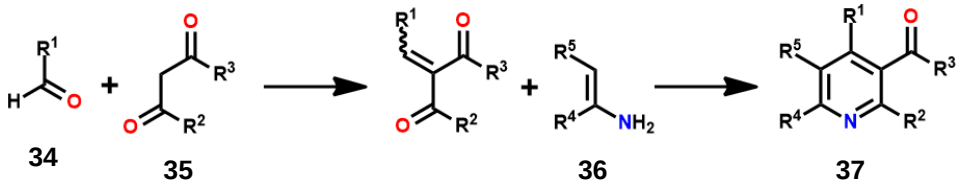
2.2 Common Methodologies for the Synthesis of Pyridines

The condensation of an aldehyde **30**, with two equivalents of a 1,3-dicarbonyl **29**, and ammonia **31** yields a 1,4-dihydropyridine **32** which can be readily oxidized to give substituted pyridines **33**; this methodology is known as the Hantzsch pyridine synthesis (**Scheme 22**).



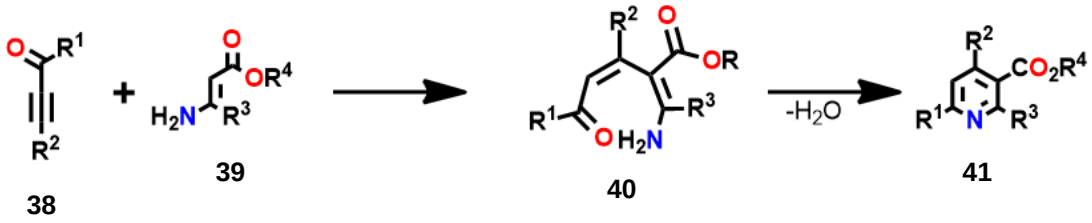
Scheme 22. General Hantzsch Pyridine Synthesis.

This procedure yields symmetrically substituted pyridines **33**; however, it is possible to access non-symmetrical pyridines **37** by combining an aldehyde **34**, a 1,3-dicabronyl derivative **35**, and a preformed enamine **36** (**Scheme 23**).



Scheme 23. Hantzsch pyridine synthesis with enamines as partners.

Another approach for the synthesis of substituted pyridines consists of a sequence of Michael addition/cyclodehydration of an enaminoester **39** to an alkynone **38**; this is known as the Bohlmann-Rahtz pyridine synthesis (**Scheme 24**). *δ*-Aminoketones **40** can be isolated and subjected to heating (>120 °C) to promote the cyclodehydration step to afford 2,3,4,6-substituted pyridines **41**. A variation of this reaction is the *in situ* formation of the enaminoester by condensing an ammonia source and a *β*-ketoester.



Scheme 24. General Bohlmann-Rahtz pyridine synthesis.

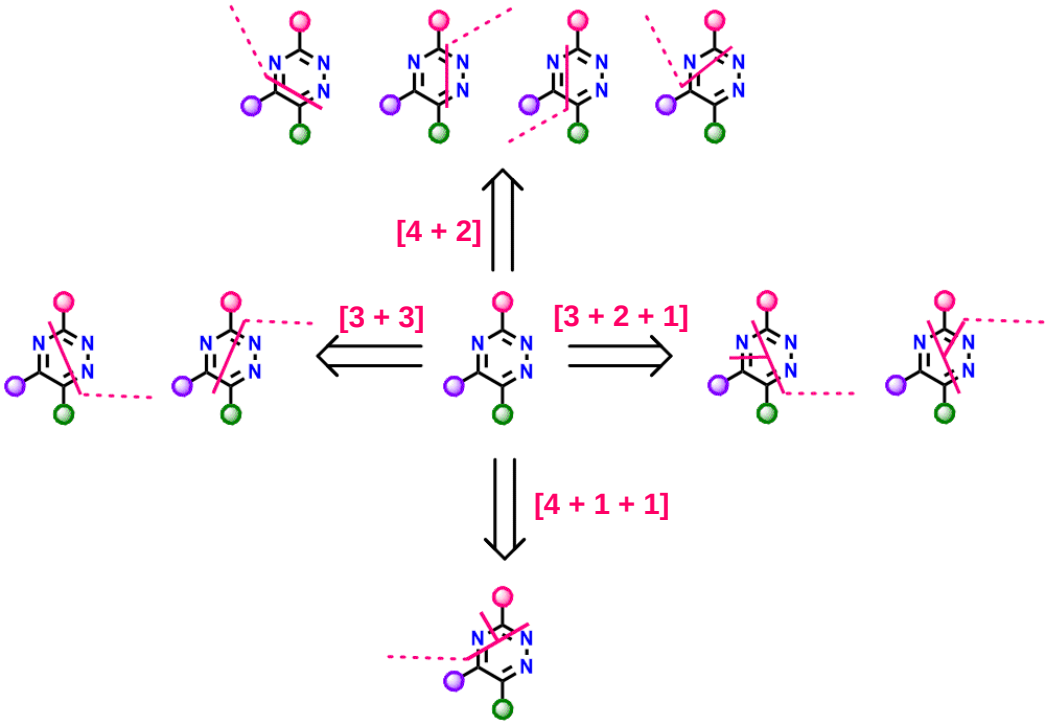
Other traditional strategies for the synthesis of pyridines include the Chichibabin reaction, the Kröhnke and the Guareschi-Thorpe pyridine syntheses, the Pretenko-Kritschenko piperidone synthesis, along with several multicomponent, metal-catalysed, and pericylic approaches.[111,113,114]

2.3 Synthesis of 3,4,5-Substituted-1,2,4-Triazines

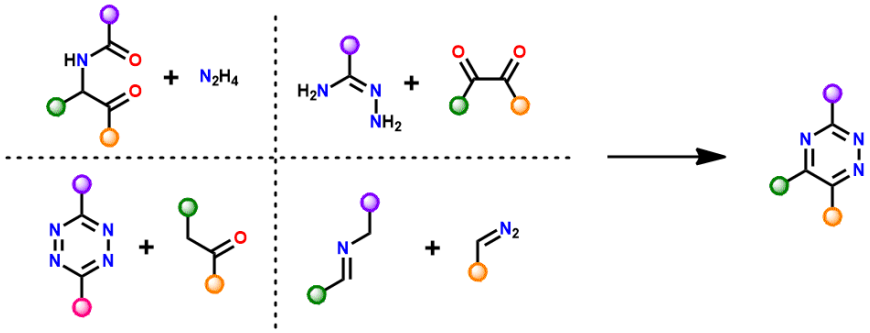
Triazines are six-membered heterocycles that contain three nitrogen atoms and there are three possible regioisomers for these compounds: 1,2,4-triazines (*a*-triazines), 1,2,3-triazines (*v*-triazines) and 1,3,5-triazines (*s*-triazines).[115] Just like pyridines, triazines are aromatic and planar, and the combined inductive effects of the nitrogen atoms make them even more susceptible to nucleophilic attack compared to pyridines.

Figure 1. Structures of triazines.

For this project, only 1,2,4-triazines (*a*-triazines) are of interest and only their synthesis and properties will be discussed. In general, there are four approaches for the synthesis of 1,2,4-triazines: [4 + 2], [3 + 3], [4 + 1 + 1], and [3 + 2 + 1] annulation reactions. The most widely explored approach has been the [4 + 2] annulation methodology, which involves the condensation of an amidrazone with 1,2-dicarbonyl compounds.



Scheme 25. General disconnections for the synthesis of 1,2,4-triazines.

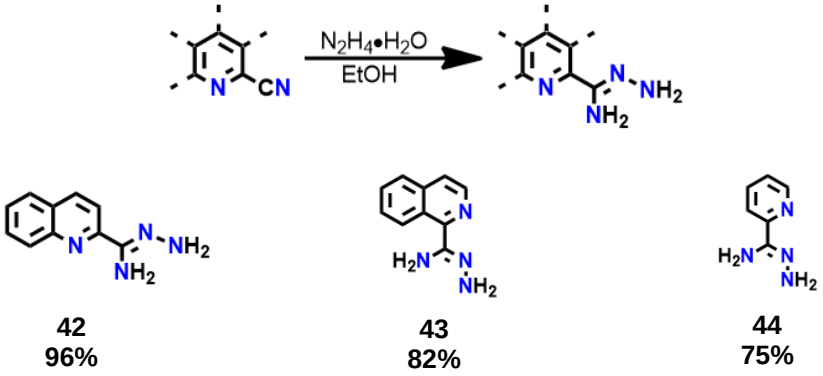


Scheme 26. Common strategies for the synthesis of *a*-triazines.

1,2,4-Triazine chemistry is dominated by its use as an electron-deficient dienophile in inverse-electron-demand Diels Alder cycloaddition reactions for the synthesis of pyridines. This application of 1,2,4-triazines was independently discovered in 1969 by Neunhoeffer & Sauer.[116,117] The first examples reported for this reaction were those of triazines with enamines as electron-rich dienes.

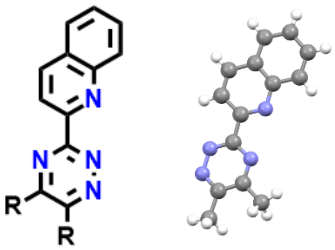
2.4 Results and Discussion

We commenced with the synthesis of amidrazones as starting materials for the preparation of triazines with a view to carrying out a condensation reaction with simple commercially available 1,2-dicarbonyl compounds. The synthesis of amidrazones is relatively straightforward, as it only involves the addition of hydrazine to a nitrile.

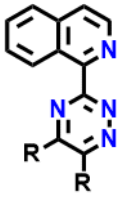


Amidrazones could be obtained in very good yields. The reaction generally requires an excess of hydrazine and several hours to days to maximize conversion. Amidrazones are quite insoluble solids, permitting facile isolation by simple vacuum filtration. Solid amidrazones **42**, **43**, and **44** were then first washed with Et_2O to remove any organic residue, followed by deionized water washed to remove the excess of hydrazine.

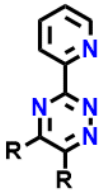
The next step was the condensation of the amidrazones with 1,2-dicarbonyl compounds. The prepared amidrazones were condensed with 2,3-butanedione and benzil to synthesize simple substituted triazines.



45, R = Me, 90% [X-Ray]
46, R = Ph, 91%



47, R = Me, 90%
48, R = Ph, 85%



49, R = Me, 95%
50, R = Ph, 85%

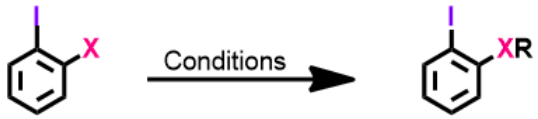
The condensation of amidrazones with 1,2-dicarbonyls was also operationally simple and the work up and isolation just requires Et_2O washes. Ethanol was chosen as the reaction solvent as triazines are generally insoluble in it and so the product precipitates upon its formation.

2.4.1 Synthesis of Potassium (Aryl)alkynyltrifluoroborates

Potassium organotrifluoroborates emerged in the 1960s, but their use was not widespread until the 1990s.[14] Interest in these reagents increased as alternatives to organoboronic acids and esters were sought for their use in the Suzuki-Miyaura cross-coupling reaction. Since then, multiple publications highlighting their applications and usefulness as bench-stable organoboron reagents have appeared in the literature.[118]

The potassium alkynyltrifluoroborates needed for this project were prepared from the corresponding terminal alkyne, which were obtained by protodesilylation of the corresponding alkynylsilane. These alkynes could be prepared by Sonogashira cross-coupling of trimethylsilylacetylene and the corresponding iodobenzene derivative. Some iodobenzene derivatives **51** were not commercially available, and these required *de novo* synthesis (**Table 3**). For example, isopropoxy-2-iodobenzene **53** was obtained by alkylation of 2-iodophenol with isopropyl bromide in the presence of K_2CO_3 in DMF at 50 °C for 3 h

(**Entry 1**). *tert*-Butoxy-2-iodobenzene **54** was prepared following a literature procedure by decomposition of Boc_2O in the presence of catalytic $Sc(OTf)_3$, which generates *in situ* the *tert*-butyl cations needed to alkylate the phenol (**Entry 2**).[119] The yield of the reaction is moderate and increasing the reaction time, temperature, and the number of equivalents of Boc_2O led to no improvement on the yield. 1-(Cyclohexyloxy)-2-iodobenzene **55** was prepared from 2-iodophenol with cyclohexanol under Mitsunobu conditions (**Entry 3**),[120] while 2-iodo *N*,*N*-dimethylaniline **56** could be easily obtained from methylation of the amino group with MeI (**Entry 4**).

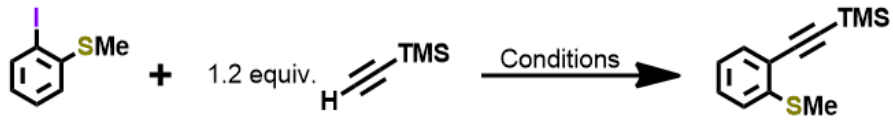


51 **52**

Entry	X	R	Conditions	Yield
1	**O**	^{i}Pr (**53**)	1.5 Br^{i}Pr, 5 equiv. K_2CO_3 DMF, 50 °C, 12 h	80%
2	**O**	^{t}Bu (**54**)	2.3 equiv. Boc_2O, 5 mol% $Sc(OTf)_3$ DCM, r.t., *ca.* 18 h	52%
3	**O**	Cy (**55**)	2 equiv. CyOH, 1.2 equiv. PPh_3 1.2 equiv. DIAD, THF, r.t., 16 h	40%
4	**NMe**	Me (**56**)	6 equiv. MeI, 4 equiv. K_2CO_3 DMF, 70 °C, 21 h	62%

Table 3. Conditions for the alkylation of 2-iodophenol and 2-iodoaniline.

With the desired iodobenzene analogues in hand, the next step was to carry out a Sonogashira cross-coupling reaction of these compounds with trimethylsilylacetylene to obtain the desired alkynylsilanes (**Table 4**).



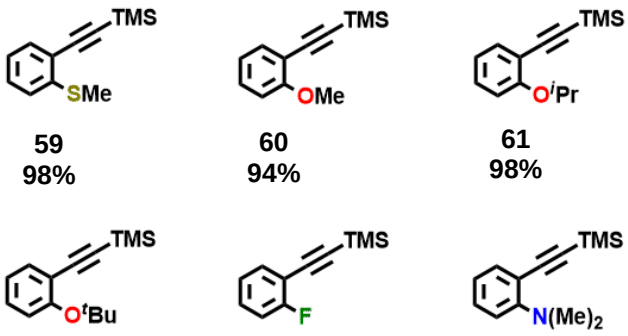
57 **58** **59**

Entry	[Pd] (mol%)	CuI (mol%)	Et_3N	Solvent	Temperature	Time	Yield
1	2	1	6 equiv.	THF	50	6 h	50%
2	2	4	6 equiv.	THF	50	6 h	52%
3	4	8	6 equiv.	THF	50	6 h	60%
4	4	8	6 equiv.	THF	50	*ca.* 18 h	62%
5	2	1	Neat	Et_3N	r.t.	4 h	0%
6	2	1	Neat	Et_3N	r.t.	20 h	37%
7	2	1	Neat	$Et_3N^{[a]}$	r.t.	20 h	57%
8	2	1	Neat	$Et_3N^{[a,b]}$	r.t.	20 h	98%

Table 4. Optimization experiments for the Sonogashira cross-coupling reaction. [Pd] = $PdCl_2(PPh_3)_2$. [*a*] = After 10 h, an extra 0.5 equiv. of trimethylsilylacetylene was added. [*b*] = Et_3N was distilled before use.

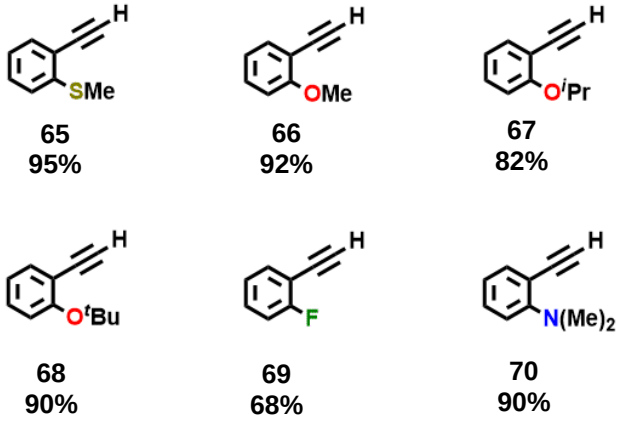
Starting from 2-thiomethyl iodobenzene **57**, previous conditions used in our research group yielded the alkynylsilane **58** in moderate 50% yield (**Entry 1**).[121] Although this methodology allowed us to access the desired alkynylsilane, it was deemed too inefficient for the generation of multigram quantities of material. Increasing the amount of Pd catalyst and CuI had almost no effect on the yield (**Entry 2**). Doubling the amount of metal reagents with respect to the previous experiment slightly improved the yield (**Entry 3**), nevertheless, there was still room for improvement, especially considering that in the literature it is common to find that the Sonogashira reaction tends to give excellent yields. An increase in the reaction time had no effect whatsoever (**Entry 4**). According to experimental procedures reported in the literature,[122] it is possible to have a high yielding reaction if the reaction is run in neat Et_3N. Carrying out the reaction in neat Et_3N with a reaction time of 4 h resulted only in isolated starting material (**Entry 5**). Extending the reaction time to 20 h yielded the desired alkynylsilane product in just 37% yield (**Entry 6**).[123] We then reasoned that there could be two factors affecting the outcome of the reaction; first, the potential loss of

trimethylsilylacetylene **58** due to evaporation and/or considerable Glaser coupling side reaction; and second, the quality of the Et_3N that was being used. Indeed, increasing the amount of trimethylsilylacetylene had a positive effect on the yield (**Entry 7**). Finally, the Sonogashira reaction provided the product in excellent yield when Et_3N was purified before use. This purification protocol consisted of stirring Et_3N with KOH pellets for 2 h at room temperature, followed by distillation over 4 Å MS, all of these carried out under a nitrogen atmosphere. This procedure was essential to obtain reproducible and high yielding results (**Entry 8**). Although in some literature procedures it is common to find that degassing may be crucial for a successful Sonogashira coupling, with these substrates degassing Et_3N (both by gas displacement and by freeze-thaw cycles) had no further effect on the yield, hence, degassing Et_3N was not carried out. With the optimised reaction conditions in hand, we then applied these to our substrates. Pleasingly, the alkynylsilanes required for this project could be obtained in excellent yields on multigram scale.



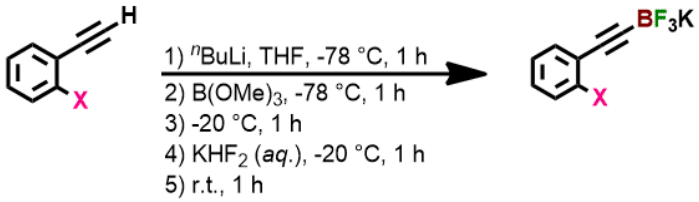
Unfortunately, 1-(cyclohexyloxy)-2-iodobenzene **55** failed to give any product and only starting material was recovered. Increasing the reaction time, the equivalents of metal reagents, and the temperature did not have any effect.

The next step consisted of a protodesilylation reaction of the prepared alkynylsilanes to obtain the corresponding terminal alkynes. The reaction was effectively done in MeOH with 2 equivalents of KOH as base at room temperature over the course of 12 h.

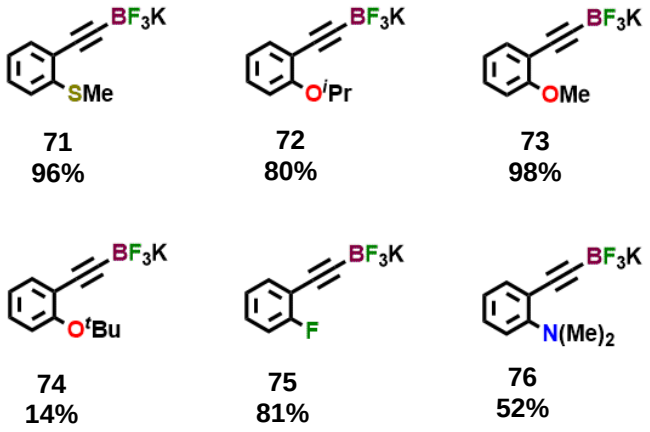


The isolation procedure of the reaction products is also operationally simple, as it only requires an aqueous work up and DCM extraction to isolate the terminal alkynes as single products. In the case of alkyne **69**, the relatively low yield was attributed to loss of material due to evaporation during the isolation process. During the first attempts to prepare this compound, we were unable to isolate any product or any material whatsoever, presumably due to evaporation of the product, however, the product could be isolated by keeping a short solvent evaporation and at room temperature. We were also pleased to find that *tert*-butyl ether **68** did not undergo base-promoted elimination, which could have reduced the yield.

Finally, the prepared aryl alkynes were used for the synthesis of (aryl)alkynyltrifluoroborate salts. Although the synthesis and use of organotrifluoroborates is becoming more widespread, their synthesis may be difficult in the laboratory.

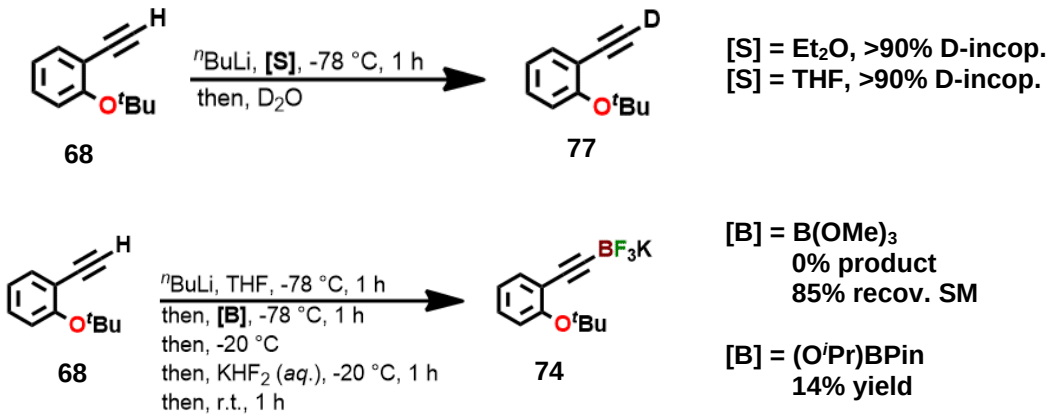


Scheme 27. Synthesis of potassium (aryl)alkynyltrifluoroborate salts.



The first step of the sequence is the deprotonation of the terminal alkyne to give the corresponding organolithium species. It is crucial that no more than 1 equivalent is used, as an excess of ^{n}BuLi can unavoidably lead to the formation of mixed potassium salts of the form $KBF_{4-x}(^{n}Bu)_{x}$, which will reduce the yield and they are almost impossible to separate from the product alkynyltrifluoroborate salts. In this step, it is important to make sure that the concentration of the ^{n}BuLi solution is not compromised. Aged ^{n}BuLi solutions are cloudy and may have precipitates. If a ^{n}BuLi solution with these characteristics is to be used, then titration with menthol and bipyridyl (as indicator) is recommended to determine the exact concentration of the solution. However, the use of fresh and clear solutions is strongly recommended over an aged bottle, where possible. The addition of the ^{n}BuLi solution should also be done slowly and dropwise. Usually, after all the required ^{n}BuLi solution has been

added, the reaction mixture will show a transition to a dark coloured solution. This experimental observation can be interpreted as a good sign that the deprotonation is taking place. Nevertheless, this can be hard to spot if the initial solution of the alkyne is already dark, hence, this statement must be taken with care. The next step is the addition of the boron source, typically $B(OMe)_3$. The addition of this reagent is also recommended to be done slowly and dropwise. Depending on the literature procedure, the use of other boron reagents such as $B(O^iPr)_3$ or $(O^iPr)BPin$ can be found. The selection of the boron reagent could influence the yield of the reaction; as the next step involves the addition of KHF_2 as an aqueous solution, the added water can trigger a protodeboronation reaction, which will regenerate the starting alkyne. In general, the stability of the organoboronic esters produced decreases in the order $RBPin > RB(O^iPr)_2 > RB(OMe)_2$, and so it should not be surprising to find that organotrifluoroborate yields are better when $(O^iPr)BPin$ is used instead of $B(OMe)_3$. The use of $B(OMe)_3$ is suggested over $(O^iPr)BPin$ only on a price and availability basis and it is encouraged to try the former first before testing the more expensive $B(O^iPr)_3$ or $(O^iPr)BPin$ reagents. For example, compound **74** was prepared using $(O^iPr)BPin$ as the boron source as $B(OMe)_3$ failed to give any product and only the starting alkyne was recovered (89% recovered starting material). It is reasonable to think that there could be a problem regarding the deprotonation of the alkyne in this case. However, the deprotonation was done in both THF and Et_2O, and after quenching with D_2O, both experiments yielded the deuterated terminal alkyne with >90% of deuterium incorporation.



Scheme 28. Experiments for the synthesis of organotrifluoroborate 66.

These experiments suggest that the stability of the alkynylboronic ester intermediate can play an important role in the outcome of the synthesis of an organotrifluoroborate salt.

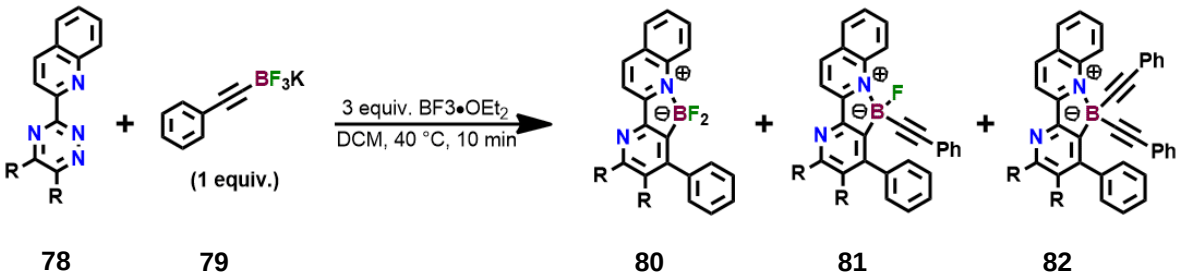
Because of the potential protodeboronation side reaction, the reaction mixture was first warmed up to –20 °C rather than immediately warming up to room temperature as some literature procedures suggest. Although doing this lengthens the synthesis, it decreases the chances of protodeboronation occurring. Indeed, adding an aqueous solution at –20 °C can lead to water freezing; to prevent this, it is important to start the reaction under diluted conditions. Empirically, it was found that a concentration of 0.15 M of alkyne in THF was effective in preventing water freezing. Also, the use of a relatively concentrated KHF_2 solution will decrease the amount of water in the mixture and hence the chances of protodeboronation. During this work, using 3.5 M KHF_2 proved to be an effective concentration with the right solubility. The isolation of the produced organotrifluoroborates can be troublesome, however, extraction of the residual solid with acetone under reflux for at least 1 h followed by hot filtration of the solid proved to be the most reliable procedure to isolate the desired organotrifluoroborates. Once isolated, organotrifluoroborates may contain water; in this sense, it can be useful to redissolve them in acetone and use a drying agent,

such as Na_2SO_4 or $MgSO_4$ to further dry them. Another alternative is drying the salt in a desiccator with P_2O_5 over the course of a few hours.

2.4.2 Boron-Directed Cycloaddition Reactions

With the desired substrates in hand, we then focused on the boron-directed cycloaddition reactions. As mentioned in **Chapter 1**, the reaction of an (aryl)alkynyltrifluoroborate with a 1,2,4-triazine linked to Lewis basic group in the presence of a fluorophilic Lewis acid yields the corresponding pyridine with the boron incorporated as BF_2 functional group. The reaction is relatively straightforward, however, the conditions for the reaction must be strictly anhydrous for its success. In this work, BF_3•OEt_2 was used as the Lewis acid to start the reaction. For the reaction to be reproducible, the distillation of the BF_3•OEt_2 is crucial. Commercial BF_3•OEt_2 has a pale-yellow to dark-yellow colour, depending on how old the sample is. After distillation under vacuum, BF_3•OEt_2 is colourless and can be kept under a continuous flow of nitrogen over the course of at least two weeks, however, a quick inspection before use should be done to ensure no yellow colouration is present. If the liquid BF_3•OEt_2 starts to turn yellow, a distillation will be needed again. As mentioned before, the organotrifluoroborate can also be a source of water that can quench the reaction, hence it is strongly suggested to dry these reagents prior use. The boron-directed cycloaddition reaction is relatively fast, and the organodifluoroboranes produced are typically stable to silica gel, air, and moisture, facilitating their isolation. We commenced the synthesis of a series of organodifluoroboranes to confirm that the presence of racemic mixtures of axially chiral pyridines is a general result. In our preliminary work, it was found that the reaction requires 3 equivalents of salt per equivalent of triazine to achieve optimal yields. When the directed-

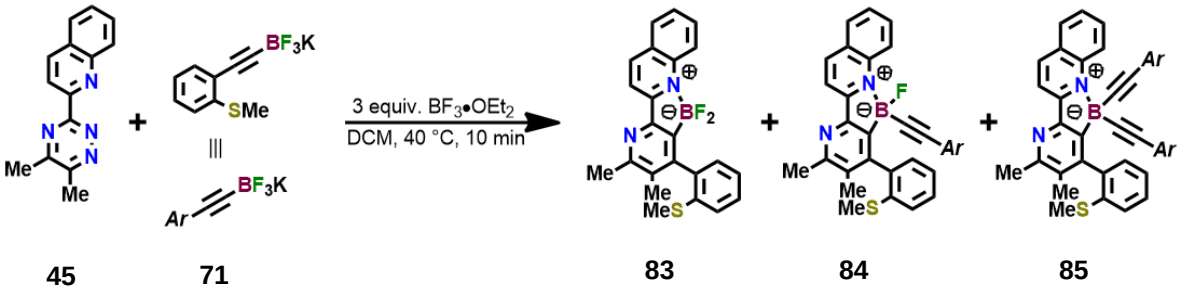
cycloaddition reaction was run with a 1:1 ratio of triazine **78** and salt **79**, alkynylated products (**81**, **82**) are formed, which lowers the yield of organodifluoroborane (**80**) and sometimes these alkynylated products cannot be separated from the product.



78 **79** **80** **81** **82**

Scheme 29. BF_3-Promoted cycloaddition of triazines.

Nevertheless, as the screening of triazines and organotrifluoroborate salts progressed, the initial reaction conditions used became impractical. The use of 3 equivalents of salt per equivalent of triazine required a considerable investment of time and work as the synthesis of the alkynyltrifluoroborates takes at least 3 to 4 synthetic steps depending on the substrate. For this reason, we decided to investigate new reaction conditions where only 1 equivalent of salt was needed to increase the efficiency of the reaction and maximize the use of feedstocks (**Table 5**).



45 71 83 84 85

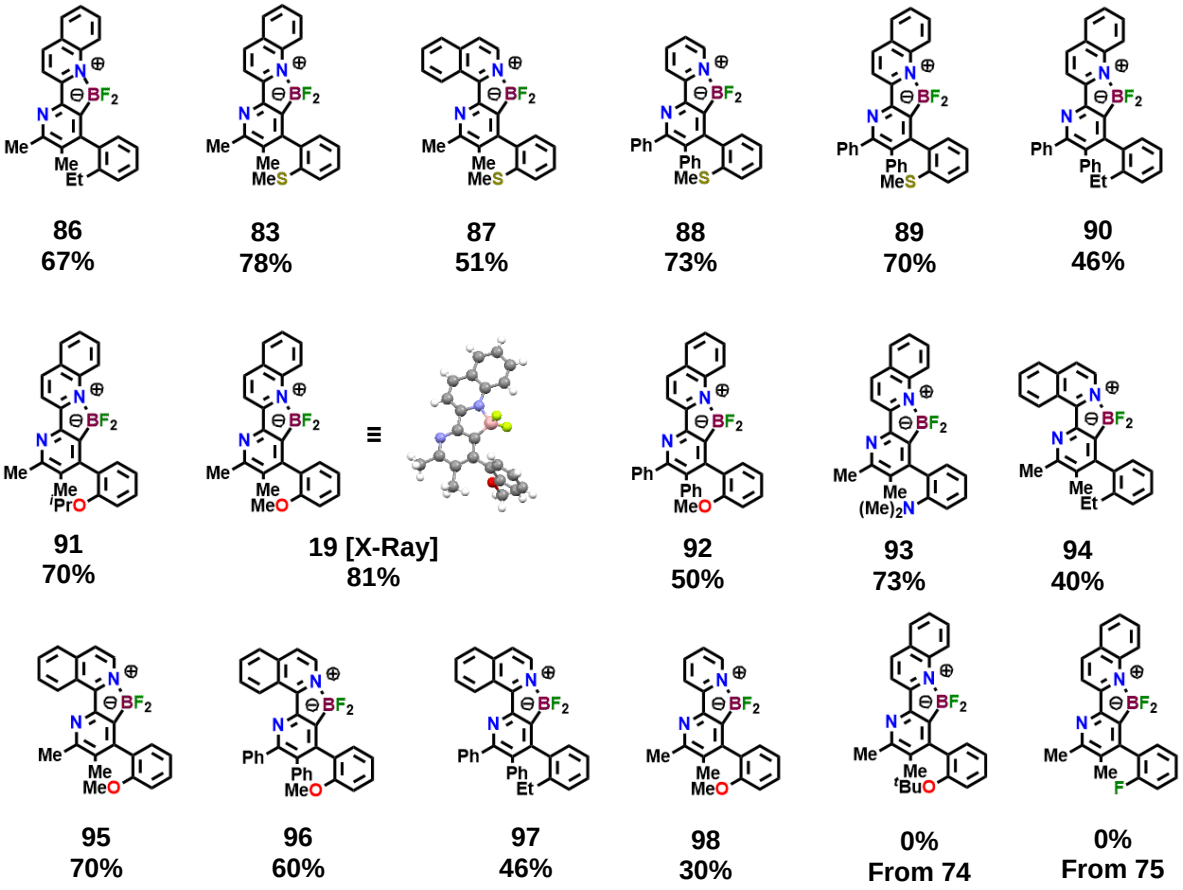
Entry	45:71:BF_3	Conditions	Product ratio (83:84:85)	Conversion (Yield)
1	1:1:0	40 °C, 24 h	0:0:0	0% (0%)
2	1:3:3	40 °C, 30 min	80:20:0	93% (67%)
3	1:3:3	40 °C, 2 h	46:46:2	88% (0%)
4	1:3:3	50 °C, 30 min	32:61:7	95% (0%)
5	1:3:3	35 °C, 1 h	77:13:10	59% (0%)
6	1:1:3	30 °C, 1 h	98:2:0	90% (78%)
7	1:1:3	30 °C, 2 h	90:6:4	90% (70%)

Table 5. Directed-cycloaddition reaction optimization experiments.

Starting from alkynyltrifluoroborate **71** and triazine **45**, mixing them in DCM at reflux for 24 h in the absence of BF_3•OEt_2 yields no product and only unreacted staring materials were recovered (**Entry 1**). In the presence of 3 equiv. BF_3•OEt_2, the desired organodifluoroborane **83** is obtained at 67% in just 30 min, however, this requires the use of 3 equiv. of alkynyltrifluoroborate (**Entry 2**). Increasing the time to 2 h favours the formation of disproportion products **84** and **85** (**Entry 3**). Increasing the temperature to 50 °C further favours disproportion product **84** (**Entry 4**). Decreasing the temperature to 35 °C had the opposite effect and favoured the formation of **75** (**Entry 5**). Further decreasing of temperature yielded organodifluoroborane **83** in very good yield and it only required the use of 1 equiv. of salt (**Entry 6**), and the formation of the organodifluorborane was clear just by inspection of the reaction mixture. A further increase of the reaction time did cause the disproportion products to form (**Entry 7**). A common feature, although not general, is that these

organodifluoroboranes show strong fluorescence emissions, hence, it is relatively easy to track them during isolation and purification procedures.

With a new set of optimized reaction conditions in hand, we then prepared a series of organodifluoroboranes.



Indeed, all the organodifluoroboranes prepared showed the expected two AB-doublets in the ^{19}F NMR spectra, setting the stage for testing our hypothesis on the resolution of these axially chiral systems. X-Ray crystallography of organodifluoroborane **19** showed that the B atom is tetracoordinated, with the directing N atom of the quinoline directing group acting as the fourth substituent. This analysis also confirmed that the southern ring lies perpendicular with respect to the planar pyridine-quinoline ring system.

Unfortunately, organotrifluoroborates **74** and **75** failed to give their corresponding organodifluoroborane products. In the case of **74**, we observed loss of the ^{t}Bu group even though the cycloaddition was operative, yielding a fluorescent solid which proved to be insoluble in all solvents, even water; as for **75**, a complex inseparable mixture of fluorescent products was obtained, hence this example was discarded.

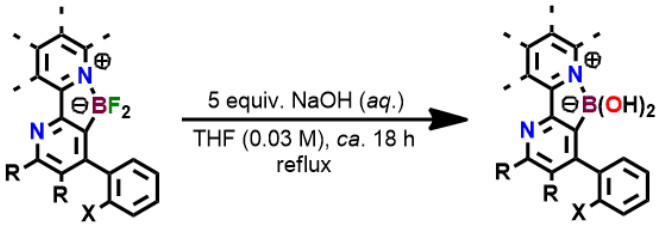
2.4.3 Esterification and Resolution of Biaryl Organodifluoroboranes

Having prepared a selection of organodifluoroboranes, which all exhibited axial chirality, we moved on to the exploration of a resolution strategy. First, we assumed that the direct reaction an organodifluoroborane and a chiral diol would give the corresponding boronic ester. However, mixing organodifluoroboranes and chiral diols in different solvents over a range of temperatures only yielded unreacted starting materials. Presumably, the organodifluoroboranes' B–F bonds in which the B atom is already tetracoordinated, are too unreactive even though the reaction could be entropically favoured due to the liberation of two molecules of HF. Hence, we decided to convert the corresponding organodifluoroborane to the corresponding organoboronic acid to favour the esterification reaction. The hydrolysis of the organodifluoroboranes proved to be a challenge. Treatment of organodifluoroborane **83** with 1 M NaOH (*aq*.) indeed yielded the corresponding organoboronic acid. Nevertheless, oxidation and protodeboronation side reactions reduced the yield of this product. It was important then to explore more optimal conditions for the reaction. Starting from organodifluoroborane **83**, treatment with 5 equiv. of NaOH yielded a mixture of organoboronic acid, along with the corresponding phenol and pyridine side products. It was not possible to determine the exact ratios of these products in the crude reaction mixture not

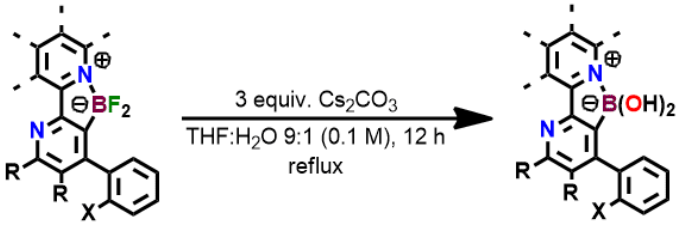
only because of the absence of diagnostic signals to distinguish each product, but also because organoboronic acids tend to form complex boroxines (boron anhydrides) which complicated both ^{1}H NMR analysis and isolation even further. Nevertheless, LCMS analysis allowed us to identify the composition of the mixture and track the outcomes of our experiments. Rather than generating a calibration curve, we decided to use qualitative information retrieved from the LC chromatograms. Taking organodifluoroborane **83** as a model system, we tested the effect of the number of equivalents of NaOH. As this number increased, the relative intensity of the protodeboronation and phenol products decreased in the LC chromatogram. When 40 equivalents of NaOH were used, the formation of side products was suppressed and the corresponding organoboronic acid was obtained as the single product. Encouraged by this result, we tested these conditions on other substrates. Unfortunately, these conditions showed to be exclusive for organodifluoroborane **83** and were not general for all substrates. Given that organodifluoroboranes are not widespread in the literature and there is scarce information regarding their reactivity and transformations, we looked at the chemistry of their closest relatives, organotrifluoroborates, as a reference. In 2012, Lloyd-Jones *et al*. reported a kinetic study about the hydrolysis of potassium organotrifluoroborate salts.[124] Briefly, this study concluded that there is no trend in the rate of hydrolysis of organotrifluoroborates, and so each of the substrates showed different hydrolysis rate profile. The identity of the substrate, the temperature, reaction time, concentration of the base, the stirring rate, and vessel shape, size, and even the active surface of the flask (whether its etched or not) are all factors that can affect the rate of hydrolysis of organotrifluoroborates. In some cases, addition of powdered glass was needed to increase the surface are of active glass, which is an intrinsic fluorophile that promotes organotrifluoroborate hydrolysis.

Ultimately, we were unable to find a single protocol for the high-yielding hydrolysis of the organodifluoroboranes used in this work. However, two different protocols could be developed, that, although not high yielding for all organoboronic acids, they proved quite useful for the obtention of these products in acceptable purity. These are summarised in 'Method A' and 'Method B' shown below.

Method A:

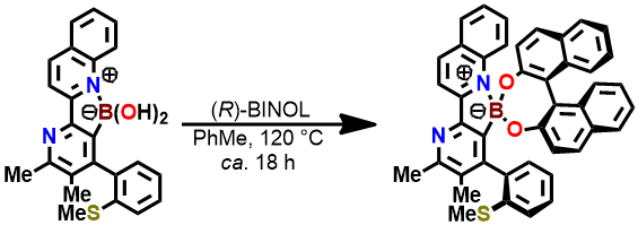


Method B:



Moving forward, we then tested the reactivity of our organoboronic acids with a selection of chiral diols to demonstrate the formation of diastereomeric organoboronic esters. (*R*)-BINOL proved to be the best chiral diol for the resolution. Other diols tested were (*R*,*R*)-tartaric acid dimethyl diester, (+)-diisopropyl L-tartrate, TADDOL (α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol), and (*R*)-(+)-3,3′-dibromo-1,1′-bi-2-naphthol; however, these diols failed to provide a satisfactory resolution due to low diastereomeric ratios which were observed. The esterification reaction of organoboronic acids with diols is a condensation

reaction in which 2 molecules of water are formed per each molecule of organoboronic ester formed. Because of this, the need for dehydrating agents in the reaction mixture is not unusual to favour the formation of the organoboronic ester product. In this sense, we chose organoboronic acid **99** as starting point for the optimisation of this reaction (**Table 6**).



99 **100**

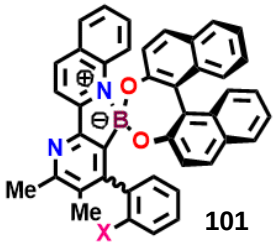
Entry	(*R*)-BINOL	Drying agent	Yield	*d.r.*
1	1 equiv.	4 Å MS	0[a]	-
2	1 equiv.	4 Å MS	31	>98:2
3	1.5 equiv.	4 Å MS	35	>98:2
4	1.5 equiv.	$MgSO_4$	12	>98:2
5	1.5 equiv.	Dean-Stark	50	>98:2
6	2 equiv.	Dean-Stark	67	>98:2

Table 6. Optimization of the esterification reaction with (*R*)-BINOL. [*a*] = The reaction was performed at room temperature.

Acid **99** was chosen as its preparation (*via* Method B) was reliable and reproducible, giving samples with good LCMS profiles. Organoboronic acids were not purified as they are not suitable for column chromatography and common subproducts, such as protodeboronation and oxidation products, showed virtually the same solubility as the target acid, therefore crude organoboronic acids were then used directly in the esterification step.

Treating organoboronic acid **99** with 1 equivalent of (*R*)-BINOL at room temperature failed to give any product (**Entry 1**). Heating the reaction mixture at 120 °C yielded the desired product albeit in just 31% yield when molecular sieves were used as the drying agent (**Entry 2**). Increasing the number of equivalents to 1.5 had a minor improvement in the yield (**Entry 3**). We decided to test other drying agents; changing molecular sieves for $MgSO_4$ reduced the

yield and the product could only be isolated in 12% yield (**Entry 4**). However, carrying out the reaction under Dean-Stark conditions increased the yield to a moderate 50% (**Entry 5**). Finally, using 2 equivalents of chiral diol afforded the desired product in 67% yield (**Entry 6**). Interestingly, in all the optimization experiments only one diastereomer was observed by ^{1}H NMR, ^{13}C NMR, and LCMS analyses (the configuration of the major diastereomer was determined by X-ray crystallography, *vide infra*). We proceeded to extend the scope of organoboronic esters and compare their diastereomeric ratios (**Table 7**).



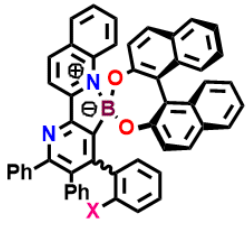
101

Entry	X	Yield	*d.r.*
1	**Et (102)**	33%	1:1
2	**OMe (103)**	57%	4:1
3	**O^{i}Pr (104)**	89%	7:1
4	**SMe (100)**	67%	>98:2
5	**N(Me)$_2$ (105)**	64%	5:1

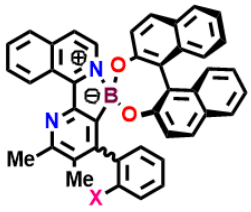
Table 7. Effect of the *ortho*-substituent (X) on the *d.r.* of organoboronic esters 100, 102-105.

First, the diastereomeric ratios of those organoboronic esters of the form **101**, were analysed. Surprisingly, when **X** = Et, the outcome was a 1:1 mixture of diastereomers (**Entry 1**). However, when **X** = OMe, a 4:1 mixture of diastereomers was observed (**Entry 2**). Going from an *ortho*-OMe group to a sterically more demanding *ortho*-O^{i}Pr favoured the resolution even further (**Entry 3**). To our surprise, the bigger thiomethyl group yielded a single diastereomer (**Entry 4**). Finally, the dimethylamino group could also provide a resolved mixture of diastereomers in a 5:1 ratio (**Entry 5**). Encouraged by these results, we extended the scope of

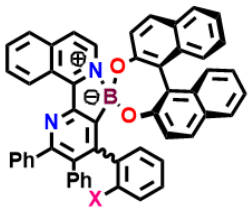
organoboronic esters, but now limiting ourselves to the substituents which afforded the most notable differences in the diastereomeric ratio, that is Et, OMe, and the SMe group.



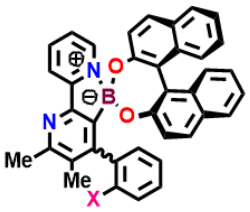
X	*d.r.*
Et (106)	1:1
OMe (107)	4:1
SMe (108) [a]	1:1



X	*d.r.*
Et (109)	1:1
OMe (110)	4:1
SMe (111)[a]	1:1



X	*d.r.*
Et (112)	1:1
OMe (113)	3:1
SMe (114)[a]	~1.9:1

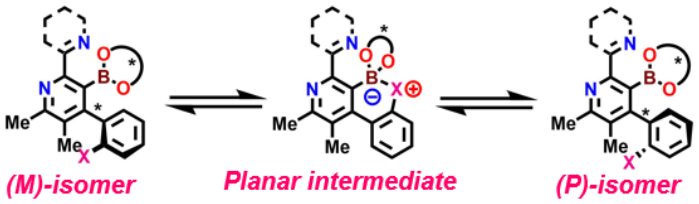


X	*d.r.*
Et (115)	1:1
OMe (116)	5.6:1
SMe (117)[a]	1:1

[a] = Diastereomeric ratios were determined from the crude reaction mixture.

In all cases, when X was an ethyl group, a 1:1 mixture of diastereomers was obtained (the *d.r.* was determined by ^{1}H-NMR). On the other hand, the methoxy group could undergo the resolution of the diastereomeric organoboronic esters quite generally. Interestingly, the thiomethyl group was not able to afford a satisfactory resolution when it was studied on other systems. The reason behind this is still not clear and is a matter that deserves further attention. Regarding the nature of the resolution, the relatively high yields (>50%) and the complete consumption of the organoboronic acid to give unequal diastereomeric ratios quickly discarded a classical kinetic resolution in these cases, and so a dynamic process must be operative. To test this hypothesis, we studied the behaviour of these compounds upon heating. We were able to obtain diastereoenriched (1:0 *d.r.*) organoboronic esters **102** (*via* preparative HPLC) and **103** (*via* precipitation of the major diastereomer). Heating diastereoenriched **102** in toluene at 120 °C overnight (*ca.* 18 h) resulted in no change in the diastereomeric ratio, while organoboronic ester **103** yielded the 4:1 ratio observed initially.

The fact that only those substituents possessing lone pairs yielded a satisfactory resolution led us to think that the resolution happens *via* a planar intermediate where the *ortho*-Lewis basic group coordinates to the B atom and, depending on the relative stability of each diastereomer, the resolution occurs, hence, being a dynamic thermodynamic resolution (**Scheme 30**).



Scheme 30. Proposed equilibrium for the epimerization of axially chiral organoboronic esters.

In 2013, Stoltz & Virgil and Fernández & Lassaletta independently proposed similar processes for the Pd-mediated construction and dynamic kinetic resolution of axially chiral biaryl systems.[125,126] The crystallization of diastereomerically pure organoboronic esters **100** and **103** allowed us to determine the configuration of the major diastereomer, which in this case was *M* (**Figure 2**).

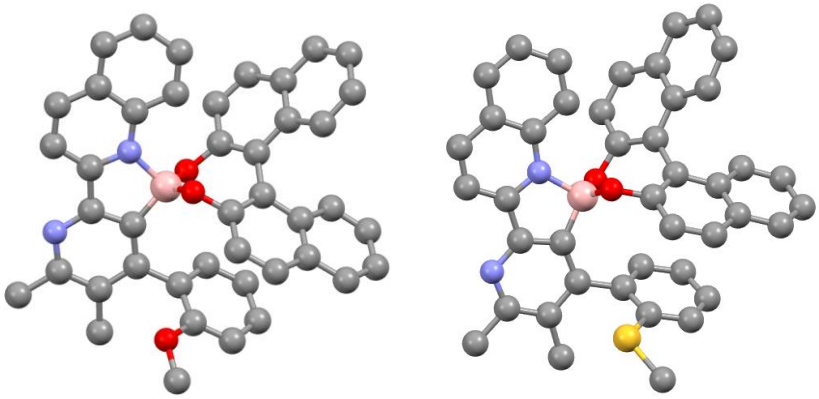


Figure 2. X-ray structures of compounds 103 and 100 (Hydrogens have been omitted for clarity).

The X-ray analysis also revealed a π-π stacking interaction between the benzene ring of the biaryl system and the southern naphthalene of the BINOL (**Figure 3**).

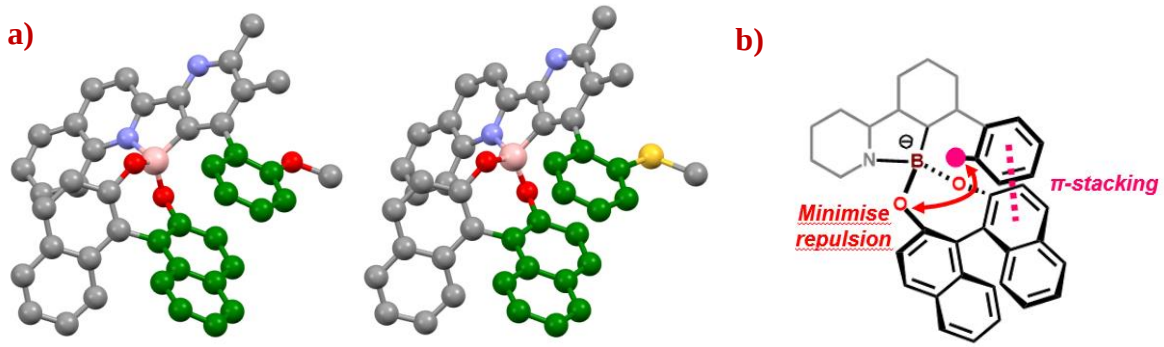
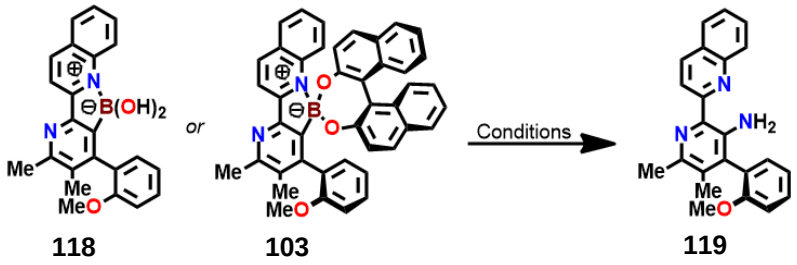


Figure 3. a) Side-on view of the X-ray structures of compounds 95 and 92. Rings engaged in π-π stacking interactions have been highlighted in green. b) Model for the rationale of the resolution stereoselectivity.

The major diastereomer is that in which the *ortho* group is orientated away from the BINOL possibly to prevent unfavourable steric interactions with one of the BINOL ester's O atoms.

2.4.4 Stereoretentive Transformations of Atropo-Resolved Organoboronic Esters

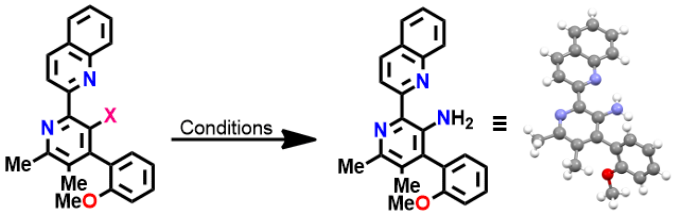
Having succeeded in resolving the biaryl axis formed from the boron-directed cycloaddition products discussed in the last sections, we were interested in studying further functionalizations and to evaluate the level of stereochemical retention after the boron ester functional group has been replaced. First, we looked at the amination of **103** (and its organoboronic acid derivative **118**) to give amine **119**.



Scheme 31. Amination reaction of compounds 103 and 118.

The amination of organoboronic acids, organoboronic esters, and organotrifluoroborate salts to give primary amines is known, although it has received considerably less attention with respect to the widely used Chan–Lam coupling which yields secondary and tertiary amines. For the synthesis of primary amines from organoboron compounds, several reagents and/or conditions are operative.[127–129] One approach has been the use of hydroxylamine derivatives, in which the OH group is converted into a leaving group (such as OBz) allowing nucleophilic attack by the nitrogen atom to the hypovalent boron atom, forming an ate complex which then undergoes 1,2-metallate rearrangement forming the desired C–N bond. Following the same idea, other reagents such as DHP (*O*-(2,4-dinitrophenyl)hydroxylamine) and HAS (hydroxylamine-*O*-sulfonic acid) have appeared in the literature as aminating reagents for organoboronic acids and esters.[130] However, the use of these reagents in our system for the transformation of organoboronic ester **103** into the desired amine **119** was unsuccessful, with recovery of the corresponding organoboronic acid. We then turned our attention to metal-mediated amination protocols, specifically, a copper-mediated amination/azidation conditions for the intended C–N bond formation, for which some reports have appeared in the literature. In 2007 Tao *et al*. reported the direct synthesis of aryl azides from aryl boronic acids under similar copper-mediated conditions,[131] while in 2010, Aldrich *et al*. reported the

conversion of aryl boronic acid to aryl azides catalyzed by $Cu(OAc)_2$ in the presence of sodium azide.[132] In 2012, Niu *et al*. reported the functionalization of 2-arylpyridines *via* sequential borylation/copper catalysis,[133] accessing both aryl azides and aryl anilines. These works were used as the starting point for our investigations (**Table 8**).

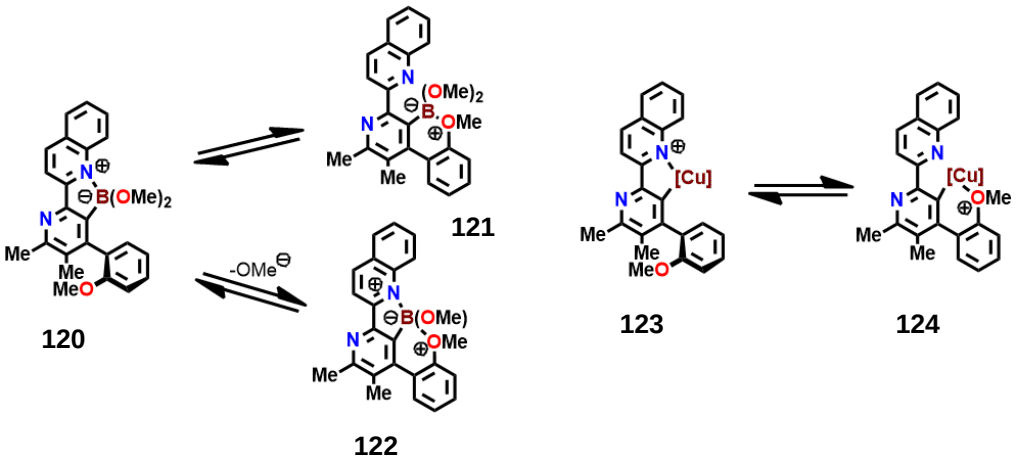


103 or 118 **(*rac*)-119 [X-Ray]**

Entry	X	Conditions	Outcome
1[a]	B(BINOL)	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, 12 h	68% 30% ee
2	BF_2	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, *ca*. 18 h	SM
3	$B(OH)_2$	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, 12 h	55%
4	B(BINOL)	1.5 equiv. NaN_3, THF:MeOH 1:1, 70 °C, 12 h	SM
5	B(BINOL)	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, THF, 70 °C, 12 h	Trace
6	B(BINOL)	1.5 equiv. NaN_3, 5 mol% $Cu(OAc)_2$, 2 equiv. (*R*)-BINOL, Et_2O, 40 °C	RSM
7	B(BINOL)	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, r.t., 12 h	SM
8[a]	B(BINOL)	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, 2 equiv. ^{t}BuOH, THF, 70 °C, 12 h	18% ee
9[a]	B(BINOL)	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, 2 equiv. (*R*)-BINOL, THF, 70 °C, 12 h	19% ee
10	B(BINOL)	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, 2 equiv. HCl•Et_2O, THF, 70 °C, 12 h	**109**
11[a]	B(BINOL)	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, 2 equiv. HFIP, THF, 70 °C, 12 h	20% ee

Table 8. Screening of amination conditions of compounds 118 and 103. [*a*] = Initial *d.r.* ≥ 98:2.

Treating organoboronic ester **103** with NaN_3 and $Cu(OAc)_2$ in a THF:MeOH 1:1 mixture for 12 h at 70 °C indeed afforded the desired amine in 68% albeit just 30% *ee* (**Entry 1**). The structure of the amine was unambiguously assigned by X-ray crystallography. With the intention of obtaining a racemic sample of amine **119**, the amination of racemic organodifluoroborane **19** was attempted, however, this failed to give any product (**Entry 2**). Using organoboronic acid **103** instead as staring material yielded the racemic amine in 55% yield (**Entry 3**). We then decided to undertake some control experiments to better understand the nature of the reaction in expectation of improving the retention of the stereochemical information. We hypothesised that possible reaction intermediates such as **120** or **123** could lead to planar species such as **121**, **122**, and **124**, hence adversely impacting the reaction's stereochemical outcome.

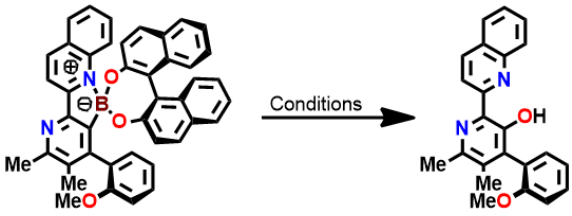


Scheme 32. Proposed intermediates for the amination of 103.

First, it was shown that $Cu(OAc)_2$ was needed, as in the absence of this no product formation occurred (**Entry 4**). The absence of methanol was also unfavourable, but it did not suppress product formation completely and traces of this could be detected by LCMS analysis (**Entry**

5). As the copper reagent was in excess, we explored the possibility of decreasing the amount of copper needed, however this only resulted in recovered hydrolysed starting material (**Entry 6**); this same outcome was observed when the reaction was attempted at room temperature (**Entry 7**). We assumed that the methanol was not only serving as solvent but also as a proton source for the formation of the amino group. With this in mind, we evaluated different proton sources. Replacing methanol for other alcohols such as ^{t}BuOH (**Entry 8**), (*R*)-BINOL (**Entry 9**), and HFIP (**Entry 11**) did not result in an improvement on the enantiomeric excess of the product; using HCl•Et_2O as proton source resulted in immediate hydrolysis of the organoboronic ester (**Entry 10**). Given the lack of success in improving the outcome of this reaction, we decided to look at other transformations.

We moved on to the oxidation of **103** to afford the corresponding phenol product **125** (**Table 9**). Like the amination reaction, there are several conditions reported for the oxidation of organoboron compounds and the most common used reagents for this transformation are *m*CPBA, H_2O_2, and $NaBO_3$.[110]



103 (*d.r.* ≥ 98:2) **125**

Entry	Conditions	Outcome
1	30% H_2O_2 (excess), THF, r.t., *ca.* 18 h	SM[a]
2	30% H_2O_2 (excess), THF, r.t., 36 h	SM[a]
3	30% H_2O_2 (excess), 3 M NaOH (*aq.*), THF, r.t., *ca.* 18 h	SM[a]
4	30% H_2O_2 (excess), 3 equiv. Cs_2CO_3, THF, r.t., *ca.* 18 h	SM[a]
5	30% H_2O_2 (excess), THF, 40 °C, *ca.* 18 h	52%
6	5 equiv. $NaBO_3•H_2O$, THF:MeOH:H_2O 1:1:0.5, r.t., 12 h	SM[a]
7	1 equiv. *m*CPBA, DCM, 0 °C to r.t., 3 h	35%
8	1.2 equiv. *m*CPBA, DCM, 0 °C to r.t., *ca.* 18 h	48%

Table 9. Condition screening for the oxidation of 95. [*a*] = Only hydrolysis of 95 was observed.

We commenced our optimization experiments using H_2O_2 as oxidizing agent. Treatment of organoboronic ester **103** with an excess of H_2O_2 in THF at room temperature resulted in recovered organoboronic acid (**Entry 1**). Increasing the reaction time to 36 h did not influence the outcome (**Entry 2**). The use of bases at room temperature also failed and only the organoboronic acid was observed (**Entries 3 & 4**). However, increasing the reaction temperature to 40 °C yielded the desired product in 52% although with moderate enantiomeric excess (62% *e.e.*) (**Entry 5**). We attributed this outcome to be a consequence of the relatively high reaction temperature and so we decided to try other oxidising agents that could do the reaction at room temperature or lower. $NaBO_3•H_2O$ also failed to give any product and the organoboronic ester was hydrolysed (**Entry 6**). Treating **103** with *m*CPBA for 3 h yielded phenol **125** with very good stereoretention (76% *e.e.*) albeit in low chemical yield

(**Entry 7**). Increasing the time of the reaction and adding an extra 0.2 equiv. had a slight increase on the chemical yield while retaining the enantiomeric excess (**Entry 8**). The identity of phenol **125** was confirmed by X-ray crystallography.

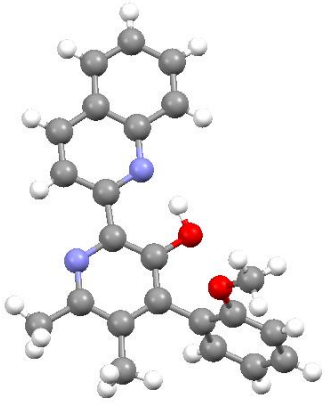
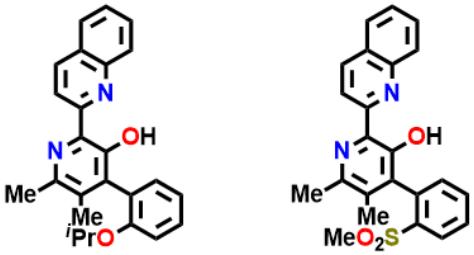


Figure 4. X-Ray structure of phenol (*rac*)-125.

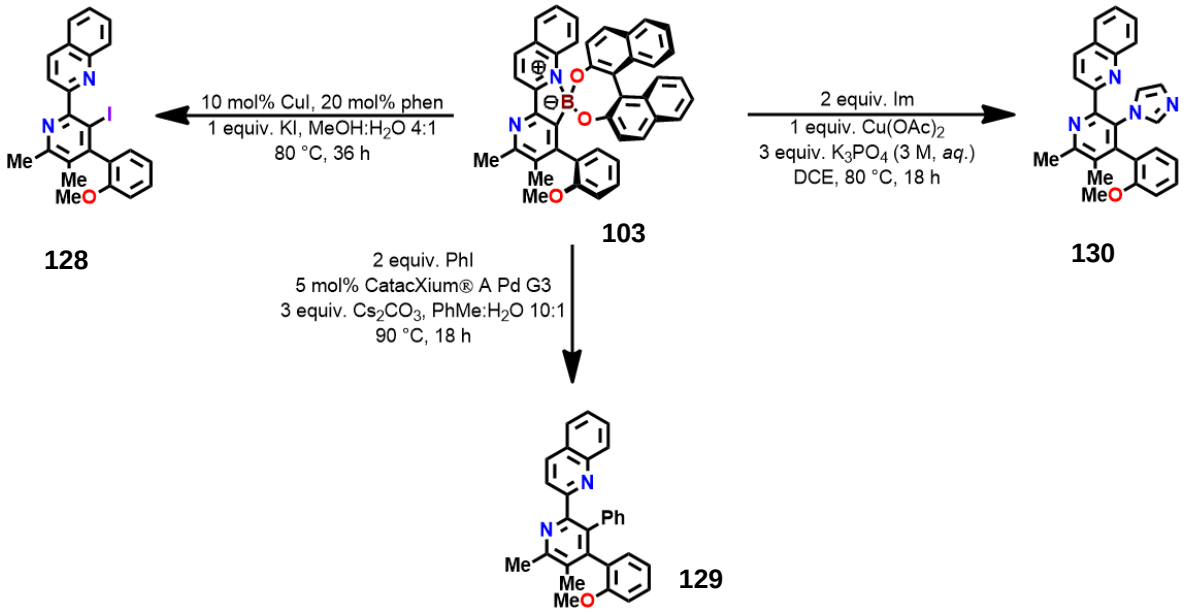
Organoboronic esters **103** and **100** underwent oxidation (**100** also oxidized at S) to give phenols **126** and **127** with similar stereoretention levels.



126
46%
88:12 *e.r.*
(from 103, 88:12 *d.r.*)

127
72%
89:11 *e.r.*
(from 100, ≥ 98:2 *d.r.*)

We also worked with other typical boron transformations such as the iodination,[134] Suzuki-Miyaura coupling, and the Chan-Lam coupling.[135]



Scheme 33. Other functionalization reactions of organoboronic ester 103.

Unfortunately, due to matters of time and problems in isolation, the samples of the products could not be properly characterised and its stereochemical outcome could not be obtained accurately.

2.4.5 Further Exploration of BINOL Derivatives

Having developed a novel strategy for the resolution of axially chiral biaryl compounds, we wanted to further improve the efficiency of the transformation to obtain higher levels of stereoretention. To this end, after careful examination of the X-ray structures of compounds **100** and **103**, we envisioned two approaches: to increase the stability of the major diastereomer, or to decrease the stability of the minor diastereomer. In order to increase the stability of the major one, we decided to integrate a Lewis acidic functional group into the

BINOL, such that this could engage in a Lewis acid-base interaction with the Lewis basic *ortho*-substituent.

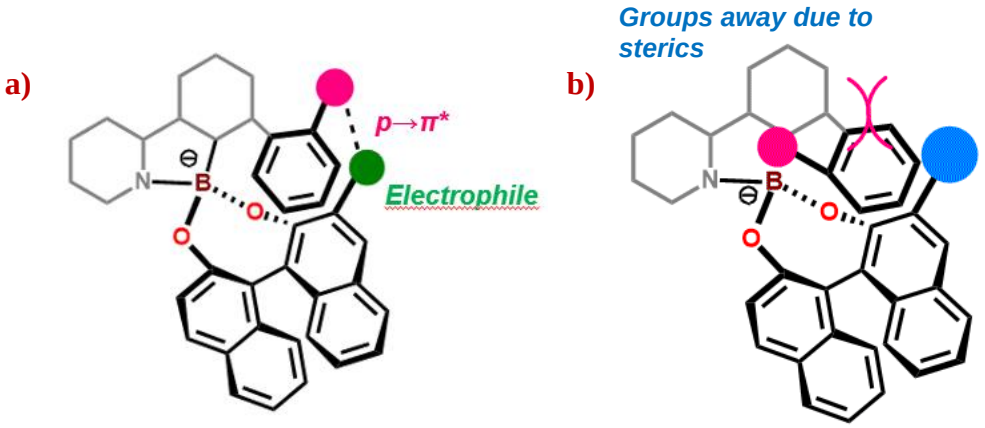


Figure 5. Rationale for the design of BINOL derivatives. a) Stabilization of the major diastereomer by attractive Lewis acid-base interactions. b) Destabilization of the major diastereomer by steric repulsions.

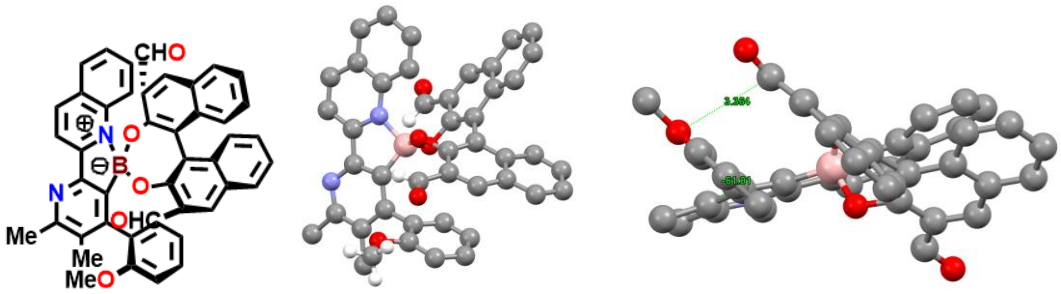
Such a Lewis-acidic group should possess empty low-lying orbitals for the *ortho*-substituent's lone pairs to engage in the hypothesised interaction. On the other hand, a destabilization of the major diastereomer to favour the opposite configuration could be achieved by increasing the size of the group attached to the BINOL, ultimately favouring the opposite configuration. We then screened a series of BINOL derivatives to evaluate the effect of substituents on the resolution (**Table 10**).

Entry	X	*d.r.*
1	H (**103**)	4:1
2	Br (**131**)	2.6:1
3	I (**132**)	2.3:1
4	Me (**133**)	5:1
5	CH_2Br (**134**)	6:1
6	CH_2NHAc (**135**)	5:1
7	CHO (**136**)	8:1
8	CH_2CN (**137**)	11:1 (>98:2)

Table 10. Diastereomeric ratios of organoboronic esters with symmetrically *ortho*-substituted BINOL derivatives.

We commenced by evaluating the effect of the halogen atoms Br and I. The Br atom reduced the efficiency of the resolution, yielding a *d.r.* of 2.6:1, while the I atom yielded a *d.r.* of 2.3:1 (**Entries 2 & 3**). These results could be a consequence of unfavourable steric interactions between the OMe group and the halogen atoms, hence destabilizing the major diastereomer. Nevertheless, introducing a Me group had the opposite effect and improved the resolution compared to BINOL (**Entry 4**). Given that the more polarizable halogen atoms reduced the diastereomeric ratio, it is unlikely that the Me would engage in favourable London dispersion forces that could increase the stability of the major diastereomer. In this scenario, it is more likely that a destabilization of the minor diastereomer is operative, however, more experimental information is needed to support this statement. Adding a methylene group between the BINOL's naphthalene ring and the Br atom improved the stereochemical outcome (**Entry 5**). We thought that thanks to the methylene group, we had reached an optimal distance to engage the OMe group in favourable non-covalent interactions. We next explored

the potential for an acetamide to engage the OMe group by H-bonding, however, this did not deliver a considerable improvement (**Entry 6**). In contrast, the use of an aldehyde group did show a considerable improvement of the diastereomeric ratio (**Entry 7**). In this case, it was possible to study the major diastereomer further thanks to X-ray crystallography.



136 [X-Ray]

Figure 7. X-Ray structure of compound 136 (All hydrogens except the aldehyde and OMe hydrogens were omitted for clarity.

The X-ray structure of **136** shows that the benzene ring carrying the OMe group has been tilted closer to the BINOL's naphthalene ring by 1.01°. It is plausible that a stronger interaction between these two systems would lead to a closer contact, however, the interaction is unlikely to come from the initially envisioned $n_O \rightarrow \pi^*_{CHO}$ interaction, as both the OMe group and the CHO group did not show a proper geometrical alignment for this to occur effectively. It is plausible that the increase in the stability of the major diastereomer is a consequence of the complementary polarities of the ring systems. The geometric distortions observed by crystallography, though, can be a consequence of the crystal packing, and not necessarily reflect the compound's true conformation in solution, hence the conclusions extracted from such data are not irrefutable.

Using an acetonitrile group further improved the resolution and gave the mixture of diastereomers in 11:1 ratio (**Entry 8**). It is plausible to think that the methylene bridge allows a better overlap of the nitrile's empty π* orbitals with the oxygen's lone pairs, increasing the stability of the major diastereomer, although an X-ray structure is needed to confirm this hypothesis. When the *ortho* group is O^{i}Pr, similar levels of diastereocontrol were observed (crude: 89:11 *d.r.*; after purification >98:2 *d.r.*).

In summary, we have set a proof of concept for a novel dynamic strategy for the resolution of axially chiral pyridine motifs. Overall, the strategy consists of a pyridine-ring construction/boron-installation in a single step using the boron-directed [4 + 2] cycloaddition reaction, followed by resolution *via* boron transesterification, and finally functional group interconversion of the boronic ester group to give diversified atropo-enantioenriched pyridines. This work has set the basis for future development of the strategy for further synthetic applications.

Chapter 3. Asymmetric Total Synthesis of Streptonigrin

3.1 Streptonigrin

Streptonigrin **138** is a secondary metabolite isolated by fermentation from *Streptomyces flocculus*, a bacterium found in soil. Its isolation was achieved in 1959 by Rao & Cullen,[101] and the determination of its structure by NMR spectroscopy and chemical derivatization was reported in 1963.[136] Streptonigrin´s structure was later confirmed by X-ray crystallography in 1975 by Chiu and Limbscomb; it is a member of a group of natural products known as *streptonigrinoids*, along with other natural products such as streptonigrone **139** and lavendamycin **140**.[137] Streptonigrin has different names; this is because its isolation has been possible from other bacteria species such as *S. rufochromogenes* and *S. echinatus* in France, here named rufochromomycin, and from *Actinomyces albus var. bruneomycini* in what was the Soviet Union, hence named bruneomycin.

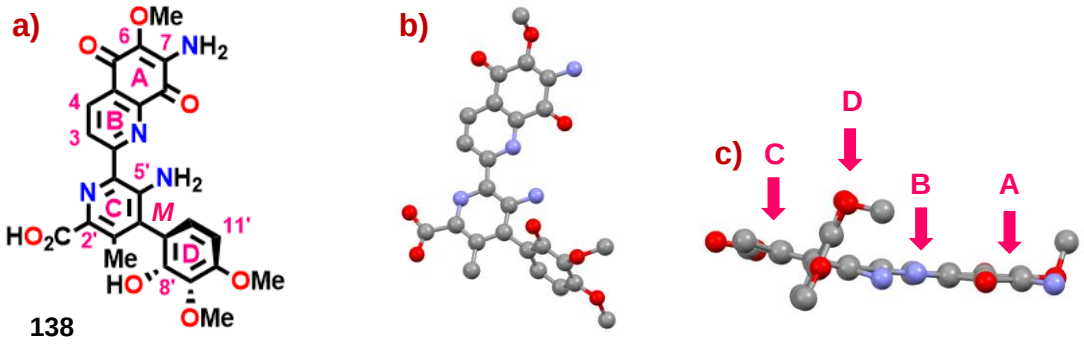


Figure 8. a) Chemical structure of streptonigrin. b) Streptonigrin's X-ray structure front view. c) Streptonigrin's X-ray structure side on view.

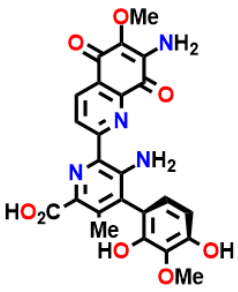
Streptonigrin is a fascinating molecule consisting of a highly functionalized quinolone ring system (denoted as A and B) connected to an atropoisomeric heterobiaryl system (denoted as C and D) (**Figure 8a**). The X-ray structure of streptonigrin revealed that the AB and C rings

are nearly coplanar, while the D ring is perpendicular to this ring array, hence, generating atropisomerism (**Scheme 8b and 8c**). Encountering axially chiral heterobiaryl systems in natural products is quite unusual even for atropisomeric natural products.[90] Rotation about the bond connecting pyridine ring C and aryl ring D is then restricted by the C3' methyl group, the C5' amino group, and the C8' hydroxy group. The methoxy groups at C9' and C10' could also "push" the C8' hydroxy group even closer to the axis, although this statement is merely speculative. With respect to the bond connecting the AB quinolone fragment with pyridine ring C, this does not generate atropisomerism as there is only one substituent *ortho* to this bond (C5´–NH_2), failing then in providing sufficient rotational rigidity. In fact, the AB and C ring systems can afford coplanarity thanks to an intramolecular hydrogen bonding between the C5' amino group and N1.[137]

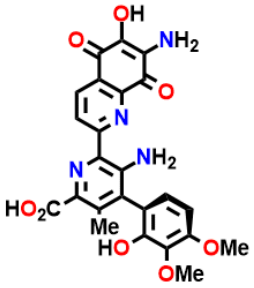
Assigning the correct configuration of the chiral axis required several efforts. The X-ray analysis could not reveal the correct stereochemistry because of the lack of a heavy atom and so it was initially misassigned.[137] In 1981, Gillard & Dholakia assigned the configuration of streptonigrin's axis to be *S* (or *P*) by circular dichroism studies.[138] Later in 1997, Tennant & Rickards reported more detailed and more accurate circular dichroism experiments which showed the correct configuration of the chiral axis to be *R* (or *M*).[139] In this study, streptonigrin was methylated with diazomethane to obtain the corresponding methyl ester; this was done with the purpose of suppressing possible experimental complications due to streptonigrin's zwitterionic nature in solution.[140]

Streptonigrinoids have been of interest for both chemists and biologists due to their high activity against Gram-positive and Gram-negative bacteria, lymphoma, melanoma, cancers of breast, cervix, head, and neck, as well as some viruses.[141] Back in the 1980s, streptonigrin made it to phase II clinical trials due its interesting biological activity, nevertheless, it showed

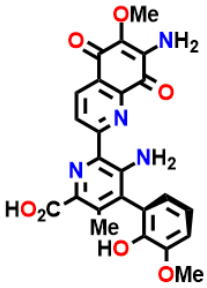
undesirable side effects, such as severe bone marrow depression.[142] Recently though, it has been reported that streptonigrin shows antitumor activity even at nanomolar concentrations, minimising secondary effects.[143]



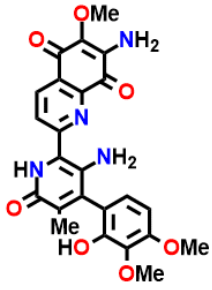
10'-*O*-Demethylstreptonigrin



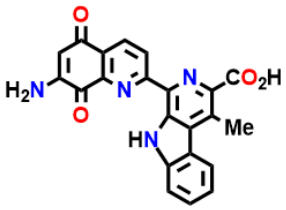
6-*O*-Demethylstreptonigrin



10'-*O*-Demethoxystreptonigrin



Streptonigrone 139



Lavendamycin 140

Figure 9. Some members of the streptonigrinoid family of natural products.

Streptonigrin's antitumor mechanisms have been extensively investigated, but the exact pathway is still not completely understood. It has been proposed that streptonigrin induces DNA single and double strand breaks, unscheduled DNA synthesis, and DNA complex formation.[142] Specifically, streptonigrin has been shown to bind irreversibly to DNA *via* ternary streptonigrin-metal-DNA complexes, although full characterization and identification of streptonigrin-metal complexes is scarce. Streptonigrin exhibits multiple metal coordination sites, and the formation of streptonigrin-metal-DNA complexes has been

proposed with metal ions such as Zn, Cu, Fe, Mn, Pt, Cd, and Au.[142,144,145] The absence of metal ions prevents the association of streptonigrin and DNA. Once the ternary streptonigrin-metal-DNA complex forms, streptonigrin starts to cause oxidative damage to DNA *via* its quinolone fragment; in fact, this fragment has been identified as the responsible for its antitumour activity.[146] DNA damage triggers the cell's mechanisms for DNA protection, such as heterochromatin formation. Briefly, heterochromatin is tightly packed DNA, and its formation has been proposed as a mechanism for both DNA protection and gene silencing. As more heterochromatin forms, more genes get silenced and the more difficult it is for the cell to carry out its vital functions, ultimately leading to cell death. Not only does streptonigrin damage DNA, but it also promotes the formation of reactive oxygen species, which is also a source of cellular damage.[147]

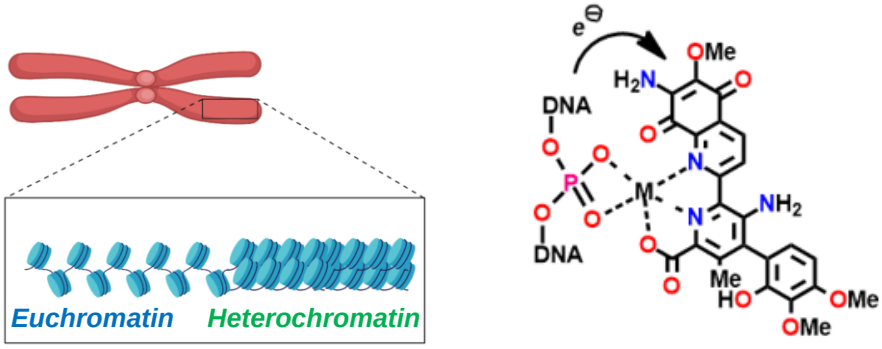
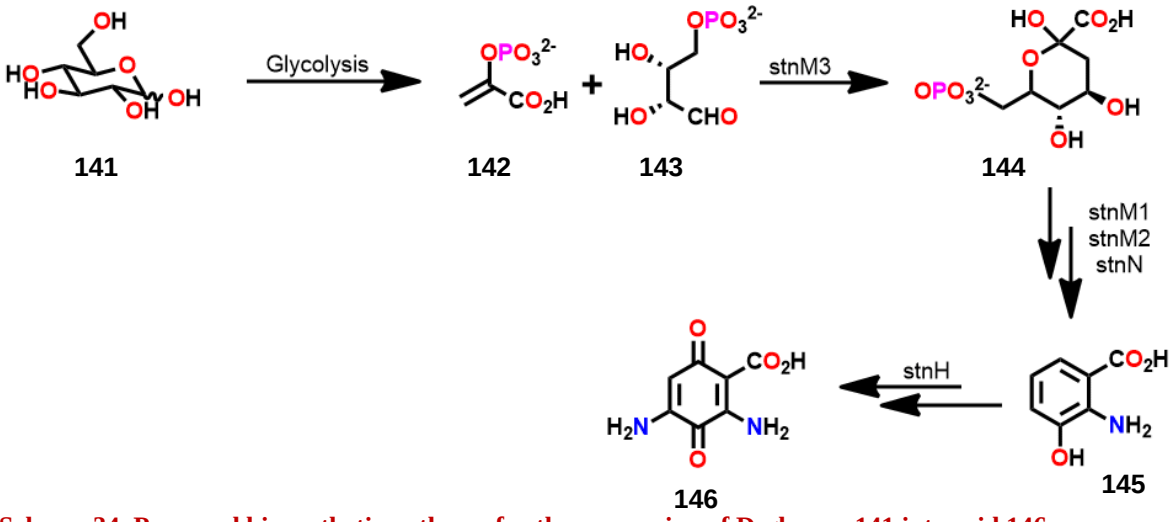


Figure 10. a) Representation of euchromatin and heterochromatin. b) DNA-metal-streptonigrin terniary complex.

3.2 Streptonigrin Biosynthesis

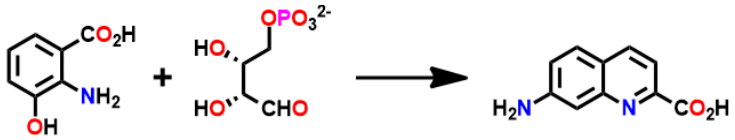
The biosynthetic origins of streptonigrin have also been deeply explored. It has been proposed that streptonigrin comes from a convergent biosynthetic pathway, where the carbon frameworks of the AB quinolone system and the CD ring system are formed prior to its

linkage.[148] ^{13}C–labelling experiments have shown that all streptonigrin's C atoms can be traced back to D-glucose **141**, which undergoes glycolysis to give D-erythrose-4-phosphate **142** and phosphoenol pyruvate **143**.[149] These glycolysis products undergo an aldol condensation/hemiacetal formation sequence mediated by stnM3 (DAHP synthase) to give hemiacetal **144**, which serves as feedstock for a modified shikimate pathway catalysed by stnM1 (anthranilate synthase), stnM2 (isochorismatase) and stnN (2,3-dihydroxybenzoate-2,3-dehydrogenase) to give anthralinic acid **145**. It has been suggested that **145** undergoes oxidation by stnH (oxidoreductase) to give **146** (Scheme 34).[150]



Scheme 34. Proposed biosynthetic pathway for the conversion of D-glucose 141 into acid 146.

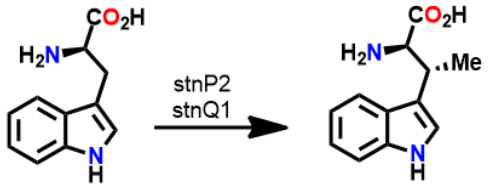
On the other hand, Gould *et al*. have proposed that anthralinic acid **146** condenses with another molecule of D-erythrose-4-phosphate **143** to give quinoline **147**. Presumably, the carboxy group of **146** is lost during the cyclization and aromatization sequence (Scheme 35). In this scenario, the introduction of the missing three oxygen substituents has been proposed to occur at a later stage.[151]



146 **143** **147**

Scheme 35. Formation of proposed quinoline intermediate 147.

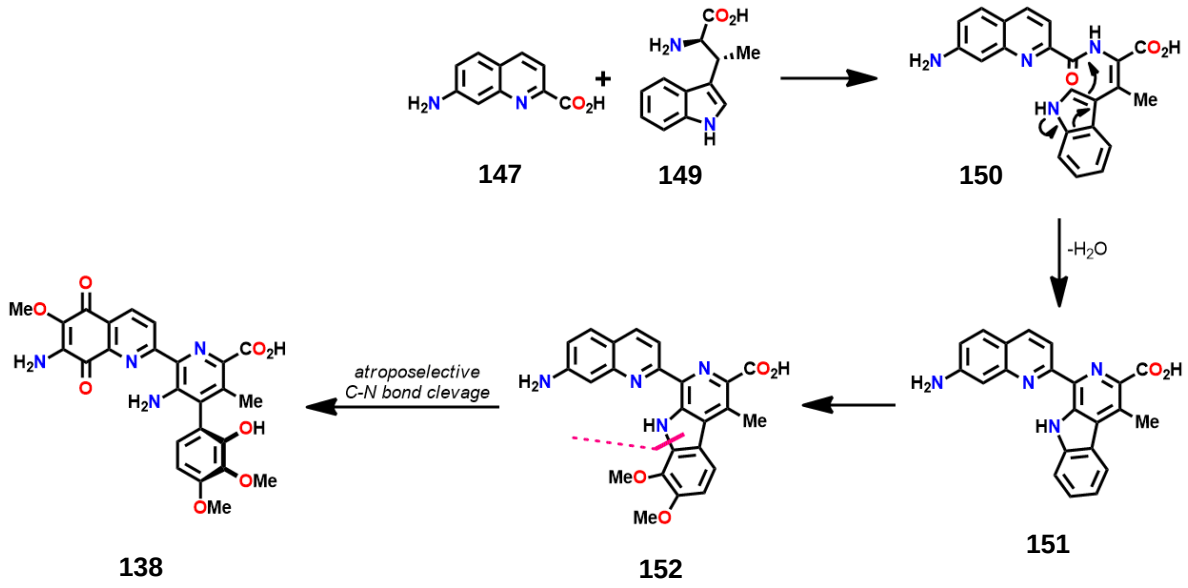
Phosphates **142** and **143** also serve as starting materials for the biosynthesis of the C and D rings. The southern D ring is thought to come from L-typtophan **148** (a product of the shikimate pathway) which first undergoes methylation at the *β*–C catalysed by stnP2 (FAD-dependent oxidoreductase) and stnQ1 (methyltransferase) (**Scheme 36**).[148,152]



148 **149**

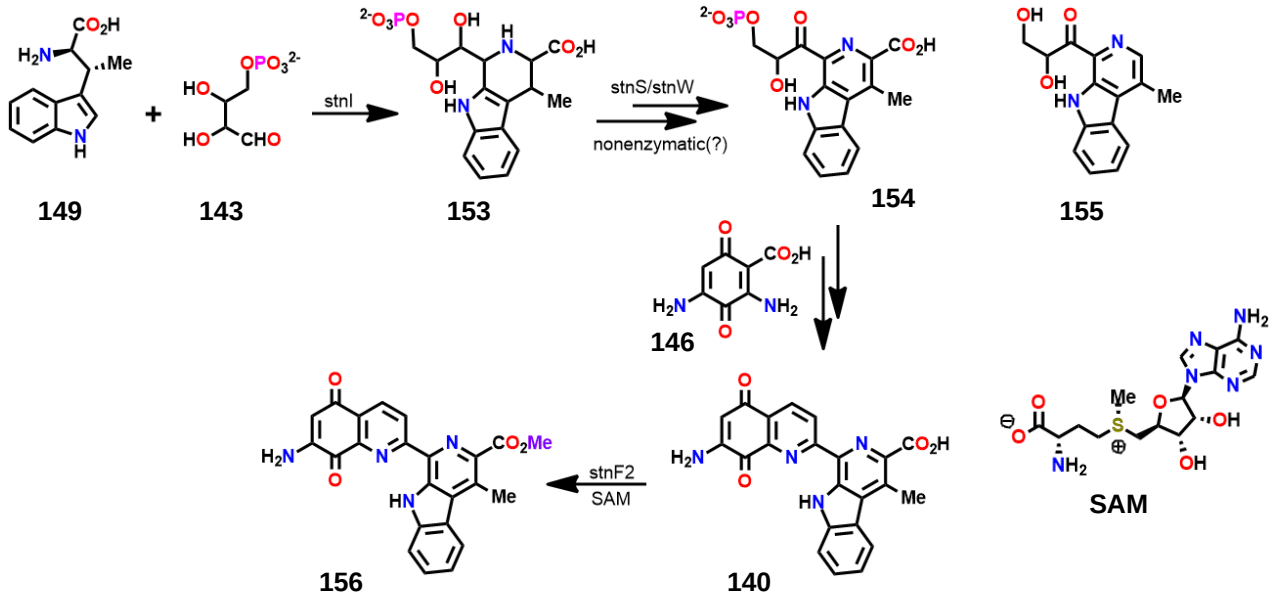
Scheme 36. *β*-Methylation of tryptophan 148.

There are two different proposals for the formation of pyridine ring C. Gould *et al*. have suggested that quinoline **147** couples with *β*-methylated L-tryptophan to give amide **150** which undergoes an intramolecular Pictet-Spengler cyclisation. Upon aromatization by water loss, pyridine ring C is then formed. Pentacyclic intermediate **151** presumably gets oxidised to incorporate the C9' and C10' hydroxyl groups. In these experiments, lavendamycin **140** was also isolated but Gould's proposal does not offer a full explanation about this experimental result. Finally, atroposelective C–N bond cleavage and incorporation of the missing oxygen substituents yield streptonigrin (**Scheme 37**).[153]



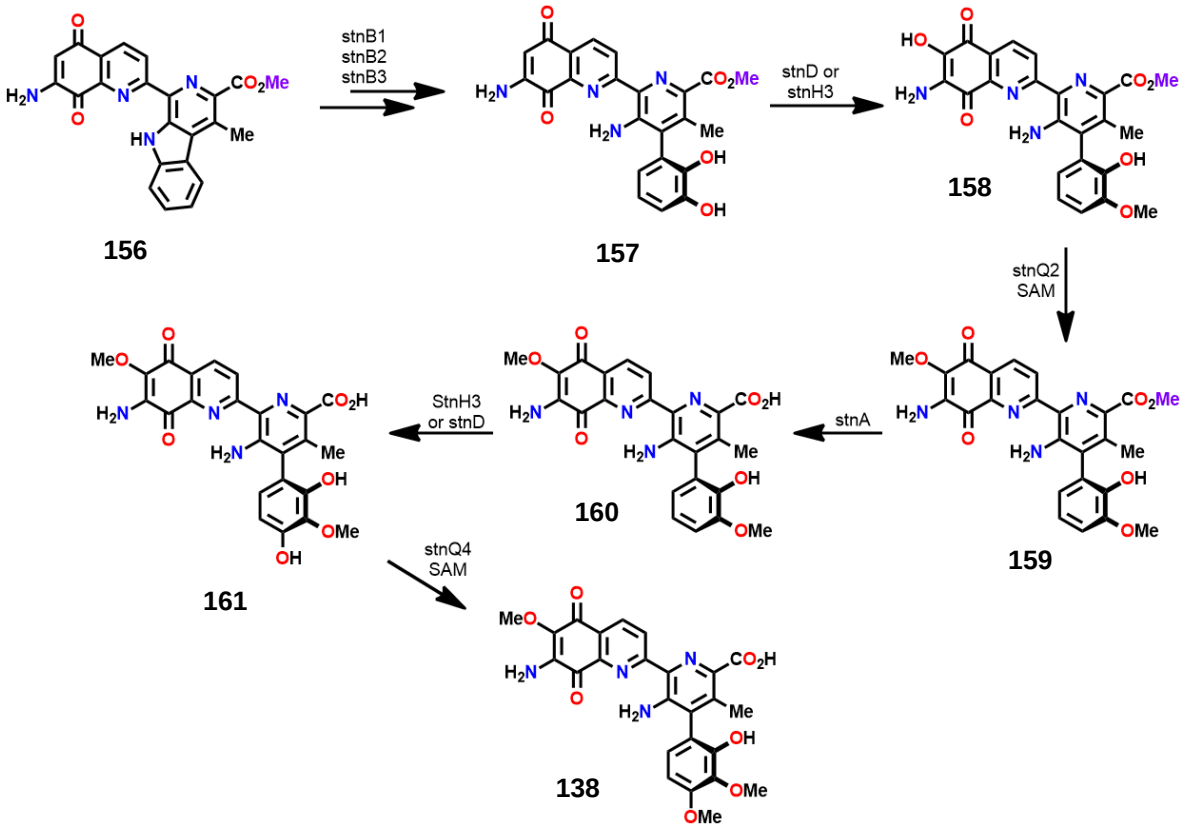
Scheme 37. Biosynthetic pathway for the synthesis of streptonigrin according to Gould *et al*.

In 2013, an alternative pathway for the formation of ring C was reported.[154] *β*-Methylated L-tryptophan **149** condenses with D-erythrose-4-phosphate **143** to give intermediate **153** after the Pictet-Spengler event (presumably catalysed by stnI, a cyclase/dehydrase). Condensed intermediate **153** is then oxidised to yield pyridine **154**; it is unknown whether this step is nonenzymatic or enzyme-catalysed by the action of stnS (which has cytochrome P450 activity) and stnW (acetyl-CoA dehydrogenase). Intermediates **154** and **146** converge in a condensation step furnishing lavendamycin **140** as a biosynthetic intermediate towards streptonigrin; the enzyme(s) involved in this transformation have not been identified yet. Lin *et al*. have proposed that lavendamycin **140** undergoes a cryptic carboxyl methylation, catalysed by stnF2, a SAM-dependent leucine carboxyl methyltransferase (**Scheme 38**).[154]



Scheme 38. Proposal for the biosynthetic synthesis of lavendamycin 140 and its cryptic methylation step.

Methylated lavendamycin **156** serves as substrate for stnB1 (aromatic ring dioxygenase *α* subunit), stnB2 (aromatic ring dioxygenase *β* subunit), and stnB3 (ferredoxin reductase). StnB1 and stnB2 also catalysed the regio- and atropo-selective C–N bond formation to give aminopyridine intermediate **157**. Methylation of the C9' hydroxyl group by SAM-mediated stnQ3 (methyltransferase), followed by C6 oxidation catalysed by either stnD (4-hydroxyphenylacetate-3-hydroxylase), stnH3 (FAD-dependent oxidoreductase), or another oxidising enzyme afford intermediate **158**. The introduced C6-hydroxyl group then gets methylated by SAM-mediated stnQ2 (catechol-*O*-methyltransferase) resulting in intermediate **159**. The next step involves the formal hydrolysis of the methyl ester group by stnA (hydrolase). Stn A has been identified and its crystal structure was reported in 2017 by Chen *et al*.[155] Finally, oxidation catalysed by stnH3 (FAD-dependent oxidoreductase) or by stnD installs the final hydroxyl group at C10', which then gets methylated by SAM-mediated stnQ4 (methyltransferase) to afford streptonigrin (**Scheme 39**).

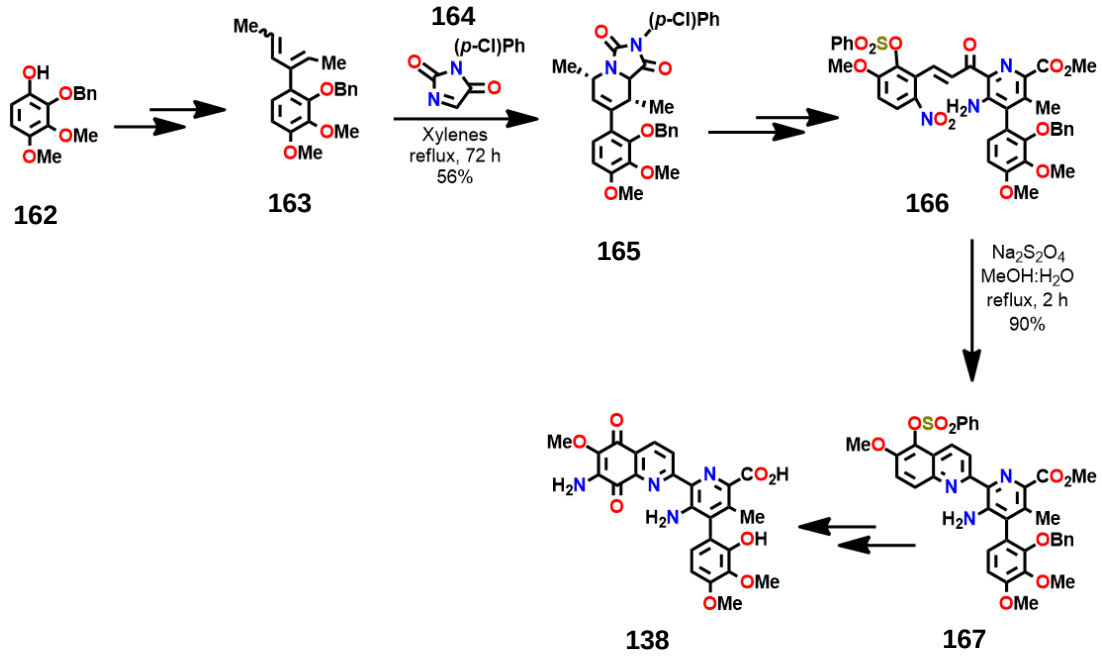


Scheme 39. Proposed biosynthetic pathway for the conversion of methylated lavendamycin 156 into streptonigrin.

3.3 Total Syntheses of Streptonigrin

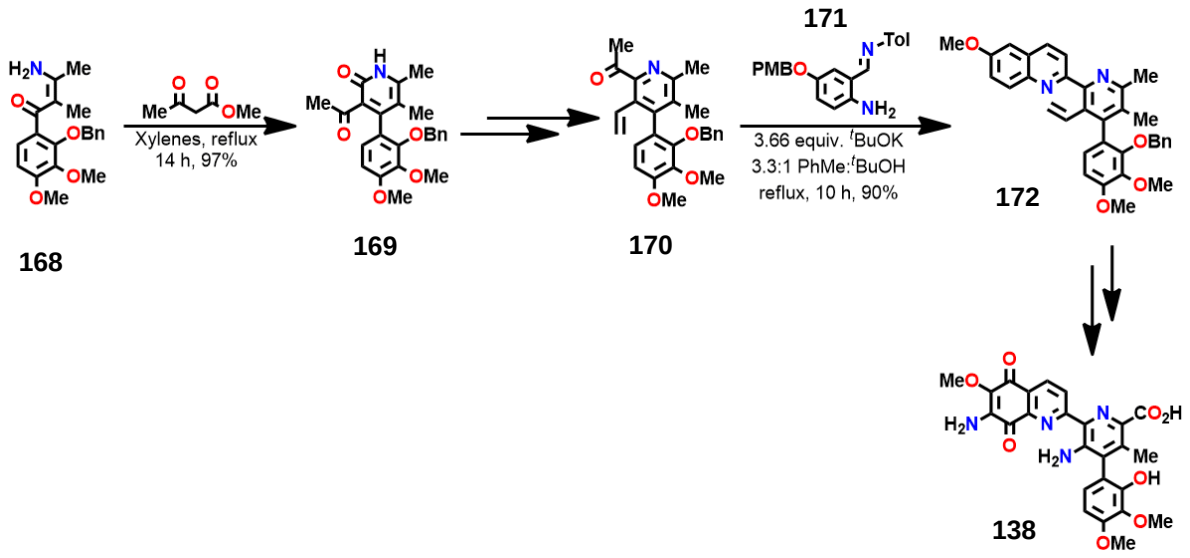
Since its discovery, there has been extensive work towards the synthesis of streptonigrin and related frameworks. Several synthetic studies, including total and partial syntheses, and studies of model systems, have provided valuable strategies for the installation of the required functional groups at the correct positions.[156–160] The first total synthesis of streptonigrin was reported back in 1980 by Steven Weinreb *et al.* (**Scheme 40**); the synthesis comprised 31 steps with an overall yield of 0.013%.[161] The synthesis features a hetero Diels-Alder cycloaddition reaction to construct key pyridine ring C and a reductive cyclization step to construct ring B. Oxidation of ring A with Frémy's salt provided the quinolone fragment with the correct

oxidation level. Finally, the northern amino group was installed by a sequence of iodination, azidation, and reduction reactions; this sequence was first introduced in 1967 with bromine being used instead of iodine.[162] The final step was the hydrolysis of the methyl ester in pyridine ring C to afford streptonigrin. The synthesis suffers from two major problems: the lack of regioselectivity in the hetero Diels-Alder step, and the length of the whole synthesis.



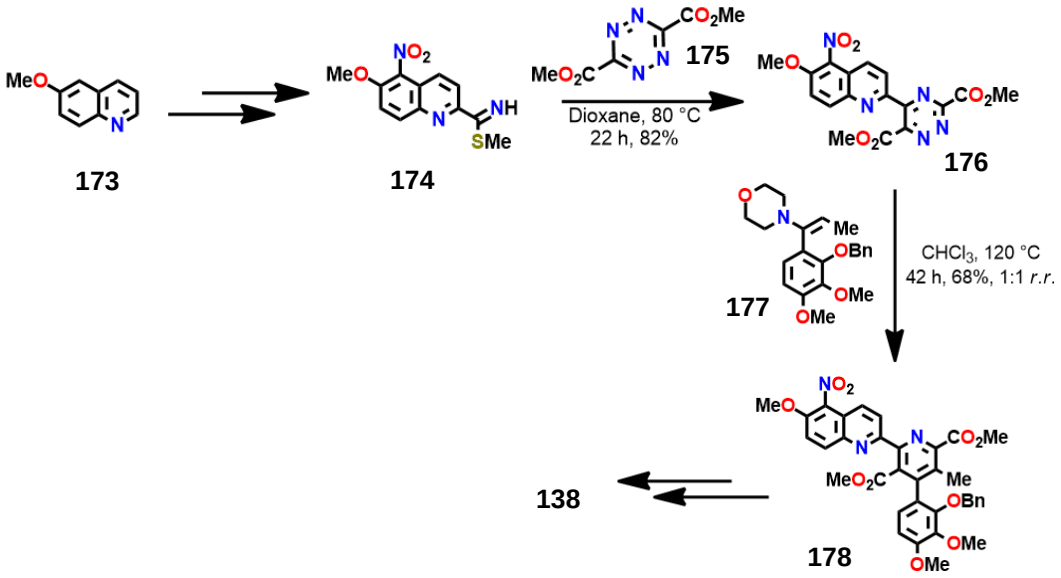
Scheme 40. Condensed overview of Weinreb's total synthesis of streptonigrin.

A year later, Kende *et al*. reported an improved synthesis obtaining streptonigrin in 19 steps with an overall yield of 1.3%. In this work, the key pyridine ring C was formed by condensation of a *β*-keto enamine **168** with methyl acetoacetate, while condensing **170** with precursor **171** afforded the quinoline ring system **172** (**Scheme 41**). The last steps were the same as those employed by Weinreb.[163]



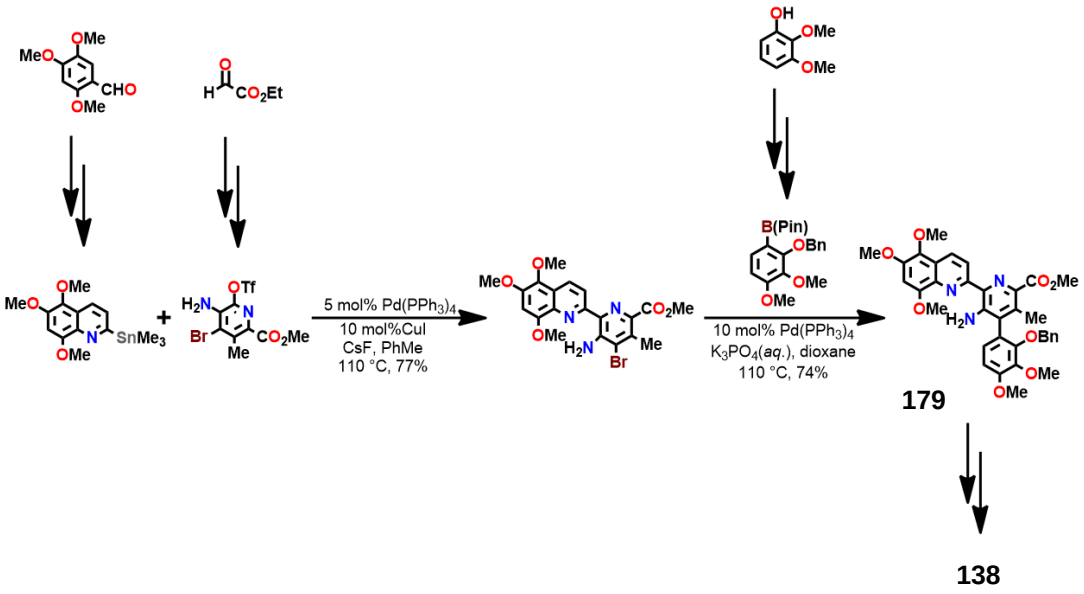
Scheme 41. Condensed overview of Kende's total synthesis of streptonigrin.

In 1985, Boger *et al*. reported their approach towards a total synthesis of streptonigrin, which focused on two sequential inverse-electron-demand Diels-Alder cycloaddition reactions to forge pyridine ring C and construct streptonigrin´s entire carbon framework; nevertheless, the second inverse-electron-demand Diels-Alder event was not regioselective (**Scheme 42**).



Scheme 42. Condensed overview of Boger's formal synthesis of streptonigrin.

In 2011, Donohoe *et al*. achieved the total synthesis of streptonigrin in 14 steps with an overall yield of 14%. In this work, streptonigrin's ring systems were synthesised individually and then linked together using modern Pd-catalysed cross-coupling chemistry (**Scheme 43**).[164]

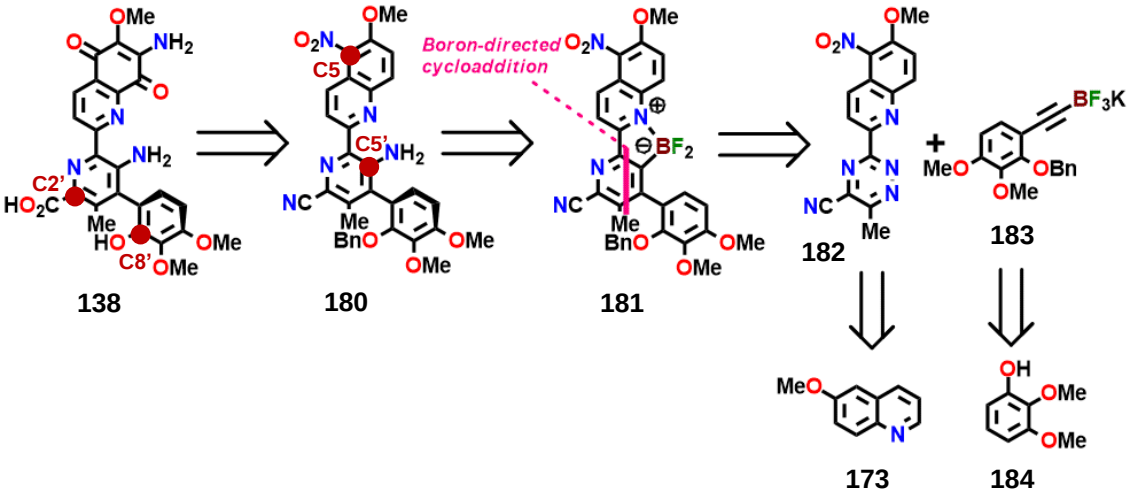


Scheme 43. Condensed overview of Donohoe's total synthesis of streptonigrin.

It is important to say that all the synthetic approaches previously described achieved the synthesis of racemic streptonigrin. In 2013, Donohoe's team published a follow-up study featuring a screening of conditions for the atroposelective formation of the axially chiral biaryl bond. This approach reported afforded intermediate **179** in 35% *ee*, setting the ground for further improvement in the stereocontrolled construction of these key biaryl axis; up to date, this is the only report of an asymmetric approach for the synthesis of streptonigrin. Hence, we set as an objective to synthesise more highly enantioenriched streptonigrin by employing our novel boron-mediated strategy for the resolution of the chiral axis.

3.4 Retrosynthetic Analysis of Streptonigrin

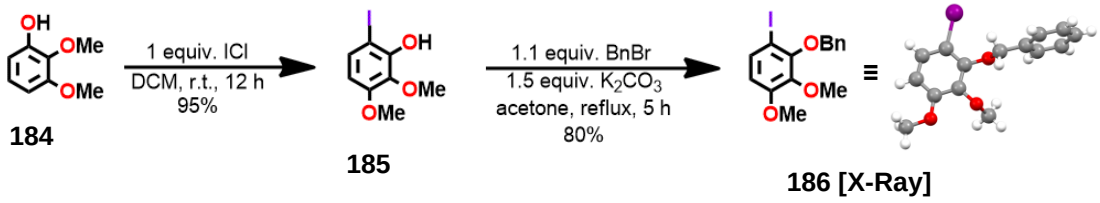
Our approach for the total synthesis of streptonigrin was centred around the construction of the key pyridine C ring *via* the directed-cycloaddition strategy studied in the previous chapter (**Scheme 44**). The main challenge was then the correct timing for installing the diverse functional groups the molecule possesses and making sure that the required transformations do not impose heating under extended time regimes that could cause racemization of the chiral axis. Thanks to previous synthetic efforts reported in the literature, we planned to install the needed functionality on the northern quinolone ring system after the introduction of a nitro group at C5.[157] We also anticipated that the carboxy group at C2' could come from the hydrolysis of a nitrile group, which could be introduced *via* an S_NAr reaction; we also contemplated to protect the phenol group at C8' with a Bn group; all of this would then require intermediate **180** to be prepared. The amino group at C5' would come from a boron functional group, ultimately resulting in intermediate **181**. The presence of the difluoroborane functional group allowed us to disconnect the molecule *via* the boron-directed cycloaddition reaction; such retrosynthetic operation yielded two fragments, triazine fragment **182** and organotrifluoroborate fragment **183**. Triazine fragment **182** could come from commercially available 6-methoxyquinoline **173**, while potassium trifluoroborate fragment could come from 2,3-dimethoxyphenol **184**.



Scheme 44. Retrosynthetic analysis of streptonigrin.

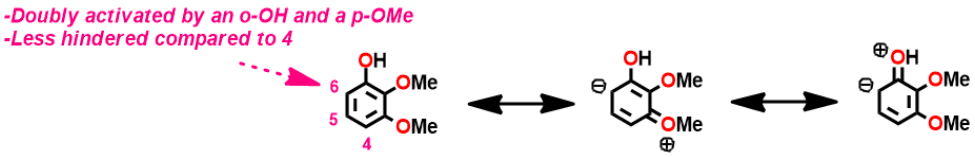
3.5 Synthesis of Organotrifluoroborate Fragment 183

With a synthetic plan in hand, the first stage of the synthesis was to prepare organotrifluoroborate fragment **183**. Starting from commercially available 2,3-dimethoxyphenol **184**, regioselective S_EAr by addition of a commercial solution of ICl (1.0 M in DCM) in DCM at room temperature in the dark for 12 h yielded aryl iodide **185** in excellent yield (95%). The phenol group in **185** was then protected with benzyl bromide (BnBr) in the presence of K_2CO_3 in acetone at reflux for 5 h, yielding aryl iodide **185** in 85% yield. This intermediate was recrystallized from DCM and both its structure, and the position of the iodine atom could be confirmed by X-ray crystallography (Scheme 45).



Scheme 45. Synthesis of X-ray structure of aryl iodide 186.

The regioselectivity of the iodination reaction can be reasoned by analysing the differences between the three available positions for electrophilic attack (**Scheme 46**). Although all three positions are being activated respectively by the oxygen atoms, position **5** is being singly activated only, while the other positions are being doubly activated. Therefore position **6** represents the most reactive site as it is less hindered compared to position **4** which has a bulkier OMe group next to it and has practically the same degree of activation.



Scheme 46. Resonance structures of phenol 184.

Then, Sonogashira cross-coupling of aryl iodide **186** with trimethylsilylacetylene under our optimized conditions afforded alkyne **187** in 98% yield, which was followed by desilylation with K_2CO_3 affording terminal alkyne **188** in 72% yield. The structure of terminal alkyne **188** was also confirmed by X-ray crystallography.

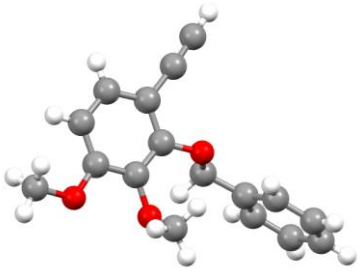


Figure 11. X-ray structure of alkynylaryl 188.

Finally, the lithiation-borylation-fluorination sequence afforded potassium organotrifluoroborate salt **189** in 85% yield (45% overall yield over 5 steps). Each of these steps could be carried out in multigram scale allowing the preparation of several grams of organotrifluoroborate salt **189** whose structure was also confirmed by X-ray crystallography. This 5-step synthesis did not present any further challenges thanks to the previous optimization experiments done, especially of the last 3 steps as described in the previous chapter (**Scheme 47**).

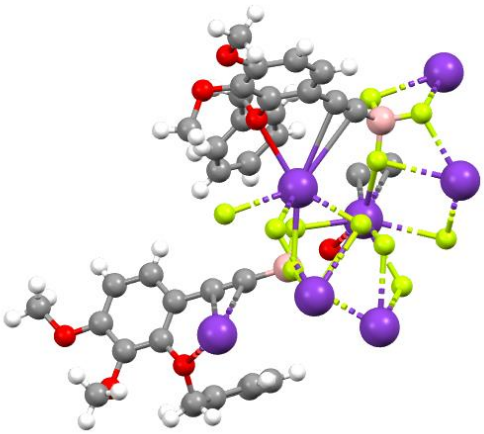
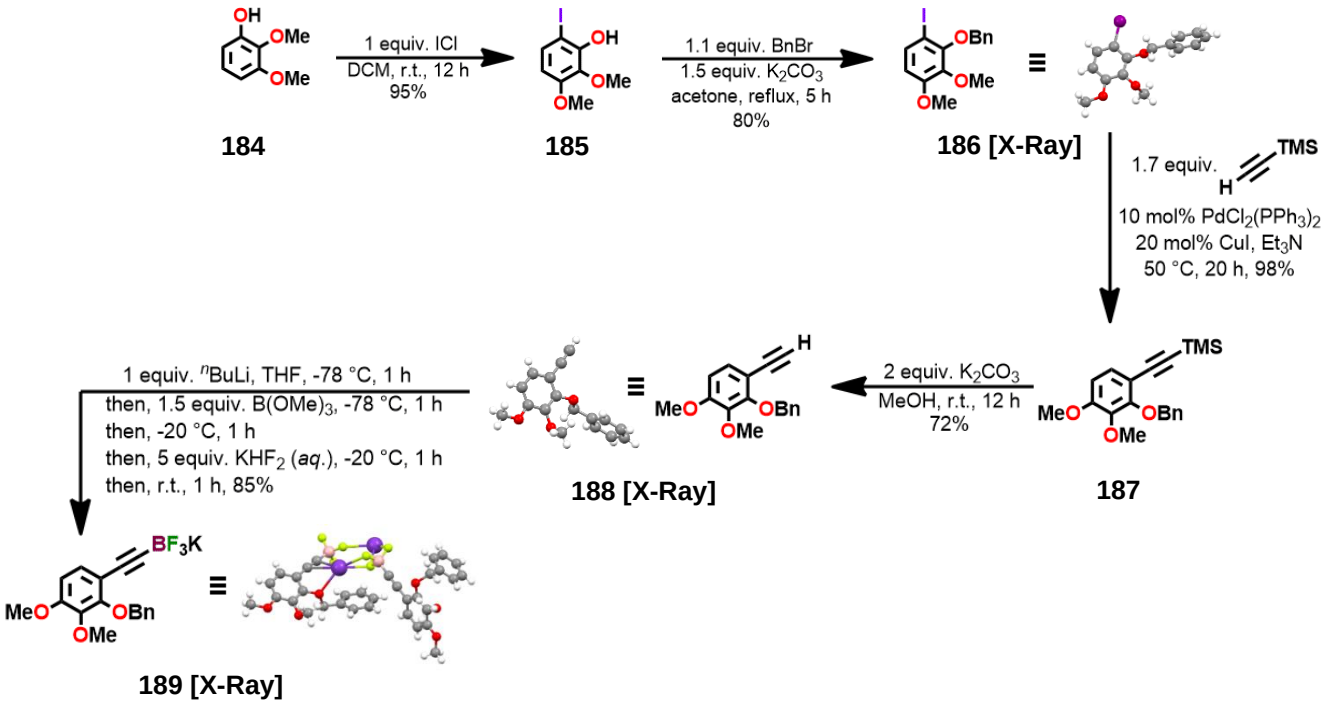


Figure 12. X-ray structure of potassium organotrifluoroborate 189.

The X-ray structure of organotrifluoroborate **189** shows a polymeric solid-state arrangement with heptacoordinated K cations. Each K cation is coordinated by 5 F atoms from BF_3 moieties, while the other two coordination sites being occupied by an alkyne and the O atom from the benzyloxy group respectively. This latter interaction between the K cations and the *ortho* substituent could explain why organotrifluoroborate **69** (**Chapter 2, Scheme 27**) was unstable, degrading over the course of a few months. Presumably, an interaction between the K cations and the *ortho* F atoms in **69** could lead to formation of KF, hence explaining the observed decomposition of this compound.



Scheme 47. 5-Step synthesis of potassium organotrifluoroborate 189 starting from 2,3-dimethoxyphenol 184.

3.6 Synthesis of Triazine Fragment 182

Next, we turned our attention to the synthesis of triazine fragment **182**. Initially, we contemplated the synthesis of this triazine to be oriented towards having an ester group instead of a nitrile group at C5 (**compound 182, Scheme 44).** One of the main challenges in the synthesis of unsymmetrically substituted triazines is the regioselectivity of the condensation step between the amidrazone and the 1,2-dicarbonyl compound. In these cases, the regioselectivity is dictated by the attack of the most electrophilic carbon with the most nucleophilic nitrogen atom of the amidrazone.

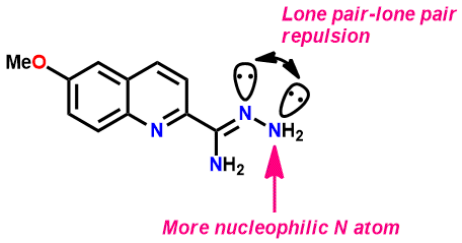
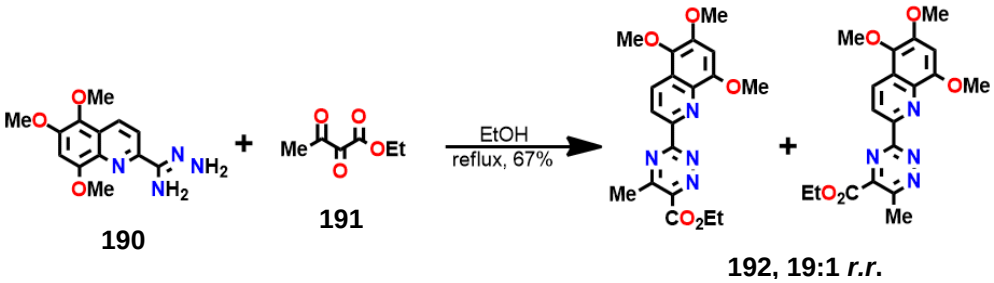


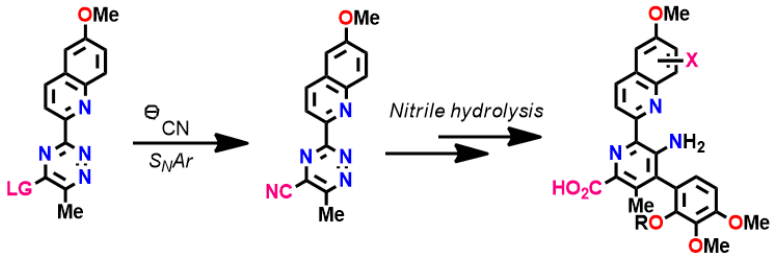
Figure 13. Amidrazone's α-effect.

The N atom at the amino group attached to the imino nitrogen is the most nucleophilic of the amidrazone's N atoms; this is because that N atom is subjected to an α-effect, which is the increased nucleophilicity of an atom due to the presence of an adjacent atom that possesses lone pairs. Previous studies done in our research group regarding the synthesis of substituted and functionalized triazines showed that the reaction of amidrazones, for example **190**, with tricarbonyl **191** yields triazine **192** with a 19:1 regioisomeric ratio (**Scheme 48**). In this scenario, the ester group ends up at C6 (C3' with respect to streptonigrin), making this approach unsuitable for the synthesis of our target.



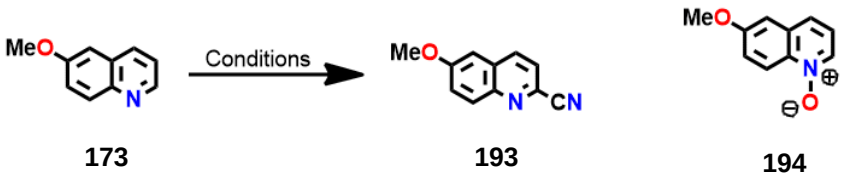
Scheme 48. Regioselectivity of the condensation of amidrazone 190 with tricarbonyl 191.

Inspired by the work of Neunhoeffer *et al.*,[165] our plan consisted then on introducing a nitrile group at C5 (C5' with respect to streptonigrin) *via* a S_NAr reaction on an appropriate triazine substrate. We anticipated that the introduced nitrile could be converted to the needed carboxy group by a hydrolysis reaction (**Scheme 49**).



Scheme 49. Proposed strategy for the introduction of streptonigrin's C2' carboxy group.

With this idea in mind, the first step was the cyanation of 6-methoxyquinoline **173** (**Table 11**). First, we attempted to introduce the nitrile substituent by activation of the quinoline *via* its *N*-oxide **194**. Oxidation of quinoline **173** with *m*CPBA yielded quinoline *N*-oxide **194** in 82% yield.[166] *N*-Oxide **194** was then heated at 80 °C with TMSCN and PIDA in DCE as solvent to give the desired product in moderate 55% yield (**Entry 1**).[167] Given the need for higher yields, another approach was to heat quinoline **173** with TMSCN under neat conditions, but this only yielded the desired product in 45% yield (**Entry 2**).[168] This approach was discarded because of the operational danger of heating toxic TMSCN at high temperatures when scaling up. We then subjected quinoline **173** to the conditions reported by Dixon *et al*. for the C–H cyanation of *N*-heteroaromatics.[169]

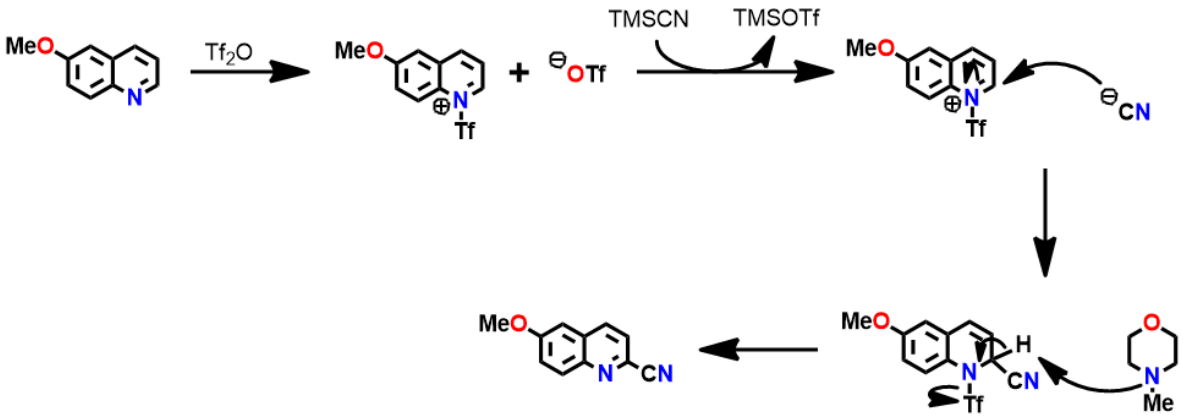


173 **193** **194**

Entry	Conditions	Outcome
1[a]	TMSCN, PIDA, DCE, 80 °C	55%
2[a]	TMSCN, 130 °C, neat	45%
3[b]	Tf_2O, $CHCl_3$, r.t., then, TMSCN, 60 °C, 3 h, then, NMM, 60 °C, 18 h	77%
4[c]	Tf_2O, $CHCl_3$, r.t., then, TMSCN, 60 °C, 3 h, then, NMM, 60 °C, 18 h	61%

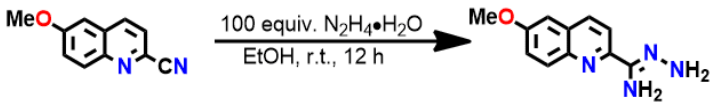
Table 11. Optimization experiments for the cyanation of quinoline 173. [a] = Via 194. Yield calculated from 161. [b] = 500 mg of 173 scale. [c] = 10 g of 173 scale.

Under such conditions, the reaction proceeds with complete conversion to give the product in 77% yield and as a 4:1 ratio of regioisomers, with the desired regioisomer formed as the major one at 500 mg scale (**Entry 3**). The reaction was scalable and, even though at multigram scale there was a drop on the yield, the amount of isolated material was still satisfactory enough (**Entry 4**). Pleasingly, the mixture of regioisomers was separable by column chromatography, allowing us to access quinoline **193** in multigram quantities The reaction proceeds *via* an addition-elimination mechanism, where the quinoline is activated by Tf_2O, followed by attack of a cyanide anion at C2 and finally the σ-complex gets deprotonated by NMM to yield the desired product (**Scheme 50**).



Scheme 50. Proposed mechanism for the cyanation of quinoline 173.

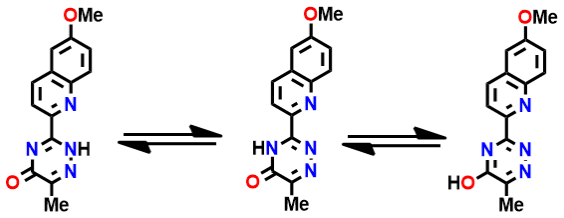
Quinoline **193** was then treated with an excess of hydrazine monohydrate, which gave amidrazone **195** in 95% yield (**Scheme 51**). The isolation of this compound was straightforward and only required filtration and washing with deionized water, however, care must be taken and the amidrazone must be washed with a generous amount of deionized water to wash up any residual hydrazine, which may pose a problem for the next step.



193 **195**

Scheme 51. Synthesis of amidrazone 195.

Amidrazone **195** was then treated with pyruvic acid to afford triazinone **196a** in 95% yield. In general, the reaction proceeded smoothly and was operationally simple, however, the quality of the pyruvic acid was quite important for the success of the reaction. Fresh pyruvic acid has a light-yellow colour, over time, this can change to orange. This chemical must be kept in a freezer and protected from light to ensure its quality and purity. The solubility of triazinone **196** was quite limited, being only sparingly soluble in DMF and DMSO. In principle, triazinone **196** could exist as 3 different tautomers: **196a**, **196b**, or **196c** (Scheme 52).



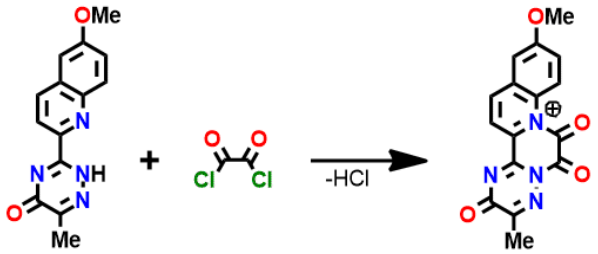
196a **196b** **196c**

Scheme 52. Possible tautomers of triazinone 196.

Although the identity of the tautomer obtained is unknown, tautomer **172c** was discarded because of a strong vibration at 1732 cm^{-1} observed by infrared spectroscopy, which suggests the presence of a C=O bond. In general, pyridines with an oxygen atom at positions 2 or 4 exist predominantly as their carbonyl tautomers. Because of this, it is reasonable to think that triazinone **196** most likely exists as either **196a** or **196b**. An exhaustive study to determine the

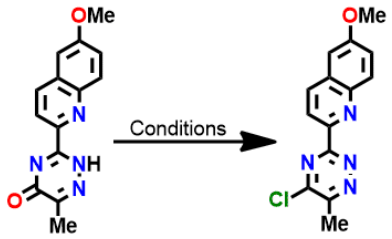
real identity of this compound was not carried out as its identity was considered inconsequential for our objectives. Previous studies on the nature of these type of compounds have shown that the dominant tautomeric structure can be different in solution and in the solid state, and is also a function of the triazinone's substituents.[170]

In order to introduce the cyano substituent at C5 of the triazine core, the exchange of the oxo group of triazinone **196** into a leaving group was needed, and so we aimed for a well-known deoxychlorination reaction. This reaction represented a considerable challenge as several conditions had to be tested until a reliable, scalable, and reproducible methodology could be found. Our starting point was Neunhoeffer's work,[165] and so the common chlorinating agents $SOCl_2$, $POCl_3$ and $(COCl)_2$ were tested first. Unfortunately, under Neunhoeffer's reported conditions only complex mixtures with no sign of product formation were obtained. We then turn our attention to other chlorinating agents such as PCl_3, PCl_5, NCS, BTC (with catalytic DMF),[171] and $POCl_3$ (with catalytic DMF).[172] All of them were unsuccessful in giving the desired product under a wide range of solvents (including DCM, DMF, DMSO, neat conditions), temperatures (–78 °C, 0 °C, room temperature, reflux, microwave heating), and reaction times (minutes to days).[173–176] Even the quality of the reagents was tested (fresh reagents, distilled, and/or dried over 4 Å MS), however, all experiments ended up in failure. From these extensive screening of chlorinating conditions, we noticed that the only conditions able to provide traces of product were those when $(COCl)_2$ was used in the presence of a catalytic amount of DMF. A screening of solvents, temperatures, and reaction times also failed to give high-yielding and reproducible results. Nevertheless, a common result from these experiments was the presence of a cation with a mass of 323 au, which we attributed to species **197** (**Scheme 53**). We suspected that the problem relied on the triazinone being more reactive than DMF towards $(COCl)_2$, hence causing the reaction to fail.



196 **197**

Scheme 53. Proposed side reaction for the synthesis of triazinone with $(COCl)_2$.



196 **198**

Entry	Conditions	Outcome
1[a]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*s*), DCM, r.t., 4 h	< 5%
2[a]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*s*), DCM, 0 °C, 4 h	< 5%
3[b]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*DCM*), DCM, r.t., 1 h	15%
4[b]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*DCM*), DCM, r.t., 2 h	0% (85% SM)
5[b]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*DCM*), DCM, r.t., 1 h	34%
6[b]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*DCM*), DCM, r.t., 30 min	60%
7[b]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*DCM*), DCM, r.t., 15 min	74%
8[b,c]	2 equiv. $[(CH_3)_2NCHCl]Cl$ (*DCM*), DCM, r.t., 15 min	74%

Table 12. Optimization experiments for the chlorination reaction of triazinone 196 with preformed Vilsmeier reagent. [a] = Solid commercial Vilsmeier reagent was used. [b] = A pre-made Vilsmeier reagent solution (0.1 F) was used. [c] = Reaction run at 2 g scale.

Based on this hypothesis, we decided to try commercial Vilsmeier reagent $[(CH_3)_2NCHCl]Cl$ instead of trying to prepare it *in situ* (**Table 12**). Treating triazinone **172** with commercial Vilsmeier reagent for 4 h at room temperature led to the desired chloride in low yield (**Entry 1**). Decreasing the temperature to 0 °C did not offer an improvement on the reaction yield (**Entry 2**). The Vilsmeier reagent is quite hygroscopic, which caused problems with its

manipulation hence leading to low yielding outcomes. Up to this point, we concluded that it was better to prepare the Vilsmeier reagent in solution under a nitrogen atmosphere beforehand to prevent the reagent's decomposition. Indeed, adding DMF to a solution of $(COCl)_2$ in DCM under a nitrogen atmosphere proceeded with immediate evolution of bubbles (CO and CO_2) and precipitation of the Vilsmeier reagent as a solid. Treating triazinone **196** with freshly prepared Vilsmeier reagent solution afforded the product in 15% yield over 1 h (**Entry 3**). Extending the reaction time reduced the yield and over the course of 2 h no product was obtained (85% SM was recovered) (**Entry 4**). Aging the Vilsmeier reagent solution proved to be beneficial; this is because the reagent forms first as a solid which precipitates instantly, but over the course of a few days it dissolves into the DCM. An overnight (*ca*. 18 h) aging was enough for a successful chlorination reaction, however, the older the solution is, the more concentrated it gets and hence less solution is required for a successful reaction. Empirically, the rate of solubilization of the Vilsmeier reagent also depends on the ambient temperature, the lower the temperature the slower the solubilization and *vice versa*. For this reaction, time played an important role. Over the course of 1 h, triazine chloride **198** was obtained in 34% yield when an aged Vilsmeier reagent solution was used (**Entry 5**). Decreasing the reaction time favoured the outcome; presumably, this happened because the triazine chloride is quite a soft and reactive electrophile, and rapidly reacts with DMF to give the triazinone back. Decreasing the time to 30 min afforded triazine chloride in 60% yield (**Entry 6**). Finally, a reaction time of 15 min was enough to obtain the desired target in 74% yield (**Entry 7**). This methodology was found to be scalable and up to 2 g of triazinone **196** could be converted to the chlorinated product without affecting the yield (**Entry 8**). The identity of the product was unequivocally confirmed by X-ray crystallography.

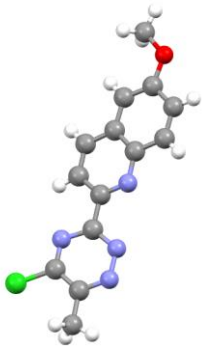
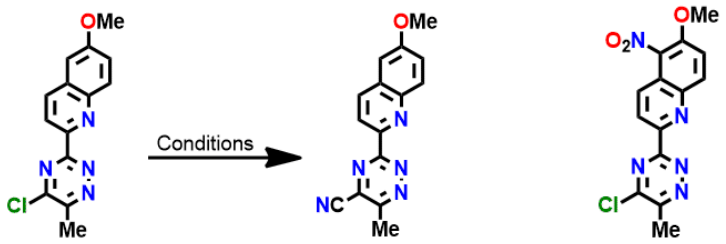


Figure 13. X-ray structure of triazine chloride 198.

We treated triazine chloride with DMF to confirm if this led back to the triazinone. Indeed, after 1 h, triazinone **196** was generated back, confirming our hypothesis, and providing an explanation for the problems observed in our initial optimization studies. As a final note, bromination and triflation of triazinone **196** were also attempted but these experiments were unsuccessful.

With triazine chloride **198** in hand and available in multigram quantities, we proceeded to study the S_NAr reaction to install the desired nitrile at the triazine core. Our initial plan was to use a mixture of TBACN and TBAF as a source of cyanide ions, however, treating triazine chloride **198** with this mixture in different ratios and reaction times led to complex mixtures with only traces of product formed. From our initial experiments we noticed that controlling the reaction time was key, as only a few minutes were needed before the reaction got out of control (**Table 13**).



198 199 200

Entry	Conditions	Outcome
1	2.5 equiv. TMSCN, 2.5 equiv. TBAF[a], DCM, r.t., 5 min	1:0.2 Product:SM 32% yield[d]
2	2.5 equiv. TMSCN, 2.5 equiv. TBAF[b], DCM, r.t., 5 min	1:0.8 Product:SM
3	2.5 equiv. TMSCN, 2.5 equiv. TBAF[c], DCM, r.t., 5 min	1:0.5 Product:SM
4	2.5 equiv. TMSCN, 2.5 equiv. TBAF[a], DCM, r.t., 30 min	1:3.75 Product:Impurity
5	2.5 equiv. TMSCN, 2.5 equiv. TBAF[a], DCM, r.t., 2 min	1:0.4 Product:SM
6	2.5 equiv. KCN, 2.5 equiv. TBACl, DMF, r.t., 1 h	1:3.8 Product:SM
7	2.5 equiv. KCN, 2.5 equiv. TBACl, DMF, r.t., 5 h	1:3.6 Product:SM
8	2.5 equiv. KCN, 2.5 equiv. TBACl, DMF, reflux, 2 h	Complex mixture
9	2.5 equiv. TMSCN, 2.5 equiv. TBAF, DCM, –78 °C, 5 min	SM
10	2.5 equiv. TMSCN, 2.5 equiv. TBAF, DCM, –78 °C, 1 h	SM
11	2.5 equiv. TMSCN, 2.5 equiv. TBAF, DCM, –40 °C, 1 h	SM
12	2.5 equiv. TMSCN, 2.5 equiv. TBAF, DCM, –40 °C, 2 h	1:12 Product:SM
13	2.5 equiv. TMSCN, 2.5 equiv. TBAF, DCM, 0 °C, 1 h	1:12 Product:SM (Complex)
14	2.5 equiv. TMSCN, 2.5 equiv. TBAF, DCM, 0 °C, 2 h	21% yield[d]
15	2.5 equiv. TMSCN, 2.5 CsF, DCM, r.t., *ca.* 18 h	1:3.2 Product:SM
16	1.2 equiv. Tf_2O, DCM, r.t., 1 h, then, 5 equiv. TMSCN, reflux, 12 h	Complex (mostly SM)
17	2.5 equiv. KCN, 2.5 equiv. TBACl, DMF, 45 °C, 5 h	1:7.2 Product:SM
18	2.5 equiv. TMSCN, 2.5 equiv. CsF, DMF, r.t., 2 h	Complex
19	10 equiv. TMSCN, 10 equiv. CsF, DCM, r.t., *ca.* 18 h	1:3 Product:SM
20	2.5 equiv. TMSCN, 2.5 equiv. TBAF, DCM, 0 °C, 2 h	Complex[e]

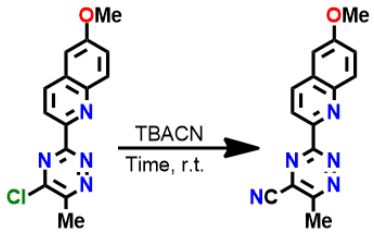
Table 13. Condition screening towards the cyanation of triazine chloride 198. [a] = Dried over 4 Å MS. [b] = Dried over $MgSO_4$. [c] = Premixed TMSCN and TBAF were used. [d] = The product was isolated with another impurity. [e] = Nitro triazine 200 was used as starting material.

We thought that the basicity of TBAF was affecting the outcome of our experiments. Because of this, we decided to dry the reagent before use with 4 Å MS (**Entry 1**) and $MgSO_4$ (**Entry 2**). These experiments did not give the desired product in satisfactory yields. Furthermore, the separation of the product and the starting material was impossible, hence imposing the condition that the starting material must be consumed completely. Premixing TBAF and

TMSCN and then adding this to the triazine chloride did not result in complete starting material consumption (**Entry 3**). Using "dried" TBAF, increasing the reaction time to 30 min resulted in loss of the starting material, however, another impurity was formed which was also impossible to separate from the product (**Entry 4**). Decreasing the reaction time from 5 min to 2 min yielded a 1:0.4 mixture of product to staring material (**Entry 5**). We then decided to look at other cyanating reagents such as KCN. In the literature, KCN is commonly used as a cyanide source in DMF as solvent. The use of DMF represented a problem for our system because it reacts with the triazine chloride, however, the reaction is not immediate and so there was a window of opportunity. Treating the triazine chloride with KCN in the presence of TBACl afforded a 3.8:1 mixture of starting material and product (**Entry 6**). Formation of the triazinone was observed as well. Increasing the reaction time from 1 h to 5 h did not show a considerable improvement (**Entry 7**) and most of the material was converted to the triazinone. Heating the reaction mixture to reflux also failed to give any product and only a complex mixture was obtained (**Entry 8**), and applying a lower temperature was not beneficial either (**Entry 17**). We then decided to start again with the TMSCN/TBAF combination, changing this time the reaction temperature. All reactivity shut down at –78 °C and only the starting material was recovered (**Entries 9 & 10**). At –40 °C, only starting material was obtained after 1 h (**Entry 11**), but after 2 h the reaction starts and a 1:12 product:SM was observed along with other impurities (**Entry 12**), and at 0 °C the same result was obtained after 1 h (**Entry 13**). We then decided to extend the reaction time to 2 h, after this time the starting material disappeared but the product was isolated with an impurity that could not be identified (**Entry 14**). As it was not possible to use the reaction time to control the reaction, we decided to look back at TMSCN, but this time, using CsF as the fluoride source (**Entry 15**), but unfortunately, the reaction stopped at ~25% conversion. Further experiments with CsF failed to give any

satisfactory results (**Entries 18 & 19**). We also tried Dixon´s cyanation conditions employed for the synthesis of quinoline intermediate **193**, however these failed to give any product and mostly starting material was recovered along other unidentified side products (**Entry 16**). We then opted for the use of nitro triazine chloride **200** as starting material to compare its reactivity with **198**. Nitro triazine chloride **176** was prepared by nitration of **198** in 67% yield. However, treating **200** with the TMSCN/TBAF combination at 0 °C for 2 h gave back a complex mixture with no sign of product (**Entry 20**).

Discouraged by these results we discarded the use of TMSCN/TBAF combination and turned our attention to TBACN, a commercially available reagent that is soluble in organic solvents such as DCM (**Table 14**).



198 **199**

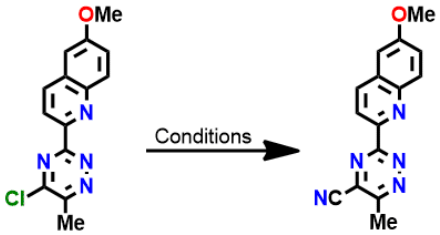
Entry	TBACN	Time	Outcome
1	2 equiv.	12 h	Complex
2	2 equiv.	5 min	3:1 Product:SM
3	2 equiv.	15 min	5:1 Product:SM
4	2 equiv.	1 h	8:1 Product:SM
5	2 equiv.	3 h	7%
6	4 equiv.	5 min	54%
7	6 equiv.	5 min	28%

Table 14. Condition screening for the cyanation of 198 with TBACN.

Treating triazine chloride **198** with 2 equiv. of TBACN over 12 h yielded a complex mixture of unidentified products (**Entry 1**). Decreasing the reaction time to 5 min yielded a mixture of product and starting material, but this time the desired nitrile triazine was the major product.

Increasing the reaction favored the formation of **199** (**Entries 3 & 4**), nevertheless, complete consumption of staring material occurred only after 3 h (**Entry 5**). As TBACN was yielding cleaner results, we decided to increase the number of equivalents to evaluate the effect of reagent stoichiometry. Indeed, increasing the number of equivalents to 4 afforded complete consumption of the starting material and the product could be isolated in moderate 54% yield after column chromatography (**Entry 6**). Increasing the number equivalents led to a decrease in the yield (**Entry 7**). We were also pleased to find out that the reaction could be scaled up starting with 1 g of triazine chloride without any change in the yield (54%). Nevertheless, this protocol was far from perfect; in the first place, the reaction time must be precisely adhered to, as well as the following work up and purification steps; second, after 5 min, the yield starts to drop dramatically and so it had to be worked up immediately after this time. The purification of the reaction crude also had to be performed just after drying and evaporation to prevent further decomposition of the product. Finally, care must be taken when handling TBACN; this compound, although a solid, is highly hygroscopic and must be used quickly and used immediately after weighing. Another factor to keep in mind is that the quality and appearance of this chemical is different depending on the supplier it is obtained from. At the time this project was done, only two providers offered this chemical, Merck® and Fluorochem®. The appearance of commercial TBACN can go from a white crystalline solid to a sticky white paste, and naturally the reproducibility was directly linked to the quality of the reagent. As TBACN was too unreliable, both in terms of quality and availability, an alternative methodology for the synthesis of **199** was urgently needed. We decided to explore a Negishi cross-coupling reaction for the synthesis of **199**. To this end, we chose $Pd(PPh_3)_4$ as the catalyst and $Zn(CN)_2$ as cyanide source; these reagents are the most

common chemicals reported in the literature for the desired transformation hence were used as starting points (**Table 15**).



198 **199**

Entry		Conditions	Outcome
1	1.5 equiv. $Zn(CN)_2$ 15 mol% $Pd(PPh_3)_4$	THF, 85 °C, 8 h	Mostly SM
2		MeCN, 85 °C, 8 h	1:1 SM:Prd.
3		Dioxane, 85 °C, 8 h	Mostly SM
4		PhMe, 85 °C, 8 h	Mostly SM
5		1.5 equiv. CuCN, dioxane, 85 °C, 8 h	SM
6		MeCN, 85 °C, 12 h	55% yield
7		DCM, 85 °C, 8 h	2:1 SM: Prd.
8		NMP, 85 °C, 8 h	Mostly SM

Table 15. Condition screening for the Pd-catalyzed cyanation of 198 with $Zn(CN)_2$.

We screened a series of common solvents to evaluate their effect in the reaction outcome. Indeed, the reaction showed a high dependency on the solvent; THF (**Entry 1**), dioxane (**Entries 3 & 5**), PhMe (**Entry 4**), and NMP (**Entry 8**) yielded mostly starting material back. MeCN proved to be the best solvent and, although the reaction was also operative in DCM, the reaction was slower in this solvent (**Entry 7**). It must be pointed out that the quality of the Pd catalyst can have an influence in the reaction outcome. $Pd(PPh_3)_4$ is a yellow and crystalline solid that has to be kept in a fridge (2 – 8 °C) to prolong its shelf life. However, the quality of commercial samples of this catalyst can be compromised, and it is not uncommon to find samples that either have lost their crystallinity or color, turning from bright yellow to dark orange. When samples of $Pd(PPh_3)_4$ with these characteristics were used, an

increase in the reaction time (from 12 h to 18 h) was needed to obtain reproducible yields. The reaction time should not be increased if a Pd catalyst with a high level of purity is already being used, as this will lead to a drop in the yield (from 55% to ≤ 15%). Finally, the identity of this nitrile triazine was confirmed by X-ray crystallography.

With nitrile triazine in hand, the last step for obtaining our required synthetic intermediate consisted of a nitration reaction. Suspending triazine **199** in H_2SO_4, followed by addition of HNO_3 afforded the desired triazine **182** in 81% yield. The product could be crystallized from a saturated DCM solution, confirming both the identity of the triazine and the position of the introduced nitro group by X-ray crystallography (**Figure 14**).

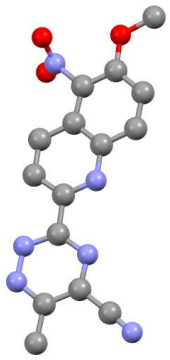
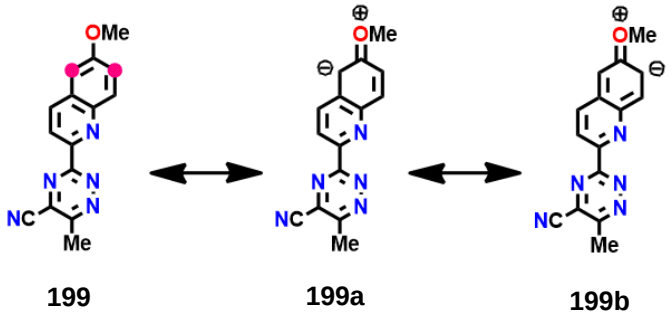


Figure 14. X-ray structure of nitro triazine 182 (Hydrogens have been omitted for clarity).

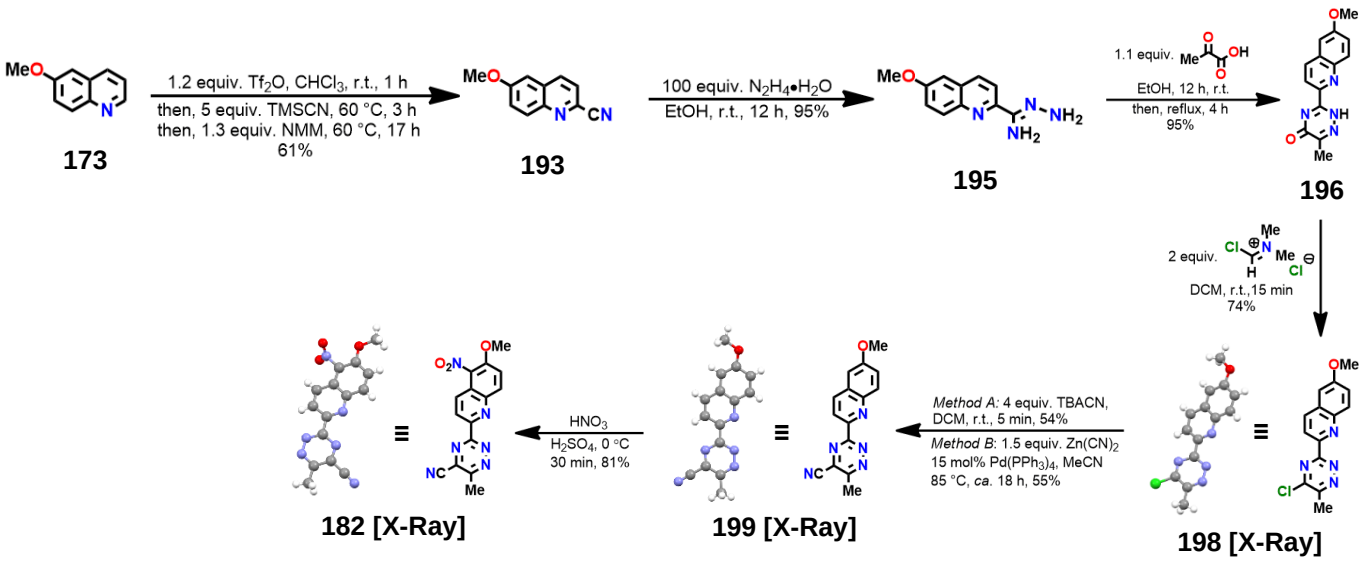
In principle, two nitrated regioisomers might be expected from this reaction. Although both positions *ortho* to the methoxy group (C5 and C7) are activated by it, the reaction is regioselective affording just one product. Presumably, this is because the observed regioisomer allows the maintenance of one aromatic ring in the Wheland intermediate, while formation of the other regioisomer involves complete loss of aromaticity. This causes

resonance structure **199b** to contribute to a lesser extent to the resonance hybrid, and so the overall reactivity is mostly dictated by resonance structure **199a** (Scheme 54).



Scheme 54. Resonance structures of triazine 199.

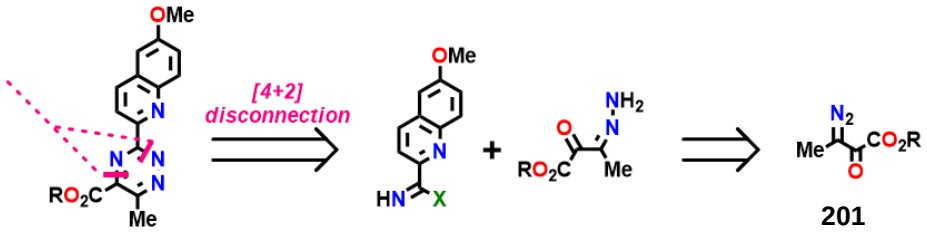
The neutralization of the reaction mixture must be done carefully, and no strong bases (such as NaOH) must be used. This is because it was observed that at high pH values, no product was isolated and only complex mixtures were obtained. Experimentally, it is quite challenging to neutralize a strong acid with a strong base as the pH abruptly "jumps" when this is done and is easy to end up with a highly basic solution if this is not performed carefully enough. For this reason, the neutralization of the acidic reaction mixture was carried out with saturated $NaHCO_3$ (*aq*.). Finally, the required synthetic intermediate could be obtained from commercially available 6-methoxyquinoline in 18% yield over 6 steps (Scheme 55).



Scheme 55. 6-step sequence for the synthesis of triazine 182 from quinoline 173.

3.7 Other Attempted Approaches for the Synthesis of Triazine Fragment 182

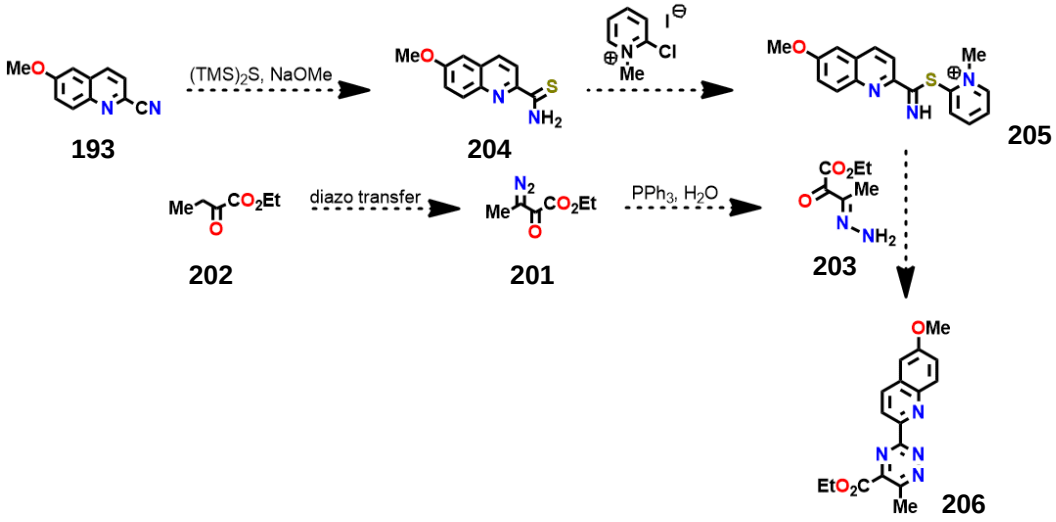
Simultaneous to the optimization of our initial plan to prepare triazine fragment **182**, we evaluated other possible strategies for that end. To circumvent the regioselectivity problem of the conventional amidrazone/1,2-dicarbonyl condensation, Neunhoeffer and Ohsumi reported the synthesis of triazines with an ester group at C5 using diazo compounds **201** as starting materials (**Scheme 56**).[177]



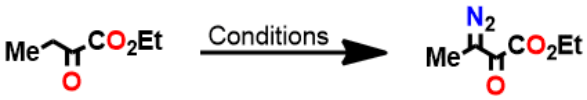
Scheme 56. Alternative approach towards the synthesis of regiocontrolled triazines.

We expected then to apply the same strategy to our system; ethyl-oxobutanoate **202** would then be subjected to a Regitz diazo transfer reaction to get diazo compound **201**, followed by

a Staudinger-type reduction to give hydrazone **203**. On the other hand, the cyano group of quinoline **193** would then be converted to thioamide **204**. Activation of this amide with Mukaiyama's reagent would give intermediate **205**, and its reaction with hydrazone **203** would give the desired triazine **206** with the correct regiochemistry (**Scheme 57**). Unfortunately, this approach was quickly abandoned as the key Regitz diazo transfer reaction was unsuccessful (**Table 16**).



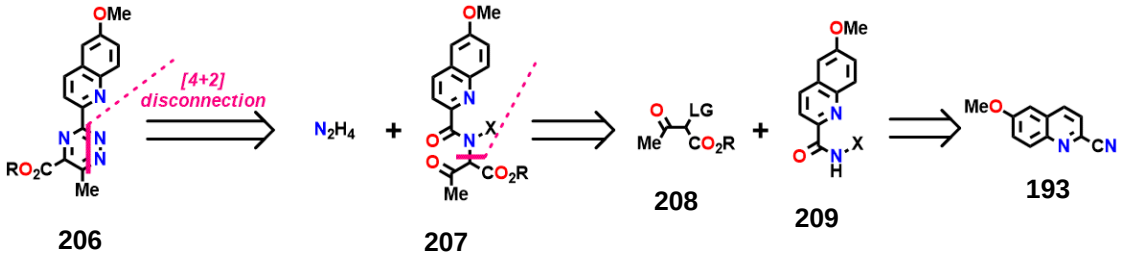
Scheme 57. Proposed synthetic plan for an alternative triazine precursor.



Entry	Conditions	Outcome
1	TsN_3, K_2CO_3, TBACl, THF	Complex mixtures without signs of product
2	MsN_3, Et_3N, TBACl, THF	
3	MsN_3, K_2CO_3, TBACl, THF	
4	LiHMDS, $(CF_3CO)_2O$, THF, –78 °C, then, TsN_3, Et_3N, H_2O, MeCN, r.t.	
5	LiHMDS, THF, –78 °C, 30 min, then MsN_3, r.t.	
6	LiHMDS, THF, –78 °C, 30 min, then TsN_3, r.t.	

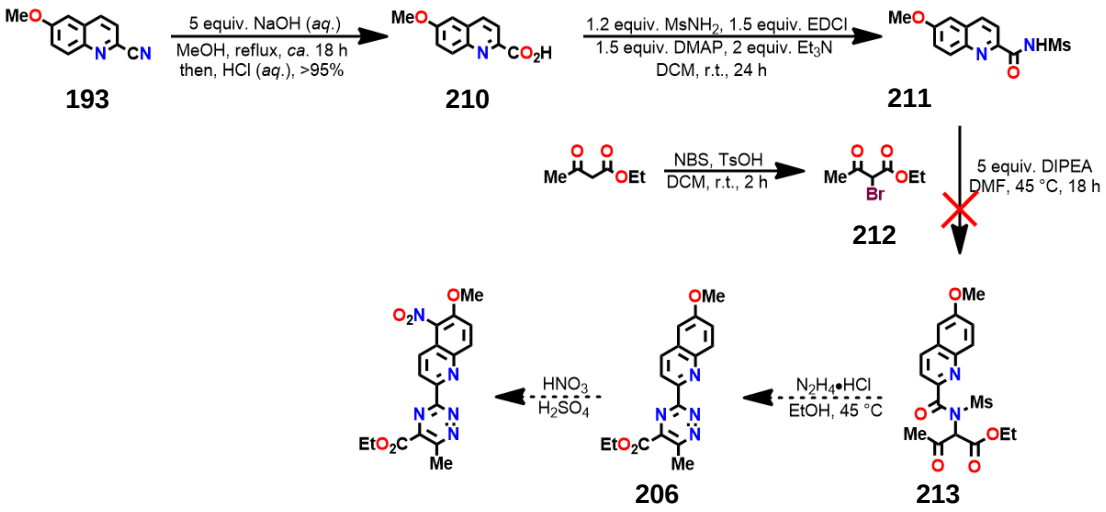
Table 16. Condition screening for the synthesis of diazo compound 201.

Having discarded this approach, we then contemplated the possibility of building triazine **206** by a different [4 + 2] approach where hydrazine could be the 2-atom component. Such [4 + 2] disconnection yields amide intermediate **207**, which could be prepared *via* an S_N2 reaction with an appropriate *β*-ketoester **208**. Finally, amide **209** could come from known quinoline **193** (Scheme 58).



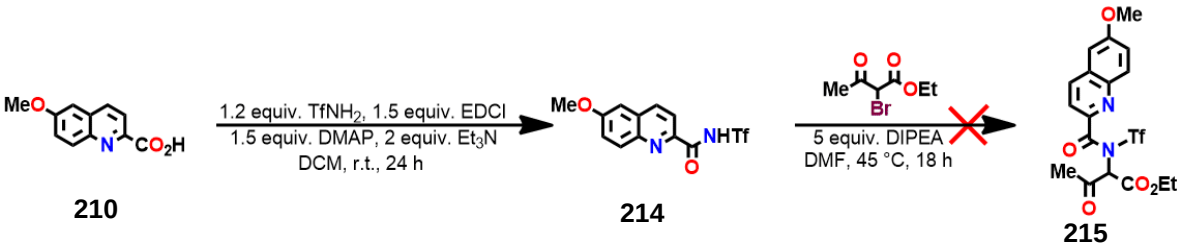
Scheme 58. Second alternative approach for the synthesis of triazine 206.

We started by subjecting quinoline **193** to basic hydrolysis to give carboxylic acid **210**, which was then coupled with methanesulfonamide to get amide **211** in moderate (50%) yield. With amide **211** in hand, we attempted to link it with *β*-ketoester **212** to give intermediate **213**. However, all experiments met with failure, and only starting materials were recovered back in each case (Scheme 59).



Scheme 59. Second-generation synthetic plan for the preparation of triazine 206.

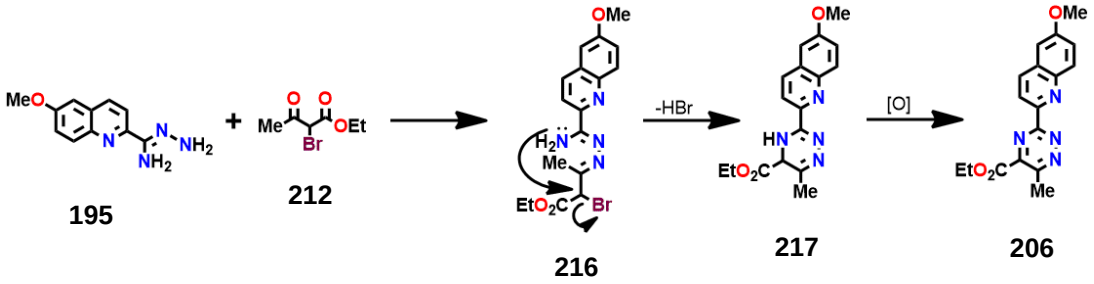
We thought that sulfonamide **211** was not acidic enough for a mild base to deprotonate it, hence the mesyl group was replaced for a triflyl group in expectance of enhancing the acidity of the amide. Unfortunately, this also proved to be unproductive and only the starting trifluorosulphonamide was recovered (**Scheme 60**).



Scheme 60. Attempted S_N2 reaction of triflyl amide 214 with bromo-β-ketoester 212.

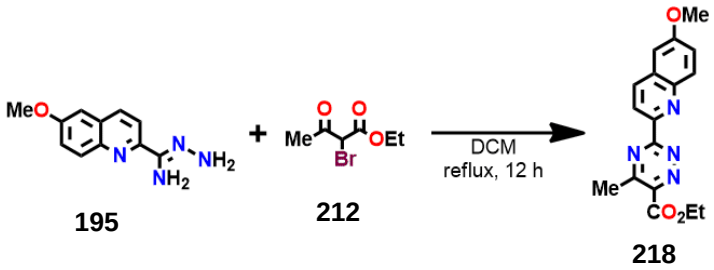
In principle, these failures suggest that the central C atom of **214** is too hindered for the S_N2 reaction to take place. With this scenario in mind, we thought that the reaction of β-ketoester **212** with amidrazone **195** would give the correct triazine regiochemistry, as the more reactive carbon centre would be the ketone one, forming imine intermediate **216**, which could undergo

an intramolecular S_N2 to give partially saturated triazine **217**. Finally, an oxidizing agent would give the aromatized triazine (**Scheme 61**).



Scheme 61. Reaction of amidrazone 195 with *β*-ketoester 212.

Indeed, the direct reaction of amidrazone **195** with **212** afforded (34% yield) an already aromatic triazine product without the need of an oxidizing agent, although, after careful examination of the compound's spectra, we concluded that the incorrect regioisomer was formed (**Scheme 62**).

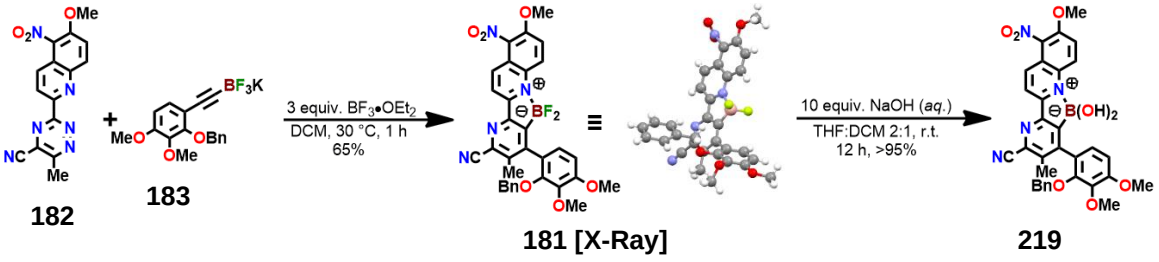


Scheme 62. Formation of the undesired triazine 218.

Even though the attempted approaches could be useful for the synthesis of functionalized triazines, these were not suitable for our objectives.

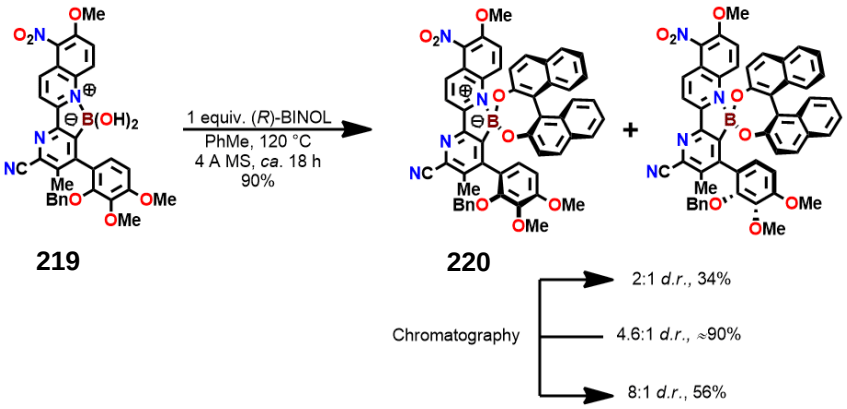
3.8 Construction and Resolution of Streptonigrin´s Carbon Framework

With both triazine **182** and organotrifluoroborate **183** in hand, the next step of our synthetic plan was to combine them *via* our boron-directed cycloaddition methodology. Mixing **182** and **183** in the presence of 3 equivalents of BF_3•OEt_2 yielded the desired organodifluoroborane intermediate **181** in 65% yield (Scheme 63). Thanks to the optimization experiments carried out before, the use of 3 equivalents of valuable organotrifluoroborate was not necessary and only 1 could be used for a satisfactory yield. The identity of the organodifluoroborane was confirmed by X-ray crystallography, and, similar to the organodifluoroboranes described in the previous chapter, this also showed the AB doublet pattern observed in the ^{19}F NMR spectrum. Then, hydrolysis of the organodifluoroborane afforded the corresponding organoboronic acid **219** in excellent yield, and the formation of oxidation and protodeboronation side products was suppressed by running the reaction under a nitrogen atmosphere.



Scheme 63. Synthesis of organoboronic acid 219 from precursors 182 and 183.

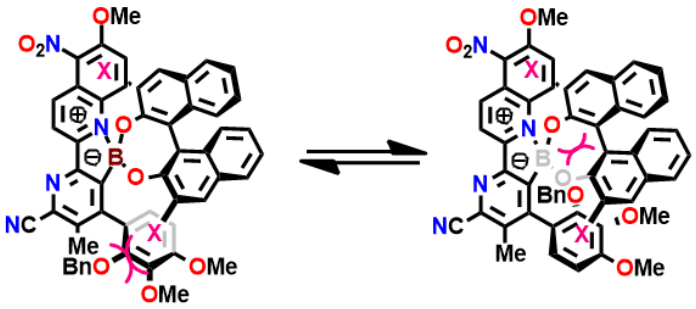
Organoboronic acid **219** was then esterified with (*R*)-BINOL to give organoboronic ester **220** as a 4.6:1 mixture of diastereomers. This diastereomeric ratio could be improved by column chromatography up to an 8:1 *d.r.* (Scheme 64).



Scheme 64. Esterification and resolution of streptonigrin precursor 219.

Another fraction with a 2:1 *d.r.* could also be isolated, and, upon heating to 120 °C, the mixture went back to the thermodynamic ratio, allowing the material to be recycled.

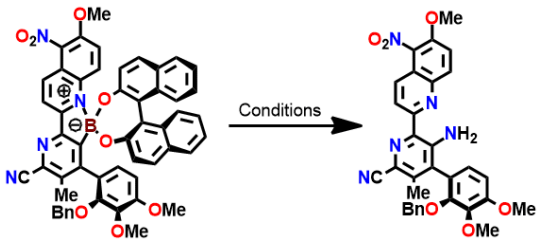
Encouraged by these results, we decided to test if the use of functionalized BINOL derivatives would improve the thermodynamic ratio of diastereomers. It was surprising to find that neither the CHO-BINOL nor the CN-CH_2-BINOL improved the diastereomeric ratio. In the case of CHO-BINOL, a 2:1 mixture of diastereomers was obtained, while the use of CN-CH_2-BINOL yielded a 1:1 mixture. Attempting to improve the diastereomeric ratio of the organoboronic esters, we heated the samples at 150 °C in toluene, but unfortunately the samples decomposed. One possible explanation for these outcomes could be because that the potential $O_p \rightarrow CHO_{\pi^*}$ interaction between the OBn group and the CHO group could be disfavoured by steric interactions (**Scheme 65**).



Scheme 65. Equilibrium between diastereomeric organoboronic acids with functionalized BINOL derivatives.

3.9 Endgame by Functional Group Interconversions

With streptonigrin's carbon framework assembled and with the chiral axis resolved, the last stage of our synthesis was the introduction of the remaining functional groups, and so the next step was the amination of our organoboron intermediates. Having a set of conditions to start with (**Table 17**), subjecting organoboronic acid **219** and organoboronic ester **220** to the conditions described before gave the desired amine in 28% and 35% yield respectively (**Entry 1**). As the yields observed were quite low, we decided to look for more efficient conditions.



220 180

Entry	Conditions	Yield
1	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, 12 h	35%
2[a]	1.5 equiv. NaN_3, 1 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, 12 h	25%
3	3 equiv. NaN_3, 2 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, 12 h	35%
4	3 equiv. NaN_3, 2 equiv. $Cu(OAc)_2$, THF:MeOH:H_2O 1:1:1, 70 °C, 12 h	30%
5	3 equiv. NaN_3, 2 equiv. $Cu(OAc)_2$, DCM:MeOH 1:1, 70 °C, 12 h	15%
6	3 equiv. NaN_3, 2 equiv. $Cu(OTf)_2$, THF:MeOH 1:1, 70 °C, 12 h	0%
7	3 equiv. NaN_3, 2 equiv. $CuCl_2$, THF:MeOH 1:1, 70 °C, 12 h	0%
8	3 equiv. NaN_3, 2 equiv. $Cu(OAc)_2$, 2 equiv. $B(OH)_3$ THF:MeOH 1:1, 70 °C, 12 h	50%
9[a]	3 equiv. NaN_3, 2 equiv. $Cu(OAc)_2$, 2 equiv. $B(OH)_3$ THF:MeOH 1:1, 70 °C, 12 h	28%

Table 17. Screening of reaction conditions for the amination of 220. [*a*] = 150 mg scale experiments, all other experiments were carried out at a 50 mg scale.

At 150 mg scale, the yield of the reaction reduced to just 25%, hence, affecting the material throughput efficiency (**Entry 2**). Doubling up the number of equivalents of $Cu(OAc)_2$ and NaN_3 had no effect on the reaction outcome (**Entry 3**). We hypothesized that the organoboronic ester was too unreactive and the transesterification with MeOH could be slow, and so water was added to promote its hydrolysis. Unfortunately, no improvement was observed (**Entry 4**). In principle, this could be anticipated from the result when organoboronic acid **219** was used as substrate. In this case, we contemplated the possibility of the organoboron anhydride (boroxine) to be the predominant species, lowering the organoboronic acid's reactivity towards the desired transformation. This experiment suggested that speciation due to boron was not a problem. Replacing THF for DCM afforded

amine **180** in just 15% yield (**Entry 5**). Other copper salts, such as $Cu(OTf)_2$ and $CuCl_2$, suppressed all product formation (**Entries 6 & 7**). Given the lack of reported insights about this transformation, we look at its closest relative, the Chan-Lam coupling. In 2017, Watson *et al*. published a spectroscopic study of the Chan-Lam reaction of organoboronic esters.[178] One of the findings of this study was that, when pinacol organoboronic esters were used as substrates, the liberated pinacol can have an inhibitory effect on the efficiency of the reaction by coordination of the diol with Cu(II) cations. To suppress this inhibitory pathway, $B(OH)_3$ can be used as a diol scavenger to improve the yield of the reaction. Indeed, the use of $B(OH)_3$ as additive for our reaction afforded the desired product in 50% yield (**Entry 8**). Nevertheless, these conditions were not scalable, limiting the efficient conversion of materials (**Entry 9**). The identity of amine **180** was unambiguously confirmed by X-ray crystallography. A comparison of the X-ray structures of compounds **(*rac*)-120**, **(*rac*)-180**, and **138** revealed that they all share an intramolecular H bonding between the amino group at C5' and quinoline's N1, confirming that thanks to this interaction the quinoline and the pyridine rings can be coplanar (**Figure 15**).

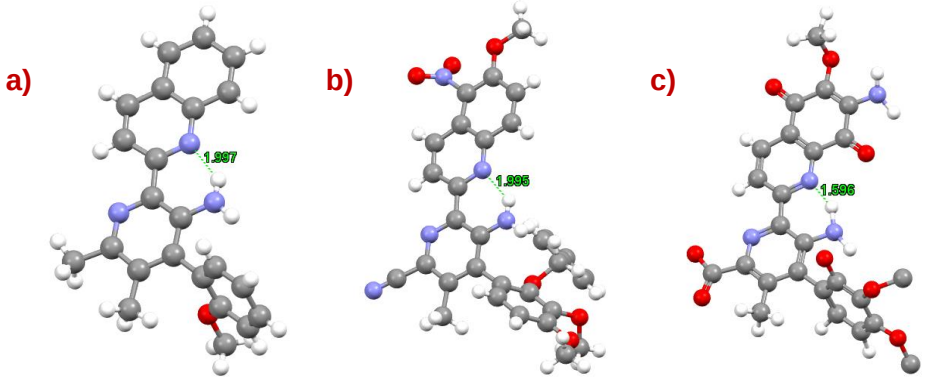
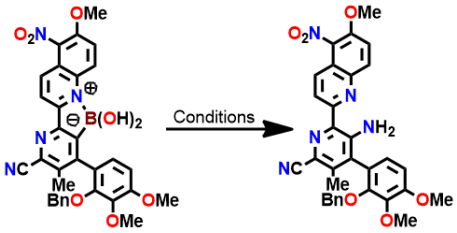


Figure 15. a) X-Ray structure of (*rac*)-120 b) X-Ray structure of (*rac*)-180. c) X-Ray structure of 138.

Although these amination conditions allowed us to access decent amounts of valuable amine intermediate, these were unable to satisfy our demand for bigger amounts of this intermediate and more optimization experiments had to be done. We further explored different conditions for this reaction, now, using organoboronic acid **219** as substrate (**Table 18**).



219 **180**

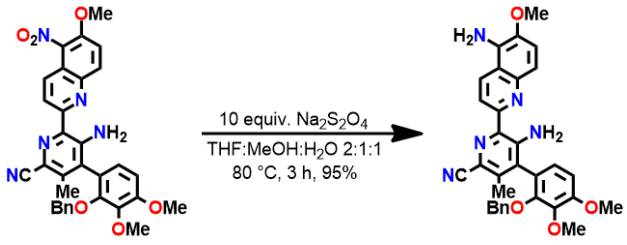
Entry	Conditions	Yield
1	3 equiv. NaN_3, 2 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, 12 h	28%
2	3 equiv. NaN_3, 2 equiv. $Cu(OAc)_2$, THF:MeOH 1:1, 70 °C, 12 h	25%
3	3 equiv. NaN_3, 2 equiv. CuOAc, THF:MeOH 1:1, 70 °C, 12 h	(40-50) %
4	3 equiv. NaN_3, 2 equiv. CuOAc, THF:MeOH 1:1, 70 °C, 12 h	(28-35) %
5	3 equiv. NaN_3, 2 equiv. $Cu(MeCN)_4BF_4$, THF:MeOH 1:1, 70 °C, 12 h	11%
6	3 equiv. NaN_3, 2 equiv. CuTC, THF:MeOH 1:1, 70 °C, 12 h	8%
7	3 equiv. NaN_3, 2 equiv. CuI, THF:MeOH 1:1, 70 °C, 12 h	54%
8	3 equiv. NaN_3, 2 equiv. CuBr, THF:MeOH 1:1, 70 °C, 12 h	34%
9	3 equiv. NaN_3, 2 equiv. $CuBr{\bullet}SMe_2$, THF:MeOH 1:1, 70 °C, 12 h	53%
10	3 equiv. NaN_3, 2 equiv. $Cu(MeCN)_4PF_6$, THF:MeOH 1:1, 70 °C, 12 h	0%
11	3 equiv. NaN_3, 2 equiv. CuI, THF:MeOH 1:1, 70 °C, 12 h	52%
12	3 equiv. NaN_3, 2 equiv. CuI, THF:MeOH 1:1, 70 °C, 12 h	30%
13	3 equiv. NaN_3, 2 equiv. CuI, MeCN:MeOH 1:1, 70 °C, 12 h	70%
14	3 equiv. NaN_3, 2 equiv. CuI, 1 equiv. phen, THF:MeOH 1:1, 70 °C, 12 h	77%
15	3 equiv. NaN_3, 2 equiv. CuI, 1 equiv. PPh_3, THF:MeOH 1:1, 70 °C, 12 h	89%

Table 18. Optimization experiments for the amination of 219 using Cu(I) salts.

Under the previously optimized conditions, organoboronic acid yielded amine **219** in poor 28% yield at test scale (**Entry 1**), and at bigger scales the outcome was a bit lower (**Entry 2**). Changing $Cu(OAc)_2$ for CuOAc showed an important improvement of up to 50% yield of isolated product at test scale (**Entry 3**), however at bigger scales this was not reproducible

(**Entry 4**). Given that the use of Cu(I) was beneficial for the reaction's yield, we decided to test the effect of the counterion; $[Cu(MeCN)_4]BF_4$, CuTC, CuI, CuBr, $CuBr{\bullet}SMe_2$, $[Cu(MeCN)_4]PF_6$ salts were tested and CuI and $CuBr{\bullet}SMe_2$ achieved the maximum yields observed at this stage (**Entries 5-10**). We then tested if the promising yields obtained when using CuI were reproducible on larger scales, the reaction was scaled up to 125 mg and 500 mg. Again, the yield dropped when a scale up was tested, although the improvement was encouraging. Next we decided to test other solvents, and pleasingly, amine **180** was isolated in 70% yield when the reaction was conducted in MeCN:MeOH 1:1. The yield was even better when phen and PPh_3 were used as additives (**Entries 14 & 15**), nevertheless the products contained an impurity that was impossible to wash out and hence not using these additives was preferred. The use of MeCN as co-solvent also allowed the reaction to be reproducible at bigger scales, allowing high material throughput.

The next step of our plan was the reduction of the nitro group to give the corresponding diamine **221** (**Scheme 66**). This process could be readily done with the use of sodium dithionite $Na_2S_2O_4$. Interestingly, attempts to carry out this reduction under dissolving metal (Fe, Zn, and In were tried) protocols failed to give any desired product.

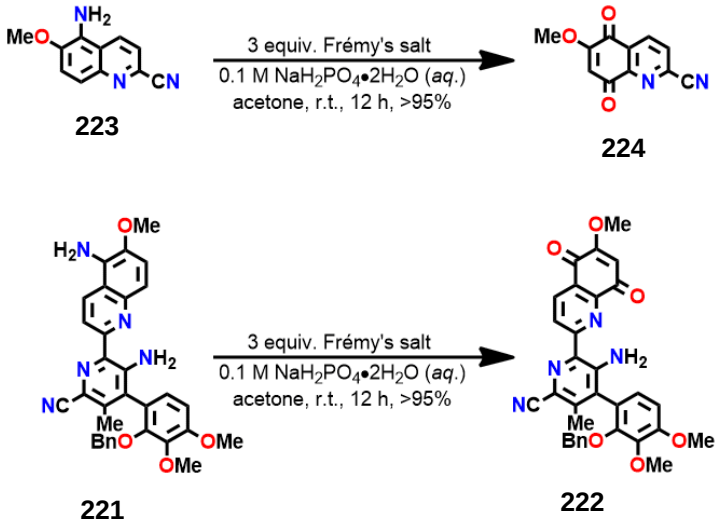


180 **221**

Scheme 66. Reduction of 180 nitro group.

Sodium dithionite is a white crystalline solid with a sulphurous odour. Over the course of time, it can be oxidised by the action of air to give an off-white rock-like solid, which is completely unreactive; it is important to check the quality before use.

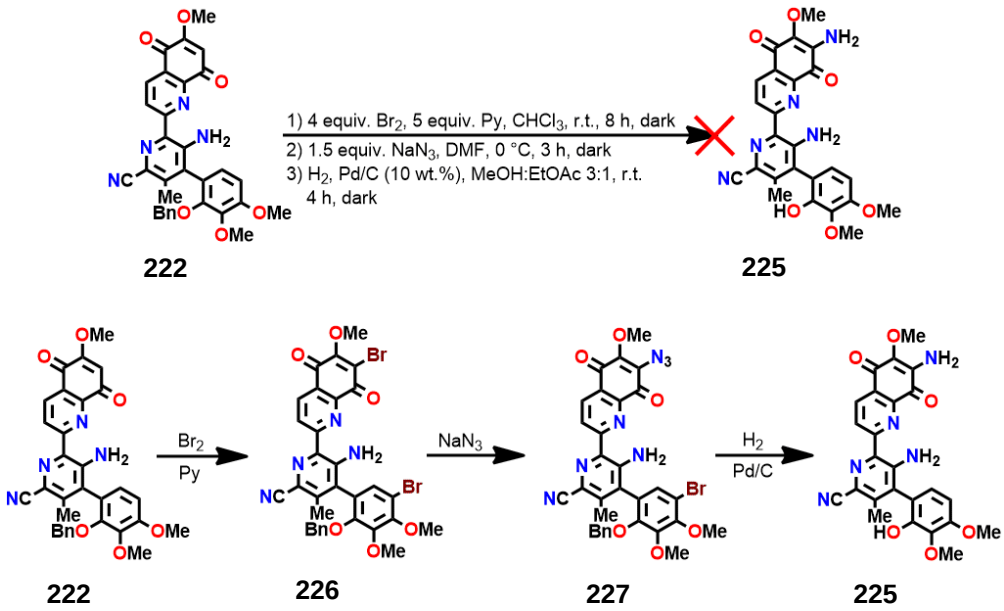
Then, diamine **221** was oxidized with Frémy's salt to give the corresponding quinolone **222** according to Kende's and Weinreb's works. This transformation was attempted first on a model system **223** to confirm its effectiveness (**Scheme 67**).



Scheme 67. Teuber oxidation of compounds 221 and 223.

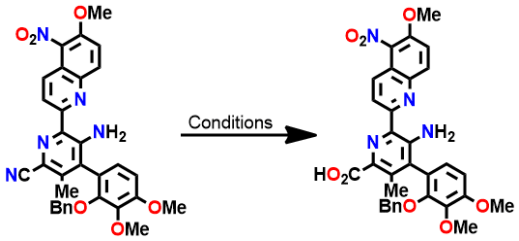
The oxidation proceeds under very mild conditions, and both the model **223** and the working systems **221** could be readily oxidized. Frémy's salt is an orange solid and is commercially available. Nevertheless, it must be stored in a freezer as this compound decomposes at room temperature. Orange Frémy's salt then starts to change into a white solid which lacks the oxidative properties. In older literature, this transformation is referred as the Teuber oxidation.

With quinolone **222** in hand, the next step was to introduce the northern amino group to give intermediate **225**. The introduction of this amino group would occur as a result of three consecutive reactions on quinolone **222**: bromination, azidation and hydrogenolysis/reduction. Treatment of quinolone **222** with Br_2 and Py would give dibromide intermediate **226**; in the literature, the halogenation of C7 has been reported with both bromine and iodine, however, Donohoe *et al*. reported reproducibility issues with the iodination protocol employed by Kende and Weinreb and used bromine instead. Then, substitution of the alkenyl bromine atom with sodium azide would yield azide intermediate **227**; finally, hydrogenolysis would carry out three transformations at once: reduction of the azide group, debenzylation of the phenol group, and reduction of the extra C11'–Br bond. We decided to follow Donohoe's reported experimental conditions for the introduction of the missing amino group, however, these conditions failed to give any product and only complex mixtures were observed, hence we were facing a dead end (**Scheme 68**).



Scheme 68. Attempted synthesis for the introduction of the amino group at C7.

Considering that the only difference between Donohoe's intermediate and ours was the identity of the substituent at C2', it was straightforward to conclude that we needed to convert the nitrile group into a methyl ester group to reproduce the reported methodology. In this sense, we attempted the hydrolysis of the nitrile *en route* to the methyl ester (**Table 19**).



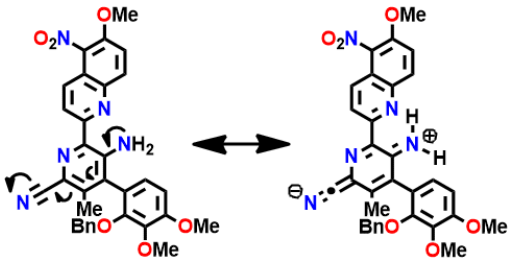
180 **228**

Entry	Conditions	Outcome
1	5 equiv. NaOH (*aq.*), DCM:MeOH 2:1, 60 °C, 12 h	SM
2	5 equiv. TBAOH (*aq.*) DCM:MeOH 2:1, 60 °C, 12 h	SM
3	20 equiv. NaOH (*aq.*), DCM:MeOH 2:1, 60 °C, 12 h	SM
4	40 equiv. NaOH (*aq.*), DCM:MeOH 2:1, 60 °C, 12 h	SM
5	1 equiv. TsOH•H_2O, DCM:MeOH 2:1, 60 °C, 12 h	SM
6	40 equiv. NaOH (*aq.*), DMF, 100 °C, 12 h	SM
7	1 equiv. TsOH•H_2O, DMF, 100 °C, 12 h	SM
8	40 equiv. NaOH (*aq.*), DMF, 120 °C, 12 h	SM
9	40 equiv. HCl (*aq.*), DMF, 100 °C, 12 h	SM*
10	40 equiv. TBAOH (*aq.*), DMF, 120 °C, 12 h	SM
11	10 equiv. TBAOH (*aq.*), DMF, 120 °C, 12 h	SM
12	10 equiv. NaOH (*aq.*), DMF, 120 °C, 12 h	SM

Table 19. Screening of conditions for the hydrolysis of amine 180. * = Debenzylation occurred.

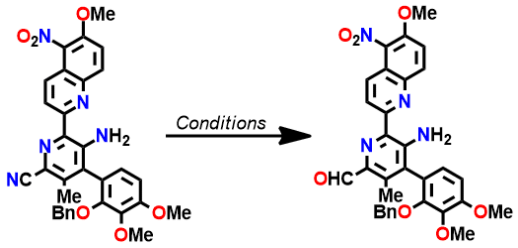
Piconitrile **180** was treated with NaOH (*aq.*) in a 1:1 mixture of DCM and MeOH, however, this left the starting material untouched (**Entry 1**). Changing NaOH for TBAOH expecting the TBA cation to improve solubility of the base also led to unreacted starting material (**Entry 2**). Increasing the amount of NaOH did not have any effect either (**Entries 3 & 4**). *p*-Toluenesulfonic acid also failed to give any product at 60 °C (**Entry 5**), and the use of other

acids such as HCl (**Entry 9**) and H_2SO_4 (not shown) only led to debenzylation. We decided to try DMF as solvent to favour the solubility of the reaction components, however, all experiments carried out in DMF and with extended heating failed as the nitrile was inert towards hydrolysis (**Entries 8 – 12**). The reactivity of the nitrile group is influenced both by the pyridine's N1' atom and the amino group located at C5'. The X-ray structure of piconitrile **180** suggests that the amino group is in complete resonance with the pyridine ring, which is likely to be the cause of the inertness of the nitrile group towards the hydrolysis by a mesomeric effect (**Scheme 68**).



Scheme 68. Resonance structures of amine 180.

We decided then to discard the possibility of hydrolysing the nitrile group and so we looked to the alternative of reducing it to an aldehyde group. We therefore explored the reduction of the nitrile group with DIBAL-H as the reducing agent (**Table 20**).



180 **229**

Entry	Conditions	Outcome
1[a,b]	1.5 DIBAL-H, DCM, –78 °C, 2 h	Complex NMR but the product was observed.
2[a,b]	1.5 DIBAL-H, DCM, –78 °C, 5 min	50% conversion
3[a,b]	1.5 DIBAL-H, DCM, –78 °C, 15 min	80% conversion
4[a,b,c]	1.5 DIBAL-H, DCM, –78 °C, 1 h	>90% conversión 35% yield
5[a,b,d]	1.5 DIBAL-H, DCM, –78 °C, 1 h	>90% conversion 74% yield
6[a,b]	2 DIBAL-H, DCM, –78 °C, 1 h	95% conversion
7[a,f]	2 DIBAL-H, DCM, –78 °C, 1 h	Complete conversion
8[e,f]	4 DIBAL-H, DCM, –78 °C, 1 h	70% conversion
9[e,f]	4 DIBAL-H, DCM, –20 °C, 1 h	Complex NMR
10[e,f]	4 DIBAL-H, DCM, –45 °C, 1 h	Complex NMR
11[e,f,g]	4 DIBAL-H, DCM, –78 °C, 1 h	~83% conversion
12[e,f,g]	4 DIBAL-H, DCM, –78 °C, 2 h	~88% conversion
13[e,f,g]	6 DIBAL-H, DCM, –78 °C, 2 h	>90% conversion
14[e,f,g]	8 DIBAL-H, DCM, –78 °C, 2 h	Complete conversion

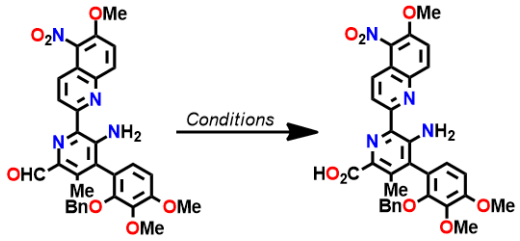
Table 20. Optimization experiments for the reduction of 180 with DIBAL-H. [a] = The reaction was done in test scale (50 mg of SM). [b] = 1 M DIBAL-H in THF was used. [c] = The product was isolated by column chromatography on silica gel. [d] = The product was isolated by column chromatography on Fluorisil®. [e] = The reaction was done in 100 mg scale of SM. [f] = 1 M DIBAL-H in DCM was used. [g] = The initial concentration was reduced 0.02 mol/L → 0.007 mol/L.

We commenced by treating amine **180** with 1.5 equivalents of DIBAL-H for 2 h at –78 °C in DCM (**Entry 1**). DCM was chosen as the solvent for this reaction given the high solubility of amine **180** in this solvent. This experiment yielded a complex NMR spectrum; however, the aldehyde signal of the product could be observed. We opted for decreasing the reaction time to just 5 min, resulting in a 50% conversion (**Entry 2**). Increasing the reaction time to 15 min had a slight improvement on the conversion to 80% (**Entry 3**). A further increase in the

reaction time to 1 h was accompanied with an excellent conversion (>90%), nevertheless, only 34% of pure aldehyde **229** could be isolated by column chromatography on silica gel (**Entry 4**). By changing the solid phase of the chromatography to Fluorisil® the yield could be improved to 74% (**Entry 5**), but still far from the >90% conversion observed in the crude ^{1}H NMR spectrum, presumably due to degradation of the product during the purification procedure. Given that no other decomposition or side products were observed, we thought that it would be possible to obtain a complete conversion of the SM and so we could avoid the problematic purification step. To achieve that, we increased the stoichiometry of DIBAL-H to two equivalents, however, complete conversion of the SM was still not observed (**Entry 6**). We then decided to test the effect of the DIBAL-H solution's solvent; using DIBAL-H as a DCM solution afforded complete conversion of the SM to the aldehyde (**Entry 7**). Encouraged by this result, we then tried to scale up these conditions to access a bigger quantity of this compound. Unfortunately, scaling the reaction up (from 50 mg to 100 mg) brought incomplete conversion of the SM (**Entry 8**). Increasing the reaction temperature had a negative effect and complex mixtures of products were observed when this was attempted (**Entries 9 & 10**). Detailed inspection of the reaction mixture before DIBAL-H addition revealed that the SM was precipitating from the solvent upon cooling. Although amine **180** shows a high solubility in DCM at room temperature, that is not the case at lower temperatures. Hence, an increase of the reaction volume (or concentration decrease) was tested. We were pleased to observe that doing this brought an improvement of the conversion upon higher SM scales (**Entry 11**). Increasing the reaction time was also beneficial, increasing the conversion ratio from 5:1 to 7:1 with respect to the previous experiment (**Entry 12**). Finally, a further increase in the number of equivalents of the reducing agent was needed to achieve complete conversion (**Entries 13 & 14**). These experiments showed the importance of

solubility on the outcome for this reaction. Indeed, it was also needed to allow the starting amine to solubilise completely before cooling down the solution and/or adding the reducing agent to observe reproducible results.

With an optimised reduction protocol in hand, the next step was to oxidise the newly formed aldehyde to the carboxylic acid, but first, we attempted to convert it into the methyl ester in one step (**Table 21**).



229 **230**

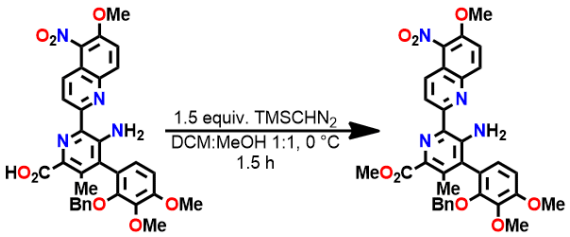
Entry	Conditions	Outcome
1	3 equiv. NaCN, 5 equiv. MnO_2, 1.5 equiv. AcOH, MeOH:DCM 2:1, 0 °C to r.t., 12 h	SM recovered
2	5 equiv. $NaClO_2$, 7.5 equiv. $NaH_2PO_4 \bullet H_2O$, 12 equiv. 2-Me-2-butene, ^tBuOH:THF:H_2O 1:1:1, r.t., 1 h	Mostly SM, Product was detected by LCMS.
3	5 equiv. $NaClO_2$, 7.5 equiv. $NaH_2PO_4 \bullet H_2O$, 12 equiv. 2-Me-2-butene, ^tBuOH:THF:H_2O 1:1:1, r.t., 5 h	Incomplete conversion
4	5 equiv. $NaClO_2$, 7.5 equiv. $NaH_2PO_4 \bullet H_2O$, 12 equiv. 2-Me-2-butene, ^tBuOH:THF:H_2O 1:1:1, r.t., 12 h	Incomplete conversion
5	5 equiv. $NaClO_2$, 7.5 equiv. $NaH_2PO_4 \bullet H_2O$, 12 equiv. 2-Me-2-butene, DCM:^tBuOH:THF:H_2O 2:1:1:1, r.t., 12 h	Complete conversion. No side-products
6	5 equiv. $NaClO_2$, 7.5 equiv. $NaH_2PO_4 \bullet H_2O$, 12 equiv. 2-Me-2-butene, THF, H_2O, ^tBuOH, r.t., *ca.* 18 h	Complete conversion. No side-products

Table 21. Optimization experiments for the oxidation of aldehyde 229.

Aldehydes can be converted to methyl esters by treatment with NaCN and activated MnO_2 in MeOH. Attack of the cyanide anion into the aldehyde, followed by oxidation of the formed alcohol with MnO_2 yields an acyl cyanide, which is attacked by methanol, collapsing with the liberation of the cyanide anion to give the desired methyl ester.[179] This protocol was not

productive for our substrate, and it was discarded in favour of a Pinnick oxidation (**Entry 1**). Applying a set of oxidation conditions obtained from the literature for 1 h provided a mixture of starting aldehyde and the corresponding carboxylic acid as judged from LCMS analysis (**Entry 2**).[180] Analysis by NMR spectroscopy was difficult because of overlapping signals and the absence of the H–OCOR signal in DCM due to fast exchange. In other solvents, such as d^6–DMSO, although much more informative, the product could not be extracted back from the d^6–DMSO, likely due to its zwitterionic nature. For this reason, all tracking was done solely by qualitative LCMS analysis. Increasing the reaction time further to 12 h did not afford complete conversion (**Entry 3**). Similar to the previous reduction step, it was observed that the reaction mixture was more like a suspension rather than a two-phase system. As we suspected that the problem for an incomplete conversion was a solubility issue, DCM was used as co-solvent. Indeed, this led to a homogenous organic phase with no suspended solid and complete conversion could be achieved in 12 h (**Entry 4**). However, these conditions only worked for test scale (50 mg) experiments. To achieve complete conversion when more than 100 mg of SM were used, extending the reaction time overnight (*ca*. 18 h) was enough to get complete oxidation of the aldehyde without signs of side-products (**Entry 5**).

The next step was to methylate carboxylic acid intermediate **206**; even though doing this lengthens the synthetic route, we anticipated that continuing with the free carboxylic acid would impose solubility, isolation, purification, and analysis difficulties. To do this transformation, carboxylic acid **206** was methylated with $TMSCHN_2$ in a mixture of DCM: MeOH 1:1 for 1.5 h at 0 °C (**Scheme 70**).

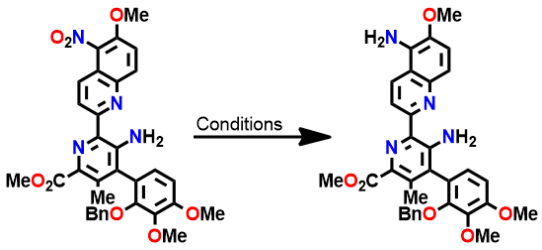


230 **231**

Scheme 70. Esterification of picolinic acid 230 with $TMSCHN_2$.

Again, DCM had to be used as co-solvent, as other common solvents reported for this transformation such as PhMe and THF failed to give satisfactory conversions. Methylation with $TMSCHN_2$ is straightforward and chemoselective although care must be taken when handling this chemical as it is extremely toxic and if inhaled can be fatal. Attempts to purify the product by column chromatography only yielded 47% of product even though the reaction proceeds with >95% conversion. We then decided to skip any purification and use the crude for the following step.

With the methyl ester installed, the next step was to reduce the nitro group just as it was done before (**Table 22**).



231 **232**

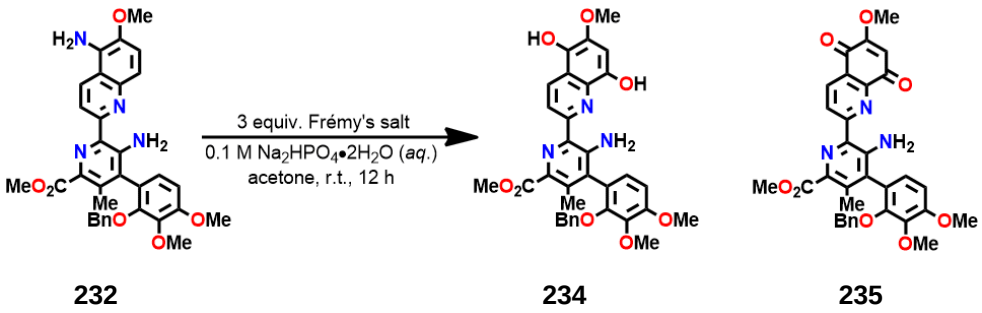
Entry	Conditions	Outcome
1	10 equiv. $Na_2S_2O_4$, THF:MeOH:H_2O 2:1:1, 80 °C, 3 h	60% conversion
2	10 equiv. $Na_2S_2O_4$, THF:MeOH:H_2O 2:1:1, 80 °C, (+ 3 h)	85% conversion
3	10 equiv. $Na_2S_2O_4$, THF:MeOH:H_2O 2:1:1, 80 °C, (+ 1 h), 7 h total	100% conversion
4	10 equiv. $Na_2S_2O_4$, DCM:THF:MeOH:H_2O 2:1:1:1, 80 °C, 3 h	10% conversion
5	20 equiv. $Na_2S_2O_4$, THF:MeOH:H_2O 2:1:1, 80 °C, 3 h	100% conversion

Table 22. Optimization experiments for the nitro group reduction of methyl ester 231.

Nevertheless, subjecting methyl ester **231** to our initial reduction conditions resulted in 60% conversion (**Entry 1**). As the reaction yielded only a mixture of SM and product, the previous crude was subjected to the reaction conditions for an extra 3 h which resulted in 85% conversion (**Entry 2**). Subjecting the mixture to the reducing conditions for one more hour (7 h in total) yielded complete conversion to the desired diamine **232** (**Entry 3**). At this point of the synthesis, it was crucial to prevent heating for an extended period to prevent racemization of the resolved chiral axis. Aiming for a complete conversion in a shorter time, we decided to add DCM to the solvent mixture to test if that could improve the conversion. This was not the case, and the use of DCM had a negative effect on the conversion (**Entry 4**). Finally, starting the reaction with 20 equivalents of $Na_2S_2O_4$ instead of 10 allowed us to get complete conversion on a test scale (50 mg) (**Entry 5**). It was observed though that upon scaling up,

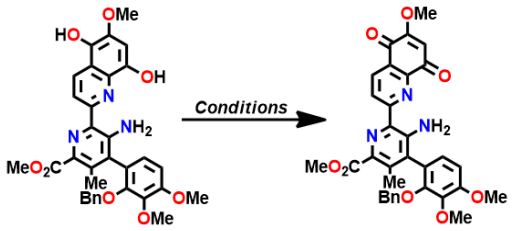
considerable hydrolysis of the methyl ester group happened (≤ 35%). The hydrolysed diamine was detected in the aqueous phase during the extraction procedure. Approximately 75% of the hydrolysed material could be recovered by acidifying the aqueous phase, however, an optimal pH value for the complete recovery of this compound could not be determined. Such diamine picolinic acid could then be readily methylated with $TMSCHN_2$ and the resulting material could be recycled for the synthesis.

The next step was then to oxidize aminoquinoline **232** to the corresponding quinolone. Subjecting diamine **232** to Frémy's salt resulted in what we initially concluded was the quinolone, however, after careful examination of the experimental data we concluded that we were isolating the corresponding dihydroquinoline **234** (Scheme 71).



Scheme 71. Incomplete Teuber oxidation of diamine 232.

In the literature, however, the oxidation of anilines to quinolines with Frémy's salt is quite common and no reports could be found regarding the need for a two-step oxidation protocol when using this reagent. We decided then to optimise the reaction conditions for this transformation (**Table 23**).



234 **235**

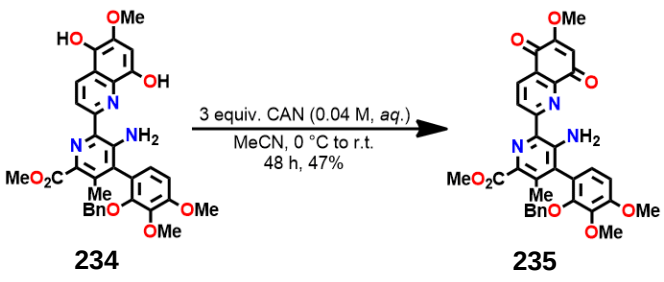
Entry	Conditions	Outcome
1	3 equiv. Frémy´s salt, 3 equiv. $Na_2HPO_4•2H_2O$, acetone:H_2O 1:1, r.t., 12 h	0% conversion (Recovered SM)
2	10 equiv. Frémy´s salt, 10 equiv. $Na_2HPO_4•2H_2O$, acetone:H_2O 1:1, r.t., 12 h	44% conversion
3	30 equiv. Frémy´s salt, 10 equiv. $Na_2HPO_4•2H_2O$, acetone:H_2O 1:1, r.t., 12 h	46% conversion
4	50 equiv. Frémy´s salt, 10 equiv. $Na_2HPO_4•2H_2O$, acetone:H_2O 1:1, r.t., 12 h	48% conversion
5	50 equiv. Frémy´s salt, 10 equiv. $Na_2HPO_4•2H_2O$, MeOH:H_2O 1:1, r.t., 12 h	50% conversion
6	280 equiv. Frémy´s salt, 0.05 M $Na_2HPO_4•2H_2O$:MeOH 1:1, 10 min (0.4 mM)	55% conversion
7	280 equiv. Frémy´s salt, 0.05 M $Na_2HPO_4•2H_2O$:MeOH 1:1, 1 h (0.4 mM)	74% conversion
8	280 equiv. Frémy´s salt, 0.05 M $Na_2HPO_4•2H_2O$:MeOH 1:1, *ca*. 18 h (0.4 mM)	80% conversion

Table 23. Conditions tested for the oxidation of dihydroquinoline 234.

Treating dihydroquinoline **234** with 3 equiv. of Frémy's salt yielded no conversion to the quinolone and only starting material was recovered (**Entry 1**). Increasing to 10 the number of equivalents resulted in a 44% conversion to the quinolone (**Entry 2**). When 30 equivalents of Frémy's salt were used the conversion barely had any improvement (**Entry 3**), and a bigger amount did not show a considerable improvement neither (**Entry 4**). In the literature it is common to find that oxidations with Frémy's salt can be carried out in MeOH, hence, we decided to replace the acetone for MeOH, however, the increase in the conversion was negligible (**Entry 5**). Following Kende's conditions also failed to give the expected oxidation with complete conversion (**Entry 6**). Increasing the reaction time to 1 h improved the

conversion further (**Entry 7**), and leaving the reaction overnight afforded an 80% conversion to the quinolone (**Entry 8**). The high excess of Frémy's salt needed for an acceptable conversion made this set of conditions impractical though, and side hydrolysis of the methyl ester was considerable too.

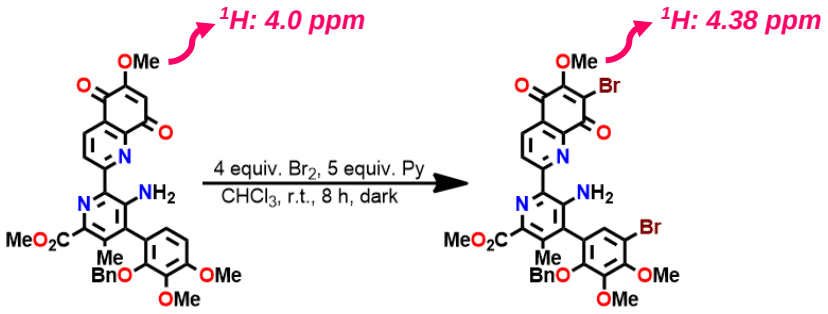
We decided to explore other options to promote this oxidation step. The use of iodine oxidants PIDA and IBX only led to decomposition and very low yields (≤ 10%). Next, we tested CAN as it is a common reagent used for this transformation (**Scheme 72**). In a work published in 2013, Donohoe *et al*. described that using a freshly prepared CAN solution led to considerable decomposition. We observed this same trend, and at the test scale (50 mg) the yield of the reaction was just ≤ 28%, on bigger scales the yield was even lower. It was observed though that the CAN solution must be aged for at least 2 weeks to obtain acceptable yields (~50%). Similar issues when handling CAN have not been pointed out in other experimental procedures surveyed in the literature; this suggests that this type of systems is susceptible to decomposition in the presence of CAN. The reaction's yield was also a function of whether the solution was allowed to age in the dark or not. Aging the CAN solution in the dark resulted in worse results, however, the exact reason behind this is not understood. Overall, we were not able to reproduce the high yields reported by Donohoe *et al.* regardless of how the CAN solution was allowed to age.



234 **235**

Scheme 72. Oxidation of dihydroquinoline 234 with aqueous CAN.

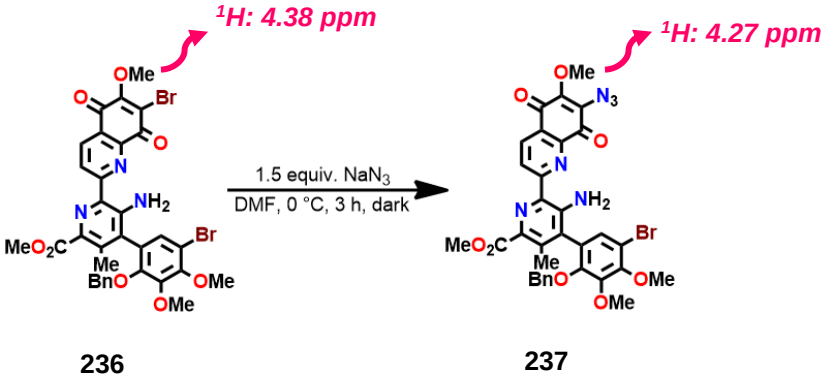
With a protocol to prepare quinolone **235**, we were in position to repeat the experimental conditions for the introduction of the northern amino group. Unfortunately, even with the methyl ester in place, we were unable to isolate any product and only complex mixtures were obtained. We decided to study each step individually to try to detect where the problem was lying. We noted straightway that the bromination step yielded considerable decomposition/degradation of the starting material. To prevent this, it was vital to premix the bromine and the pyridine first, rather than adding these reagents directly to the chloroform solution of quinolone; also, it was essential to prevent heating samples at any time of the synthesis procedure, including the rotary evaporation steps. This is, all reaction set up, isolation, and evaporation had to be done strictly in the dark and at room temperature to prevent decomposition. By employing these changes to the experimental protocol, we were able to obtain a relatively clean ^{1}H NMR spectrum of the reaction crude; one of the OMe signals shifted considerably, and the appearance of an aromatic singlet revealed the integration of the expected two Br atoms as previously described (**Scheme 73**).



Scheme 73. Bromination of quinolone 235.

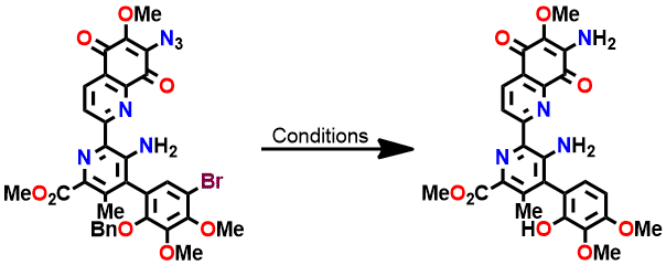
We also found that bromide intermediate **236** could be stored overnight by protecting it from light and keeping it in a freezer. Next, we studied the azidation reaction. Similar to the

bromination step, it was essential to carry out all manipulations in the dark and at room temperature to prevent decomposition. *In vacuo* drying of the reaction crudes at temperatures higher than 25 °C resulted in sudden colour changes, and naturally, complex NMR spectra were obtained when this happened. After the azidation reaction, the OMe signal has a slight upfield displacement in the ^{1}H NMR spectrum, suggesting the substitution of the Br atom for an azide group at C7 (this result was also supported by HRMS analysis) (**Scheme 74**).



Scheme 74. Bromine substitution with azide of intermediate 236.

Finally, we tested the hydrogenation step. It was quickly noticed that the debenzylation and the reduction of the southern Ar–Br bond were not efficiently proceeding (**Table 24**).

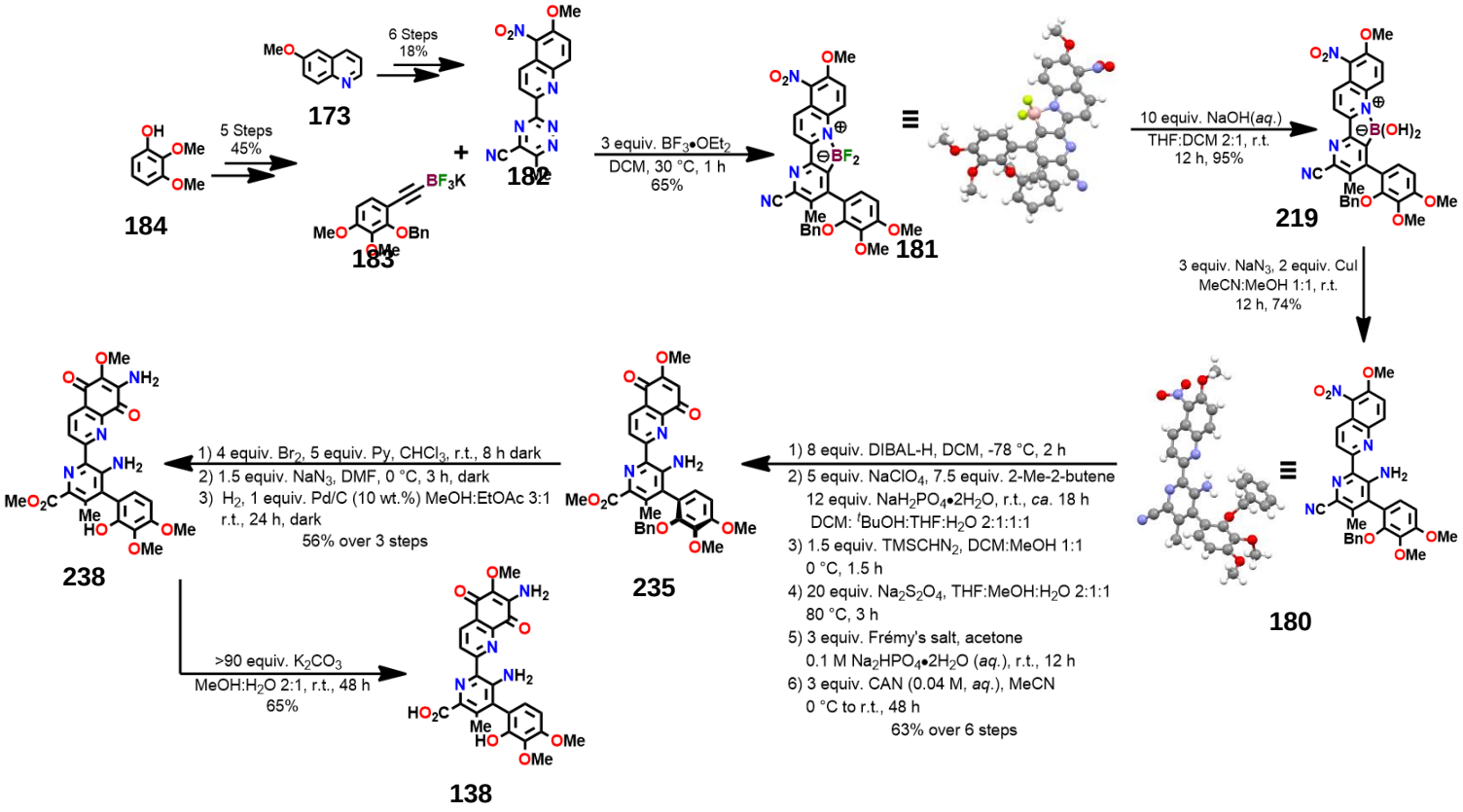


237 **238**

Entry	Conditions	Outcome
1	H_2, 10 mol% Pd/C, MeOH:EtOAc 3:1, r.t., 4 h	No deprotection
2	H_2, 10 mol% Pd/C, MeOH:EtOAc 3:1, r.t., 12 h	No deprotection
3	H_2, 10 mol% Pd/C, MeOH:EtOAc 3:1, r.t., 24 h	Partial deprotection (0.5:1 Prd:SM)
4	H_2, 0.5 equiv. Pd/C, MeOH:EtOAc 3:1, r.t., 24 h	Partial deprotection (1:1 Prd:SM)
5	H_2, 1 equiv. Pd/C, MeOH:EtOAc 3:1, r.t., 24 h	Partial deprotection (3:1Prd:SM)
6	H_2, 1 equiv. Pd/C, MeOH:EtOAc 3:1, r.t., 24 h [0.8 mmol/L] → [1.6 mmol/L]	Complete deprotection

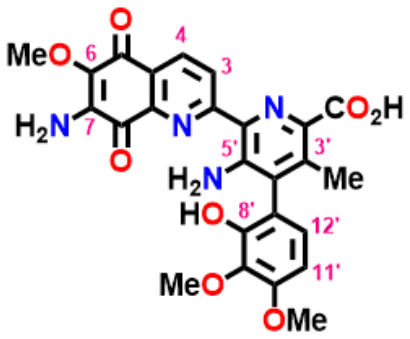
Table 24. Condition screening for the hydrogenolysis/reduction of compound 237.

First, we replicated Donohoe's hydrogenation conditions, which did not yield debenzylation at all (**Entry 1**). Increasing the reaction time to 12 h did not result in any change (**Entry 2**). Increasing the reaction time further to 24 h resulted in 33% debenzylation (**Entry 3**). We then increased the amount of catalyst to 0.5 equiv. which resulted in 50% conversion (**Entry 4**) and increasing the catalyst charge further resulted in 75% conversion (**Entry 5**). Finally, increasing the concentration allowed the debenzylation to proceed completely (**Entry 6**). Unfortunately, these reaction conditions are only suitable for scales no higher than ~100 mg of starting material. With streptonigrin's methyl ester **238** in hand, the final step was the hydrolysis of the methyl ester group to afford racemic streptonigrin in 65% yield. Overall, our route consists of 24 steps with a 2% yield (**Scheme 75**).



Scheme 75. Our developed total synthesis of racemic streptonigrin 138.

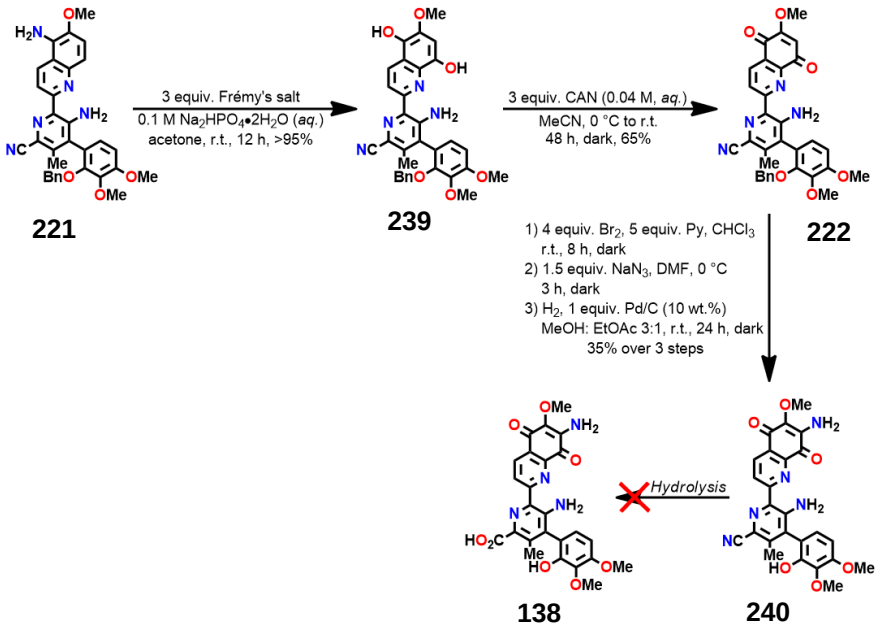
Because of its zwitterionic nature, the silica gel used for streptonigrin's isolation had to be buffered to pH 6.8. This was done by stirring silica gel in a commercial phosphate buffer solution for 5 min, followed by vacuum filtration; the silica was then kept in an oven until use.



Atom Number	^{1}H NMR (d^{6} – DMSO)			^{13}C NMR (d^{6} – DMSO)		
	Harrity	*Donohoe*	*Literature*	*Harrity*	*Donohoe*	*Literature*
1	–	–	–	–	–	–
2	9.01 (d, 8.4)	9.01 (d, 8.4)	9.01 (d)	144.1	144.1	144.1
3	8.36 (d, 8.4)	8.36 (d, 8.5)	8.36 (d)	126.0	125.9	125.9
4	–	–	–	133.4	133.4	133.4
4a	–	–	–	126.7	126.7	126.7
5	–	–	–	175.9	175.9	175.9
6	–	–	–	135.7	135.7	135.7
6–OMe	3.82 (s)	3.81 (s)	3.81 (s)	59.7	59.7	59.7
7	–	–	–	141.6	141.6	141.6
7–NH$_2$	6.91 (s, br)	6.92 (s, br)	6.93 (s, br)	–	–	–
8	–	–	–	180.3	180.3	180.3
8a	–	–	–	159.9	159.8	159.8
1'	–	–	–	–	–	–
2'	–	–	–	136.2	136.2	136.2
2'–CO$_2$H	12.28 (s, br)	12.32 (s, br)	12.22 (s, br)	167.0	167.0	167.1
3'	–	–	–	134.6	134.5	134.8
3'–Me	2.18 (s)	2.18 (s)	2.17 (s)	17.0	17.0	17.0
4'	–	–	–	134.0	134.0	133.9
5'	–	–	–	145.7	145.7	145.7
6'	–	–	–	129.5	129.5	129.5
7'	–	–	–	114.9	114.9	114.8
8'	–	–	–	148.1	148.1	148.1
8'–OH	8.92 (s)	8.92 (s)	8.94 (s, br)	–	–	–
9'	–	–	–	136.9	136.9	136.9
9'–OMe	3.76 (s)	3.76 (s)	3.76 (s)	60.3	60.3	60.3
10'	–	–	–	153.1	153.1	153.1
10'–OMe	3.85 (s)	3.85 (s)	3.85 (s)	55.7	55.7	55.7
11'	6.70 (d, 8.5)	6.70 (d, 8.6)	6.70 (d)	104.4	104.4	104.4
12'	6.74 (d, 8.5)	6.73 (d, 8.5)	6.73 (d)	124.6	124.6	124.6

Table 25. Comparison of ^{1}H and ^{13}C NMR data for natural and synthetic streptonigrin

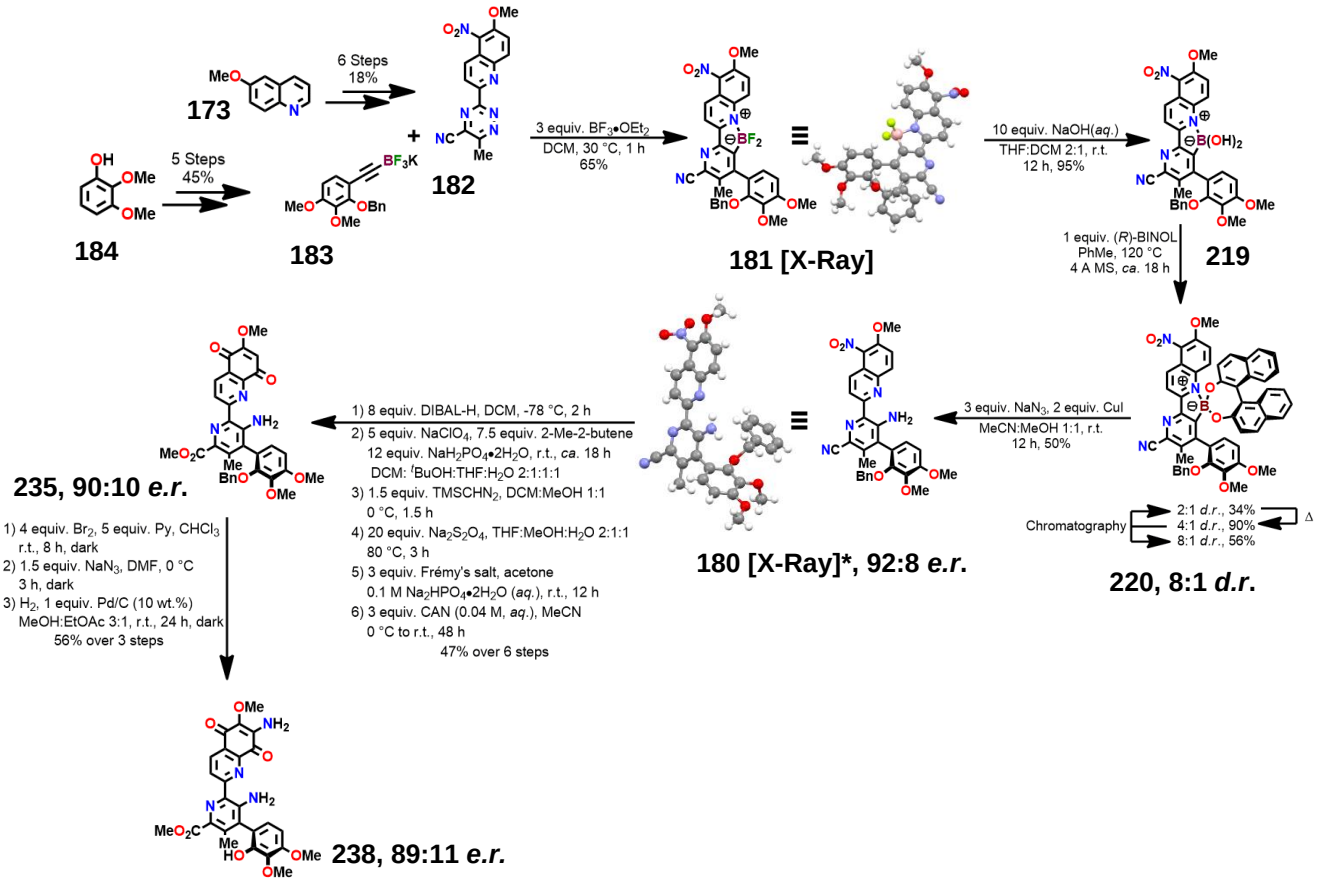
Looking back at attempts to oxidise the quinoline **221** and elaborate to streptonigrin (**Scheme 68**), it is reasonable to think that the failure of this route was because the oxidation level was not the expected quinone but the hydroquinone instead. We therefore exposed **239** to optimised oxidation conditions with aqueous CAN and were pleased to find that the quinolone **222** was formed. This was clear from the ^{1}H NMR spectrum of **222**, in which protons H3 and H7 show basically the same NMR shifts as those of analogue **238**. this compound was subjected to the bromination/azidation/reduction sequence previously described. The reaction yielded streptonigrin derivative **240** in 35% yield from **222**. Sadly however, the nitrile of this species also proved to be inert towards all room temperature hydrolysis attempts (**Scheme 76**).



Scheme 76. Attempted synthesis of streptonigrin from intermediate 240.

Having developed a synthetic route for racemic streptonigrin, we then worked on the asymmetric approach. Subjecting organoboronic ester **220** (8:1 *d.r.*) to the optimized amination conditions yielded axially chiral amine **180** with a 92:8 *e.r.* in 50% yield. Even

though the yield turned out to be lower for the organoboronic ester than the acid, attempts to increase the reaction yield resulted in complex mixtures and very low yields (< 5%). Then, formation of axially chiral quinolone **235** from enantioenriched amine **180** (92:8 *e.r*) proceeded with minimal stereochemical loss and comparable overall yield (90:10 *e.r.*). Finally, streptonigrin's methyl ester **238** was obtained in enantioenriched fashion (89:11 *e.r.*) with a 55% yield. We did not elaborate the enantioenriched ester to streptonigrin as all attempts to separate racemic streptonigrin by chiral HPLC analysis failed, and hence we had no means of assaying the enantiopurity against a standard sample. In this regard, it is notable that there are no reports of the optical rotation value of natural streptonigrin, thereby negating this as an alternative means of assessing the enantiopurity of our synthetic sample of the natural product.



Scheme 77. Asymmetric total synthesis of (*P*)-streptonigrin methyl ester 238. * = X-ray of the racemic sample.

The configuration of the chiral axis was determined by comparing the HPLC chromatograms of our enantioenriched sample with streptonigrin's methyl ester prepared from a commercial sample of streptonigrin. It was therefore demonstrated then that we have prepared the unnatural enantiomer of streptonigrin's methyl ester (**Figure 16**).

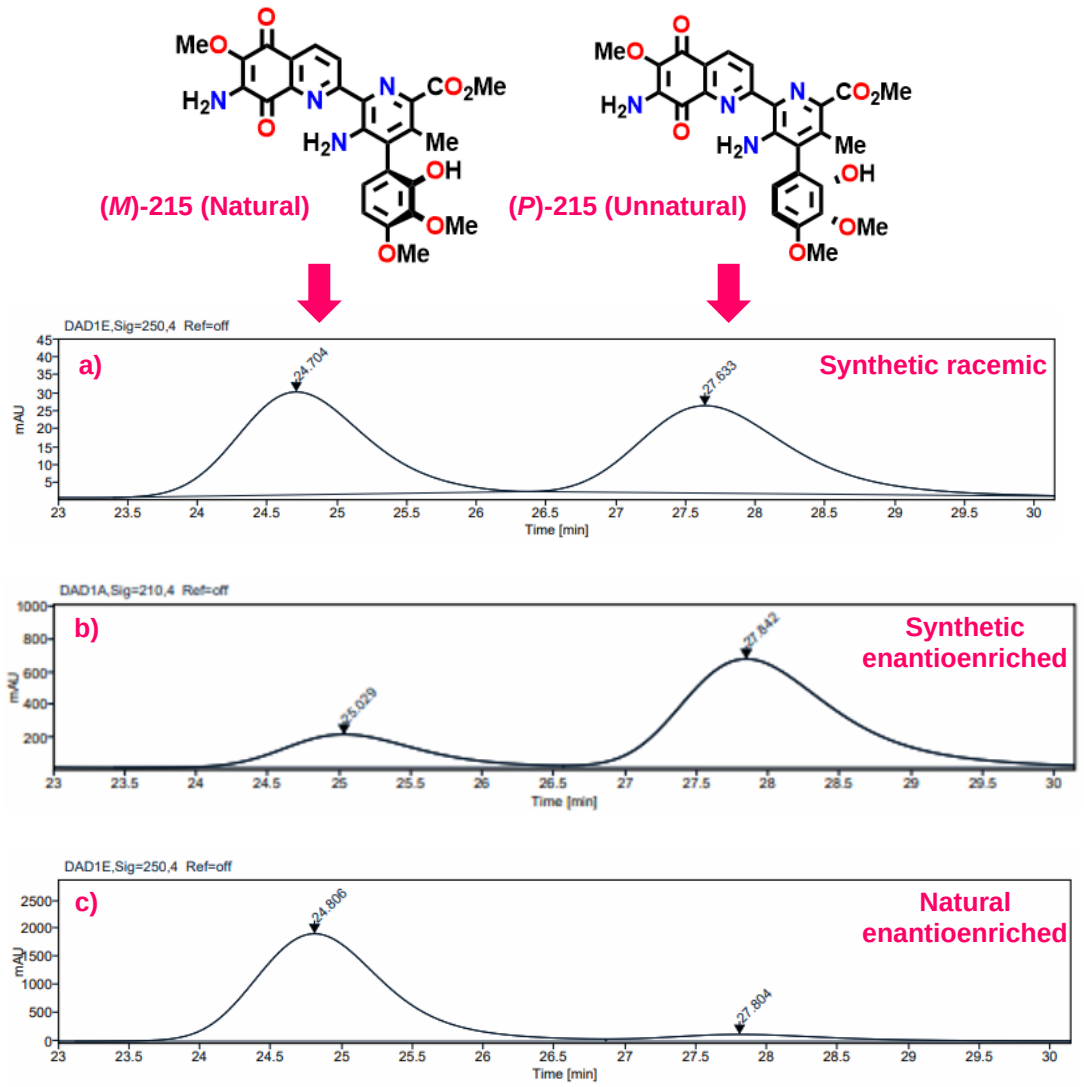


Figure 16. HPLC chromatograms (Chiral Art amylose-SC S-5 µm column [*n*-hexane/^{i}PrOH (60:40), flow rate = 0.7 mL/min, 40 °C]; t_{major} = 27.8 min, *t*minor = 25 min (89.2:10.8)) of streptonigrin's methyl ester 238. a) Synthetic racemic mixture prepared from organoboronic acid 219. b) Synthetic enantioenriched mixture prepared from organoboronic ester 220. c) Enantioenriched mixture prepared from a natural sample of streptonigrin.

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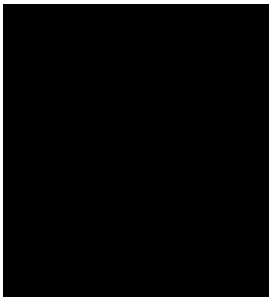

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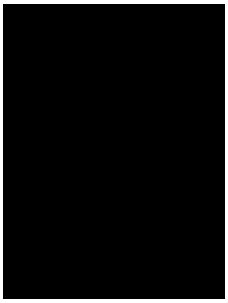

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4.5 Conclusions

- Axially chiral pyridyl organoboronic compounds with *ortho* Lewis groups can be satisfactorily resolved by forming the corresponding organoboronic ester with BINOL derivatives with the potential of isolating diastereomerically pure compounds with excellent levels of stereoretention upon functionalization. This approach takes advantage of several properties of boron's chemistry
- The boron-mediated resolution strategy developed in this work proceeds under thermodynamic control, allowing material recycling and represents the first methodology for the resolution of atropisomers in its class.
- The resolution strategy was successfully applied in the asymmetric synthesis of the natural product streptonigrin's methyl ester, offering the first strategy to deliver this product with high levels of enantiocontrol. The strategy can be extended to other streptonigrinoids as well. Promising results regarding the synthesis of other natural products, such as streptonigrone, and the multiple areas in which this strategy could be applied offer potential ground for further optimisation and applications of this methodology.

Chapter 5. Experimental Section

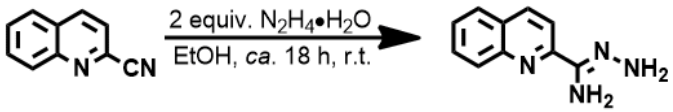
5.1 General Considerations

All reactions were carried out in flame-dried glassware under high vacuum, unless stated otherwise. For reactions carried out under an inert atmosphere, solvents were purified using a PureSolv MD purification system and transferred under nitrogen. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon FTIR spectrometer (ν_{max}/cm^{-1}). Samples were recorded neat as thin films. ^{1}H-NMR spectra were recorded on a Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz) or Bruker AMX400 (400 MHz). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane, using the residual protic solvent resonance as the internal reference: ($CHCl_3$: δ 7.26 ppm, d^6-DMSO: δ xx ppm, C_6D_6: δ xx ppm) unless otherwise stated. Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) coupling constant (Hz), integration). ^{13}C–NMR spectra were recorded on a Bruker AVIII HD 400 (101 MHz), Bruker AVI 400 (101 MHz) or Bruker AMX-400 (101 MHz) with broadband proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.16). ^{11}B–NMR spectra were recorded on a Bruker AVIII HD 400 (128 MHz). ^{19}F–NMR spectra were recorded on a Bruker AVIII HD 400 (128 MHz). High resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on a Micromass LCT operating in electrospray mode (TOF, ESI+, ESI–). Thin layer chromatography (TLC) was performed on aluminium-backed plates pre-coated with silica (0.2 mm, Merck 60 F254) which were developed using standard visualizing agents: UV light, potassium permanganate or vanillin. Flash chromatography was performed on silica gel

(Merck 40-63 µm) or Florisil® (60-100 mesh). Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected.

5.2 Experimental Procedures

Synthesis of 2-Quinolylamidrazone (42)[109]

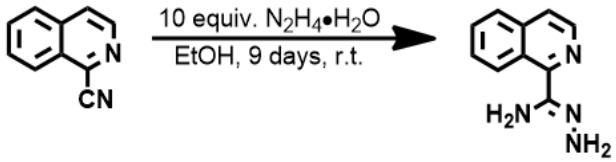


Quinoline-2-carbonitrile (500 mg, 3.2 mmol, 1 equiv.) and hydrazine monohydrate (N_2H_4•H_2O, N_2H_4 64-65%, 0.32 mL, 6.5 mmol, 2 equiv.) were stirred overnight (*ca*. 18 h) at room temperature. Then, the mixture was filtered, and the filtrate was washed with deionized water (50 mL). The product was obtained as an amorphous yellow solid (579 mg, 96%).

Note: Hydrazine monohydrate (N_2H_4•H_2O) is a highly toxic, carcinogenic, explosive, and volatile liquid. It must be handled with care and always inside a well-ventilated fume hood.

^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 8.23 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 5.86 (s, 2H), 5.60 (s, 2H).
^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 152.1, 146.7, 136.1, 130.1, 129.0, 128.2, 127.9, 126.8, 118.0, 107.2.

Synthesis of Isoquinoline-1-carbohydrozanomide (43)[109]



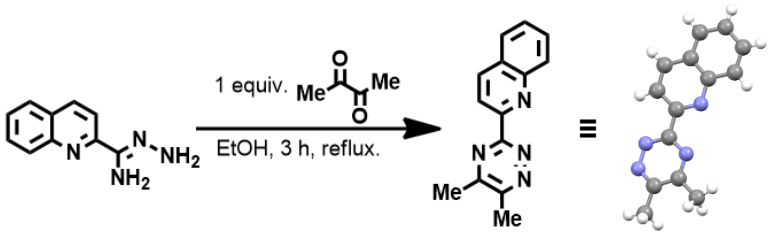
Isoquinoline-1-carbonitrile (200 mg, 1.3 mmol, 1 equiv.) and hydrazine monohydrate (N_2H_4•H_2O, 0.63 mL, 13 mmol, 10 equiv.) were stirred for 9 days at room temperature. Then,

the mixture was filtered, and the filtrate was washed with deionized water (50 mL). The product was obtained as an amorphous yellow solid (200 mg, 82%).

Note: Hydrazine monohydrate (N_2H_4•H_2O) is a highly toxic, carcinogenic, explosive, and volatile liquid. It must be handled with care and always inside a well-ventilated fume hood.

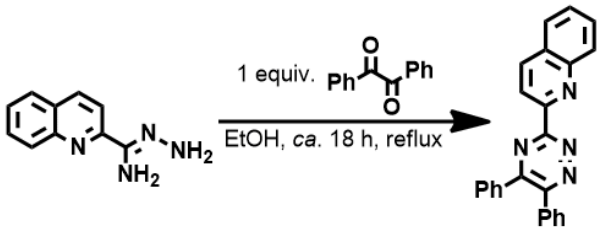
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (d, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 5.5 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.72 – 7.56 (m, 3H), 5.36 (s, 2H), 4.81 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 150.4, 149.8, 140.5, 137.2, 130.0, 128.7, 127.9, 126.9, 126.3, 122.0.

Synthesis of 5,6-Dimethyl-3-(2-quinolyl)-1,2,4-triazine (45)



To a stirred suspension of 2-quinolylamidrazone (1.00 g, 5.4 mmol, 1 equiv.) in EtOH (0.2 M) was added 2,3-butanedione (0.47 mL, 5.4 mmol, 1 equiv.) and the reaction mixture was stirred at reflux for 3 h. After cooling down to room temperature, the resulting precipitate was filtered and washed with Et_2O (50 mL) to afford the product was obtained as a yellow solid (1.28 g, 90%).
M.P. (189–191) °C recrystallized from DCM.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 8.0 Hz, 1H), 8.38 (d, *J* = 4.0 Hz, 1H), 8.36 (m, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.82 – 7.73 (m, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 2.80 (s, 3H), 2.74 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 161.6, 159.8, 157.2, 153.1, 148.3, 137.3, 130.8, 129.9, 128.8, 127.9, 127.6, 120.7, 22.3, 19.7.
HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{14}H_{13}N_4$ 273.1140, found 273.1149.
AR-FTIR (neat, cm^{-1}): 1595, 1527, 1429, 1394, 1366, 1162.

Synthesis of 2-(5,6-Diphenyl-1,2,4-triazin-3-yl)quinoline (46)



To a stirred suspension of 2-quinolylamidrazone (1.00 g, 5.4 mmol, 1 equiv.) in EtOH (0.2 M) was added benzil (1.13 g, 5.4 mmol, 1 equiv.) and the reaction mixture was stirred at reflux overnight. After cooling down to room temperature, the resulting precipitate was filtered and washed with Et_2O (50 mL) to afford the product as an amorphous yellow solid (1.76 g, 91%).

M.P. (192–194) °C not recrystallized.

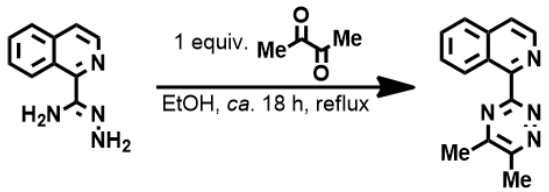
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, *J* = 7.5 Hz, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.84 – 7.78 (m, 1H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.70 – 7.61 (m, 3H), 7.49 – 7.36 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9, 156.7, 156.5, 152.9, 148.6, 137.4, 135.8, 135.4, 131.0, 130.2, 130.1, 130.0, 129.8, 128.9, 128.8, 128.7, 128.1, 127.7, 121.0.

HRMS: (ESI) *m*/*z* $[M+Na]^+$ $C_{24}H_{16}N_4Na$ calculated for 383.1267, found 383.1275.

AR-FTIR (neat, cm^{-1}): 1594, 1506, 1370, 1145.

Synthesis of 1-(5,6-Dimethyl-1,2,4-triazin-3-yl)isoquinoline (47)



To a stirred suspension of isoquinoline-1-carbohydrazonamide (1.00 g, 4.23 mmol, 1 equiv.) in EtOH (0.2 M) was added 2,3-butanedione (0.23 mL, 4.23 mmol, 1 equiv.) and the reaction mixture was stirred at reflux overnight. After cooling down to room temperature, the resulting

precipitate was filtered and washed with Et_2O (50 mL) to afford the product was obtained as an amorphous black solid (1.14 g, 90%).

M.P. (184–186) °C not recrystallized.

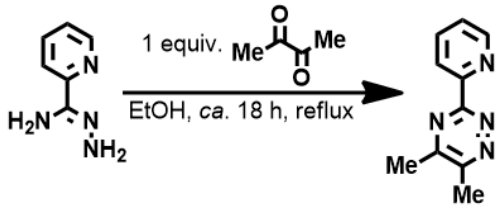
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 5.5 Hz, 1H), 8.51 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 5.5 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 2.80 (s, 3H), 2.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 159.9, 156.9, 153.9, 142.5, 137.1, 130.4, 128.2, 127.13, 127.07, 122.4, 22.1, 19.7. (*1C missing*)

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{14}H_{13}N_4$ 237.1135, found 237.1140.

AR-FTIR (neat, cm^{-1}): 3054, 1682, 1583, 1153.

Synthesis of 5,6-Dimethyl-3-(pyridin-2-yl)-1,2,4-triazine (49)



To a stirred suspension of picolinohydrazonamide (1.00 g, 7.35 mmol, 1 equiv.) in EtOH (0.2 M) was added 2,3-butanedione (0.65 mL, 7.35 mmol, 1 equiv.) and the reaction mixture was stirred at reflux overnight. After cooling down to room temperature, the resulting precipitate was filtered and washed with Et_2O (50 mL) to afford the product was obtained as an amorphous beige solid (1.30 g, 95%).

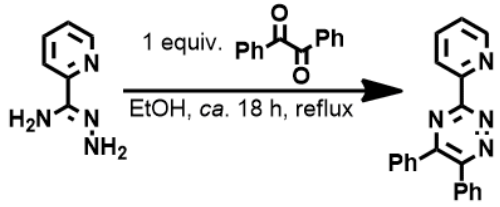
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, *J* = 4.5 Hz, 1H), 8.64 (d, *J* = 8.0 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 1H), 7.48 – 7.41 (m, 1H), 2.78 (s, 3H), 2.70 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): 161.6, 159.8, 157.2, 153.1, 150.4, 137.3, 125.4, 123.9, 22.2, 19.8.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{10}H_{11}N_4$ 187.0978, calculated 187.0983.

AR–FTIR (neat, cm^{-1}): 2194, 1573, 1209.

Synthesis of 5,6-Diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (50)



To a stirred suspension of picolinohydrazonamide (1.00 g, 7.35 mmol, 1 equiv.) in EtOH (0.2 M) was added benzil (1.55 g, 7.35 mmol, 1 equiv.) and the reaction mixture was stirred at reflux overnight. After cooling down to room temperature, the resulting precipitate was filtered and washed with Et_2O (50 mL) to afford the product was obtained as an amorphous orange solid (1.93 g, 85%).

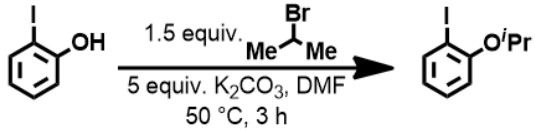
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 – 8.89 (m, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 7.94 (td, *J* = 8.0, 2.0 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.66 – 7.62 (m, 2H), 7.49 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 7.47 – 7.33 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.8, 156.6, 156.4, 152.9, 150.5, 137.1, 135.7, 135.3, 130.7, 130.0, 129.8, 129.6, 128.7, 128.6, 125.4, 124.2.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{20}H_{15}N_4$ 311.1291, found 311.1290.

AR–FTIR (neat, cm^{-1}): 3056, 1584, 1502, 1389, 1367.

Synthesis of 1-Iodo-2-*iso*propoxybenzene (53)[197]



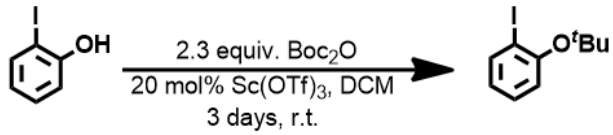
To a stirred suspension of 2-iodophenol (1.2 g, 5.5 mmol,1 equiv.) and potassium carbonate (K_2CO_3, 3.76 g, 27.3 mmol, 5 equiv.) in dry DMF (50 mL) was added 2-bromopropane (0.8 mL, 8.9 mmol). The mixture was heated at 50 °C and stirred for 3 h. After this time, the reaction mixture was cooled down to room temperature. The mixture was diluted with EtOAc

(20 mL) and washed with water (5 x 25 mL) and brine (20 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography over silica gel with a mixture of hexane:EtOAc 3:1 as eluent to afford the product as a colourless oil (1.2 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.76 (m, 1H), 7.31 – 7.25 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.74 – 6.66 (m, 1H), 4.57 (hept, *J* = 6.0 Hz, 1H), 1.40 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.8, 139.6, 129.3, 122.5, 114.4, 88.7, 72.1, 22.2.

Synthesis of 1-(*tert*-Butoxy)-2-iodobenzene (54)



Following a literature procedure[119], to a stirred solution of 2-iodophenol (5.0 g, 23 mmol, 1 equiv.), and di-*tert*-butyl dicarbonate (Boc_2O, 12 mL, 52.3 mmol, 2.3 equiv.) in DCM under a nitrogen atmosphere, was added scandium triflate ($Sc(OTf)_3$, 559 mg, 1.14 mmol, 20 mol%). The mixture was left to stir for 3 days at room temperature. The reaction mixture was washed with water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography on silica gel with hexanes:EtOAc 3:1 as eluent to afford the product as a colourless oil (3.5 g, 56%).

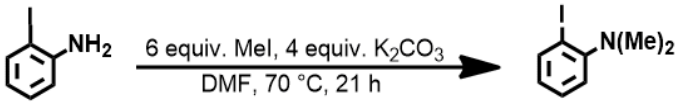
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.08 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.76 (td, *J* = 8.0, 1.5 Hz, 1H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.2, 139.5, 128.9, 124.5, 121.8, 94.9, 81.4, 29.4.

HRMS: (ESI) *m*/*z* $[M]^+$ calculated for $C_{10}H_{13}IO$ 276.0006, found 276.0007.

AR-FTIR (neat, cm^{-1}): 2978, 1577, 1289, 1238, 1157, 1142, 1017.

Synthesis of 2-Iodo-*N*,*N*-dimethylaniline (56)[198]

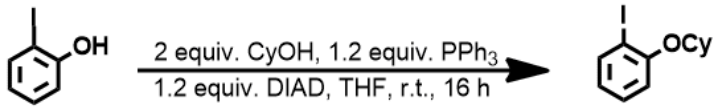


2-Iodoaniline (5.0 g, 23 mmol, 1 equiv.) and potassium carbonate (K_2CO_3, 12.6 g, 91.3 mmol, 4 equiv.) were dissolved in dry DMF (75 mL). Then, iodomethane (8.5 mL, 138 mmol, 6 equiv.) was added dropwise. The mixture was heated up to 70 °C and stirred for 21 h. Then, deionized water (50 mL) was added. The mixture was washed with brine (20 mL) and extracted with EtOAc (3 x 25 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. Purification by column chromatography over silica gel with petrol:EtOAc 95:5 as eluent afforded the product as a yellow oil (4.7 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.09 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.77 (td, *J* = 8.0, 1.5 Hz, 1H), 2.77 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 140.2, 129.1, 125.0, 120.5, 97.2, 45.0.

Synthesis of 1-(Cyclohexyloxy)-2-iodobenzene (55)[199]



Triphenylphosphine (PPh_3, 7.13 g, 27.2 mmol, 1.2 equiv.) and diisopropyl azodicarboxylate (DIAD, 5.35 mL, 27.2 mmol, 1.2 equiv.) were mixed in dry THF (50 mL). The mixture was heated up to 40 °C and stirred for 30 min. Then, 2-iodophenol (5 g, 22.7 mmol, 1 equiv.) and cyclohexanol (CyOH, 4.8 mL, 45.5 mmol, 2 equiv.) were added and the mixture was stirred for 16 h at 40 °C. The mixture was then allowed to cool down to room temperature and volatiles were evaporated *in vacuo*. The residue was redissolved in EtOAc (30 mL) and washed with water (3 x 25 mL) and brine (1 x 25 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography on silica gel with a mixture hexane:EtOAc 9:1 to afford the product as a yellow oil (2.71 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.30 – 7.21 (m, 1H), 6.84 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.68 (td, *J* = 8.0, 1.5 Hz, 1H), 4.36 (td, *J* = 8.0, 4.0 Hz, 1H), 1.96 – 1.79 (m, 4H), 1.77 – 1.66 (m, 2H), 1.61 – 1.48 (m, 1H), 1.49 – 1.32 (m, 3H).

Synthesis of Trimethyl((2-(methylthio)phenyl)ethynyl)silane (59)[200]

To a stirred mixture of 2-iodothioanisole (5.00 g, 20 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 281 mg, 0.4 mmol, 2 mol%) and copper(I) iodide (CuI, 38 mg, 0.2 mmol, 1 mol%) in ***freshly distilled*** Et_3N (0.4 M) under a nitrogen atmosphere at room temperature, trimethylsilylacetylene (3.4 mL, 24 mmol, 1.2 equiv.) was added dropwise. After 10 h, an extra 0.5 equiv. of trimethylsilylacetylene were added and the reaction mixture was stirred further for 10 h. Then, water (20 mL) was added to the reaction mixture and washed with NH_4Cl (*aq.*) (30 mL) and extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the crude product. Purification by column chromatography on silica gel with petrol afforded the product as a yellow oil (4.35 g, 98%).

Note: Triethylamine (Et_3N) was first stirred with KOH pellets over 2 h, followed by distillation over 4 Å MS under a nitrogen atmosphere before use.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.28 (td, *J* = 8.0, 1.0 Hz, 1H), 7.13 (d, *J* = 8.0, 1H), 7.06 (td, *J* = 7.0, 1.0 Hz, 1H), 2.47 (s, 3H), 0.30 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.1, 132.7, 129.0, 124.1, 124.0, 121.2, 102.2, 101.4, 15.0, 0.1.

Synthesis of ((2-*Iso*propoxyphenyl)ethynyl)trimethylsilane (61)[201]

To a stirred mixture of 1-iodo-2-isopropoxybenzene (5.00 g, 19.1 mmol, equiv.), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 268 mg, 0.4 mmol, 2 mol%) and copper(I) iodide (CuI, 36 mg, 0.2 mmol, 1 mol%) in freshly distilled Et_3N (0.4 M) under a nitrogen atmosphere at 50 °C, trimethylsilylacetylene (3.4 mL, 23 mmol, 1.2 equiv.) was added dropwise. After 10 h, an extra 0.5 equiv. of trimethylsilylacetylene were added and the reaction mixture was stirred further for 10 h. Then, water (20 mL) was added to the reaction mixture and washed with NH_4Cl(*aq.*) (30 mL) and extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the crude product. Purification by column chromatography over silica gel with petrol afforded the product as a yellow oil (4.2 g, 98%).

Note: Triethylamine (Et_3N) was first stirred with KOH pellets over 2 h, followed by distillation over 4 Å MS under a nitrogen atmosphere before use.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.30 – 7.22 (m, 1H), 6.94 – 6.88 (m, 2H), 4.59 (hept, *J* = 6.0 Hz, 1H), 1.39 (d, *J* = 6.0 Hz, 6H), 0.28 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 133.8, 129.7, 120.9, 116.0, 101.8, 98.2, 72.3, 22.2, 0.0.

Synthesis of ((2-Methoxyphenyl)ethynyl)trimethylsilane (60)[202]

To a stirred mixture of 2-iodoanisole (5.00 g, 21 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 300 mg, 0.4 mmol, 2 mol%) and copper(I) iodide (CuI, 41 mg, 0.2 mmol, 1 mol%) in freshly distilled Et_3N (0.4 M) under a nitrogen atmosphere at room temperature, trimethylsilylacetylene (3.6 mL, 27 mmol, 1.2 equiv.) was added dropwise. After 10 h, an extra 0.5 equiv. of trimethylsilylacetylene were added and the reaction mixture was stirred further for 10 h. Then, water (20 mL) was added to the reaction mixture and washed with NH_4Cl (*aq.*) (30 mL) and extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the crude product. Purification by column chromatography over silica gel with petrol afforded the product as a yellow oil (4.08 g, 94%).

Note: Triethylamine (Et_3N) was first stirred with KOH pellets over 2 h, followed by distillation over 4 Å MS under a nitrogen atmosphere before use.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.27 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.88 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 0.28 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 160.3, 134.2, 130.0, 120.3, 112.4, 110.7, 101.3, 98.4, 55.8, 0.1.

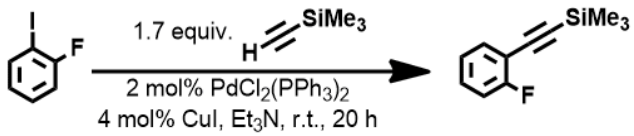
Synthesis of ((2-*tert*-Butyloxyphenyl)ethynyl)trimethylsilane (62)

To a stirred mixture of 1-(*tert*-butoxy)-2-iodobenzene (3.5 g, 12.6 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 180 mg, 0.4 mmol, 2 mol%) and copper(I) iodide (CuI, 49 mg, 0.2 mmol, 1 mol%) in freshly distilled Et_3N (0.4 M) under a nitrogen atmosphere at room temperature, trimethylsilylacetylene (2.15 mL, 15.1 mmol, 1.2 equiv.) was added dropwise. After 10 h, an extra 0.5 equiv. of trimethylsilylacetylene were added and the reaction mixture was stirred further for 10 h. Then, water (20 mL) was added to the reaction mixture and washed with NH_4Cl (*aq.*) (30 mL) and extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the crude product. Purification by column chromatography over silica gel with petrol afforded the product as a yellow oil (2.8 g, 90%).

Note: Triethylamine (Et_3N) was first stirred with KOH pellets over 2 h, followed by distillation over 4 Å MS under a nitrogen atmosphere before use.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.21 (td, *J* = 7.5, 1.5 Hz, 1H), 7.05 – 6.95 (m, 2H), 1.42 (s, 9H), 0.25 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.5, 133.6, 129.1, 123.6, 123.0, 119.6, 103.1, 97.4, 80.9, 29.0, 0.0.
HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{23}OSi$ 247.1513, found 247.1519.
AR-FTIR (neat, cm^{-1}): 2977, 2901, 2158, 1248, 1160.

Synthesis of ((2-Fluorophenyl)ethynyl)trimethylsilane (63)[203]

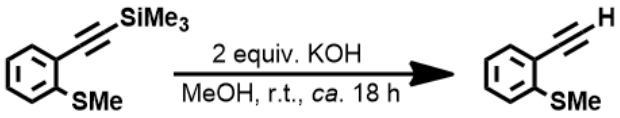


To a stirred mixture of 2-fluoroiodobenzene (5.00 g, 22.5 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 315 mg, 0.23 mmol, 2 mol%) and copper(I) iodide (CuI, 86 mg, 0.45 mmol, 4 mol%) in freshly distilled Et_3N (0.4 M) under a nitrogen atmosphere at room temperature, trimethylsilylacetylene (4.8 mL, 34 mmol, 1.5 equiv.) was added dropwise. After 10 h, an extra 0.5 equiv. of trimethylsilylacetylene were added and the reaction mixture was stirred further for 10 h. Then, water (20 mL) was added to the reaction mixture and washed with NH_4Cl (*aq.*) (30 mL) and extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the crude product. Purification by column chromatography over silica gel with petrol afforded the product as a yellow oil (3.34 g, 95%).

Note: Triethylamine (Et_3N) was first stirred with KOH pellets over 2 h, followed by distillation over 4 Å MS under a nitrogen atmosphere before use.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (td, *J* = 8.0, 1.5 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.10 – 7.02 (m, 2H), 0.28 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0 (d, *J* = 252.0 Hz), 131.0 (d, *J* = 8.0 Hz), 130.2, 123.8 (d, *J* = 3.5 Hz), 115.5 (d, *J* = 21.0 Hz), 111.8 (d, *J* = 16.0 Hz), 100.1 (d, *J* = 3.0 Hz), 98.0, 0.1.
^{19}F NMR (377 MHz, $CDCl_3$): δ –109.6 (s).

Synthesis of (2-Ethynylphenyl)(methyl)sulfane (65)[204]

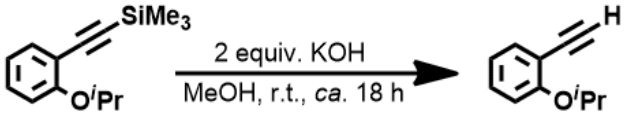


To a stirred solution of trimethyl((2-(methylthio)phenyl)ethynyl)silane (4.35 g, 0.02 mol, 1 equiv.) in MeOH (100 mL, 0.7 M), potassium hydroxide (KOH, 1.10 g, 0.04 mol, 2 equiv.) was added. The mixture was stirred overnight (*ca*. 18 h) at room temperature. The reaction mixture was washed with water (20 mL) and brine (20 mL), extracted with DCM (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a yellow oil (2.62 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.31 (td, *J* = 7.5, 1.0 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 3.48 (s, 1H), 2.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.0, 133.2, 129.4, 124.3, 120.2, 83.6, 81.1, 15.2.

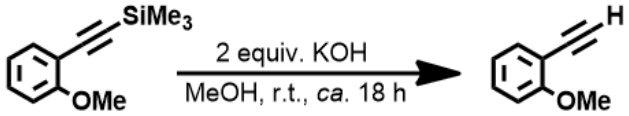
Synthesis of 1-Ethynyl-2-*iso*propoxybenzene (67)[201]



To a stirred solution of ((2-isopropoxyphenyl)ethynyl)trimethylsilane (4.2 g, 18 mmol, 1 equiv.) in MeOH (100 mL), potassium hydroxide (KOH, 2 g, 36 mol, 2 equiv.) was added. The mixture was stirred overnight (*ca*. 18 h) at room temperature. Then, the reaction mixture was washed with water (20 mL) and brine (20 mL), extracted with DCM (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a yellow oil (2.7 g, 92%).

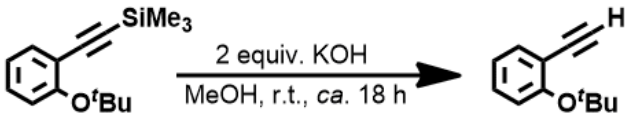
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.27 (td, *J* = 8.0, 1.5 Hz, 1H), 6.93 – 6.86 (m, 2H), 4.59 (hept, *J* = 6.0 Hz, 1H), 3.25 (s, 1H), 1.38 (d, *J* = 6.0 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 134.3, 130.0, 121.6, 114.7, 80.8, 80.4, 71.8, 22.1.

Synthesis of 1-Ethynyl-2-methoxybenzene (66)[205]



To a stirred solution of ((2-methoxyphenyl)ethynyl)trimethylsilane (3.54 g, 17.4 mmol, 1 equiv.) in MeOH (100 mL), potassium hydroxide (KOH, 2 g, 36 mol, 2 equiv.) was added. The mixture was stirred overnight (*ca*. 18 h) at room temperature. Then, the reaction mixture was washed with water (20 mL) and brine (20 mL), extracted with DCM (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a yellow oil (1.9 g, 82%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.37 – 7.27 (m, 1H), 6.95 – 6.85 (m, 2H), 3.90 (s, 3H), 3.31 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 160.6, 134.2, 130.3, 120.5, 111.2, 110.7, 81.1, 80.1, 55.8.

Synthesis of 1-Ethynyl-2-*tert*-butyloxybenzene (68)



To a stirred solution of ((2-*tert*-butyloxyphenyl)ethynyl)trimethylsilane (2.8 g, 12 mmol, 1 equiv.) in MeOH (100 mL), potassium hydroxide (KOH, 1.3 g, 23 mol, 2 equiv.) was added. The mixture was stirred overnight (*ca*. 18 h) at room temperature. Then, the reaction mixture was washed with water (20 mL) and brine (20 mL), extracted with DCM (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a yellow oil (1.8 g, 90%).

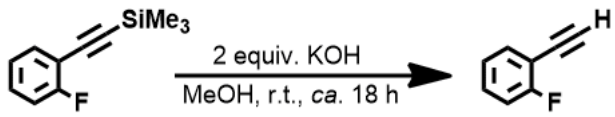
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.03 – 6.98 (m, 1H), 3.20 (s, 1H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7, 133.9, 129.4, 123.4, 123.0, 118.4, 81.6, 81.0, 80.4, 29.0.

HRMS: (ESI) *m/z* $[M]^+$ calculated for $C_{12}H_{14}O$ 174.1039, found 174.1047.

AR-FTIR (neat, cm^{-1}): 3298, 2978, 2197, 1240, 1155, 1101.

Synthesis of 1-Ethynyl-2-fluorobenzene (69)[206]



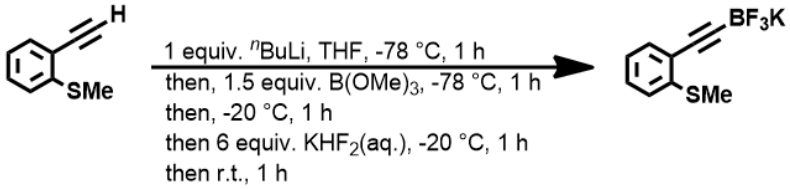
To a stirred solution of ((2-fluorophenyl)ethynyl)trimethylsilane (4.0 g, 20.7 mmol, 1 equiv.) in MeOH (100 mL), potassium hydroxide (KOH, 5.72 g, 20.7 mol, 2 equiv.) was added. The mixture was stirred overnight (*ca*. 18 h) at room temperature. Then, the reaction mixture was washed with water (20 mL) and brine (20 mL), extracted with DCM (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a yellow oil (1.7 g, 68%).

Note: Do not leave the product in the rotary evaporator for a prolonged time as the product is volatile and can be lost during this process if care is not taken.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 1H), 7.36 – 7.29 (m, 1H), 7.13 – 7.05 (m, 2H), 3.31 (s, 1H).

^{19}F NMR (377 MHz, $CDCl_3$): δ –110.1 (s).

Synthesis of Potassium ((2-(Methylthio)phenyl)ethynyl)trifluoroborate (71)



To a stirred solution of ((2-thiomethoxy)phenyl)acetylene (2.6 g, 17.4 mmol, 1 equiv.) in dry THF (0.15 M) under a nitrogen atmosphere at –78 °C, a solution of 2.5 M ^{n}BuLi in hexanes (7 mL, 17.4 mmol, 1 equiv.) was added dropwise. After 1 h, trimethyl borate ($B(OMe)_3$, 3 mL, 26.2 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. Then, the reaction mixture was warmed up to –20 °C and stirred for 1 h. A saturated solution of potassium hydrogen fluoride (KHF_2, 8.17 g, 104.6 mmol, 6 equiv.) in deionized water (3.5 M) was added and the mixture was stirred for 1 h at –20 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was then evaporated *in vacuo* and the residual solid was suspended in acetone (50 mL) and heated under reflux for 2 h. Then, the suspension was filtered while still warm and volatiles were evaporated *in vacuo*. The residual solid was washed with DCM (30 mL) and filtered to afford the product as an amorphous white solid (4.3 g, 96%).

M.P. (219–221) °C (decomposition) not recrystallized.

^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 7.26 – 7.19 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 2.39 (s, 3H).

^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 140.9, 132.1, 127.7, 124.2, 123.8, 123.5, 14.4**.** (*2 Cs missing. The signal of the carbon atom bonded to the boron atom is not observed due to quadrupolar relaxation broadening*).

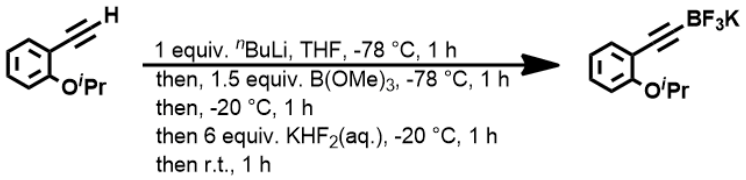
^{11}B NMR (128 MHz, *d*^{6}-DMSO): δ 1.8 (s, br).

^{19}F NMR (377 MHz, *d*^{6}-DMSO): δ –131.5 (s).

HRMS: (ESI) *m*/*z* $[M–K]^-$ calculated for $C_9H_7BF_3S$ 215.0319, found 215.0327.

AR-FTIR (neat, cm^{-1}): 2921, 2158, 1610, 1223.

Synthesis of Potassium Trifluoro((2-*iso*propoxyphenyl)ethynyl)borate (72)



To a stirred solution of 1-ethynyl-2-isopropoxybenzene (2.3 g, 14.2 mmol, 1 equiv.) in dry THF (0.15 M) under a nitrogen atmosphere at –78 °C, a solution of 2.5 M ^{n}BuLi in hexanes (6 mL, 14.2 mmol, 1 equiv.) was added dropwise. After 1 h, trimethyl borate ($B(OMe)_3$, 2.4 mL, 21.3 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. Then, the reaction mixture was warmed up to –20 °C and stirred for 1 h. A saturated solution of potassium hydrogen fluoride (KHF_2, 6.7 g, 85.2 mmol, 6 equiv.) in deionized water (3.5 M) was added and the mixture was stirred for 1 h at –20 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was then evaporated *in vacuo* and the residual solid was suspended in acetone (50 mL) and heated under reflux for 2 h. Then, the suspension was filtered while still warm and volatiles were evaporated *in vacuo*. The residual solid was washed with DCM (30 mL) and filtered to afford the product as an amorphous white solid (3.0 g, 80%).

M.P. (147–149) °C not recrystallized.

^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 7.23 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.18 – 7.11 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 4.66 – 4.52 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 158.3, 133.9, 128.2, 121.1, 117.1, 116.2, 83.6, 71.2, 22.4. (*2 Cs missing. The signal of the carbon atom bonded to the boron atom is not observed due to quadrupolar relaxation broadening*).

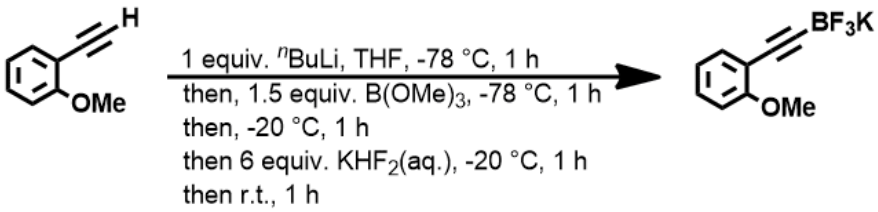
^{11}B NMR (128 MHz, *d*^{6}-DMSO): δ –1.7 (s, br).

^{19}F NMR (377 MHz, *d*^{6}-DMSO): δ –131.3 (s).

HRMS: (ESI) *m*/*z* $[M–K]^-$ calculated for $C_{11}H_{11}BF_3O$ 227.0861, found 227.0861.

AR-FTIR (neat, cm^{-1}): 2189, 1595, 1486, 1245, 1107.

Synthesis of Potassium Trifluoro((2-methoxyphenyl)ethynyl)borate (73)[207]



To a stirred solution of 1-ethynyl-2-methoxybenzene (1.9 g, 14.4 mmol, 1 equiv.) in dry THF (0.15 M) under a nitrogen atmosphere at –78 °C, a solution of 2.5 M ^{n}BuLi in hexanes (5.8 mL, 14.4 mmol, 1 equiv.) was added dropwise. After 1 h, trimethyl borate ($B(OMe)_3$, 2.4 mL, 21.6 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. Then, the reaction mixture was warmed up to –20 °C and stirred for 1 h. A saturated solution of potassium hydrogen fluoride (KHF_2, 6.7 g, 86.4 mmol, 6 equiv.) in deionized water (3.5 M) was added and the mixture was stirred for 1 h at –20 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was then evaporated *in vacuo* and the residual solid was suspended in acetone (50 mL) and heated under reflux for 2 h. Then, the suspension was filtered while still warm and volatiles were evaporated *in vacuo*. The residual solid was washed with DCM (30 mL) and filtered to afford the product as an amorphous white solid (3.4 g, 98%).

M.P. (270–272) °C not recrystallized.

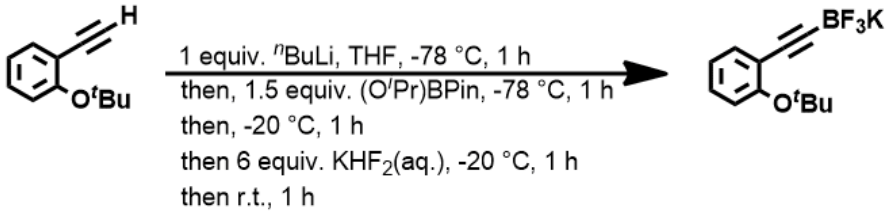
^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 7.26 – 7.15 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.83 (t, *J* = 8.0 Hz, 1H), 3.76 (s, 3H).

^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 159.9, 133.5, 128.4, 120.6, 115.1, 111.4, 55.7**.** (*2 Cs missing. The signal of the carbon atom bonded to the boron atom is not observed due to quadrupolar relaxation broadening*).

^{11}B NMR (128 MHz, *d*^{6}-DMSO): δ –1.5 (s, br).

^{19}F NMR (377 MHz, *d*^{6}-DMSO): δ –132.7 (s).

Synthesis of Potassium ((2-(*tert*-Butoxy)phenyl)ethynyl)trifluoroborate (74)



To a stirred solution of 1-ethynyl-2-*tert*-butyloxybenzene (1.4 g, 8.3 mmol, 1 equiv.) in dry THF (0.15 M) under a nitrogen atmosphere at –78 °C, a solution of 2.5 M ^{n}BuLi in hexanes (3.32 mL, 8.3 mmol, 1 equiv.) was added dropwise. After 1 h, 2-isopropoxy-4,4,5,5-

tetramethyl-1,3,2-dioxaborolane ((O^{i}Pr)B(Pin), 2.58 mL, 12.4 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. Then, the reaction mixture was warmed up to –20 °C and stirred for 1 h. A saturated solution of potassium hydrogen fluoride (KHF_2, 3.9 g, 50 mmol, 6 equiv.) in deionized water (3.5 M) was added and the mixture was stirred for 1 h at –20 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was then evaporated *in vacuo* and the residual solid was suspended in acetone (50 mL) and heated under reflux for 2 h. Then, the suspension was filtered while still warm and volatiles were evaporated *in vacuo*. The residual solid was washed with DCM (30 mL) and filtered to afford the product as an amorphous white solid (310 mg, 14%).

M.P. (240–242) °C not recrystallized.

^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 7.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.17 – 7.10 (m, 1H), 6.99 – 6.93 (m, 2H), 1.32 (s, 9H).

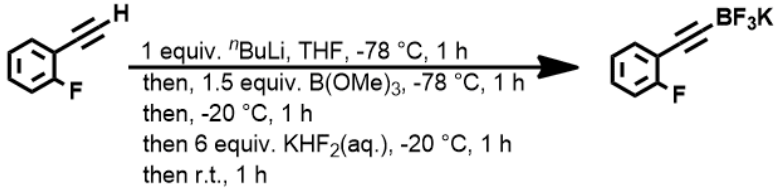
^{11}B NMR (128 MHz, *d*^{6}-DMSO): δ –1.7 (s).

^{19}F NMR (377 MHz, *d*^{6}-DMSO): δ –131.6 (s, br).

HRMS: (ESI) *m*/*z* $[M–K]^-$ calculated for $C_{12}H_{13}BF_3O$ 241.1017, found 241.1027.

AR-FTIR (neat, cm^{-1}): 2188, 1365, 1163, 1106.

Synthesis of Potassium Trifluoro((2-fluorophenyl)ethynyl)borate (75)



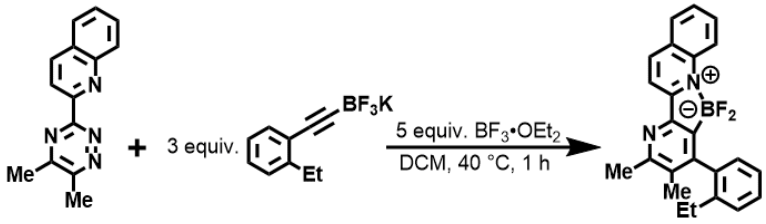
To a stirred solution of 1-ethynyl-2-fluorobenzene (1.7 g, 14.1 mmol, 1 equiv.) in dry THF (0.15 M) under a nitrogen atmosphere at –78 °C, a solution of 2.5 M ^{n}BuLi in hexanes (5.6 mL, 14.1 mmol, 1 equiv.) was added dropwise. After 1 h, trimethyl borate ($B(OMe)_3$, 2.4 mL, 21.2 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. Then, the reaction mixture was warmed up to –20 °C and stirred for 1 h. A saturated solution of potassium hydrogen fluoride (KHF_2, 6.6 g, 84.6 mmol, 6 equiv.) in deionized water (3.5 M) was added and the mixture was stirred for 1 h at –20 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction

mixture was then evaporated *in vacuo* and the residual solid was suspended in acetone (50 mL) and heated under reflux for 2 h. Then, the suspension was filtered while still warm and volatiles were evaporated *in vacuo*. The residual solid was washed with DCM (30 mL) and filtered to afford the product as an amorphous white solid (2.6 g, 81%).

Note: Over the course of a few months, this compound was found to degrade, presumably due to formation of KF and KBF_4, yielding a yellow solid.

^{1}H NMR (400 MHz, DMSO): δ 7.39 – 7.33 (m, 1H), 7.31 – 7.25 (m, 1H), 7.17 (t, *J* = 9.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H).
^{11}B NMR (128 MHz, *d*^{6}-DMSO): δ –1.6 (s).
^{19}F NMR (377 MHz, *d*^{6}-DMSO): δ –111.7 (s), –132.0 (s).
HRMS: (ESI) *m*/*z* $[M–K]^-$ calculated for $C_8H_4BF_4$ 187.0321, found 187.0342.
AR-FTIR (neat, cm^{-1}): 1573, 1489, 1250, 1209, 1101.

Synthesis of 10-(2-Ethylphenyl)-11,11-difluoro-8,9-dimethyl-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (86)



To a suspension of 5,6-dimethyl-3-(2-quinolyl)-1,2,4-triazine (100 mg, 0.423 mmol, 1 equiv.) and potassium (2-ethylphenyl)ethynyl)trifluoroborate (300 mg, 1.27 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl ethereate (BF_3•OEt_2, 0.26 mL, 2.12 mmol, 5 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$(*aq*.) (15 mL) was added and the mixture was washed with deionized water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of DCM:EtOAc 1:1 as eluent to afford the product as a beige amorphous solid (110 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 7.0 Hz, 1H), 7.85 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.42 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 2.67 (s, 3H), 2.43 (q, *J* = 7.5 Hz, 2H), 2.09 (s, 3H), 1.06 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5, 157.1, 154.6, 152.5, 152.3, 144.2, 141.2, 140.2, 138.1, 133.3, 133.2, 129.0, 128.7, 128.5, 128.0, 127.7, 125.6, 122.8, 115.4, 26.1, 23.6, 16.4, 14.6.

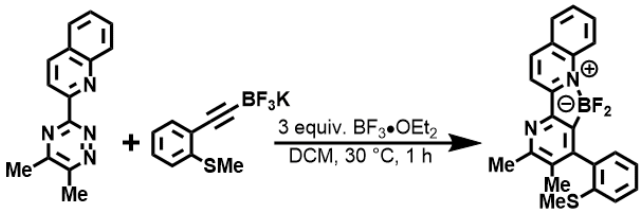
^{11}B NMR (128 MHz, $CDCl_3$): δ 8.9 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –154.9 (d, *J* = 116 Hz), –156.8 (d, *J* = 116 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{24}H_{22}BF_2N_2$ 387.1844, found 387.1841.

AR–FTIR (neat, cm^{-1}): 2961, 2925, 2874, 1597, 1447, 1269, 1087.

Synthesis of 11,11-Difluoro-8,9-dimethyl-10-(2-(methylthio)phenyl)-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (83)



To a suspension of 5,6-dimethyl-3-(2-quinolyl)-1,2,4-triazine (100 mg, 0.4 mmol, 1 equiv.) and potassium (2-thiomethoxyphenyl)ethynyltrifluoroborate salt (109 mg, 0.4 mmol, 1 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl ethereate (BF_3•OEt_2, 0.2 mL, 1.3 mmol, 3 equiv.). The mixture was stirred for 1 h at 30 °C. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reside was purified by column chromatography on silica gel with a mixture of DCM:Et_2O 98:2 as eluent to afford the product as a white solid (111 mg, 78%).

M.P. (255–257) °C recrystallized from DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 8.0 Hz, 1H), 8.49 (d, *J* = 9.0 Hz, 1H), 8.43 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.35 – 7.24 (m, 2H), 2.68 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5, 157.0, 152.5, 150.9, 144.2, 140.2, 138.7, 136.6, 133.9, 133.1, 129.1, 129.0, 128.5, 128.4, 127.7, 126.5, 125.3, 122.8, 115.4, 23.5, 16.3, 16.2.

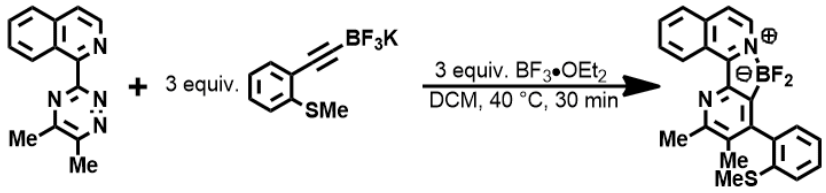
^{11}B NMR (128 MHz, $CDCl_3$): δ 8.7 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –154.1 (d, *J* = 90.0 Hz), –157.5 (d, *J* = 90.0 Hz).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{23}H_{20}BF_2N_2S$ 405.1403, found 405.1411.

AR–FTIR (neat, cm^{-1}): 2918, 1618, 1596, 1276.

Synthesis of 8,8-Difluoro-10,11-dimethyl-9-(2-(methylthio)phenyl)-8*H*-pyrido[3',2':3,4][1,2]azaborolo[5,1-a]isoquinolin-7-ium-8-uide (87)



To a suspension of 1-(5,6-dimethyl-1,2,4-triazin-3-yl)isoquinoline (116 mg, 0.5 mmol,1 equiv.) and potassium (2-thiomethoxyphenyl)ethynyltrifluoroborate salt (375 mg, 1.47 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl ethereate ($BF_3{\cdot}OEt_2$, 0.18 mL, 1.47 mmol, 3 equiv.). The mixture was stirred for 30 min at reflux. Then, saturated $NaHCO_3$(*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reside was purified by column chromatography on Fluorisil® with a gradient starting with DCM and ending in Et_2O to afford the product as an amorphous orange solid (102 mg, 51%).

M.P. (246–248) °C not recrystallized.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 6.0 Hz, 1H), 7.96 – 7.91 (m, 2H), 7.90 – 7.84 (m, 1H), 7.81 (d, *J* = 6.0 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.33 – 7.25 (m, 2H), 2.74 (s, 3H), 2.37 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9, 155.4, 154.4, 150.7, 139.6, 138.7, 136.6, 134.0, 132.9, 132.0, 130.2, 129.8, 129.1, 128.4, 127.0, 126.4, 125.3, 125.2, 122.9, 23.8, 16.3, 16.1.

(*The signal of the carbon atom bonded to the boron atom is not observed due to quadrupolar relaxation broadening*).

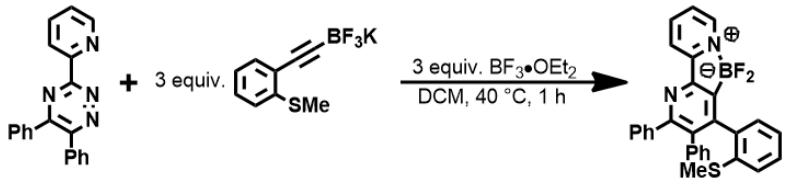
^{11}B NMR (128 MHz, $CDCl_3$): δ 7.2 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –161.4 (d, *J* = 132.0 Hz), –165.7 (d, *J* = 132.0 Hz).

HRMS: (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{23}H_{20}BF_2N_2S$ 405.1308, found 405.1358.

AR-FTIR (neat, cm^{-1}): 2921, 1553, 1437, 1277, 1090.

Synthesis of 5,5-Difluoro-4-(2-(methylthio)phenyl)-2,3-diphenyl-5*H*-[1,2]azaborolo[1,5-*a*:4,3-*b*']dipyridin-6-ium-5-uide (88)



To a suspension of 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (102 mg, 0.33 mmol,1 equiv.) and potassium (2-thiomethoxyphenyl)ethynyltrifluoroborate salt (225 mg, 0.97 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl ethearate (BF_3·OEt_2, 0.11 mL, 9.7 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$(*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reside was purified by column chromatography on silica gel using DCM as eluent to afford the product as an amorphous white solid (115 mg, 73%).

M.P. (227–229) °C not recrystallized.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, *J* = 5.5 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.23 (td, *J* = 8.0, 1.0 Hz, 1H), 7.66 – 7.56 (m, 1H), 7.40 – 7.33 (m, 2H), 7.25 – 7.11 (m, 8H), 7.03 – 6.94 (m, 4H), 2.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 143.9, 141.4, 140.6, 139.0, 138.8, 137.9, 137.7, 136.4, 131.2, 131.0, 130.3, 130.1, 129.8, 128.1, 127.6, 127.2, 127.0, 126.9, 126.6, 124.0 (x 2C), 119.3, 17.0. (*The signal of the carbon atom bonded to the boron atom is not observed due to quadrupolar relaxation broadening*).

^{11}B NMR (128 MHz, $CDCl_3$): δ 8.1 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –157.9 (d, *J* = 119.0 Hz), –160.9 (d, *J* = 119.0 Hz).

HRMS: (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{29}H_{22}BF_2N_2S$ 479.1566, found 479.1559.

AR-FTIR (neat, cm^{-1}): 1624, 1371, 1133, 1101.

Synthesis of 11,11-Difluoro-10-(2-(methylthio)phenyl)-8,9-diphenyl-11*H*-pyrido[3',2'3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (89)

To a suspension of 2-(5,6-diphenyl-1,2,4-triazin-3-yl)quinoline (110 mg, 0.32 mmol,1 equiv.) and potassium (2-thiomethoxyphenyl)ethynyltrifluoroborate salt (242 mg, 0.95 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl ethearate (BF_3·OEt_2, 0.12 mL, 9.5 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$(*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reside was purified by column chromatography on silica gel using DCM as eluent to afford the product as an amorphous green solid (118 mg, 70%).

M.P. (274–276) °C not recrystallized.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 8.0 Hz, 1H), 8.58 (*overlapping doublets*, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.89 (m, 1H), 7.68 (m, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.28 – 7.20 (m, 4H), 7.00 – 6.89 (m, 6H), 6.66 (d, *J* = 8.0 Hz, 1H), 3.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8, 156.6, 155.8, 150.7, 144.3, 140.8, 140.2, 138.7, 138.5, 133.3, 130.8, 130.2 (x4 C), 129.3, 129.2, 128.6, 128.02 (x4 C), 127.98, 127.6, 127.5, 126.9, 126.4, 123.0, 120.1, 115.8, 110.4, 55.0. (*The signal of the carbon atom bonded to the boron atom is not observed due to quadrupolar relaxation broadening*).

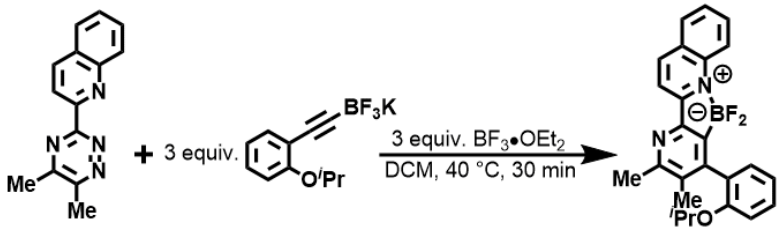
^{11}B NMR (128 MHz, $CDCl_3$): δ 9.0 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –151.5 (d, *J* = 102 Hz), –158.0 (d, *J* = 102 Hz).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{33}H_{24}BF_2N_2S$ 529.1716, found 529.1736.

AR-FTIR (neat, cm^{-1}): 1597, 1438, 1294, 1103.

Synthesis of 11,11-Difluoro-10-(2-*iso*propoxyphenyl)-8,9-dimethyl-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (91)



To a suspension of 5,6-dimethyl-3-(2-quinolyl)-1,2,4-triazine (100 mg, 0.4 mmol,1 equiv.) and potassium trifluoro((2-isopropoxyphenyl)ethynyl)borate (338 mg, 1.3 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.16 mL, 1.3 mmol, 3 equiv.). The mixture was stirred for 30 min at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reside was purified by column chromatography on silica gel with a gradient starting with DCM, ending in Et_2O to afford the product as an amorphous white solid (130 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 8.5 Hz, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 8.44 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.38 – 4.25 (m, 1H), 2.67 (s, 3H), 2.17 (s, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 157.4, 154.9, 152.3, 150.2, 144.2, 140.3, 134.7, 133.3, 131.1, 130.6, 129.3, 129.1, 128.6, 127.8, 123.0, 121.4, 116.2, 115.5, 71.5, 23.7, 22.2, 16.8.

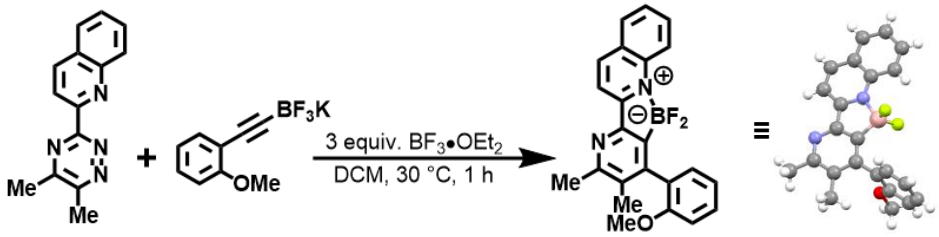
^{11}B NMR (128 MHz, $CDCl_3$): 9.0 (s).

^{19}F NMR (377 MHz, $CDCl_3$): δ –151.0 (d, *J* = 94.5 Hz), –158.4 (d, *J* = 94.5 Hz).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{25}H_{24}BF_2N_2O$ 417.1944, found 417.1944.

AR–FTIR (neat, cm^{-1}): 2915, 1600, 1523, 1227, 1102.

Synthesis of 11,11-Difluoro-10-(2-methoxyphenyl)-8,9-dimethyl-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (19)



To a suspension of 5,6-dimethyl-3-(2-quinolyl)-1,2,4-triazine (99 mg, 0.42 mmol, 1 equiv.) and potassium (2-methoxyphenyl)ethynyltrifluoroborate salt (100 mg, 0.42 mmol, 1 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.15 mL, 1.26 mmol, 3 equiv.). The mixture was stirred for 1 h at 30 °C. Then, saturated $NaHCO_3$(*aq*.) (15 mL) was added and the mixture was washed with deionized water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reside was purified by column chromatography on silica gel with a mixture of hexane:EtOAc 6:4 as eluent to afford the product as a white solid (132 mg, 81%).

M.P. (263–265) °C recrystallized from DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 8.5 Hz, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 8.44 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.85 (ddd, *J* = 8.5, 7.5, 1.0 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.42 (td, *J* = 8.0, 1.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.12 (td, *J* = 7.5, 1.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 2.66 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.3, 157.3, 156.5, 152.4, 149.6, 144.2, 140.3, 134.4, 133.2, 130.7, 129.4, 129.1, 128.6, 128.4, 127.7, 122.9, 120.8, 115.5, 111.1, 55.8, 23.7, 16.5.

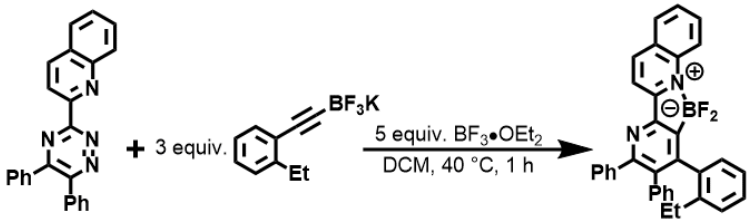
^{11}B NMR (128 MHz, $CDCl_3$): δ 8.7 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –152.2 (d, *J* = 91.5 Hz), –158.6 (d, *J* = 91.5 Hz).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{23}H_{20}BF_2N_2O$ 389.1637, found 389.1640.

AR–FTIR (neat, cm^{-1}): 1599, 1558, 1381, 1187, 1083.

Synthesis of 10-(2-Ethylphenyl)-11,11-difluoro-8,9-diphenyl-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (90)



To a suspension of 5,6-diphenyl-3-(2-quinolyl)-1,2,4-triazine (85 mg, 0.24 mmol, 1 equiv.) and potassium ((2-ethylphenyl)ethynyl)trifluoroborate salt (139 mg, 0.59 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.15 mL, 1.2 mmol, 5 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the mixture was washed with water (20 mL) and extracted with DCM (4 x 10 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The product was slowly precipitated from DCM to afford it as an amorphous beige solid (55 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 8.0 Hz, 1H), 8.61 – 8.56 (m, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.91 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.21 (m, 5H), 7.18 – 7.10 (m, 1H), 7.08 – 6.90 (m, 5H), 2.51 – 2.35 (m, 1H), 2.23 – 2.09 (m, 1H), 1.02 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 156.6, 154.2, 153.4, 144.5, 140.9, 140.8, 140.3, 138 .0, 137.9, 137.6, 133.5, 130.3 (x 2C), 129.9, 129.5, 128.7, 128.2, 127.9, 127.8 (x 2C), 127.7, 127.4, 127.3 (x 2C), 126.7, 124.8, 123.0, 115.9, 26.0, 14.2.

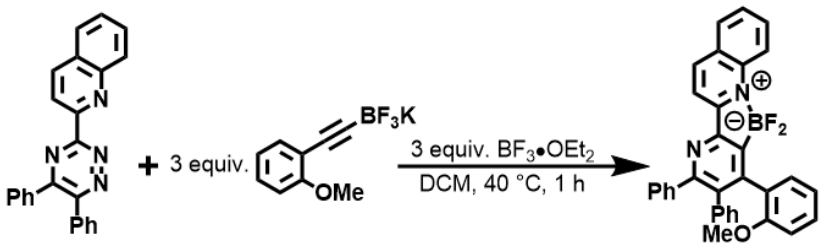
^{11}B NMR (128 MHz, $CDCl_3$): δ 7.3 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –153.4 (d, *J* = 139.0 Hz), –155.9 (d, *J* = 139.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{34}H_{26}BF_2N_2$ 511.2157, found 511.2166.

AR–FTIR (neat, cm^{-1}): 3273, 2924, 1628, 1553, 1492, 1243, 1089.

Synthesis of 11,11-Difluoro-10-(2-methoxyphenyl)-8,9-diphenyl-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (92)



To a suspension of 5,6-diphenyl-3-(2-quinolyl)-1,2,4-triazine (85 mg, 0.24 mmol,1 equiv.) and potassium((2-ethylphenyl)ethynyl)trifluoroborate salt (139 mg, 0.59 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.15 mL, 1.2 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The product was slowly precipitated from DCM and washed with Et_2O (15 mL) to afford the product as an amorphous pale grey solid (60 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 8.5 Hz, 1H), 8.62 – 8.55 (m, 2H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.90 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.47 – 7.39 (m, 1H), 7.41 – 7.36 (m, 2H), 7.25 – 7.20 (m, 5H), 7.03 – 6.90 (m, 5H), 6.66 (d, *J* = 7.5 Hz, 1H), 3.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8, 156.6, 155.9, 154.3, 151.0, 145.0, 144.5, 140.7, 140.3, 138.9, 138.5, 133.5, 130.9, 130.3 (x2 C), 129.4, 128.7, 128.2, 128.1, 127.8 (x2 C), 127.0, 126.6, 123.1, 120.2, 116.1, 110.5, 55.1.

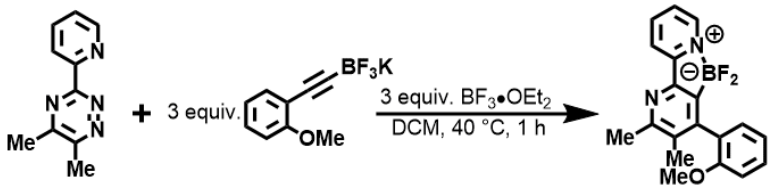
^{11}B NMR (128 MHz, $CDCl_3$): δ 9.2 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –151.5 (d, *J* = 102.0 Hz), –158.0 (d, *J* = 102.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{33}H_{24}BF_2N_2O$ 513.1950, found 513.1959.

AR–FTIR (neat, cm^{-1}): 2925, 1597, 1240, 1103, 1006.

Synthesis of 5,5-Difluoro-4-(2-methoxyphenyl)-2,3-dimethyl-5*H*-[1,2]azaborolo[1,5-*a*:4,3-*b*']dipyridin-6-ium-5-uide (98)



To a suspension of 5,6-diphenyl-3-(2-quinolyl)-1,2,4-triazine (100 mg, 0.424 mmol,1 equiv.) and potassium ((2-methoxyphenyl)ethynyl)trifluoroborate (197 mg, 1.06 mmol, 3 equiv.) in DCM (4 mL) was added freshly distilled boron trifluoride diethyl etherate (BF_3•OEt_2, 0.13 mL, 1.06 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel using EtOAc as eluent to afford the product as an amorphous pale-yellow solid (60 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 5.5 Hz, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.15 (t, *J* = 7.5 Hz, 1H), 7.56 – 7.46 (m, 1H), 7.39 (t, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 2.63 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.3, 156.4, 156.0, 151.9, 149.9, 143.8, 141.3, 133.9, 130.6, 129.4, 128.4, 124.3, 120.8, 118.6, 111.0, 55.8, 23.7, 16.5.

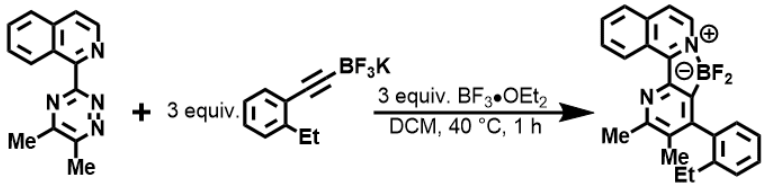
^{11}B NMR (128 MHz, $CDCl_3$): δ 7.6 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –156.2 (d, *J* = 90.0 Hz), –163.2 (d, *J* = 90.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{19}H_{18}BF_2N_2O$ 339.1480, found 339.1486.

AR–FTIR (neat, cm^{-1}): 2923, 1626, 1560, 1486, 1244, 1077.

Synthesis of 9-(2-Ethylphenyl)-8,8-difluoro-10,11-dimethyl-8*H*-pyrido[3',2'3,4][1,2]a-zaborolo[5,1-*a*]isoquinolin-7-ium-8-uide (94)



To a suspension of 5,6-dimethyl-3-(2-isoquinolyl)-1,2,4-triazine (100 mg, 0.424 mmol,1 equiv.) and potassium ((2-ethylphenyl)ethynyl)trifluoroborate (290 mg, 1.27 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.26 mL, 2.14 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on Fluorisil® with a mixture of hexane:EtOAc 4:1 as eluent to afford the product as an amorphous pale yellow solid (66 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.58 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.27 (d, *J* = 6.5 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.93 – 7.87 (m, 1H), 7.84 (d, *J* = 6.5 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.32 – 7.27 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 2.74 (s, 3H), 2.43 (q, *J* = 7.5 Hz, 2H), 2.09 (s, 3H), 1.07 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.8, 155.2, 154.4, 152.1, 141.2, 139.6, 138.2, 134.0, 132.4, 132.0, 130.1, 130.0, 128.7, 128.0, 127.9, 127.0, 125.5, 125.2, 123.0, 60.4, 26.1, 23.9, 21.1.

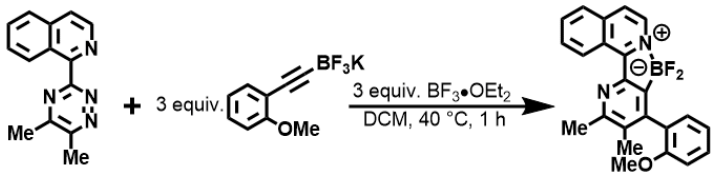
^{11}B NMR (128 MHz, $CDCl_3$): δ 7.3 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –162.46 (d, *J* = 131.0 Hz), –164.74 (d, *J* = 131.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{24}H_{22}BF_2N_2$ 387.1844, found 387.1845.

AR–FTIR (neat, cm^{-1}): 2961, 2925, 2874, 1597, 1447, 1269, 1087.

Synthesis of 8,8-Difluoro-9-(2-methoxyphenyl)-10,11-dimethyl-8*H*-pyrido[3',2':3,4][1,2]azaborolo[5,1-*a*]isoquinolin-7-ium-8-uide (95)



To a suspension of 5,6-dimethyl-3-(2-isoquinolyl)-1,2,4-triazine (100 mg, 0.424 mmol, 1 equiv.) and potassium ((2-methoxyphenyl)ethynyl)trifluoroborate (250 mg, 1.07 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.13 mL, 1.07 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The product was slowly precipitated from DCM to afford the product as an amorphous pale brown solid (130 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (d, *J* = 8.0 Hz, 1H), 8.30 (d, *J* = 6.0 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.94 – 7.88 (m, 1H), 7.85 (d, *J* = 6.0 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.13 (td, *J* = 8.0, 1.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.75 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.4, 156.3, 155.2, 154.6, 149.4, 139.5, 134.0, 133.4, 132.0, 130.6, 130.3, 129.7, 129.2, 128.4, 126.9, 125.2, 122.8, 120.7, 111.0, 55.7, 23.7, 16.3.

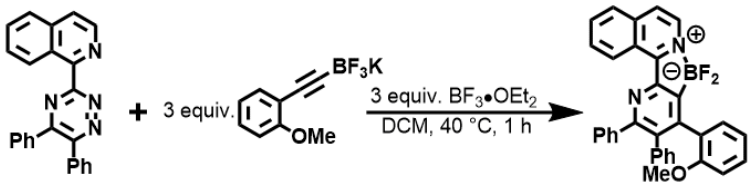
^{11}B NMR (128 MHz, $CDCl_3$): δ 7.3 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –159.7 (d, *J* = 125.0 Hz), –166.8 (d, *J* = 123.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{23}H_{20}BF_2N_2O$ 389.1637, found 389.1632.

AR–FTIR (neat, cm^{-1}): 3079, 2953, 2836, 1600, 1553, 1494, 1353, 1243, 1089.

Synthesis of 8,8-Difluoro-9-(2-methoxyphenyl)-10,11-diphenyl-8*H*-pyrido[3',2':3,4][1,2]azaborolo[5,1-a]isoquinolin-7-ium-8-uide (96)



To a suspension of 5,6-diphenyl-3-(2-isoquinolyl)-1,2,4-triazine (121 mg, 0.336 mmol,1 equiv.) and potassium ((2-methoxyphenyl)ethynyl)trifluoroborate (240 mg, 1.00 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.13 mL, 1.00 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The product was slowly precipitated from DCM to afford the product as an amorphous pale-yellow solid (104 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (d, *J* = 8.0 Hz, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 8.04 – 7.85 (m, 4H), 7.51 – 7.42 (m, 3H), 7.32 – 7.21 (m, 4H), 7.09 – 6.93 (m, 6H), 6.67 (d, *J* = 8.0 Hz, 1H), 3.41 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1, 157.4, 155.9, 154.0, 150.6, 141.3, 139.8, 138.6, 137.9, 134.3, 132.2, 131.0, 130.4 (x2 C), 130.3, 129.2, 128.1, 127.8 (x2 C), 127.5, 127.2, 127.0, 126.6, 125.4, 123.7, 120.2, 110.4, 55.1.

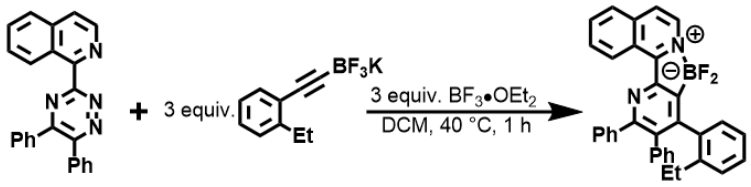
^{11}B NMR (128 MHz, $CDCl_3$): δ 7.8 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –158.8 (d, *J* = 114.0 Hz), –165.9 (d, *J* = 114.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{33}H_{24}BF_2N_2O$ 513.1950, found 513.1961.

AR–FTIR (neat, cm^{-1}): 3057, 2838, 1547, 1243, 1109, 1009.

Synthesis of 9-(2-Ethylphenyl)-8,8-difluoro-10,11-diphenyl-8*H*-pyrido[3',2':3,4][1,2]a-zaborolo[5,1-*a*]isoquinolin-7-ium-8-uide (98)



To a suspension of 5,6-diphenyl-3-(2-isoquinolyl)-1,2,4-triazine (85 mg, 0.236 mmol, 1 equiv.) and potassium ((2-ethylphenyl)ethynyl)trifluoroborate (139 mg, 0.590 mmol, 3 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.15 mL, 1.18 mmol, 3 equiv.). The mixture was stirred for 1 h at reflux. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The product was slowly precipitated from DCM to afford the product as an amorphous pale-yellow solid (55 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (d, *J* = 8.5 Hz, 1H), 8.40 (d, *J* = 6.5 Hz, 1H), 8.07 – 7.88 (m, 4H), 7.51 – 7.45 (m, 2H), 7.34 – 7.18 (m, 6H), 7.15 – 7.08 (m, 1H), 7.06 – 6.89 (m, 5H), 2.46 – 2.34 (m, 1H), 2.19 – 2.07 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.4, 157.0, 153.7, 153.2, 141.1, 140.7, 139.7, 137.8, 137.5, 137.1, 134.2, 132.2, 130.2 (x2 C), 130.2, 130.1, 129.8, 127.7 (x2 C), 127.5, 127.2 (x2 C), 127.1, 126.6, 125.4, 124.7, 123.7, 25.8, 14.1.

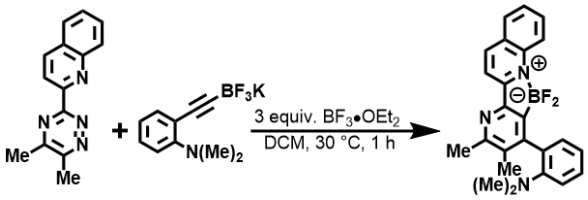
^{11}B NMR (128 MHz, $CDCl_3$): δ 7.3 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –161.0 (d, *J* = 111.0 Hz), –163.9 (d, *J* = 111.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{34}H_{26}BF_2N_2$ 511.2152, found 511.2167.

AR–FTIR (neat, cm^{-1}): 3272, 2925, 1628, 1552, 1493, 1243, 1089.

Synthesis of 10-(2-(Dimethylamino)phenyl)-11,11-difluoro-8,9-dimethyl-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (93)



To a suspension of 5,6-dimethyl-3-(2-quinolyl)-1,2,4-triazine (100 mg, 0.42 mmol, 1 equiv.) and potassium trifluoro((2-dimethylaminophenyl)ethynyl)borate (106 mg, 0.42 mmol, 1 equiv.) in DCM (4 mL) was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 0.16 mL, 1.27 mmol, 3 equiv.). The mixture was stirred for 1 h at 30 °C. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the reaction mixture was washed with water (20 mL) and extracted with DCM (4 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 2:1 as eluent to afford the product as an amorphous white solid (124 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 8.5 Hz, 1H), 8.45 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.86 (t, *J* = 8.0, Hz, 1H), 7.68 – 7.60 (m, 1H), 7.40 – 7.32 (m, 2H), 7.16 – 7.07 (m, 2H), 2.67 (s, 3H), 2.55 (s, 6H), 2.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.4, 157.4, 151.9, 150.3, 144.2, 142.4, 133.3, 132.8, 131.42, 131.39, 129.2, 128.9, 128.7, 127.8, 123.0, 122.9, 121.7, 117.7, 115.5, 43.7 (x2 C), 23.9, 16.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ 8.9 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –150.5 (d, *J* = 89.0 Hz), 158.3 (d, *J* = 89.0 Hz).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{24}H_{22}BF_2N_3$ 402.1948, found 402.1962.

AR–FTIR (neat, cm^{-1}): 3923, 1596, 1523, 1451, 1382, 1264, 1100, 1082.

General Procedures for the Synthesis of Boronic Esters

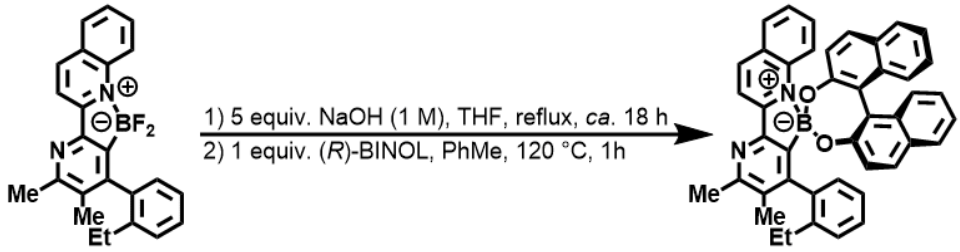
Procedure 1

To a solution of aryl difluoroborane (1 equiv.) in THF (0.03 M) was added NaOH (1.0 M in water, 5 equiv.). The reaction was stirred *ca*. 18 h at reflux. Then, the mixture was allowed to cool down to room temperature and concentrated *in vacuo*. The concentrate was washed with water and 1.0 M HCl (*aq*.) (10 mL) and extracted with DCM (3 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The crude material was dissolved in PhMe (0.03 M) and then (*R*)-(+)-1,1'-bi(2-naphtol) ((*R*)-BINOL, 1 equiv.) was added. The reaction was stirred for 1 h at 120 °C. Then, the mixture was allowed to cool down to room temperature and the volatiles were evaporated to dryness *in vacuo* at ***35 °C***. The residue was purified by column chromatography or by recrystallization to afford the title compound.

Procedure 2

Aryl difluoroborane (1 equiv.) and Cs_2CO_3 (3 equiv.) were dissolved in a mixture of THF:H_2O 9:1 (0.1 M). The mixture was stirred at reflux for 12 h. Then, the mixture was allowed to cool down to room temperature and was concentrated *in vacuo*. The concentrate was washed with deionized water (15 mL) and 1 M HCl (*aq*.) and extracted with DCM. The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was redissolved in PhMe and (*R*)-BINOL (1 equiv.) was added. The mixture was heated at 120 °C for 12 h under Dean-Stark conditions. Then, the mixture was allowed to cool down to room temperature and the volatiles were evaporated *in vacuo* at ***35 °C***. The residue was purified by column chromatography or by recrystallization to afford the title compound.

Synthesis of (4*S*,10'*R*,11b*R*)-10'-(2-Ethylphenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2'3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (102)



Following general procedure 2, aryl difluoroborane **9a** (90 mg, 0.23 mmol, 1 equiv.) and (*R*)-BINOL (133 mg, 0.47 mmol, 2 equiv.) were used to afford the crude product, which was purified by column chromatography on silica gel with a mixture hexane:Et_2O 1:1 as eluent to afford the product as a 1:1 mixture of diastereomers (101 mg, 69%). The compound could not be generated in pure form due to rapid hydrolysis of the organoboronic ester, and the sample contains ~25% BINOL. The yield has been corrected against this impurity.

^{1}H NMR (400 MHz, C_6D_6): δ 8.39 (d, *J* = 8.5 Hz, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.75 – 7.42 (m, 9H), 7.38 – 7.19 (m, 9H), 7.12 – 6.92 (m, 10H), 6.85 (t, *J* = 8.5 Hz, 2H), 6.68 – 6.56 (m, 4H), 6.47 – 6.31 (m, 4H), 6.28 – 6.22 (m, 1H), 6.19 (t, *J* = 7.5 Hz, 1H), 2.70 – 2.40 (m, 10H), 1.81 (s, 3H), 1.79 (s, 3H), 1.26 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).

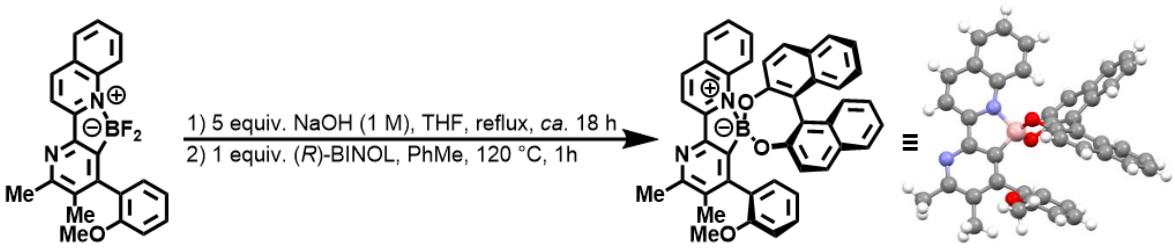
^{13}C NMR (101 MHz, C_6D_6): δ 158.2, 158.2, 158.0, 157.9, 156.2, 155.8, 155.7, 153.3, 153.2, 152.8, 152.5, 143.5, 143.4, 141.6, 141.2, 141.0, 139.5, 138.8, 138.6, 134.5, 134.4, 134.3, 133.9, 133.8, 131.3, 131.0, 130.8, 130.7, 130.5, 130.3, 129.8, 129.7, 129.4, 129.2, 129.1, 127.5, 127.2, 127.0, 126.7, 126.6, 126.5, 126.4, 125.9, 125.7, 125.6, 125.2, 125.1, 125.0, 124.9, 124.1, 124.0, 123.9, 123.8 (x 2C), 123.6, 123.5, 123.3 (x 2C), 122.6, 121.3, 121.1, 115.8, 26.3, 26.1, 23.6, 23.5, 16.9, 16.6, 14.6, 14.0.

^{11}B NMR (128 MHz, C_6D_6): δ 13.6 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{44}H_{34}BN_2O_2$ 633.2708, found 633.2710.

AR–FTIR (neat, cm^{-1}): 3055, 2963, 2934, 1593, 1505, 1466, 1339, 1254, 1098, 1023.

Synthesis of (4*S*,10'*R*,11b*R*)-10'-(2-Methoxyphenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (103)



Following general procedure 1, difluoroborane **9b** (53 mg, 0.13 mmol), and (*R*)-BINOL (39 mg, 0.13 mmol) were combined to give the crude boronic ester. The residue was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 7:3 as eluent to afford the product as a 4:1 mixture of diastereomers (49 mg, 57%).

Diastereomer enrichment by precipitation: Following general procedure 2 with difluoroborane **9b** (100 mg, 0.26 mmol, 1 equiv.), caesium carbonate (Cs_2CO_3, 252 mg, 0.78 mmol, 3 equiv.) and (*R*)-BINOL (148 mg, 0.52 mmol, 2 equiv.). The product was slowly precipitated from MeCN and was obtained as a yellow solid (108 mg, 66%, ≥98:2 *d.r.*).

$[\alpha]_D^{20}$ = –862 [1.0 *c* in $CHCl_3$].

M.P. 175–177 °C (decomposition) recrystallized from PhMe.

^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer): δ 8.58 (d, *J* = 8.5 Hz, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 7.80 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.17 – 7.09 (m, 4H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.67 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 6.30 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.25 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 5.86 (td, *J* = 7.5, 1.0 Hz, 1H), 3.80 (s, 3H), 2.65 (s, 3H), 1.94 (s, 3H).

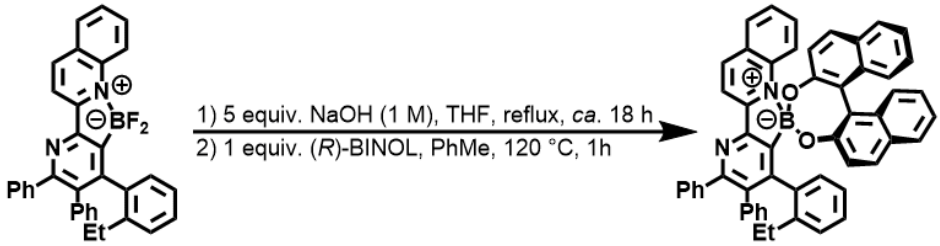
^{13}C NMR (101 MHz, $CDCl_3$, major diastereomer): δ 158.2, 157.6, 155.4, 155.1, 155.0, 143.7, 141.1, 135.0, 133.7, 133.5, 131.6, 131.5, 130.4, 130.2, 129.3, 129.2, 129.1, 128.5, 128.2, 127.9, 127.8, 127.7, 127.6, 127.3, 126.9, 125.2, 124.6, 124.4, 124.0, 123.8, 123.7, 123.2, 123.0, 122.6, 122.4, 121.3, 119.0, 115.8, 109.6, 54.9, 23.8, 16.5.

^{11}B NMR (128 MHz, C_6D_6): δ 13.2 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{43}H_{32}BN_2O_3$ 635.2508, found 635.2511.

AR–FTIR (neat, cm^{-1}): 3059, 2952, 1594, 1523, 1253.

Synthesis of (4*S*,10'*R*,11b*R*)-10'-(2-Ethylphenyl)-8',9'-diphenylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (107)



Following general procedure 1, aryl difluoroborane **9c** (50 mg, 0.1 mmol, 1 equiv.), and (*R*)-BINOL (28 mg, 0.1 mmol, 1 equiv.) were combined to give the crude product. The residue was purified by column chromatography on silica gel using a mixture of petrol:EtOAc 7:3 as eluent to afford the title compound as a 1:1 mixture of diastereomers (34 mg, 46%).

^{1}H NMR (400 MHz, C_6D_6): δ 8.43 – 8.36 (m, 2H), 8.18 (d, *J* = 9.0 Hz, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.74 – 7.62 (m, 7H), 7.62 – 7.39 (m, 9H), 7.38 – 7.19 (m, 8H), 7.13 – 6.96 (m, 17H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.74 – 6.53 (m, 9H), 6.44 – 6.13 (m, 7H), 3.05 – 2.93 (m, 1H), 2.60 – 2.48 (m, 1H), 2.45 – 2.32 (m, 1H), 2.30 – 2.17 (m, 1H), 1.04 – 0.93 (m, 6H).

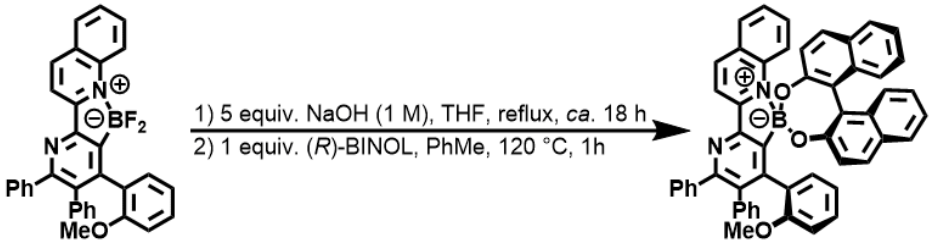
^{13}C NMR (101 MHz, C_6D_6): δ 159.2, 159.1, 157.6, 157.5, 156.1, 155.8, 155.7, 155.5, 155.3, 154.8, 154.5, 153.3, 143.7, 143.6, 142.1, 141.9, 141.8, 141.4, 140.7, 139.4, 139.3, 139.2, 138.7, 138.4, 138.1, 134.5, 134.4, 134.3, 134.2, 132.3, 131.9, 131.8, 131.5, 131.4, 131.1, 131.0, 130.9 (x2 C), 130.8 (x2 C), 130.7, 130.6, 129.9, 129.8, 129.6, 129.5, 129.4, 128.6 (x2 C), 127.6, 127.4, 127.3, 127.0, 126.9, 126.8, 126.7, 126.6, 126.5, 125.8, 125.7, 125.5, 125.3, 125.1, 124.8, 124.4, 124.2, 124.1, 124.0 (x2 C), 123.7 (x2 C), 123.6, 123.5, 123.4, 123.3, 123.2, 122.9, 121.1, 120.8, 118.3, 116.0, 26.0, 25.9, 13.6, 13.5.

^{11}B NMR (128 MHz, C_6D_6): δ 13.7 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{54}H_{38}BN_2O_2$ 759.2813, found 759.2781.

AR–FTIR (neat, cm^{-1}): 3057, 2971, 2929, 2924, 1619, 1596, 1544, 1339, 1252, 1098.

Synthesis of (4*S*,10'*R*,11b*R*)-10'-(2-Methoxyphenyl)-8',9'-diphenylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (108)



Following general procedure 1, aryl difluoroborane **9d** (140 mg, 0.27 mmol, 1 equiv.), and (*R*)-BINOL (78 mg, 0.27 mmol, 1 equiv.) were combined to give the crude product. The residue was purified by column chromatography on silica gel with DCM as eluent to afford the title compound as a 4:1 mixture of diastereomers (111 mg, 54%)

^{1}H NMR (400 MHz, C_6D_6, major diastereomer): δ 8.31 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.60 – 7.55 (m, 3H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.33 – 7.18 (m, 5H), 7.14 – 6.97 (m, 8H), 6.84 (t, *J* = 7.0 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.71 – 6.62 (m, 2H), 6.36 (t, *J* = 8.5 Hz, 1H), 6.18 (t, *J* = 8.0 Hz, 1H), 5.99 (t, *J* = 7.5 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 2.96 (s, 3H).

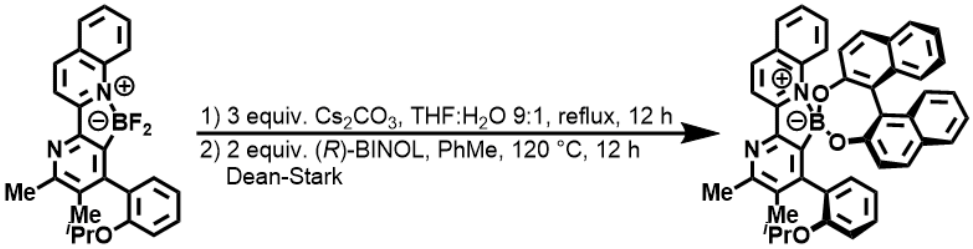
^{13}C NMR (101 MHz, C_6D_6, major diastereomer): δ 158.5, 157.8, 156.2, 156.1, 155.4, 155.1, 151.3, 143.6, 142.3, 141.4, 139.7, 139.6, 134.5, 132.6, 132.2, 131.3, 131.0, 130.9 (x 2C), 130.7, 129.7, 129.5, 127.5, 126.8, 126.6, 126.2, 125.8, 125.0, 124.5, 124.2, 123.6, 123.4, 123.2, 121.6, 118.8, 116.0, 109.7, 53.7. (*A complete assignment could not be achieved due to a large number of overlapping signals*).

^{11}B NMR (128 MHz, C_6D_6): δ 14.3 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{53}H_{36}BN_2O_2$ 759.2819, found 759.2781.

AR–FTIR (neat, cm^{-1}): 3057, 2971, 2929, 2924, 1619, 1596, 1544, 1339, 1252, 1098.

Synthesis of (4*S*,10'*R*,11b*R*)-10'-(2-*Iso*propoxyphenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (104)



Following general procedure 2 with difluoroborane **9e** (158 mg, 0.38 mmol, 1 equiv.), Cs_2CO_3 (371 mg, 1.14 mmol, 3 equiv.) and (*R*)-BINOL (217 mg, 0.76 mmol, 2 equiv.). The residual crude was purified by column chromatography on silica gel using a mixture of hexane:Et_2O 1:1 as eluent to afford the product as an amorphous yellow solid (225 mg, 89%, 7:1 *d.r.*).

M.P. 176–178 °C (decomposition) recrystallized from EtOAc.

^{1}H NMR (400 MHz, C_6D_6, major diastereomer): δ 8.30 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.70 – 7.64 (m, 3H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.39 – 7.18 (m, 7H), 7.13 – 7.02 (m, 2H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.60 (t, *J* = 7.5 Hz, 1H), 6.37 – 6.30 (m, 1H), 6.27 (t, *J* = 8.0 Hz, 1H), 5.91 (t, *J* = 7.5 Hz, 1H), 4.28 (hept, *J* = 6.0 Hz, 1H), 2.61 (s, 3H), 2.01 (s, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H).

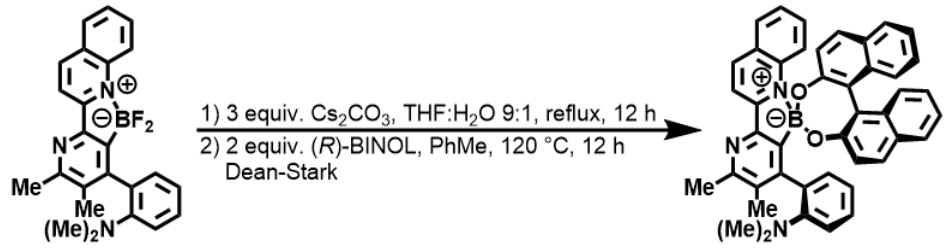
^{13}C NMR (101 MHz, C_6D_6, major diastereomer): δ 158.5, 157.3, 156.3, 156.2, 154.3, 153.0, 150.4, 143.3, 141.4, 134.9, 134.5, 134.3, 132.7, 131.3, 131.2, 131.0, 130.9, 130.7, 129.7, 129.6, 129.4, 129.3, 129.1, 126.7, 126.4, 125.7, 125.1, 124.5, 124.2, 124.1, 123.6, 123.4, 123.2, 119.4, 115.8, 112.2, 69.1, 23.7, 22.8, 21.7, 17.1.

^{11}B NMR (128 MHz, C_6D_6): δ 14.3 (s, br).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{45}H_{36}BN_2O_3$ 663.2813, found 663.2809.

AR–FTIR (neat, cm^{-1}): 2975, 2278, 1593, 1226.

Synthesis of (4*S*,10'*R*,11b*R*)-10'-(2-(dimethylamino)phenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (105)



Following general procedure 2 with difluoroborane **9f** (100 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (246 mg, 0.75 mmol, 3 equiv.) and (*R*)-BINOL (143 mg, 0.50 mmol). The residual crude was purified by column chromatography on silica gel using a mixture of hexane:Et_2O 1:1 as eluent to afford the product as an amorphous yellow solid (103 mg, 64%, 6:1 *d.r.*).

^{1}H NMR (400 MHz, C_6D_6, major diastereomer): δ 8.44 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 7.79 – 7.70 (m, 3H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 2H), 7.13 – 7.05 (m, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.95 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 6.71 – 6.66 (m, 1H), 6.66 – 6.56 (m, 2H), 6.20 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 5.75 (td, *J* = 7.5, 1.0 Hz, 1H), 2.62 (s, 3H), 2.56 (s, 6H), 1.97 (s, 3H).

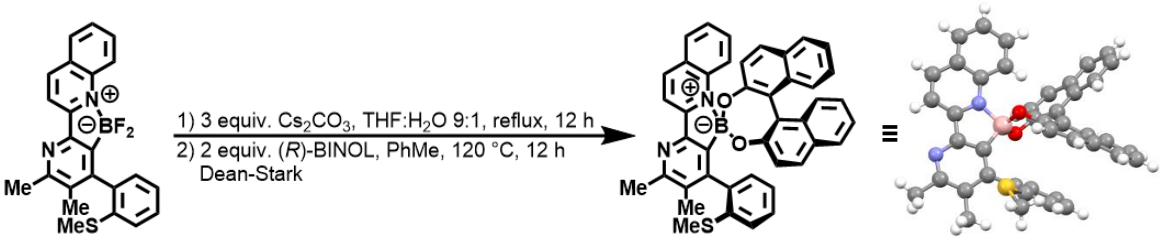
^{13}C NMR (101 MHz, C_6D_6, major diastereomer): δ 158.5, 158.0, 156.4, 156.1, 153.6, 153.2, 152.4, 150.8, 143.4, 141.9, 134.6, 134.5, 134.2, 132.8, 131.3, 130.7, 130.6, 129.8, 129.3, 128.8, 126.3, 125.9, 125.8, 125.3, 124.9, 124.0, 123.8, 123.6, 123.3, 121.1, 118.5, 116.8, 115.8, 43.7, 23.8, 16.7. (*A complete assignment could not be achieved due to a large number of overlapping signals*).

^{11}B NMR (128 MHz, C_6D_6): δ 15.0 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{44}H_{35}BN_3O_2$ 648.2817, found 648.2823.

AR–FTIR (neat, cm^{-1}): 3062, 2960, 2929, 1593, 1431, 1343, 1253, 1230, 1082.

Synthesis of (4*S*,10'*R*,11b*R*)-8',9'-Dimethyl-10'-(2-(methylthio)phenyl)spiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (100)



Following general procedure 2 with difluoroborane **9g** (50 mg, 0.12 mmol, 1 equiv.), Cs_2CO_3 (121 mg, 0.37 mmol, 3 equiv.) and (*R*)-BINOL (71 mg, 0.25 mmol, 2 equiv.). The product was slowly precipitated from MeCN and filtered to afford it as a yellow solid (54 mg, 67%, >98:2 *d.r.*). The product was further recrystallized from benzene.

$[\alpha]_D^{25}$ = –570 [1.0 *c* in $CHCl_3$].

M.P. 164–166 °C (decomposition) recrystallized from benzene.

^{1}H NMR (400 MHz, C_6D_6, single diastereomer): δ 8.30 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.70 – 7.59 (m, 3H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.33 (m, 3H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.0 Hz, 1H), 6.93 (m, 2H), 6.60 (t, *J* = 7.5 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.26 (m, 2H), 6.11 (t, *J* = 7.0 Hz, 1H), 2.58 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H).

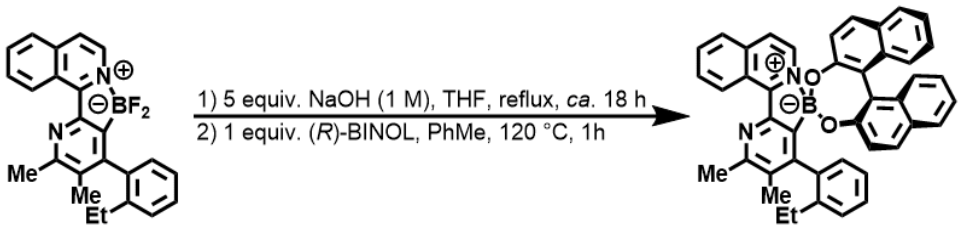
^{13}C NMR (101 MHz, C_6D_6, single diastereomer): δ 158.3, 158.1, 156.2, 155.9, 153.4, 150.8, 143.3, 141.5, 137.8, 136.9, 134.8, 134.4, 134.2, 131.1, 130.8, 129.4, 129.3, 129.2, 127.2, 126.4, 125.7, 125.0, 124.1, 124.0, 123.8, 123.7, 123.6, 123.4, 123.1, 121.4, 115.7, 23.7, 16.6, 14.7 (*Some signals are overlapped with the solvent signal*).

^{11}B NMR (128 MHz, C_6D_6): δ 14.0 (s, br).

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{43}H_{32}BN_2O_2S$ 651.2272, found 651.2299.

AR–FTIR (neat, cm^{-1}): 2920, 2852, 1590, 1465, 1252.

Synthesis of (4*S*,11b*R*)-9'-(2-Ethylphenyl)-10',11'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,8'-pyrido[3',2':3,4][1,2]azaborolo[5,1-*a*]isoquinolin]-7'-ium-23-uide (109)



Following general procedure 1, difluoroborane **9h** (80 mg, 0.21 mmol, 1 equiv.), and (*R*)-BINOL (59 mg, 0.21 mmol, 1 equiv.) were combined to give the crude product. The residue was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 7.5:2.5 as eluent to afford the title compound as a 1:1 mixture of diastereomers (120 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.72 (d, *J* = 8.0 Hz, 2H), 7.95 – 7.84 (m, 8H), 7.83 – 7.74 (m, 2H), 7.73 – 7.68 (m, 2H), 7.56 – 7.46 (m, 3H), 7.45 – 7.37 (m, 2H), 7.37 – 7.27 (m, 5H), 7.25 – 6.99 (m, 10H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 6.61 – 6.39 (m, 4H), 5.97 (t, *J* = 7.5 Hz, 1H), 2.74 (s, 3H), 2.74 (s, 3H), 2.56 – 2.39 (m, 2H), 2.28 (q, *J* = 7.5 Hz, 2H), 2.00 (s, 3H), 1.95 (s, 3H), 1.30 (d, *J* = 7.5 Hz, 3H), 0.74 (t, *J* = 7.5 Hz, 3H).

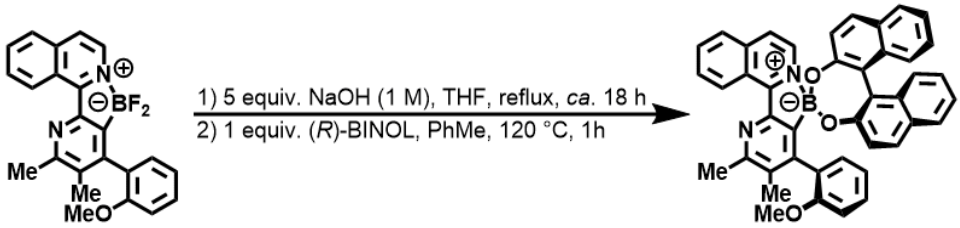
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.5, 157.4, 155.8, 155.3, 154.6 (x 2C), 154.5, 154.4, 154.2, 152.7, 151.9, 141.1, 139.8, 139.6, 139.5, 138.3 (x 2C), 133.8, 133.7, 133.5 (x 2C), 133.2 (x 2C), 133.1 (x 2C), 132.9, 132.8, 130.5, 130.2, 130.1, 130.0, 129.9, 129.6, 129.5, 129.4, 129.1, 128.8, 128.7, 128.4, 128.1, 128.0, 127.8, 127.7, 127.4, 127.3, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6 (x 2C), 125.6, 125.5, 125.3, 125.2, 125.0, 124.7, 124.6, 124.5, 123.6, 123.5, 123.4, 123.3, 123.2, 123.1, 122.8, 122.7, 122.6, 122.2, 121.9, 121.6, 120.6, 120.5, 25.8, 25.7, 24.1, 24.0, 16.8, 16.7, 14.2, 14.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 11.0 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{44}H_{34}BN_2O_2$ 633.2708, found 633.2710.

AR–FTIR (neat, cm^{-1}): 3055, 2963, 2934, 1593, 1505, 1466, 1339, 1254, 1098, 1023.

Synthesis of (4*S*,9'*R*,11b*R*)-9'-(2-Methoxyphenyl)-10',11'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,8'-pyrido[3',2':3,4][1,2]azaborolo[5,1-*a*]isoquinolin]-7'-ium-23-uide (110)



Following general procedure 1, difluoroborane **9i** (70 mg, 0.18 mmol, 1 equiv.), and (*R*)-BINOL (52 mg, 0.18 mmol, 1 equiv.) were combined to give the crude product**.** The residue was purified by column chromatography on silica gel using a mixture of petrol:EtOAc 7.5:2.5 as eluent to afford the title compound as a 4:1 mixture of diastereomers (89 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer): δ 10.72 (d, *J* = 7.5 Hz, 1H), 7.94 – 7.82 (m, 4H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.42 – 7.27 (m, 3H), 7.24 – 7.07 (m, 5H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.43 (t, *J* = 7.5 Hz, 1H), 5.78 (t, *J* = 7.5 Hz, 1H), 3.86 (s, 3H), 2.73 (s, 3H), 2.02 (s, 3H).

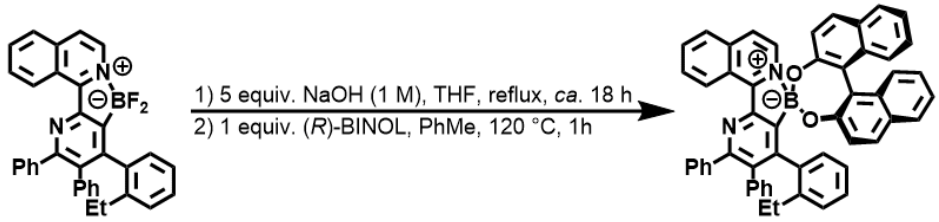
^{13}C NMR (101 MHz, $CDCl_3$, major diastereomer): δ 157.0, 155.8, 155.7, 154.8, 154.7, 154.6, 149.4, 139.5, 134.0, 133.7, 133.6, 133.2, 133.1, 132.1, 130.6, 130.2, 130.1, 129.5, 129.4, 128.8, 128.2, 128.1, 127.8, 127.7, 127.4, 127.0, 126.9, 125.4, 125.2, 124.7, 123.6, 123.4, 123.0, 122.8, 122.3, 121.7, 121.0, 119.2, 109.8, 55.1, 24.1, 16.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ 11.3 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{43}H_{32}BN_2O_3$ 635.2506, found 635.2496.

AR–FTIR (neat, cm^{-1}): 3054, 3002, 2953, 1593, 1551, 1339, 1253, 1078, 1024.

Synthesis of (4*S*,11b*R*)-9'-(2-ethylphenyl)-10',11'-diphenylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,8'-pyrido[3',2':3,4][1,2]azaborolo[5,1-*a*]isoquinolin]-7'-ium-23-uide (112)



Following general procedure 1, difluoroborane **9j** (70 mg, 0.14 mmol, 1 equiv.), and (*R*)-BINOL (39 mg, 0.14 mmol, 1 equiv.) were combined to give the crude product. The residue was purified by column chromatography on silica gel using a mixture of petrol:EtOAc 7.5:2.5 as eluent to afford the title compound as a 1:1 mixture of diastereomers (59 mg, 57%).

^{1}H NMR (400 MHz, C_6D_6): δ 10.76 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.81 – 7.58 (m, 11H), 7.57 – 7.48 (m, 4H), 7.47 – 7.39 (m, 2H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.29 – 7.17 (m, 8H), 7.15 – 6.95 (m, 20H), 6.94 – 6.88 (m, 2H), 6.87 – 6.77 (m, 2H), 6.76 – 6.64 (m, 5H), 6.52 (t, *J* = 7.5 Hz, 1H), 6.44 – 6.41 (m, 3H), 6.38 (d, *J* = 6.0 Hz, 1H), 6.24 (t, *J* = 7.5 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.64 – 2.51 (m, 1H), 2.45 – 2.34 (m, 1H), 2.30 – 2.17 (m, 1H), 1.06 – 0.94 (m, 6H).

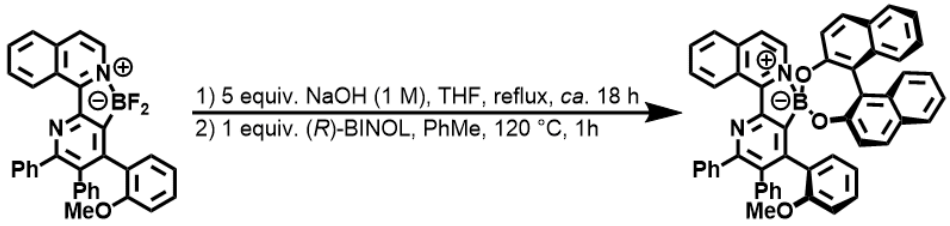
^{13}C NMR (101 MHz, C_6D_6): δ 158.5, 158.4, 158.2, 157.8, 155.9, 155.8, 155.4, 155.3, 154.2, 153.8, 153.2, 142.4, 142.2, 141.1, 139.6, 139.5 (x 2C), 139.1, 138.6, 138.4, 138.3, 137.6, 134.4, 134.3, 134.1, 133.9, 133.7, 133.6, 133.3, 133.2, 132.3 (x 2C), 132.0, 130.8, 130.7, 130.6 (x 2C), 130.5, 130.4, 130.3, 130.1, 129.9, 129.6, 129.5, 129.2, 129.1, 127.5, 127.4, 127.3, 127.1, 126.9 (x 2C), 126.7, 126.6, 126.1, 126.0, 125.9, 125.8, 125.7, 125.6, 125.3, 125.2, 124.6, 124.4, 124.2, 124.1, 124.0, 123.9, 123.8, 123.7, 123.6, 123.2, 123.1 (x 2C), 122.4, 122.1, 120.9, 120.8, 26.1, 26.0, 13.9, 13.5.

^{11}B NMR (128 MHz, C_6D_6): δ 12.0 (s, br).

HRMS: (ESI) *m/z* $[M+Na]^+$ calculated for $C_{54}H_{38}BN_2NaO_2$ 779.2846, found 779.2846.

AR–FTIR (neat, cm^{-1}): 3055, 2963, 2934, 1593, 1505, 1466, 1339, 1254, 1098, 1023.

Synthesis of (4*S*,9'*R*,11b*R*)-9'-(2-Methoxyphenyl)-10'-11'-diphenylspiro[dinaphto[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,8'-pyrido[3',2':3,4][1,2]azaborolo[5,1-*a*]isoquinolin]-7'-ium-23-uide (113)



Following general procedure 1, difluoroborane **9k** (100 mg, 0.2 mmol, 1 equiv.), and (*R*)-BINOL (56 mg, 0.2 mmol, 1 equiv.) were combined to give the crude product. The residue was purified by column chromatography on silica gel using a mixture of petrol:EtOAc 7.5:2.5 as eluent to afford the title compound as a 3:1 mixture of diastereomers (124 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 3:1): δ 10.74 – 10.65 (m, 4H), 7.99 – 7.69 (m, 21H), 7.65 (d, *J* = 8.0 Hz, 3H), 7.58 – 7.46 (m, 9H), 7.45 – 7.23 (m, 36H), 7.23 – 7.10 (m, 15H), 7.05 – 6.78 (m, 20H), 6.77 – 6.60 (m, 7H), 6.54 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.51 – 6.44 (m, 1H), 6.37 – 6.31 (m, 3H), 6.28 (t, *J* = 7.5 Hz, 1H), 6.11 (d, *J* = 8.0 Hz, 3H), 5.73 – 5.66 (m, 4H), 3.27 (s, 9H), 3.24 (s, 3H).

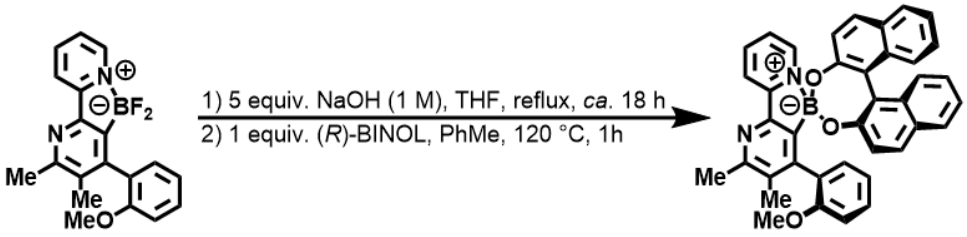
^{13}C NMR (101 MHz, $CDCl_3$, major diastereomer): δ 158.0, 157.8, 155.1, 154.8, 154.5, 154.0, 150.4, 141.7, 139.5, 138.9, 138.3, 133.9, 133.7, 133.3, 133.1, 132.4, 130.5, 130.4 (x 2C), 130.1 (x 2C), 130.0, 129.5, 129.4, 128.9, 128.4, 128.1, 127.7 (x 2C), 127.6 (x 2C), 127.5, 127.4, 127.3 (x 2C), 127.1, 126.9, 126.5, 126.2, 125.5, 125.3, 124.7, 123.5 (x 2C), 123.3, 122.8, 122.4, 122.1, 120.8, 118.8, 109.5, 54.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 11.4 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{53}H_{36}BN_2O_3$ 759.2819, found 759.2844.

AR–FTIR (neat, cm^{-1}): 3056, 2966, 2932, 1593, 1540, 1505, 1339, 1253, 1099.

Synthesis of (4*S*,4'*R*,11b'*R*)-4-(2-Methoxyphenyl)-2,3-dimethylspiro[[1,2]azaborolo[1,5-*a*:4,3-*b*']dipyridine-5,4'-dinaphto[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepin]-6-ium-14-uide (117)



Following general procedure 1, difluoroborane **9l** (60 mg, 0.18 mmol, 1 equiv.), and (*R*)-BINOL (51 mg, 0.18 mmol, 1 equiv.) were combined to give the crude product. The residue was purified by column chromatography on silica gel using a mixture of petrol:EtOAc 6:4 as eluent to afford the title compound as a 5.6:1 mixture of diastereomers (60 mg, 58%).

^{1}H NMR (400 MHz, C_6D_6, major diastereomer): δ 7.98 – 7.92 (m, 1H), 7.79 – 7.72 (m, 2H), 7.69 – 7.62 (m, 2H), 7.61 – 7.57 (m, 2H), 7.38 – 7.33 (m, 1H), 7.33 – 7.26 (m, 2H), 7.22 – 7.18 (m, 1H), 7.13 – 7.07 (m, 3H), 7.04 – 6.98 (m, 1H), 6.79 – 6.73 (m, 1H), 6.45 (t, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 5.94 (t, *J* = 7.5 Hz, 1H), 5.87 (t, *J* = 7.5 Hz, 1H), 3.43 (s, 3H), 2.56 (s, 3H), 1.98 (s, 3H).

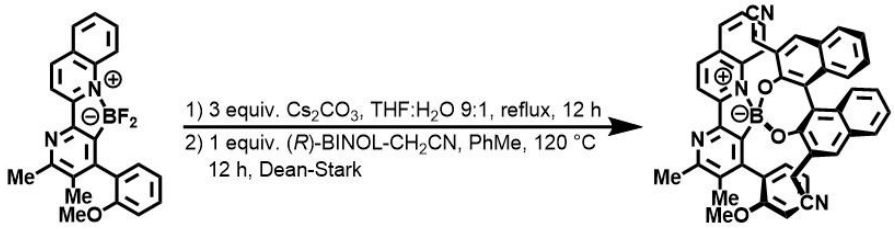
^{13}C NMR (101 MHz, C_6D_6, major diastereomer): δ 157.4, 156.3, 156.2, 155.8, 155.3, 153.0, 150.4, 142.5, 141.7, 134.4, 134.2, 133.9, 132.6, 130.7, 130.6, 129.8, 129.0, 128.6, 128.5, 128.4, 127.5, 125.9, 125.2, 124.0, 123.9, 123.8, 123.1, 123.0, 122.5, 121.5, 119.8, 118.1, 110.2, 54.7, 23.6, 16.5 (*A complete assignment could not be achieved due to a large number of overlapping signals*).

^{11}B NMR (128 MHz, C_6D_6): δ 12.2 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{39}H_{30}BN_2O_3$ 585.2344, found 585.2358.

AR–FTIR (neat, cm^{-1}): 3056, 2995, 2924, 2832, 1624, 1492, 1466, 1339, 1252, 1076.

Synthesis of (10'*R*,11b*R*)-2,6-Bis(cyanomethyl)-10'-(2-methoxyphenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (137)



Following general procedure 2 with difluoroborane **9b** (53 mg, 0.14 mmol, 1 equiv.), Cs_2CO_3 (133 mg, 0.40 mmol, 3 equiv.) and (*R*)-BINOL-CH_2CN (50 mg, 0.13 mmol, 1 equiv.). The residue was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 7:3 as eluent to afford the product as an amorphous yellow solid (82 mg, 84%, >98:2 *d.r.*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69–8.59 (m, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.72 (s, 1H), 7.65–7.54 (m, 2H), 7.42–7.33 (m, 3H), 7.23–7.12 (m, 3H), 7.10–7.01 (m, 2H), 6.70 (t, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 7.5 Hz, 1H), 6.26 (t, *J* = 8.0 Hz, 1H), 5.77 (t, *J* = 7.0 Hz, 1H), 3.89 (s, 3H), 3.67 (d, *J* = 19.0 Hz, 1H), 3.58–3.42 (m, 2H), 2.85 (d, *J* = 19.0 Hz, 1H), 2.69 (s, 3H), 1.94 (s, 3H).

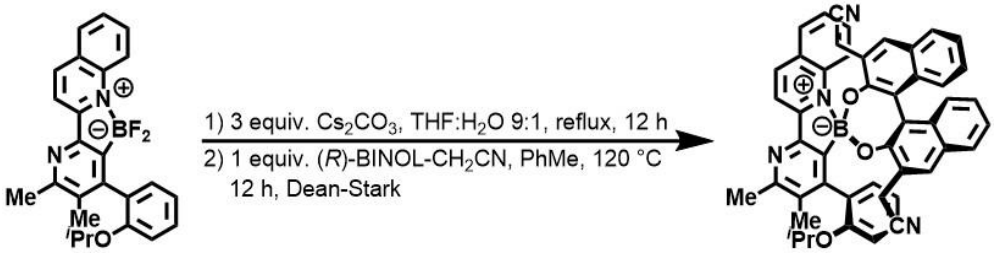
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2, 158.0, 155.3, 152.3, 152.1, 149.5, 144.5, 140.7, 135.4, 133.4, 133.1, 131.9, 131.8, 130.1, 129.6, 129.4, 128.8, 128.1, 128.0, 127.9, 127.8, 127.4, 127.1, 127.0, 126.9, 126.8, 125.9, 125.2, 124.2, 123.9, 123.6, 123.3, 122.5, 121.1, 119.1, 118.9, 117.7, 115.9, 109.6, 55.5, 23.9, 20.3, 19.2, 16.6.

^{11}B NMR (128 MHz, $CDCl_3$): δ 12.7 (s, br).

HRMS: (ESI) $[M+H]^+$ calculated for $C_{47}H_{33}BN_4O_3$ 713.2718, found 713.2239.

AR–FTIR (neat, cm^{-1}): 3062, 2999, 2920, 2836, 2253, 1598, 1522, 1428, 1342, 1260, 1243, 1066.

Synthesis of (10'*R*,11b*R*)-2,6-Bis(cyanomethyl)-10'-(2-isopropoxyphenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide



Following general procedure 2 with difluoroborane **9e** (158 mg, 0.38 mmol, 1 equiv.), Cs_2CO_3 (371 mg, 1.14 mmol, 3 equiv.) and (*R*)-BINOL-CH_2CN (138 mg, 0.38 mmol, 1 equiv.). The residual crude was purified by column chromatography on silica gel using a mixture of petrol:EtOAc 7:3 as eluent to afford the product as an amorphous yellow solid (202 mg, 72%, >98:2 *d.r.*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66–8.58 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.83–7.72 (m, 2H), 7.64 (s, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.55 (s, 1H), 7.42–7.35 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22–7.15 (m, 3H), 7.15–7.09 (m, 2H), 6.60–6.48 (m, 2H), 6.33 (t, *J* = 8.0 Hz, 1H), 5.55 (t, *J* = 7.5 Hz, 1H), 4.80–4.70 (m, 1H), 3.73 (d, *J* = 19.0 Hz, 1H), 3.57–3.38 (m, 2H), 2.77–2.63 (m, 4H), 2.01 (s, 3H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H).

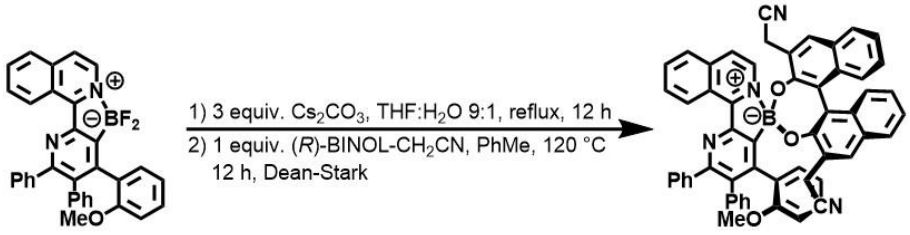
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1, 158.0, 153.4, 152.4, 152.3, 152.1, 149.5, 144.4, 140.9, 135.3, 133.5, 133.3, 132.7, 131.6, 130.0, 129.8, 129.3, 128.6, 128.4, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3, 127.0, 126.9, 126.0, 125.3, 124.3, 123.9, 123.5, 123.2, 122.9, 122.4, 120.7, 118.9, 118.6, 117.7, 115.8, 111.1, 68.8, 23.9, 23.5, 20.8, 20.0, 18.9, 17.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ 12.9.

HRMS: (ESI) $[M+H]^+$ calculated for $C_{49}H_{37}BN_4O_3$ 741.3031, found 741.3037.

AR–FTIR (neat, cm^{-1}): 3061, 2978, 2923, 2252, 1597, 1429, 1360, 1343, 1260, 1220, 1108, 1065.

Synthesis of (9'*R*,11b*R*)-2,6-Bis(cyanomethyl)-9'-(2-methoxyphenyl)-10',11'-diphenylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,8'-pyrido[3',2':3,4][1,2]azaborolo[5,1-*a*]isoquinolin]-7'-ium-23-uide



Following general procedure 2 with difluoroborane **9k** (102 mg, 0.2 mmol, 1 equiv.), Cs_2CO_3 (194 mg, 0.6 mmol, 3 equiv.) and (*R*)-BINOL-CH_2CN (73 mg, 0.2 mmol, 1 equiv.) were combined to give the crude product. The residue was purified chromatographically over silica gel using a mixture of petrol:EtOAc 7.5:2.5 as eluent to afford the product as an amorphous yellow solid (100 mg, 60%, >98:2 *d.r.*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (d, *J* = 8.0 Hz, 1H), 8.04–7.89 (m, 5H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.65 (d, *J* = 6.5 Hz, 1H), 7.53 (d, *J* = 6.5 Hz, 1H), 7.46–7.39 (m, 4H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.32–7.27 (m, 3H), 7.24–7.15 (m, 3H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.06–6.78 (m, 4H), 6.71–6.57 (m, 1H), 6.37 (t, *J* = 8.0 Hz, 1H), 6.23 (d, *J* = 7.5 Hz, 1H), 5.55 (t, *J* = 7.0 Hz, 1H), 3.72 (d, *J* = 19.5 Hz, 1H), 3.61 (s, 2H), 3.22 (s, 3H), 2.99 (d, *J* = 19.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2, 157.6, 154.7, 153.8, 151.9, 151.6, 150.1, 141.4, 139.8, 138.6, 138.4, 134.6, 133.3, 132.9, 132.8, 131.9, 130.6, 130.4, 130.3 (x 2C), 129.8, 129.7, 129.1, 128.2, 127.8 (x 3C), 127.6, 127.4, 127.2, 127.1, 127.0, 126.7 (x 2C), 126.5, 126.4, 126.0, 125.5, 125.3, 124.5, 123.7, 123.5, 123.4, 123.1, 122.9, 120.6, 119.1, 118.9, 118.1, 109.9, 55.2, 20.4, 19.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ 11.1 (s, br).

HRMS: (ESI) $[M+H]^+$ calculated for $C_{57}H_{37}BN_4O_3$ 837.3031, found 837.3049.

AR–FTIR (neat, cm^{-1}): 3058, 2923, 2853, 2254, 1710, 1454, 1430, 1360, 1261, 1106, 1094, 1022.

Synthesis of 4-(2-Methoxyphenyl)-5,6-dimethyl-2-(quinolin-2-yl)pyridin-3-ol (125)

(4*S*,10'*R*,11b*R*)-10'-(2-Methoxyphenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]di-oxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (**10b**) (40 mg, 0.06 mmol, 1 equiv., 5:1 *d.r.*), was dissolved in DCM (8 mL) at 0 °C, then 3-chloroperbenzoic acid (*m*CPBA, 17 mg, 0.10 mmol, 1.2 equiv.) was added portion-wise. The mixture was stirred under a nitrogen atmosphere at room temperature overnight (*ca*. 18 h). Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the mixture was extracted with DCM (3 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel with a gradient of elution of petrol:EtOAc 19:1 → 2:1 to afford the product as a yellow solid (10.8 mg, 48% yield, 84% *ee*, 92:8 *e.r.*).

$[\alpha]_D^{21.5}$ = +65 [1.0 *c* in $CHCl_3$].

M.P. 182 – 184 °C recrystallized from DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.11 (br, 1H), 8.85 (d, *J* = 9.0 Hz, 1H), 8.29 (d, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.5, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.44 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.23 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.13 (t, *J* = 7.5, Hz, 1H), 7.08 (d, *J* = 8.0, Hz, 1H), 3.80 (s, 3H), 2.62 (s, 3H), 2.07 (s, 3H).

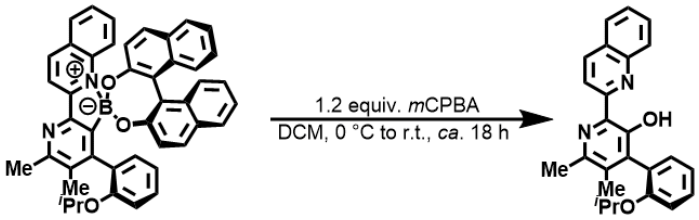
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 156.8, 154.0, 147.1, 144.6, 137.3, 135.7, 134.3, 132.8, 130.9, 130.2, 129.5, 127.8, 127.5, 127.4, 126.6, 124.7, 120.9, 118.9, 111.4, 55.8, 23.2, 16.8.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{23}H_{21}N_2O_2$ 357.1598, found 357.1600.

AR–FTIR (neat, cm^{-1}): 3014, 2934, 1594, 1496, 1459, 1420, 1243, 1184, 1113.

Chiral HPLC: The *ee* was determined by HPLC using a Chiralpak IA column [*n*-hexane/^{i}PrOH (99:1)]; τ_{major} = 20.67 min, τ_{minor} = 24.35 min (91.7:8.3).

Synthesis of 4-(2-Isopropoxyphenyl)-5,6-dimethyl-2-(quinolin-2-yl)pyridin-3-ol (126)



(4*S*,10'*R*,11b*R*)-10'-(2-*Iso*propoxyphenyl)-8',9'-dimethylspiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (**10e**) (20 mg, 0.03 mmol, 7:1 *d.r.*), was dissolved in DCM (8 mL) at 0 °C, then 3-chloroperbenzoic acid (*m*CPBA, 7 mg, 0.04 mmol, 1.2 equiv.) was added portion-wise. The mixture was stirred under a nitrogen atmosphere at room temperature (*ca*. 18 h). Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added and the mixture was extracted with DCM (3 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel with a gradient of elution of petrol:EtOAc 19:1 → 2:1 to afford the product as a yellow solid (5.4 mg, 46% yield, 76% *ee*, 88:12 *e.r.*)**.**

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.03 (br. s, 1H), 8.85 (d, *J* = 9.0 Hz, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.68 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.38 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.0, Hz, 1H), 4.48–4.37 (m, 1H), 2.61 (s, 3H), 2.08 (s, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H).

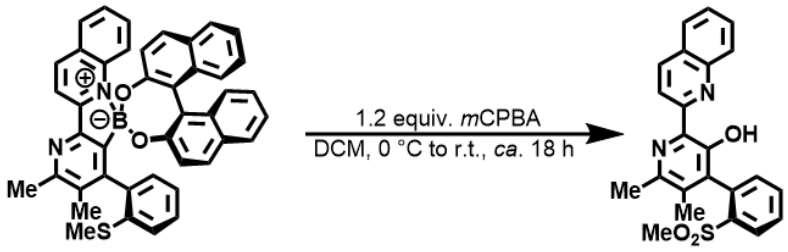
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 155.4, 154.1, 147.0, 144.7, 137.3, 136.1, 134.3, 132.6, 131.3, 130.2, 129.3, 127.8, 127.5, 127.4, 126.6, 126.4, 121.0, 118.8, 115.3, 71.2, 23.2, 22.3, 22.2, 16.9.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{25}H_{25}N_2O_2$ 385.1911, found 385.1915.

AR–FTIR (neat, cm^{-1}): 2970, 2919, 1600, 1443, 1372, 1232, 1114.

Chiral HPLC: The *ee* was determined by HPLC using a Cellulose-1 column [*n*-hexane/^{i}PrOH (95:5)]; flow rate 1.0 mL/min; t_{major} = 5.37 min, t_{minor} = 6.36 min (87.6:12.4).

Synthesis of 5,6-Dimethyl-4-(2-(methylsulfonyl)phenyl)-2-(quinolin-2-yl)pyridin-3-ol (127)



(4*S*,10'*R*,11b*R*)-8',9'-Dimethyl-10'-(2-(methylthio)phenyl)spiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (**10g**) (64.9 mg, 0.1 mmol, 49:1 *d.r.*), was dissolved in DCM (5 mL) at 0 °C, then 3-chloroperbenzoic acid (*m*CPBA, 51.8 mg, 0.3 mmol, 1.2 equiv.) was added portion-wise. The mixture was stirred under a nitrogen atmosphere at room temperature (*ca*. 18 h). Then, saturated $NaHCO_3$ (*aq*.) (20 mL) was added and the mixture was extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 4:1 as eluent to afford the product as an amorphous yellow solid (29.1 mg, 72% yield, 78% *ee*, 89:11 *e.r.*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.40 (br. s, 1H), 8.89 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 3.01 (s, 3H), 2.63 (s, 3H), 2.04 (s, 3H).

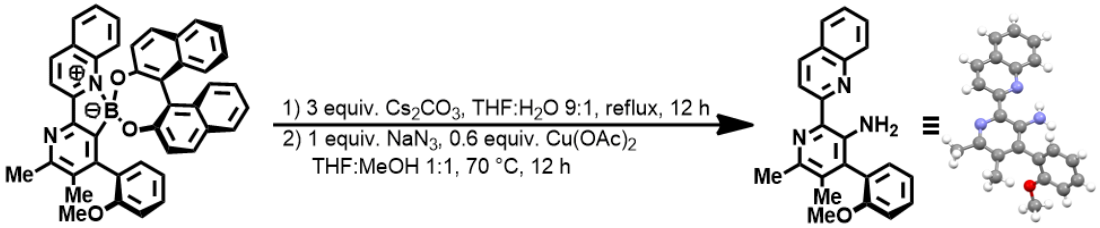
^{13}C NMR (101 MHz, $CDCl_3$): δ 152.9, 147.8, 144.4, 139.5, 137.8, 136.4, 135.4, 134.0, 132.7, 132.5, 131.8, 130.5, 129.8, 129.0, 128.0, 127.7, 127.3, 127.0, 119.0, 43.9, 22.9, 17.8.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{23}H_{21}N_2O_3S$ 405.1267, found 405.1281.

AR–FTIR (neat, cm^{-1}): 2971, 2920, 1738, 1466, 1301, 1259, 1149.

Chiral HPLC: The *ee* was determined by HPLC using a Cellulose-1 column [*n*-hexane/^{i}PrOH (90:10)]; flow rate 1.0 mL/min; t_{major} = 14.67 min, t_{minor} = 21.42 min (88.6:11.4).

Synthesis of 4-(2-Methoxyphenyl)-5,6-dimethyl-2-(quinolin-2-yl)pyridin-3-amine (119)



A suspension 2-(3-(difluoroboranyl)-4-(2-methoxyphenyl)-5,6-dimethylpyridin-2-yl)quinoline (50 mg, 0.12 mmol, 1 equiv.) and cesium carbonate (Cs_2CO_3, 125 mg, 0.39 mmol, 3 equiv.) in a mixture THF:H_2O 9:1 (10 mL) was heated up to reflux and left to stir overnight. After that, the mixture was washed with water and 1 M HCl (*aq*.), and then extracted with DCM. The organic extract was dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo*. The resulting crude was dissolved in a mixture of THF:MeOH 1:1 (2 mL) and mixed with sodium azide (NaN_3, 7.7 mg, 0.12 mmol, 1 equiv.) and copper(II) acetate ($Cu(OAc)_2$, 14.3 mg, 0.08 mmol, 0.6 equiv.). The mixture was heated up to 70 °C and left to stir overnight. The mixture was allowed to cool down to room temperature, washed with water (10 mL), and extracted with EtOAc (3 x 15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The resulting crude was purified by column chromatography on silica gel with a gradient of elution starting in DCM and ending in EtOAc. The product was obtained as an amorphous orange solid (31 mg, 68%). The enantioenriched sample was prepared by subjecting 50 mg of 2-(3-(dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepin-4-yl)-4-(2-methoxyphenyl)-5,6-dimethylpyridin-2-yl)quinoline (20:1 *d.r*.) to the amination conditions and afforded the product (31 mg, 68%) as a 65:35 mixture of atropo-enantiomers.

$[\alpha]_D^{21.5}$ = +40 [1.0 *c* in $CHCl_3$].

M.P. (174 – 176) °C recrystallized from DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.50 – 7.41 (m, 2H), 7.17 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.58 (s, 2H), 3.77 (s, 3H), 2.57 (s, 3H), 1.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1, 157.0, 146.4, 144.6, 141.2, 135.7, 133.6, 132.7,

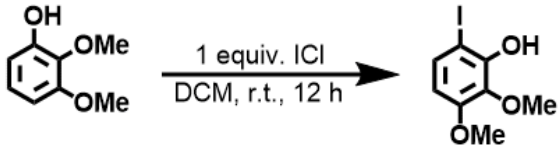
132.0, 131.0, 129.7, 129.1, 128.7, 127.5, 126.8, 125.8, 124.9, 121.5, 120.7, 111.6, 31.0, 23.0, 16.7.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{23}H_{22}N_3O$ 356.1757, found 356.1750.

AR-FTIR (neat, cm^{-1}): 3472, 3262, 2928, 2599, 1434, 1095.

The *ee* was determined by HPLC using a Chiralpak IA column [*n*-hexane/^{i}PrOH (60:40)]; τ_{major} = 6.45 min, τ_{minor} = 7.13 min.

Synthesis of 6-iodo-2,3-dimethoxyphenol (185)



To a stirred solution of 2,3-dimethoxyphenol (5 mL, 38.4 mmol, 1 equiv.) in DCM (100 mL) at room temperature was added dropwise a commercial solution of iodine monochloride (1 M ICl in DCM, 38.4 mL, 38.4 mmol, 1 equiv.). The mixture was stirred for 12 h at room temperature in the dark. The reaction mixture was quenched with $Na_2S_2O_3$ (*aq*.) (100 mL) and washed with water (40 mL). The aqueous layer was extracted with DCM (2 x 50 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography on silica gel with a mixture of DCM:petrol 1:1 as eluent to provide the product as a yellow solid (10.22 g, 95%).

M.P. 50–52 °C recrystallized from DCM.

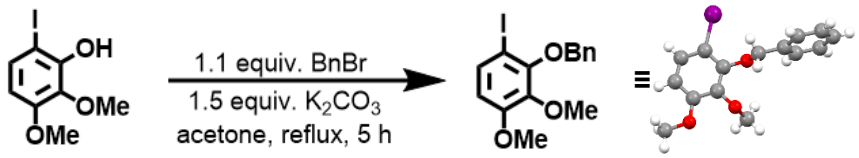
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 9.0 Hz, 1H), 6.35 (s, 1H), 6.30 (d, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.9, 149.3, 135.5, 132.7, 106.5, 71.8, 61.1, 56.1.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_8H_{10}IO_3$ 280.9675, found 280.9679.

AR–FTIR (neat, cm^{-1}): 3401, 2937, 2833, 1583, 1292, 1201.

Synthesis of 2-benzyloxy-1-iodo-2,3-dimethoxybenzene (186)



To a stirred solution of 6-iodo-2,3-dimethoxybenzene (10.2 g, 36.5 mmol, 1 equiv.) in acetone (170 mL) was added benzyl bromide (BnBr, 4.8 mL, 40.1 mmol, 1.1 equiv.) and potassium carbonate (K_2CO_3, 7.6 g, 54.8 mmol, 1.5 equiv.). Then, the mixture was stirred for 5 h at reflux. After cooling down to room temperature, the reaction mixture was filtered, and volatiles were evaporated *in vacuo*. The residue was redissolved in DCM (50 mL) and washed with water (50 mL) and brine (50 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. Purification by column chromatography on silica gel with a mixture of petrol:EtOAc 95:5 as eluent afforded the product as a white solid (10.82 g, 80%).

M.P. 71–73 °C recrystallized from DCM.

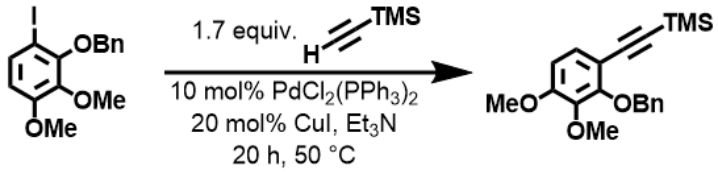
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.56 (m, 2H), 7.47 – 7.31 (m, 4H), 6.53 (d, *J* = 9.0 Hz, 1H), 5.06 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.5, 152.3, 143.0, 137.0, 132.8, 128.7, 128.4, 128.2, 110.0, 81.9, 75.2, 61.2, 56.2.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{16}IO_3$ 371.0144, found 371.0159.

AR–FTIR (neat, cm^{-1}): 2933, 1571, 1475, 1418, 1289, 1217.

Synthesis of (2-benzyloxy-2,3-dimethoxyphenylethynyl)trimethylsilane (187)



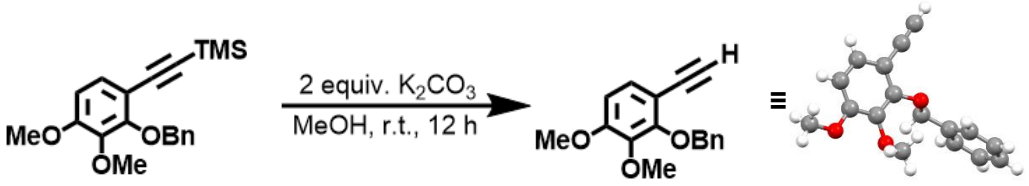
To a stirred suspension of 2-(benzyloxy)-1-iodo-2,3-dimethoxybenzene (10.3 g, 27.9 mmol, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 1.96 g, 2.79 mmol,

0.1 equiv.), copper(I) iodide (CuI, 1.1 g, 5.6 mmol, 0.2 equiv.) in ***freshly distilled*** trimethylamine (Et_3N, 0.4 M) under a nitrogen atmosphere at 50 °C, trimethylsilylacetylene (4.8 mL, 33.5 mmol, 1.2 equiv.) was added dropwise. After 10 h, an extra 0.5 equiv. of trimethylsilylacetylene was added and the reaction mixture was stirred further for 10 h. Then, the mixture was cooled down to room temperature and filtered thorugh a Celite™ pad and washed with DCM (50 mL). The filtrate was washed with saturated NH_4Cl (*aq*.) (50 mL) and extracted with DCM (3 x 40 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The resulting crude was triturated with petrol (100 mL) and filtered out. The filtrate was evaporated to dryness *in vacuo* and was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 95:5 as eluent to afford the product as a yellow oil (9.28 g, 98%).

Note: Triethylamine was stirred at room temperature with KOH pellets under a nitrogen atmosphere for 2 h, followed by distillation over 4 Å MS under a nitrogen atmosphere before use.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.55 (m, 2H), 7.40 – 7.31 (m, 3H), 7.18 (d, *J* = 9.0 Hz, 1H), 6.62 (d, *J* = 9.0 Hz, 1H), 5.17 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 0.24 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 154.1, 137.5, 128.6, 128.3, 127.9, 110.9, 107.4, 101.3, 97.0, 75.4, 61.1, 56.1, 0.1.
HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{20}H_{25}O_3Si$ 341.1573, found 341.1581.
AR–FTIR (neat, cm^{-1}): 2959, 2151, 1592, 1492, 1427, 1295.

Synthesis of 2-Benzyloxy-1-ethynyl-2,3-dimethoxybenzene (188)



To a stirred solution of (2-benzyloxy-2,3-dimethoxyphenylethynyl)trimethylsilane (9.20 g, 27.1 mmol, 1 equiv.) in MeOH (100 mL), potassium carbonate (K_2CO_3, 7.49 g, 54.2 mmol, 2 equiv.) was added. The mixture was stirred for 12 h at room temperature. Then, volatiles

were evaporated *in vacuo*, and the resulting crude was washed with water (20 mL), brine (20 mL), and extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a brown solid (5.22 g, 72%).

M.P. 69–71 °C recrystallized from DCM.

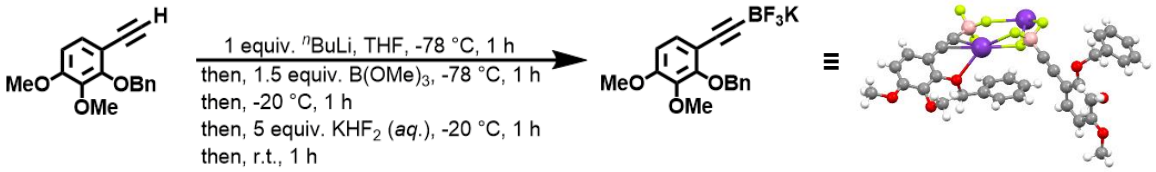
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.55 (m, 2H), 7.42 – 7.33 (m, 3H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 5.17 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.21 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8, 154.3, 142.5, 137.4, 128.7, 128.5, 128.3, 128.0, 107.6, 80.0, 76.7, 71.2, 71.1, 61.1, 56.1.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{17}H_{17}O_3$ 269.1178, found 269.1174.

AR–FTIR (neat, cm^{-1}): 3283, 2939, 2104, 1037, 1594, 1491, 1453, 1294, 1098.

Synthesis of Potassium ((2-(benzyloxy)-3,4-dimethoxyphenyl)ethynyl)trifluoroborate (189)



To a stirred solution of 2-benzyloxy-1-ethynyl-2,3-dimethoxybenzene (5.00 g, 18.7 mmol) in dry THF (0.15 M) under a nitrogen atmosphere at –78 °C, a solution of ^{n}BuLi (2.5 M in hexanes, 7.5 mL, 18.7 mmol, 1 equiv.) was added dropwise. After 1 h, trimethyl borate ($B(OMe)_3$, 3.1 mL, 28.1 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. Then, the reaction mixture was warmed up to –20 °C and stirred for 1 h. A solution of potassium hydrogen fluoride (KHF_2, 7.3 g, 93.5 mmol, 5 equiv.) in deionized water (3.5 M) was added and the resulting mixture was stirred for 1 h at –20 °C. Then, the reaction was warmed up to room temperature and stirred for 1 h. Volatiles were evaporated *in vacuo* and the residual solid was suspended in acetone (75 mL) and heated at reflux for 1 h. Then, the suspension was filtered while still warm and volatiles were evaporated *in vacuo*. The residual solid was washed with cold Et_2O (50 – 100 mL) and filtered to afford the product as a white solid (5.28 g, 85%).

M.P. 210–212 °C (decomposition) recrystallized from acetone.

^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 7.63 – 7.61 (m, 2H), 7.38 – 7.32 (m, 3H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 5.07 (s, 2H), 3.78 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 153.4, 153.1, 142.4, 138.0, 129.1, 128.6, 128.3, 127.9, 113.3, 108.4, 74.8, 65.4, 61.0, 56.3.

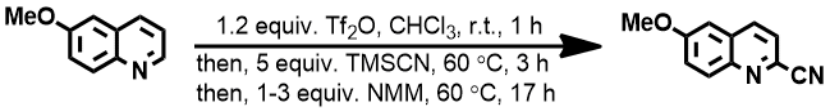
^{11}B NMR (128 MHz, *d*^{6}-DMSO): δ –1.5 (s, br).

^{19}F NMR (377 MHz, *d*6-DMSO): δ –131.7 (s).

HRMS: (ESI) *m/*z $[M–K]^-$ calculated for $C_{17}H_{15}BF_3O_3$ 335.1072, found 335.1060.

AR–FTIR (neat, cm^{-1}): 2942, 2183, 1594, 1490, 1295, 1051.

Synthesis of 2-Cyano-6-methoxyquinoline (193)[169]

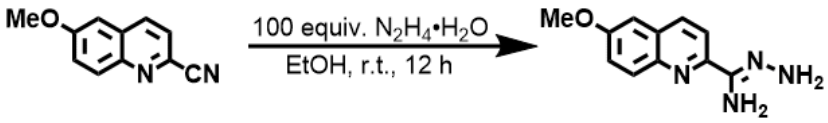


To a stirred solution of 6-methoxyquinoline (10.00 g, 62.8 mmol) in dry $CHCl_3$ (630 mL) under a nitrogen atmosphere was added trifluoromethanesulfonic anhydride (Tf_2O, 12.7 mL, 75.4 mmol, 1.2 equiv.) and the mixture was stirred at room temperature for 1 h. Then, trimethylsilyl cyanide (TMSCN, 39.3 mL, 314 mmol, 5 equiv.) was added and the mixture was heated up to 60 °C and left to stir for 3 h. Finally, *N*-methyl morpholine (NMM, 8.9 mL, 81.6 mmol, 1.3 equiv.) was added and the mixture was stirred at 60 °C for 17 h. The mixture was ***slowly*** quenched with saturated $NaHCO_3$ (*aq*.) (***warning:*** *gas liberation!*) and allowed to cool down to room temperature. The reaction mixture was extracted with DCM (6 x 40 mL) and washed with brine (6 x 40 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The residual solid was purified by column chromatography on silica gel with a mixture of DCM:Et_2O 95:5 as eluent to afford the product as an amorphous yellow solid (6.99 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 139.8, 130.9, 126.8, 126.0, 125.6, 119.9, 119.1, 113.1, 99.9, 51.1.

Synthesis of 6-methoxyquinoline-2-carbohydrazonamide (195)



6-Methoxyquinoline-2-carbonitrile (1.00 g, 5.43 mmol, 1 equiv.) and hydrazine monohydrate (N_2H_4•H_2O, N_2H_4 64–65%, 26.4 mL, 543 mmol, 100 equiv.) in EtOH (20 mL) were stirred for 12 h at room temperature. The product was filtered and washed with deionized water (150 mL) to afford it as an amorphous yellow solid (1.12 g, 95%).

Note: Hydrazine monohydrate (N_2H_4•H_2O) is a highly toxic, carcinogenic, explosive and volatile liquid. It must be handled with care and always inside a well-ventilated fume hood.

M.P. 219 – 221 °C (decomposition) not recrystallized.

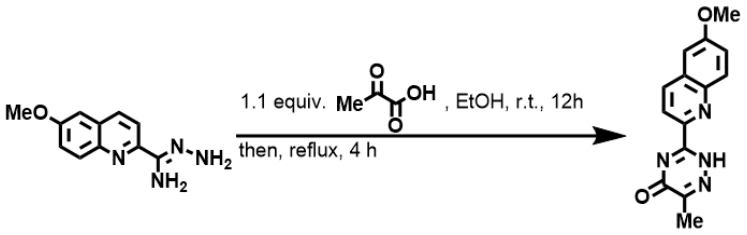
^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 8.14 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.39 – 7.34 (m, 2H), 5.83 (s, 2H), 5.42 (s, 2H), 3.89 (s, 3H).

^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 157.2, 149.5, 143.2, 142.0, 134.6, 130.0, 128.6, 121.6, 117.8, 106.0, 55.5.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{11}H_{13}N_4O$ 217.1084, found 217.1087.

AR–FTIR (neat, cm^{-1}): 3220, 1635, 1501, 1390, 1230, 1164, 1023.

Synthesis of 3-(6-methoxyquinolin-2-yl)-6-methyl-1,2,4-triazin-5(2*H*)-one (196)



To a stirred suspension of 6-methoxyquinoline-2-carbohydrazonamide (2.00 g, 9.5 mmol, 1 equiv.) in EtOH (100 mL) was added pyruvic acid (0.72 mL, 10.2 mmol, 1.1 equiv.) and the mixture was stirred at room temperature for 12 h. Then, the mixture was heated to 98 °C and

stirred further for 4 h. After cooling down to room temperature, the resulting precipitate was filtered and washed with Et_2O (50 mL) to afford the product as an amorphous white solid (2.36 g, 95%).

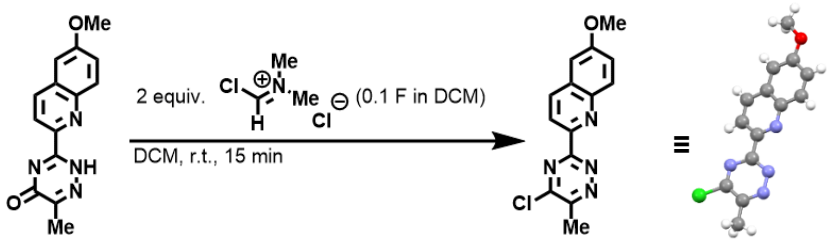
^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 14.03 (s, br, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.50 (s, 1H), 3.94 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 159.4, 143.1, 137.1, 131.3, 131.1, 124.7, 119.7, 106.3, 56.3, 17.8. (*4 signals missing; weak spectrum due to low solubility*).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{14}H_{13}N_4O_2$ 269.1033, found 269.1039.

AR–FTIR (neat, cm^{-1}): 3293, 1732, 1535, 1477, 1383, 1232, 1024.

Synthesis of 2-(5-chloro-6-methyl-1,2,4-triazin-3-yl)-6-methoxyquinoline (198)



To a suspension of 3-(6-methoxyquinolin-2-yl)-6-methyl-1,2,4-triazin-5(2*H*)-one (2.00 g, 7.5 mmol, 1 equiv.) in dry DCM (200 mL) was slowly added a solution of Vilsmeier reagent ((chloromethylene)dimethyliminium chloride, 150 mL, 0.1 F in DCM, 2 equiv.) via a dropping funnel. After the addition, the mixture was stirred at room temperature for 15 min. Then, the reaction was quenched with saturated $NaHCO_3$ (*aq*.) (40 mL) and the mixture was washed with 1 M NaOH (*aq*.) (120 mL). The mixture was extracted with DCM (3 x 50 mL) and the organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography on silica gel with a mixture of DCM:EtOAc 7:3 as eluent to afford the product as a yellow solid (1.58 g, 74%).

Initial suspension of triazinone in DCM.

While adding the Vilsmeier regaent solution.

After addition of the Vilsmeier reagent solution (t = 0 min).

After stirring for 15 min.

Note: The (chloromethylene)dimethyliminium chloride solution was prepared by adding 2.3 mL of dry DMF dropwise to a solution of 2.5 mL of oxalyl chloride $(COCl)_2$ in 300 mL of dry DCM under a nitrogen atmosphere. The mixture was stirred overnight and left to stand at room temperature under a nitrogen atmosphere until use.

M.P. 152–154 °C (decomposition) recrystallized from DCM.

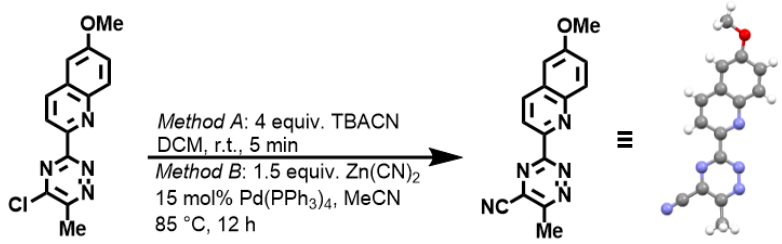
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 9.0 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 7.42 (dd, J = 9.0, 3.0 Hz, 1H), 7.12 (d, J = 3.0 Hz, 1H), 3.96 (s, 3H), 2.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.9, 159.2, 158.5, 157.3, 148.9, 144.5, 135.9, 132.3, 130.3, 123.2, 121.1, 104.8, 55.7, 20.0.

HRMS: (ESI) m/z $[M+H]^+$ calculated for $C_{14}H_{12}ClN_4O$ 287.0694, found 287.0699.

AR–FTIR (neat, cm^{-1}): 3005, 1619, 1478, 1399, 1227, 1111, 1028.

Synthesis of 3-(6-methoxyquinolin-2-yl)-6-methyl-1,2,4-triazine-5-carbonitrile (199)



Method A: 2-(5-Chloro-6-methyl-1,2,4-triazin-3-yl)-6-methoxyquinoline (1.00 g, 3.50 mmol, 1 equiv.) was added to a flame-dried three necked 250 mL flask equipped via a dropping funnel under a nitrogen atmposphere. Then, the dropping funnel was filled with 100 mL of dry DCM. Tetrabutylammonium cyanide (TBACN, 3.85 g, 14 mmol, 4 equiv.) was added and the tap of the funnel was quickly opened. The mixture was stirred for 5 min at room temperature and then ***immediately*** washed with brine (80 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purfied by column chromatography on silica gel with a mixture of DCM:EtOAc 9:1 as eluent to afford the product as an orange solid (523 mg, 54%).

Method B: A mixture of 2-(5-chloro-6-methyl-1,2,4-triazin-3-yl)-6-methoxyquinoline (500 mg, 1.75 mmol, 1 equiv.), zinc cyanide ($Zn(CN)_2$, 308 mg, 2.62 mmol, 1.5 equiv.), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 303 mg, 0.26 mmol, 15 mol%) in dry MeCN (24 mL) was heated to 85 °C and stirred for 12 h. Then, the mixture was cooled down to room temperature and filtered through a Celite™ pad eluting with DCM (200 mL). Volatiles were evaporated *in vacuo* and the resulting crude was purfied by column chromatography on silica gel with a mixture of DCM:EtOAc 9:1 as eluent to afford the product as a yellow solid (266 mg, 55%).

M.P. 167–169 °C (decomposition) recrystallized from DCM.

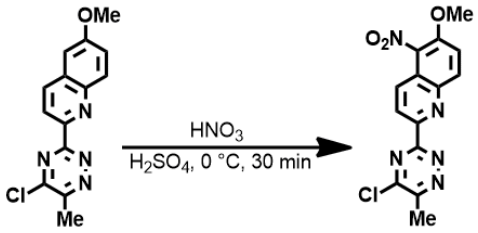
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.5 Hz, 1H), 8.27 (d, *J* = 3.0 Hz, 1H), 8.25 (d, *J* = 3.0 Hz, 1H), 7.45 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H), 3.97 (s, 3H), 3.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7, 159.5, 157.9, 148.3, 144.7, 136.2, 135.7, 132.3, 130.5, 123.6, 121.0, 113.6, 104.8, 55.7, 19.5.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{12}N_5O$ 278.1036, found 278.1041.

AR–FTIR (neat, cm^{-1}): 2999, 2008, 1615, 1223, 1163, 1092, 1022.

Synthesis of 2-(5-Chloro-6-methyl-1,2,4-triazin-3-yl)-6-methoxy-5-nitroquinoline (200)



To a stirred suspension of 2-(5-chloro-6-methyl-1,2,4-triazin-3-yl)-6-methoxyquinoline (500 mg, 1.75 mmol, 1 equiv.) in sulfuric acid (H_2SO_4, 5 mL) at 0 °C was added nitric acid (HNO_3, 0.9 mL). The mixture was ***vigorously*** stirred for 30 min at 0 °C. Then, the mixture was poured into crushed ice and ***carefully*** neutralised with saturated $NaHCO_3$ (*aq.*). The mixture was washed with water (20 mL) and brine (20 mL) and extracted with DCM (3 x 25 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as an orange solid (388 mg, 67%).

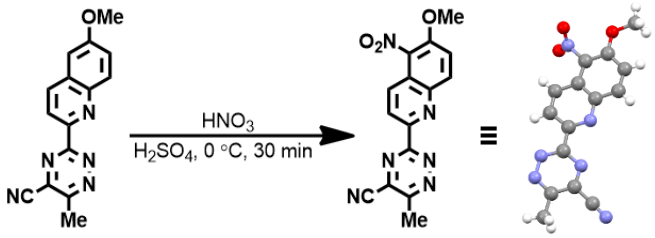
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 9.0 Hz, 1H), 8.56 (d, *J* = 9.5 Hz, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 9.5 Hz, 1H), 4.13 (s, 3H), 2.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 150.7, 148.7, 142.3, 135.5, 130.7, 123.2, 117.0, 57.3, 20.1. (*4C's missing, weak spectrum due to low solubility*).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{14}H_{10}ClN_5O_3$ 332.0545, found 332.0558

AR–FTIR (neat, cm^{-1}): 2923, 1689, 1627, 1529, 1350, 1271.

Synthesis of 3-(6-Methoxy-5-nitroquinolin-2-yl)-6-methyl-1,2,4-triazine-5-carbonitrile



To a stirred suspension of 3-(6-methoxyquinolin-2-yl)-6-methyl-1,2,4-triazine-5-carbonitrile (500 mg, 2.19 mmol) in sulfuric acid (H_2SO_4, 5 mL) at 0 °C was added nitric acid (HNO_3, 0.8 mL). The mixture was ***vigorously*** stirred for 30 min at 0 °C. Then, the mixture was poured into crushed ice and ***carefully*** neutralised with saturated $NaHCO_3$ (*aq.*). DCM (30 mL) was added and the mixture was washed with water (20 mL) and brine (20 mL) and extracted with DCM (2 x 25 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a yellow solid (570 mg, 81%).

Note: While neutralising the mixture, ***do not*** use strong bases (such as NaOH). At high pH values (>7) the product undergoes unspecified decomposition and cannot be recovered.

M.P. (170–172) °C (decomposition) recrystallized from DCM.

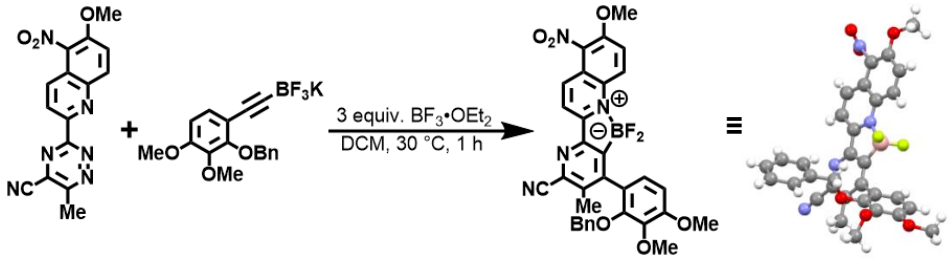
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 9.0 Hz, 1H), 8.55 (d, *J* = 9.0 Hz, 1H), 8.33 (d, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 4,14 (s, 3H), 3.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9, 158.6, 150.8, 150.1, 142.4, 135.8, 135.5, 131.0, 123.1, 122.3, 117.3, 113.4, 57.3, 19.6. (*1C missing*).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{11}N_6O_3$ 323.0887, found 323.0983.

AR-FTIR (neat, cm^{-1}): 2996, 2159, 1627, 1524, 1270, 1117.

Synthesis of 10-(2-(benzyloxy)-3,4-dimethoxyphenyl)-8-cyano-11,11-difluoro-3-methoxy-9-methyl-4-nitro-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (181)



To a stirred suspension of 3-(6-methoxy-5-nitroquinolin-2-yl)-6-methyl-1,2,4-triazine-5-carbonitrile (1.10 g, 3.42 mmol, 1 equiv.) and potassium ((2-(benzyloxy)-3,4-dimethoxyphenyl)ethynyl)trifluoroborate salt (1.14 g, 3.42 mmol, 1 equiv.) in dry DCM (34.2 mL, 0.1 mol/L) at ***30 °C*** under a nitrogen atmosphere was added ***freshly distilled*** boron trifluoride diethyl etherate (BF_3•OEt_2, 1.3 mL, 10.3 mmol, 3 equiv.) dropwise and the mixture was stirred at ***30 °C*** for 1 h. Then, saturated $NaHCO_3$ (*aq*.) (15 mL) was added, and the reaction mixture was cooled down to room temperature. The reaction mixture was washed with deionized water (20 mL) and extracted with DCM (3 x 20 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purfied by column chromatography on silica gel with a mixture of DCM:Et_2O 99:1 as eluent to afford the product as a pale yellow solid (1.35 g, 65%).

M.P. 258–260 °C recrystallized from DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 9.5 Hz, 1H), 8.63 – 8.52 (m, 2H), 7.78 (d, *J* = 9.5 Hz, 1H), 7.16 – 7.09 (m, 4H), 6.97 – 6.84 (m, 3H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.14 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.5, 154.0, 153.5, 151.6, 150.6, 150.1, 142.6, 141.9, 137.9, 137.3, 135.0, 134.4, 128.1, 127.7, 127.5, 127.4, 124.4, 124.3, 124.2, 123.0, 120.3, 118.5, 116.8, 107.9, 75.8, 61.3, 57.6, 56.0, 17.4.

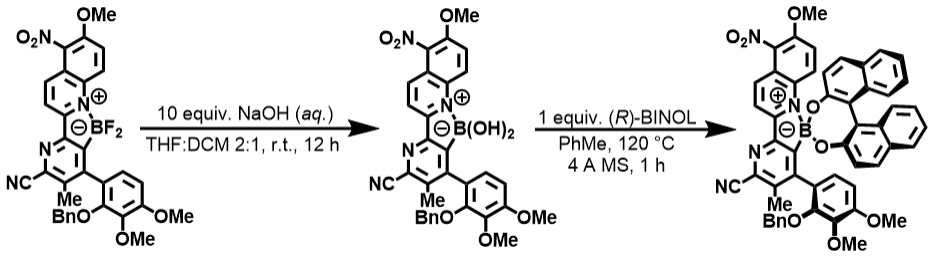
^{11}B NMR (128 MHz, $CDCl_3$): δ 8.79 (s, br).

^{19}F NMR (377 MHz, $CDCl_3$): δ –147.2 (d, *J* = 140 Hz), –154.7 (d, *J* = 140 Hz).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{32}H_{26}BF_2N_4O_6$ 611.1908, found 611.1930.

AR–FTIR (neat, cm^{-1}): 1598, 1529, 1344, 1273, 1126, 1093.

Synthesis of (4*S*,11b*R*)-10'-(2-(benzyloxy)-3,4-dimethoxyphenyl)-8'-cyano-3'-methoxy-9'-methyl-4'-nitrospiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (220)



To a stirred solution of 10-(2-(benzyloxy)-3,4-dimethoxyphenyl)-8-cyano-11,11-difluoro-3-methoxy-9-methyl-4-nitro-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-*a*]quinolin-12-ium-11-uide (1.10 g, 1.8 mmol, 1 equiv.) in a mixture of THF:DCM 2:1 (18 mL in total, 0.1 M) under a nitrogen atmosphere was added 1 M NaOH (*aq*.) (10.8 mL, 10.8 mmol, 10 equiv.). The mixture stirred for 12 h at room temperature under a nitrogen atmosphere. Then, the mixture was concentrated *in vacuo*, extracted with DCM (5 x 25 mL), washed with water (30 mL) and 1 M HCl (*aq*.) (25 mL in total, adding 5 mL per DCM extraction). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the corresponding aryl boronic acid as an amorphous beige solid which was used without further purification.

Note 1: Protodeboration and oxidation side reactions occur if the reaction is carried out the in the absence of an inert atmosphere.

Characterization of the picolinitrile boronic acid intermediate:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (d, *J* = 9.5 Hz, 1H), 8.57 (d, *J* = 9.0 Hz, 1 H), 8.47 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 9.5 Hz, 1H), 7.16 – 7.11 (m, 3H), 7.10 – 6.83 (m, 4H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.11 (s, 3H), 4.01 (s, 3H), 3.96 (s, 3H), 2.08 (s, 3H). (*Wet acetone was added to the sample to obtain a cleaner spectrum. Presumably, water prevents the formation of boroxines which yield complex NMR spectra*).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2, 153.4, 152.3, 150.2, 150.0, 149.7, 148.6, 142.8, 140.0, 136.6, 135.3, 135.0, 133.9, 129.0, 128.33, 128.27, 128.2, 124.5, 124.0, 122.9, 119.0, 118.7, 117.0, 108.0, 75.5, 61.1, 57.5, 56.1, 17.2.

^{11}B NMR (128 MHz, $CDCl_3$): δ 12.9 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{32}H_{28}BN_4O_8$ 607.1995, found 607.2014.

AR–FTIR (neat, cm^{-1}): 2159, 1976, 1597, 1530, 1496, 1354, 1274, 1093, 1003.

The aryl boronic acid (500 mg, 0.83 mmol, 1 equiv.) obtained in the previous step was added to a flame-dried two-neck flask (connected to a condenser) charged with activated 4 Å MS under a nitrogen atmosphere and dissolved in PhMe (15 mL), then (*R*)-(+)-1,1'-bi(2-naphtol) ((*R*)-BINOL, 237 mg, 0.83 mmol, 1 equiv.). The mixture was then heated to 120 °C and left to stir overnight (*ca*. 18 h). The reaction mixture was cooled down to room temperature, filtered and volatiles were evaporated to dryness *in vacuo*. ^{1}H NMR spectrum of the crude sample showed that the corresponding boronic ester was obtained as a 4.6:1 mixture of diastereomers. The reaction crude was purified by column chromatography on silica gel with a mixture of DCM:Et_2O 99.5:0.5 as eluent to obtain the product as a 8:1 mixture of diastereomers (amorphous orange solid, 396 mg, 56%).

Note 2: A second fraction of product was also isolated (240 mg, 34%, 2:1 *d.r.*) which could be equilibrated back to the thermodynamic ratio of 4.6:1 by subjecting it to the conditions just described, hence, allowing the recycle of material.

$[\alpha]_D^{21.5}$ = –310 [1.0 *c* in $CHCl_3$].

^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer): δ 8.73 (d, *J* = 9.0 Hz, 1H), 8.54 (dd, *J* = 9.0, 1.0 Hz, 1H), 8.04 –7.88 (m, 3H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.46 – 7.22 (m, 9H), 7.17 – 7.12 (m, 3H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.47 (d, *J* = 8.7 Hz, 1H), 5.94 (d, *J* = 10.0 Hz, 1H), 5.31 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 3.97 (s, 3H), 3.68 (s, 3H), 3.25 (s, 3H), 2.42 (s, 3H). (*The compound partially hydrolyses to its corresponding boronic acid in $CDCl_3$ due to traces of HCl).*

^{1}H NMR (400 MHz, C_6D_6, major diastereomer): δ 8.06 – 7.94 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.64 – 7.50 (m, 5H), 7.33 – 6.92 (m, 11H), 6.57 (d, *J* = 8.5

Hz, 1H), 5.53 – 5.38 (m, 2H), 5.16 (d, *J* = 11.0 Hz, 1H), 5.08 (d, *J* = 11.0 Hz, 1H), 3.82 (s, 3H), 2.91 (s, 3H), 2.71 (s, 3H), 2.33 (s, 3H).

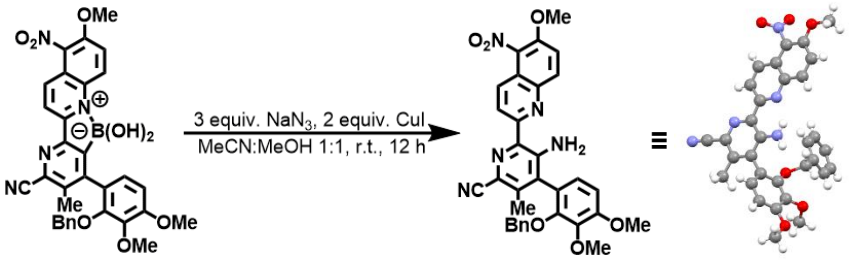
^{13}C NMR (101 MHz, C_6D_6, major diastereomer): δ 155.2, 155.0, 154.5, 154.2, 153.8, 150.9, 149.7, 148.7, 142.0, 141.8, 137.8, 136.1, 135.1, 134.7, 134.3, 134.0, 133.6, 131.1, 130.7, 130.0, 126.6, 129.3, 128.4, 127.7, 127.5, 127.22, 127.15, 127.1, 126.8, 125.8, 125.7, 125.2, 124.5, 123.8, 123.63, 123.56, 123.2, 123.0, 122.3, 120.3, 118.3, 118.0, 116.4, 106.4, 75.6, 60.4, 55.7, 54.5, 17.5.

^{11}B NMR (128 MHz, C_6D_6): δ 14.8 (s, br).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{52}H_{38}BN_4O_8$ 857.2777, found 857.2783.

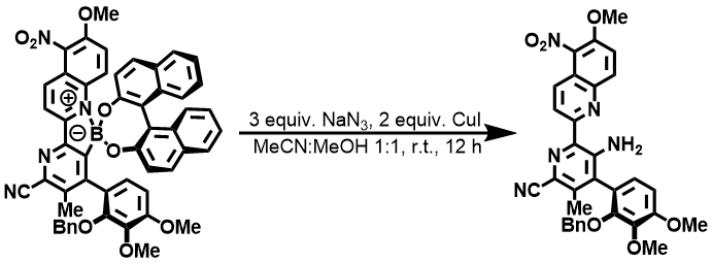
AR–FTIR (neat, cm^{-1}): 2939, 2387, 1597, 1534, 1279, 1251, 1094.

Synthesis of 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5-nitroquinolin-2-yl)-3-methylpicolinonitrile (180)



Racemic synthesis:

A suspension of 10-(2-(benzyloxy)-3,4-dimethoxyphenyl)-8-cyano-11,11-dihydroxy-3-methoxy-9-methyl-4-nitro-11*H*-pyrido[3',2':3,4][1,2]azaborolo[1,5-a]quinolin-12-ium-11-uide (500 mg, 0.83 mmol, 1 equiv.), sodium azide (NaN_3, 161 mg, 2.48 mmol, 3 equiv.), copper(I) iodide (CuI, 316 mg, 1.66 mmol, 2 equiv.) in a mixture of MeCN:MeOH 1:1 (40 mL in total) was stirred at room temperature for 12 h. Then, the reaction mixture was filtered through a Celite^{TM} pad eluting with EtOAc (25 mL). The filtrate was evaporated to dryness *in vacuo* and the resulting crude was purified by column chromatography on silica gel with a mixture of DCM:EtOAc 99:1 as eluent to afford the product as a yellow solid (352 mg, 74%).



Enantioenriched synthesis:

A suspension of (4*S*,11b*R*)-10'-(2-(benzyloxy)-3,4-dimethoxyphenyl)-8'-cyano-3'-methoxy-9'-methyl-4'-nitrospiro[dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaborepine-4,11'-pyrido[3',2':3,4][1,2]-azaborolo[1,5-*a*]quinolin]-12'-ium-26-uide (300 mg, 0.35 mmol, 1 equiv.), sodium azide (NaN_3, 68.3 mg, 1.05 mmol, 3 equiv.), copper(I) iodide (CuI, 133.3 mg, 0.7 mmol, 2 equiv.) in a mixture of MeCN:MeOH 1:1 (24 mL in total) was stirred at room temperature for 12 h. Then, the reaction mixture was filtered through Celite™ eluting with EtOAc (25 mL). The filtrate was evaporated to dryness *in vacuo* at ***35 °C*** and the resulting crude was purified by column chromatography on silica gel with a mixture of DCM:EtOAc 99:1 as eluent to afford the product as a yellow solid (101 mg, 50%, 92:2 *e.r.*, 84% *ee*).

$[\alpha]_D^{18.5}$ = +62.5 [1.0 *c* in $CHCl_3$].

M.P. 230–232 °C recrystallized from DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, *J* = 9.0 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 9.5 Hz, 1H), 7.51 (d, *J* = 9.5 Hz, 1 H), 7.13 – 7.04 (m, 3H), 6.97 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.06 (s, 3H), 3.97 (*overlapping singlets*, 6H), 2.10 (s, 3H).

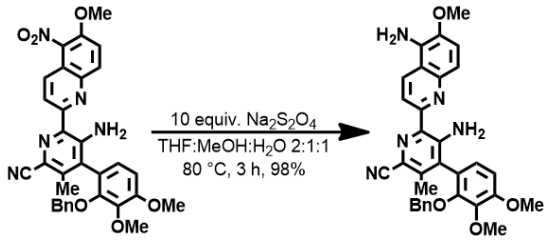
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.3, 154.7, 150.3, 149.3, 145.9, 143.5, 139.9, 138.9, 136.9, 135.0, 134.0, 132.9, 132.0, 129.3, 128.3 (x 2C), 128.1, 128.0 (x 2C), 124.7, 123.1, 120.7, 120.3, 120.2, 118.1, 116.1, 108.7, 75.4, 61.1, 57.2, 56.2, 17.2.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{32}H_{28}N_5O_6$ 578.2034, found 578.2060.

AR–FTIR (neat, cm^{-1}): 3450, 2527, 2218, 2014, 1583, 1524, 1450, 1357, 1266, 1076.

Chiral HPLC: The *ee* was determined by HPLC using a Chiral Art amylose-SA S-5 µm column [*n*-hexane/*i*PrOH (50:50), flow rate = 1.0 mL/min]; t_{major} = 10.1 min, t_{minor} = 11.7 min (91.8:8.2).

Synthesis of 5-Amino-6-(5-amino-6-methoxyquinolin-2-yl)-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-3-methylpicolinonitrile (221)



A suspension of 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5-nitroquinolin-2-yl)-3-methylpicolinonitrile (112 mg, 0.19 mmol, 1 equiv.) and sodium dithionite (techn. ≥85% $Na_2S_2O_4$, 397 mg, 1.9 mmol, 10 equiv.) in a mixture of THF:MeOH:H_2O 2:1:1 (4 mL in total) was heated to 80 °C and stirred for 3 h. Then, the reaction mixture was allowed to cool down to room temperature, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (*aq*.) (3 x 25 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as a yellow solid (105 mg, 98%).

Note 1: Key for a successful reaction is the freshness of $Na_2S_2O_4$. Older samples failed to give any product, as the reactant oxidizes over time. Fresh $Na_2S_2O_4$ is a crystalline white solid, while oxidized $Na_2S_2O_4$ is a rock-solid off-white solid.

Note 2: Extraction must be done with EtOAc to prevent emulsification.

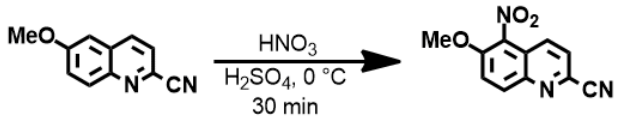
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 9.0 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.15 – 7.05 (m, 3H), 7.01 – 6.95 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 3.98 (s, 2H), 3.96 (s, 3H), 3.96 (s, 3H), 2.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 154.5, 150.4, 145.8, 143.5, 143.1, 141.5, 138.3, 136.9, 135.5, 131.4, 129.6, 129.4, 128.6, 128.5, 128.3 (x 2C), 128.0 (x 2C), 124.7, 120.7, 120.1, 118.7, 118.5, 117.2, 116.0, 108.6, 75.3, 61.1, 56.6, 56.2, 17.1.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{32}H_{29}N_5O_4$ 548.2292, found 548.2317.

AR–FTIR (neat, cm^{-1}): 1022, 1448, 1739, 2361, 2831, 2943, 3307.

Synthesis of 2-Cyano-6-methoxy-5-nitroquinoline[160]

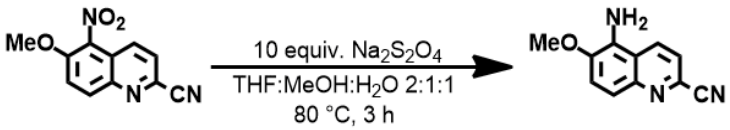


Nitric acid (0.4 mL) was added to a solution of 2-cyano-6-methoxyquinoline (500 mg, 2.7 mmol, 1 equiv.) in sulfuric acid (5 mL) at 0 °C. The mixture was stirred for 30 min and then it was poured into crushed ice. The mixture was carefully neutralized with saturated $NaHCO_3$(*aq*.) and extracted with DCM (3 x 25 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as an off-white solid (390 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 9.5 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 9.5 Hz, 1H), 4.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.6, 143.7, 131.1, 130.4, 129.3, 121.5, 120.5, 118.9, 117.9, 117.6, 56.5.

Synthesis of 5-Amino-6-methoxyquinoline-2-carbonitrile



A suspension of 2-cyano-6-methoxy-5-nitroquinoline (200 mg, 0.8 mmol, 1 equiv.) and sodium dithionite (techn. ≥85% $Na_2S_2O_4$, 1.63 g, 8 mmol, 10 equiv.) in a mixture of THF:MeOH:H_2O 2:1:1 (14 mL in total) was heated to 80 °C and stirred for 3 h. Then, the reaction mixture was allowed to cool down to room temperature, diluted with EtOAc (15

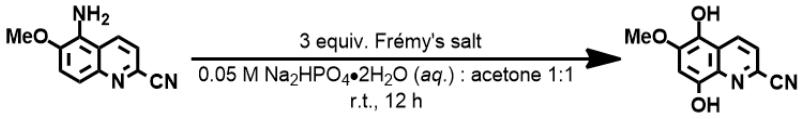
mL), and washed with saturated $NaHCO_3$ (*aq*.) (3 x 25 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as an orange solid (131 mg, 57%).

M.P. (116–118) °C (change of colour), (146–148) °C (decomposition) not recrystallized.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.57 (t, *J* = 9.0 Hz, 2H), 4.04 (s, 3H).

HRMS: (ESI) *m/z* $[M+Na]^+$ calculated for $C_{11}H_9NaN_3O$ 222.0638, found 222.0646.

Synthesis of 5,8-Dihydroxy-6-methoxyquinoline-2-carbonitrile



A suspension of 5-amino-6-methoxyquinoline-2-carbonitrile (100 mg, 0.05 mmol, 1 equiv.), potassium nitrosodisulfonate (Frémy's salt, 40 mg, 0.15 mmol, 3 equiv.), and Na_2HPO_4 (104 mg, 0.6 mmol, 3 equiv.) in a mixture of acetone:H_2O 1:1 (4 mL in total) was stirred at room temperature for 12 h. Then, the mixture was diluted with DCM (30 mL) and washed with brine (30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as an amorphous yellow solid (102 mg, 94%). The compound was used without further purification in the next step.

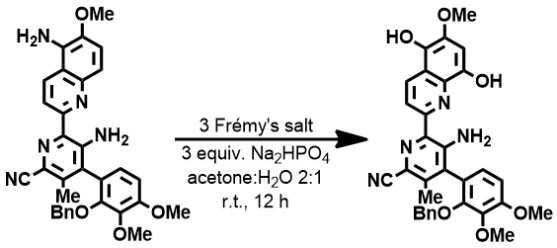
Note: Potassium nitrosodisulfonate, or Frémy's salt, is an orange solid that decomposes at room temperature, and it should always be stored in a freezer. Decomposition of this reactant yields a white solid.

M.P. (166–168) °C change of colour, (214–216) °C (decomposition) not recrystallized.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H), 8.96 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 6.21 (s, 1H), 4.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 181.4, 158.3, 157.4, 147.3, 136.8, 135.2, 131.9, 130.9, 116.3, 106.8, 57.0.

Synthesis of 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(5,8-dihydroxy-6-methoxyquinolin-2-yl)-3-methylpicolinonitrile (239)



A suspension of 5-amino-6-(5-amino-6-methoxyquinolin-2-yl)-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-3-methylpicolinonitrile (106 mg, 0.19 mmol, 1 equiv.), potassium nitrosodisulfonate (Frémy's salt, 157 mg, 0.6 mmol, 3 equiv.), and Na_2HPO_4 (104 mg, 0.6 mmol, 3 equiv.) in a mixture of acetone:H_2O 1:1 (4 mL in total) was stirred at room temperature for 12 h. Then, the mixture was diluted with DCM (30 mL) and washed with brine (30 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the product as an amorphous yellow solid (100 mg, 94%). The compound was used without further purification in the next step.

Note: Potassium nitrosodisulfonate, or Frémy's salt, is an orange solid that decomposes at room temperature, and it should always be stored in a freezer. Decomposition of this reactant yields a white solid.

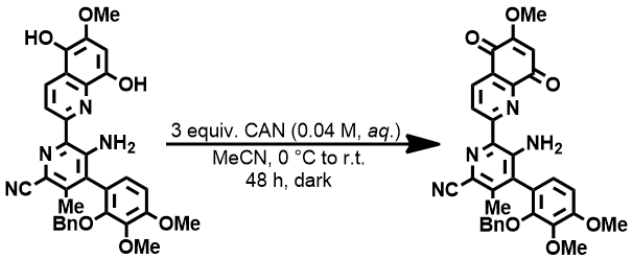
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, *J* = 8.5 Hz, 1H), 8.81 (d, *J* = 8.5 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.97 (m, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.05 (s, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 3.95 (s, 3H), 3.94 (*overlapping singlets*, 6H), 2.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 183.0, 160.4, 159.4, 157.4, 154.6, 150.4, 146.3, 144.0, 143.5, 139.1, 137.0, 133.6, 133.5, 132.2, 128.2 (x 2C), 128.0, 127.9 (x 2C), 125.2, 124.6, 120.4, 120.3, 118.2, 108.7, 105.9, 75.3, 61.1, 56.8, 56.2, 17.2. (*1C missing*).

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{32}H_{26}N_4O_6$ 563.1925, found 563.1952.

AR-FTIR (neat, cm^{-1}): 3245, 2924, 2218, 1737, 1657, 1228, 1092.

Synthesis of 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinonitrile (222)



5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(5,8-dihydroxy-6-methoxyquinolin-2-yl)-3-methylpicolinonitrile (90 mg, 0.16 mmol, 1 equiv.) was dissolved in MeCN (28 mL), cooled down to 0 °C, and protected from light with aluminium foil. Then, aqueous cerium ammonium nitrate (0.04 M CAN, 12 mL, 3 equiv.) was added dropwise, and the mixture was stirred at room temperature for 48 h in the dark. The mixture was then diluted with EtOAc (25 mL), washed with water (20 mL), and brine (20 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 1:1 as eluent to afford the product as a red solid (56 mg, 62%).

Note: The aqueous CAN solution was prepared 24 h in advance and left to stand at room temperature until use.

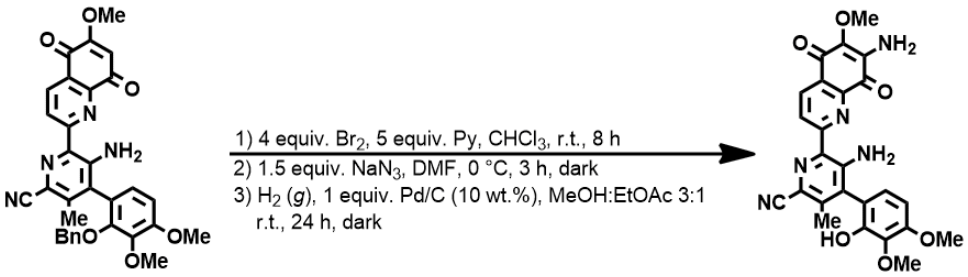
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 8.5 Hz, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 7.15 – 7.03 (m, 3H), 7.00 – 6.93 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.28 (s, 1H), 5.00 (d, *J* = 11.5 Hz, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 3.94 (*overlapping singlets*, 9H), 2.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.6, 179.3, 162.1, 160.6, 154.8, 150.4, 146.8, 145.5, 143.6, 139.6, 137.0, 134.7, 132.84, 132.82, 128.3 (x 2C), 128.2, 128.0 (x 2C), 125.8, 125.5, 124.6, 121.0, 120.1, 118.0, 110.1, 108.8, 75.4, 61.2, 56.8, 56.3, 17.3.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{32}H_{26}N_4O_6$ 563.1925, found 563.1941.

AR-FTIR (neat, cm^{-1}): 3421, 3230, 2939, 2220, 1683, 1582, 1450, 1241, 1093, 1045.

Synthesis of 5-amino-6-(7-amino-6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-4-(2-hydroxy-3,4-dimethoxyphenyl)-3-methylpicolinonitrile (225)



5-Amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinonitrile (25 mg, 0.044 mmol, 1 equiv.) was dissolved in a solution of bromine (Br_2) and pyridine (Py) in dry $CHCl_3$ (2 mL, 0.05 M Br_2, 0.06 M Py). The mixture was stirred for 8 h at room temperature in the ***dark***. Then, the mixture was diluted with $CHCl_3$ (10 mL), washed with water (10 mL), 1 M HCl (*aq.*) (10 mL) and saturated $NaHCO_3$ (*aq.*) (10 mL). The organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo* ***at room temperature in the dark***. The reaction crude was used directly in the following step without further purification.

The crude from the previous step was dissolved in dry DMF (4 mL), cooled down to 0 °C and protected from light. Sodium azide (NaN_3, 4 mg, 0.7 mmol, 1.5 equiv.) was added and the mixture was stirred for 3 h at 0 °C in the dark. Then, the mixture was diluted with EtOAc, and washed with deionized water. The organic layer was dried over Na_2SO_4, filtered, and ***evaporated to dryness in vacuo at room temperature in the dark***. The crude was directly in the following step without further purification.

The crude from the previous step was dissolved in a degassed mixture of MeOH:EtOAc 3:1. Then palladium on activated charcoal (10 mol% Pd/C, 47 mg, 0.044 mmol, 1 equiv.) was added and the system was connected to a balloon of hydrogen and protected from light. The mixture was stirred for 24 h at room temperature in the dark. The mixture was then filtered through Celite® and washed with EtOAc. The filtrate was then evaporated to dryness *in vacuo* and the resulting crude was purified by column chromatography on silica gel with a mixture of DCM:MeOH 98:2 as eluent to afford the product as a brown solid (12 mg, 55%).

Note: The bromide and azide intermediates are sensitive to light, heat, and silica gel. It is crucial to do the reaction set up and work up in the dark and at room temperature to prevent decomposition/degradation and achieve reproducible results. Nevertheless, these intermediates can be stored for the next day if necessary, by protecting them from light and keeping them in a freezer.

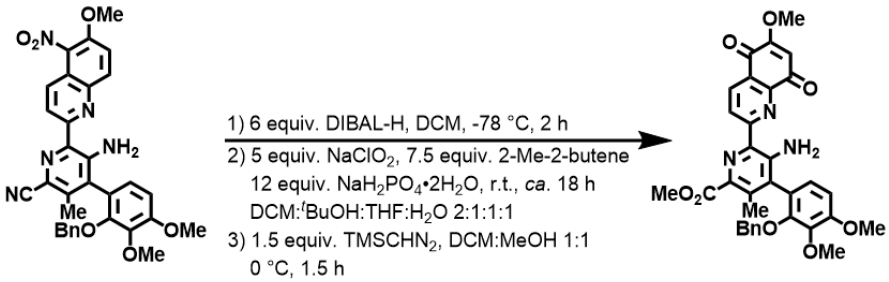
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 8.5 Hz, 1 H), 8.42 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 5.97 (s, 1H), 5.09 (s, 2H), 4.09 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 179.9, 177.4, 160.6, 153.1, 147.1, 146.3, 144.1, 139.4, 139.12, 137.5, 135.5, 134.2, 133.6, 131.6, 127.2, 126.5, 124.9, 121.1, 118.2, 112.7, 105.4, 61.4, 60.8, 56.14, 17.3.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{25}H_{22}N_5O_6$ 488.1565, found 488.1582.

AR-FTIR (neat, cm^{-1}): 3459, 2935, 2221, 1611, 1587, 1461, 1293, 1232, 1095.

Synthesis of methyl 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinate (235)[164]



Racemic synthesis:

To a stirred solution of 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5-nitroquinolin-2-yl)-3-methylpicolinonitrile (200 mg, 0.35 mmol, 1 equiv.) in DCM (50 mL) at –78 °C was added a commercial solution of diisobutylalumnium hydride (1 M DIBAL-H in DCM, 2.1 mL, 2.1 mmol, 8 equiv.). The mixture was stirred for 2 h at –78 °C and then 2

mL of EtOAc was added, followed by Rochelle's salt (*aq*.) (20 mL), and the mixture was stirred further for 1 h at room temperature. Then, the mixture was washed with deionized water (20 mL) and the aqueous phase was extracted with DCM (2 x 20 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The crude was used without further purification in the next step.

Characterization of the picolinaldehyde intermediate:

For characterization purposes, the aldehyde was purified by column chromatography on Florisil® with an elution gradient of DCM → DCM:EtOAc 98:2 to afford the product as a yellow solid (37.2 mg, 74%). The product was found to degrade on both silica gel and Florisil®.

M.P. 196 – 198 °C recrystallized from EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 9.09 (d, *J* = 9.0 Hz, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 9.5 Hz, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 7.10 – 7.01 (m, 3H), 6.97 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.93 (s, 2H), 4.08 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.3, 158.0, 154.4, 150.6, 149.2, 146.2, 143.5, 140.2, 139.8, 137.7, 137.1, 135.1, 132.9, 132.5, 129.3, 128.2, 127.8 (x 2C), 125.0, 123.1, 120.9, 120.2, 119.8, 116.1, 108.6, 75.3, 61.2, 57.2, 56.2, 16.1.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{32}H_{29}N_4O_7$ 581.2031, found 581.2059.

The aldehyde obtained in the previous step was dissolved in DCM (8 mL). Then, *tert*-butanol (^{t}BuOH, 4 mL) was added, followed by a solution of 2-methyl-2-butene (0.28 mL, 2.6 mmol, 7.5 equiv.) in THF (4 mL) and finally a solution of sodium chlorite ($NaClO_2$ technical ≥80%, 196 mg, 1.73 mmol, 5 equiv.) and sodium dihydrogen phosphate dihydrate (NaH_2PO_4•$2H_2O$, 649 mg, 4.16 mmol, 12 equiv.) in H_2O (4 mL). The mixture was stirred ***vigorously*** overnight (*ca*. 18 h) at room temperature. Then, the mixture was diluted with DCM (15 mL), and washed with water (15 mL). The aqueous phase was extracted two more times with DCM (15 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the corresponding carboxylic acid, which was used without further purification.

The carboxylic acid obtained in the previous reaction was dissolved in a mixture of DCM:MeOH 1:1 (16 mL in total) and cooled down to 0 °C. Trimethylsilyldiazomethane (2 M $TMSCHN_2$ in hexanes, 0.26 mL, 0.52 mmol, 1.5 equiv.) was added and the mixture was stirred for 1.5 h at 0 °C. Then, AcOH (2 mL) was added, and the mixture was stirred for 10 min at room temperature. The mixture was washed with brine (25 mL) and extracted with DCM (3 x 15 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the corresponding methyl ester, which was used without further purification.

Characterization of the methyl picolinate intermediate:

For characterization purposes, the methyl ester was purified by column chromatography on silica gel with an elution gradient of DCM → DCM:EtOAc 95:5 to afford the product as a yellow solid (24.8 mg, 47%). The product was found to degrade on silica gel.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, *J* = 9.0 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 8.08 (d, *J* = 9.5 Hz, 1H), 7.51 (d, *J* = 9.5 Hz, 1H), 7.11 – 7.05 (m, 3H), 7.03 – 6.97 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.93 (s, 2H), 4.06 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0, 158.2, 154.3, 150.5, 149.2, 145.3, 143.5, 140.3, 137.1, 137.1, 135.4, 135.1, 133.5, 132.9, 131.9, 129.2, 128.2, 128.0, 127.9, 125.0, 123.6, 121.6, 120.2, 116.0, 108.6, 75.2, 61.2, 57.2, 56.2, 52.2, 17.5.

These data were in accordance with the literature[208].

The crude methyl ester obtained in the previous step was dissolved in a mixture of THF:MeOH:H_2O 2:1:1 (16 mL in total) and sodium dithionite ($Na_2S_2O_4$ technical ≥85%, 1.42 g, 6.93 mmol, 20 equiv.) was added. The suspension was stirred for 3 h at 80 °C. The mixture was then cooled down to room temperature, diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ (*aq*.) (30 mL). The aqueous phase was extracted two more times with EtOAc (2 x 20 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the corresponding diamine, which was used without further purification.

The crude diamine obtained in the previous step was dissolved in a mixture of acetone:H_2O 1:1 (8 mL in total), then di-sodium hydrogen phosphate dihydrate (Na_2HPO_4•$2H_2O$, 185 mg, 1.04 mmol, 3 equiv.) and Frémy´s salt ($K_2NO(SO_3)_2$, 279 mg, 1.04 mmol, 3 equiv.) were added. The mixture was stirred at room temperature for 12 h. The mixture was then diluted with DCM (15 mL) and washed with water (15 mL) and brine (15 mL). The aqueous phase was extracted again with DCM (2 x 15 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo* to afford the corresponding dihydroxyquinoline, which was used without further purification.

The crude dihydroxyquinoline obtained in the previous step was dissolved in MeCN (80 mL), cooled down to 0 °C, and protected from light with aluminium foil. Then, aqueous cerium ammonium nitrate (0.04 M CAN, 26 mL, 1.04 mmol, 3 equiv.) was added dropwise, and the mixture was stirred at room temperature for 48 h in the dark. The mixture was then diluted with EtOAc (20 mL), washed with water (25 mL), and brine (25 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 1:1 as eluent to afford the product as a red solid (97 mg, 47% over 6 steps).

Note 5: The aqueous CAN solution was prepared 24 h in advance, and left to stand at room temperature until use.

Enantioenriched synthesis:

Enantioenriched 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5-nitroquinolin-2-yl)-3-methylpicolinonitrile (100 mg, 0.17 mmol, 1 equiv.) was used as the starting material and subjected to the six steps previously described. The final product was obtained as a red amorphous solid (28 mg, 47% over 6 steps, ~90:10 *e.r.*, 79% *ee*).

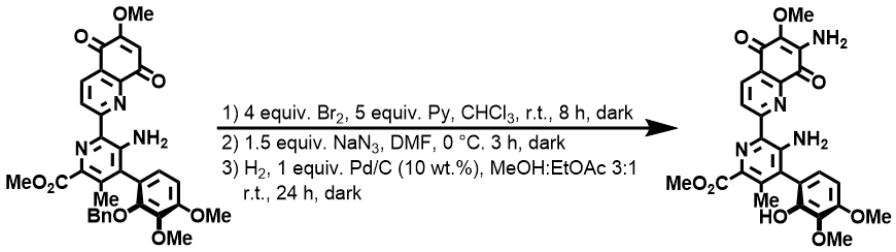
$[\alpha]_D^{20}$ = +58 [1.0 *c* in $CHCl_3$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, *J* = 8.5 Hz, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 7.09 (m, 3H), 7.00 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.27 (s, 1H), 4.94 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 11.0 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.93 (*overlapping singlets*, 6H), 2.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.8, 179.4, 166.9, 163.0, 160.5, 154.4, 150.5, 146.2, 145.5, 143.5, 137.9, 137.1, 135.6, 134.3, 133.9, 130.5, 128.2, 127.9, 127.8, 125.5, 125.4, 124.9, 121.4, 109.9, 108.6, 75.2, 61.1, 56.7, 56.2, 52.2, 17.6.

Chiral HPLC: The *ee* was determined by HPLC using a Chiral Art amylose-SA S-5 µm column [*n*-hexane/*i*PrOH (70:30), flow rate = 1.25 mL/min]; t_{major} = 12.2 min, t_{minor} = 40.7 min (89.7:10.2).

Synthesis of methyl 5-amino-6-(7-amino-6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-4-(2-hydroxy-3,4-dimethoxyphenyl)-3-methylpicolinate (238)

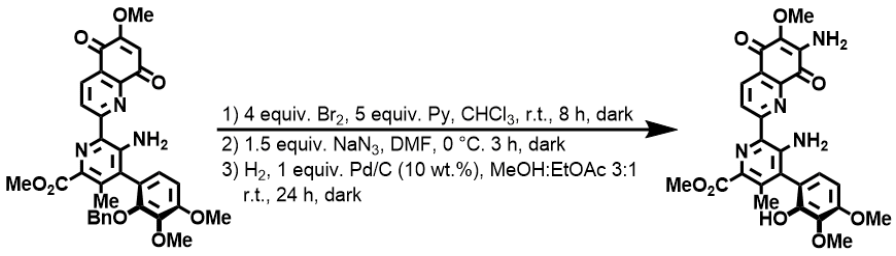


Methyl 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinate (50 mg, 0.084 mmol, 1 equiv.) was dissolved in a solution of bromine (Br_2) and pyridine (Py) in dry $CHCl_3$ (4 mL, 0.1 M Br_2, 0.12 M Py). The mixture was stirred for 8 h at room temperature in the ***dark***. Then, the mixture was diluted with $CHCl_3$ (10 mL), washed with water (10 mL), 1 M HCl (*aq*.) (10 mL) and saturated $NaHCO_3$ (*aq*.) (10 mL). The organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo* ***at room temperature in the dark***. The reaction crude was used directly in the following step without further purification.

The crude from the previous step was dissolved in dry DMF (4 mL), cooled down to 0 °C and protected from light. Sodium azide (NaN_3, 8.2 mg, 0.13 mmol, 1.5 equiv.) was added and the mixture was stirred for 3 h at 0 °C in the ***dark***. Then, the mixture was diluted with EtOAc (15 mL) and washed with deionized water (5 x 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo* ***at room temperature in the dark***. The reaction crude was used directly in the following step without further purification.

The crude from the previous step was dissolved in a degassed mixture of MeOH:EtOAc 3:1 (20 mL). Then palladium on activated charcoal (10 wt% Pd/C, 135 mg, 0.084 mmol, 1 equiv.) was added and the system was connected to a balloon of hydrogen and protected from light. The mixture was stirred for 24 h at room temperature in the ***dark***. The mixture was then filtered through Celite® and washed with EtOAc (20 mL). The filtrate was then evaporated to dryness *in vacuo* and the resulting crude was purified by column chromatography on silica gel with a mixture of DCM:MeOH 98:2 as eluent to afford the product as a brown solid (24 mg, 55%).

Note: The bromide and azide intermediates are sensitive to light, heat, and silica gel. It is crucial to do the reaction set up and work up in the dark and at room temperature to prevent decomposition/degradation and achieve reproducible results. Nevertheless, these intermediates can be stored for the next day if necessary, by protecting them from light and keeping them in a freezer.



Enantioenriched synthesis:

Enantioenriched methyl 5-amino-4-(2-(benzyloxy)-3,4-dimethoxyphenyl)-6-(6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-3-methylpicolinate (25 mg, 0.042 mol, 1 equiv.) was used as the starting material and subjected to the three steps just described. The final product was obtained as a brown solid (12 mg, 55% over 3 steps, ~89:11 *e.r.*, 79% *ee*).

$[\alpha]_D^{19}$ = +35 [5 x10^{-3} *c* in DCM]

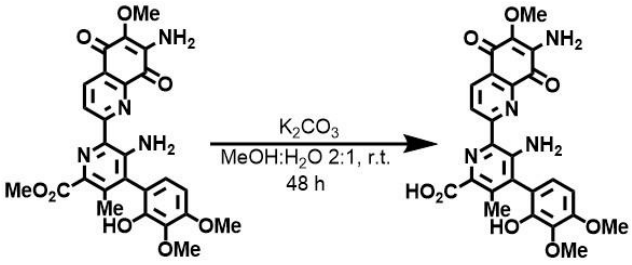
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (d, *J* = 8.5 Hz, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 5.87 (s, 1H), 5.07 (s, 2H), 4.08 (s, 3H), 3.98 (*overlapping singlets*, 6H), 3.95 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 180.1, 177.6, 167.2, 161.5, 152.8, 147.2, 145.8, 144.1, 139.1, 137.8, 137.4, 136.5, 135.6, 133.9, 132.8, 131.2, 126.8, 126.5, 125.2, 114.0, 105.2, 61.3, 60.7, 56.1, 52.3, 17.5.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{26}H_{25}N_4O_8$ 521.1667, found 521.1675.

Chiral HPLC: The *ee* was determined by HPLC using a Chiral Art amylose-SC S-5 μm column [*n*-hexane/^{i}PrOH (60:40), flow rate = 0.7 mL/min, 40 °C]; t_{major} = 27.8 min, *t*minor = 25 min (89.2:10.8).

Synthesis of Streptonigrin (138)[164]



Methyl 5-amino-6-(7-amino-6-methoxy-5,8-dioxo-5,8-dihydroquinolin-2-yl)-4-(2-hydroxy-3,4-dimethoxyphenyl)-3-methylpicolinate (35 mg, 0.067 mmol, 1 equiv) and potassium carbonate (K_2CO_3, 200 mg, 1.45 mmol, 22 equiv.) were dissolved in a mixture of MeOH:H_2O 2:1 (12 mL) and the mixture was stirred for 48 h at room temperature under an argon atmosphere. Then, MeOH was evaporated *in vacuo* at ***35 °C***. The residue was neutralized with 1 M HCl (*the aqueueos phase will turn yellow as it is acidified*) and extracted with DCM (3 x 15 mL). The organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The reaction crude was purified by column chromatography on pH (6.8) buffered silica gel with a mixture of DCM:MeOH 98:2 as eluent to afford the product as a dark-brown solid (14 mg, 65%).

Note 1: It is important to evaporate the methanol at a temperature ***no higher than 35 °C***.

Note 2: The silica gel used for the purification was stirred for 5 min with a commercial phosphate buffer solution (pH = 6.8) and filtered. Then, the buffered silica gel was kept in an oven until use.

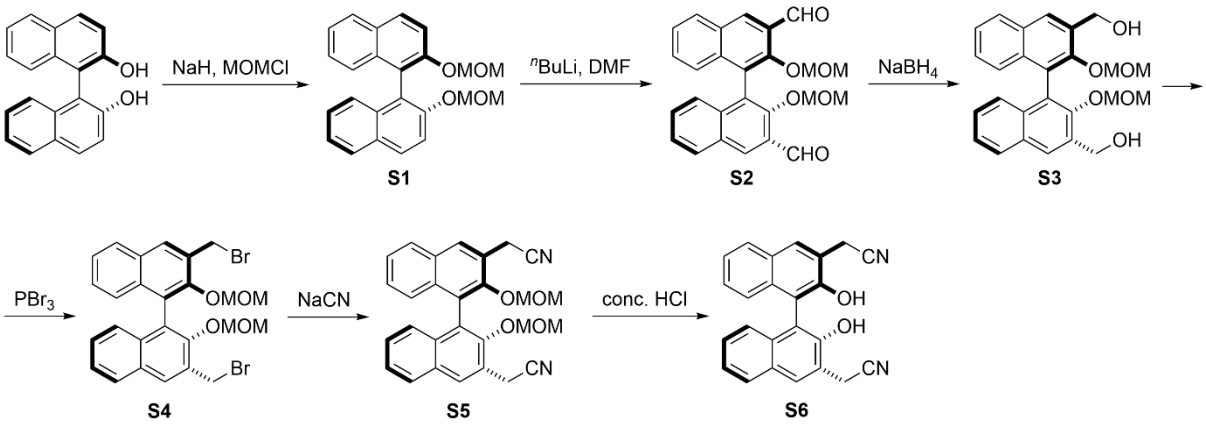
^{1}H NMR (400 MHz, *d*^{6}-DMSO): δ 12.28 (s, 1H), 9.01 (d, *J* = 8.4 Hz, 1H), 8.92 (s, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 2.18 (s, 3H).

^{13}C NMR (101 MHz, *d*^{6}-DMSO): δ 180.3, 175.9, 167.0, 159.9, 153.1, 148.1, 145.7, 144.1, 141.6, 136.9, 136.2, 135.7, 134.6, 134.0, 133.4, 129.5, 126.71 126.0, 124.6, 114.9, 104.4, 60.3, 59.7, 55.7, 17.0.

HRMS: (ESI) *m/z* $[M+H]^+$ calculated for $C_{25}H_{23}N_4O_8$ 507.1510, found 507.1523.

Synthesis of (*R*)-3,3'-Bis(cyanomethyl)-1,1'-binaphthyl-2,2'-diol

3,3'-Cyanomethyl Binol (**S6**) was synthesised according to the published procedures[1] without purification of the intermediate compounds.



Scheme S1. Synthesis of (*R*)-3,3'-bis(cyanomethyl)-1,1'-binaphthyl-2,2'-diol (S6).

Following a literature procedure[1], (*R*)-(+)-1,1'-bi(2-naphtol) ((*R*)-BINOL, 1 g, 3.5 mmol, 1 equiv.), sodium hydride (NaH 60% dispersion in mineral oil, 252 mg, 10 mmol, 3 equiv.) and chloromethyl methyl ether (MOMCl, 0.58 mL, 7.7 mmol, 2.2 equiv.) were used to afford the crude product **S1**, which was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 1:1 as eluent to afford the pure product as an amorphous white solid (1.085 g, 83%).

[1] Y. Loewer, C. Weiss, A. T. Biju, R. Fröhlich, F. Glorius, *J. Org. Chem.* **2008**, *76*, 2324–2327. (S3)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 9.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.26 – 7.15 (m, 4H), 5.09 (d, *J* = 7.0 Hz, 2H), 4.98 (d, *J* = 7.0 Hz, 2 H), 3.15 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6, 134.8, 130.2, 129.7, 128.7, 126.9, 126.0, 124.6, 121.8, 117.1, 95.2, 56.3.
These data were in accordance with the literature[1].

Following a literature procedure[1], **S1** (1 g, 2.7 mmol, 1 equiv.), a solution of ^{n}BuLi (2.5 M in hexanes, 3.3 mL, 8.3 mmol, 3.1 equiv.) and DMF (0.72 mL, 9.3 mmol, 3.5 equiv.) were used to afford the crude product **S2**, which was used in the next step without further purification.
Following a literature procedure[1], crude **S2** (2.7 mmol, 1 equiv.) and sodium borohydride ($NaBH_4$, 212 mg, 5.6 mmol, 2.1 equiv.) were used to afford the crude product **S3**, which was used in the next step without further purification.

Crude **S3** (2.7 mmol, 1 equiv.) was dissolved in $CHCl_3$ (40 mL) and the solution was cooled down to 0 ^{o}C. Phosphorus tribromide (PBr_3, 0.10 mL, 1.0 mmol, 0.4 equiv.) was added dropwise to the solution at 0 ^{o}C and the mixture was stirred overnight (*ca*. 18 h). The mixture was then poured into crushed ice and the product was extracted with DCM (3 x 30 mL). The organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the crude product **S4**, which was used in the next step without further purification.

Crude **S4** (2.7 mmol, 1 equiv.) was dissolved in 10 mL of dry DMF and then sodium cyanide (NaCN, 327 mg, 6.7 mmol, 2.5 equiv.) was added at room temperature under a nitrogen atmosphere. After stirring overnight (*ca*. 18 h) at room temperature, the solution was poured into crushed ice and left at room temperature for 1 h. The precipitate formed was filtered, washed with deionized water and dried *in vacuo* to afford crude **S5** as an amorphous beige solid.

Crude **S5** (2.7 mmol, 1 equiv.) was dissolved in 30 mL of THF and the solution was cooled down to 0 ^{o}C. Then, concentrated HCl (3 mL) was added dropwise to the solution at 0 ^{o}C. After stirring overnight (*ca*. 18 h) at room temperature, deionized water was added to the

solution and the product was extracted with DCM (3 x 30 mL). The organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to afford the crude product **S6**, which was purified by column chromatography on silica gel with a mixture of petrol:EtOAc 1:1 as eluent to afford the product as an amorphous beige solid (0.311 g, 32% over 5 steps).

$[\alpha]_D^{21}$ = +52 [0.25 *c* in MeOH].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.19 (s, 2H), 4.00 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3, 133.0, 130.7, 129.3, 128.6, 128.4, 125.2, 124.0, 119.4, 117.6, 111.1, 19.6.

HRMS: (ESI) $[M+H]^+$ *m/z* calculated for $C_{24}H_{16}N_2O_2$ 364.1285, found 365.1290.

AR–FTIR (neat, cm^{-1}): 3351, 2265, 1624, 1507, 1457, 1360, 1207, 1142, 1012, 755.

References

(1) Dimitrijevic, E.; Taylor, M. S. Organoboron Acids and Their Derivatives as Catalysts for Organic Synthesis. *ACS Catal.* **2013**, *3* (5), 945–962.

(2) Légaré, M. A.; Pranckevicius, C.; Braunschweig, H. Metallomimetic Chemistry of Boron. *Chem. Rev.* **2019**, *119* (14), 8231–8261.

(3) Fernández, E. *Synthesis and Application of Organoboron Compounds*; 2015; Vol. 49.

(4) Elschenbroich, C.; Salzer, A. *Organometallics. A Concise Introduction*, Germany.; VCH, 1992.

(5) Ishiyama, T.; Ishida, K.; Miyaura, N. Synthesis of Pinacol Arylboronates via Cross-Coupling Reaction of Bis(Pinacolato)Diboron with Chloroarenes Catalyzed by Palladium(0)-Tricyclohexylphosphine Complexes. *Tetrahedron* **2001**, *57* (49), 9813–9816..

(6) Gomez-Bengoa, E.; Helm, M. D.; Plant, A.; Harrity, J. P. A. The Participation of Alkynylboronates in Inverse Electron Demand [4 + 2] Cycloadditions: A Mechanistic Study. *J. Am. Chem. Soc.* **2007**, *129* (9), 2691–2699..

(7) Vivat, F.; Adams, H.; Harrity, J. P. A. Ambient Temperature Nitrogen-Directed Cycloaddition Reactions. *Org. Lett.* **2009**, *12* (1), 160–163.

(8) Matteson, D. S.; Waldbillig, J. O. Norborneneboronates. *J. Org. Chem.* **1963**, *28* (2), 366–369.

(9) Delaney, P. M.; Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. A [4+2] Cycloaddition Strategy to Pyridine Boronic Ester Derivatives. *Org. Lett.* **2008**, *10* (5), 781–783.

(10) Brown, H. C.; Brown, C. Simple , General Synthesis Of. *Tetrahedron* **1988**, *29* (22), 2–5.

(11) Lee, C. I.; Zhou, J.; Ozerov, O. V. Catalytic Dehydrogenative Borylation of Terminal Alkynes by a SiNN Pincer Complex of Iridium. *J. Am. Chem. Soc.* **2013**, *135* (9), 3560–3566..

(12) Hill, M. S.; Liptrot, D. J.; Weetman, C. Alkaline Earths as Main Group Reagents in Molecular Catalysis. *Chem. Soc. Rev.* **2016**, *45*, 972–988..

(13) Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis*; Wiley, 2005.

(14) Darses, S.; Genet, J. P. Potassium Organotrifluoroborates: New Perspectives in Organic Synthesis. *Chem. Rev.* **2008**, *108* (1), 288–325.

(15) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. Conversion of Arylboronic Acids into Potassium Aryltrifluoroborates: Convenient Precursors of Arylboron Difluoride Lewis Acids. *J. Org. Chem.* **1995**, *60* (10), 3020–3027.

(16) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. A 2-Pyrone Cycloaddition Route to Functionalised Aromatic Boronic Esters. *Tetrahedron* **2008**, *64* (5), 866–873.

(17) Harrity, J. P. A.; Jiang, J.; Meijer, A. J. H. M.; Nassoy, A. M. A.; Raubo, P. A Mechanistic Study of the Lewis Base-Directed Cycloaddition Of. *J. Am. Chem. Soc.* **2014**, *136*, 8642–8653.

(18) Christie, G.; Kenner, J. The Molecular Configurations of Polynuclear Aromatic Compounds. Part I. *J. Chem. Soc.* **1922**, No. 614, 614–620.

(19) Oki, K. *Recent Advances in Atropisomerism*; Allinger, N., Eliel, E., Wilen, S., Eds.; Wiley Interscience: New York, 1983.

(20) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem. Int. Ed.* **2005**, *44* (34), 5384–5427.

(21) Mislow, K.; Glass, M. A. W.; Hopfs, H. B.; Simon, E.; Wahl, G. H. The Stereochemistry of Doubly Bridged Biphenyls: Synthesis, Spectral Properties, and Optical Stability. *J. Am. Chem. Soc.* **1964**, *86* (9), 1710–1733.

(22) Kyba, E. P.; Gokel, G. W.; Jong, F. De; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. Host-Guest Complexation. 7. The Binaphthyl Structural Unit in Host Compounds. *J. Org. Chem.* **1977**, *42* (26), 4173–4184.

(23) Bringmann, G.; Busse, H.; Dauer, U.; Giissregen, S.; Stahl, M.; Chemie, O.; Wtirzburg, U.; Hubland, A. Structure and Enantiomerization of Helically Twisted Lactone--Bridged Biaryls : A T h e o r e t i c a l Study L. *Tetrahedron*, **1995**, *51* (11), 3149–3158.

(24) Bott, G.; Field, L. D.; Sternhell, S. Steric

Effects. A Study of a Rationally Designed System. *J. Am. Chem. Soc.* **1980**, *102* (17), 5618–5626.
(25) Colter, A. K.; Clemens, L. M. Solvent Effects in the Racemization of 1,1'-Binaphthyl. A Note on the Influence of Internal Pressure on Reaction Rates 1 . *J. Phys. Chem.* **2007**, *68* (3), 651–654.
(26) Meyers, A. I.; Himmelsbach, R. J. Enantioselective Synthesis of 2,2',6-Trisubstituted Biphenyls. *J. Am. Chem. Soc.* **1985**, *107* (3), 682–685.
(27) Leroux, F.; Maurin, M.; Nicod, N.; Scopelliti, R. The Remarkable Configurational Stability of Ortho,Ortho′-Tetrafluoro Substituted Biphenyls: 2,2′,4,4′,6,6′-Hexafluorobiphenyl-3, 3′-Dicarboxylic Acid as a Model. *Tetrahedron Lett.* **2004**, *45* (9), 1899–1902.
(28) Gladiali, S.; Dore, A.; Fabbri, D.; de Lucchi, O.; Valle, G. Synthesis, Crystal Structure, Dynamic Behavior and Reactivity of Dinaphtho[2,1-b:1′,2′-d]Phospholes and Related Atropisomeric Phosphacyclic Derivatives. *J. Org. Chem.* **1994**, *59* (21), 6363–6371.
(29) Adams, R.; Kornblum, N. Stereochemistry of Biphenyls. LI. Resolution of Diphenic Acids Having Many-Membered Bridges Across the 5,5′-Positions: A Novel Type of Restricted Rotation 1. *J. Am. Chem. Soc.* **1941**, *63* (1), 188–200.
(30) Mislow, K.; Hyden, S.; Schaefer, H. Stereochemistry of the 1,2,3,4-Dibenzcyclonona-1,3-Diene System.1 A Note on the Racemization Barrier in Bridged Biphenyls. *J. Am. Chem. Soc.* **1962**, *84* (8), 1449–1455.
(31) Irie, M.; Yoshida, K.; Hayashi, K. Laser Photolysis Study of the Photoracemization of 1,1′-Binaphthyl. *J. Phys. Chem.* **1977**, *81* (10), 969–972.
(32) Hattori, T.; Shimazumi, Y.; Goto, H.; Yamabe, O.; Morohashi, N.; Kawai, W.; Miyano, S. Synthesis, Resolution, and Absolute Stereochemistry of (-)-Blestriarene C. *J. Org. Chem.* **2003**, *68* (6), 2099–2108.
(33) Edwards, D. J.; Pritchard, R. G.; Wallace, T. W. Complementary Kinetic and Thermodynamic Resolution of a Chiral Biaryl Axis. *Tetrahedron Lett.* **2003**, *44* (25), 4665–4668.
(34) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115* (20), 11239–11300.
(35) Miyano, S.; Tobita, M. M.; Hashimoto, H. Asymmetric Synthesis of Axially Dissymmetric 1,1'-Binaphtyls via an Intramolecular Ullmann Coupling Reaction of (R)- and (S)-2,2'-Bis(1-Bromo-2naphthylcarbonyloxy)-1,1'-Binaphtyl. *Bull. Chem. Soc. Jpn.* **1981**, *54* (11), 3522–3526.
(36) Lipshutz, B. H.; Kayser, F.; Liu, Z. -P. Asymmetric Synthesis of Biaryls by Intramolecular Oxidative Couplings of Cyanocuprate Intermediates. *Angew. Chem. Int. Ed. English* **1994**, *33* (18), 1842–1844.
(37) Kyasnoor, R. V.; Sargent, M. V. A Formal Synthesis of Both Atropenantiomers of Desertorin C. *Chem. Inform.* **2010**, *30* (13), 2713–2714.
(38) Lipshutz, B. H.; Shin, Y.-J. Preparation of Symmetrically & Unsymmetrically Substituted Ligands. *Tetrahedron Lett.* **1998**, *39*, 7017–7020.
(39) Bringmann, G.; Keller, P.; Rolfing, K. A New Approach to Atroposelective Biaryl Synthesis, Utilizing Chiral Carbon-Carbon Bridges. *Synlett* **1994**, No. 6, 423–424.
(40) Meyers, A. I. Chiral Oxazolines. *J. Heterocycl. Chem.* **1998**, *35* (5), 991–1001.
(41) Meyers, A. I.; Meier, A.; Rawson, D. J. A Highly Stereoselective Synthesis of Axially Chiral Biaryls. Application to the Synthesis of a Potential Chiral Catalysts. *Tetrahedron Lett.* **1992**, *33* (7), 853–856.
(42) Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. Chiral Oxazoline Route to Enantiomerically Pure Biphenyls: Magnesio and Copper Mediated Asymmetric Hetero- and Homo-Coupling Reactions. *Tetrahedron* **2004**, *60* (20), 4459–4473.
(43) Nelson, T. D.; Meyers, A. I. The Asymmetric Ullmann Reaction. 2. The Synthesis of Enantiomerically Pure C2-Symmetric Binaphthyls. *J. Org. Chem.* **1994**, *59* (9), 2655–2658.
(44) Andrus, M. B.; Asgari, D.; Sclafani, J. A. Efficient Synthesis of 1,1'-Binaphthyl and 2,2'-Bi- o -Tolyl-2,2'-Bis(Oxazoline)s and Preliminary Use for the Catalytic Asymmetric Allylic Oxidation of Cyclohexene . *J. Org. Chem.* **2002**, *62* (26), 9365–9368.

(45) Kamikawa, K.; Watanabe, T.; Uemura, M. Asymmetric Synthesis of Axially Chiral Biaryls Utilizing Planar Chiral Arene Chromium Complexes. *Yuki Gosei Kagaku Kyokaishi/Journal Synth. Org. Chem.* **2001**, *59* (11), 1078–1085.

(46) Kamikawa, K.; Watanabe, T.; Daimon, A.; Ue Mura, M. Stereoselective Synthesis of Axially Chiral Natural Products, (-)-Steganone and O,O'-Dimethylkorupensamine A, Utilizing Planar Chiral (Arene)Chromium Complexes. *Tetrahedron* **2000**, *56* (15), 2325–2337.

(47) Watanabe, T.; Shakadou, M.; Uemura, M. Diastereoselective Ortho-Lithiation of Tricarbonylchromium Complexes of Chiral Benzaldehyde Acetals. *Inorganica Chim. Acta* **1999**, *296* (1), 80–85.

(48) Hattori, T.; Koike, N.; Okaishi, Y.; Miyano, S. Highly Stereospecific Conversion of Planar Chirality of a Cyclophane into Axial Chirality of Binaphthyls. *Tetrahedron Lett.* **1996**, *37* (12), 2057–2060.

(49) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition Metal Complexes. 2. Nickel- and Palladium-Catalyzed Asymmetric Grignard Cross-Coupling. *J. Am. Chem. Soc.* **1982**, *104* (1), 180–186.

(50) Yin, J.; Buchwald, S. L. A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds [29]. *J. Am. Chem. Soc.* **2000**, *122* (48), 12051–12052.

(51) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. Asymmetric Coupling of Phenols with Arylleads [2]. *J. Am. Chem. Soc.* **1999**, *121* (38), 8943–8944.

(52) Broutin, P. E.; Colobert, F. Enantiopure β-Hydroxysulfoxide Derivatives as Novel Chiral Auxiliaries in Asymmetric Biaryl Suzuki Reactions. *Org. Lett.* **2003**, *5* (18), 3281–3284.

(53) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. Enantioselective Oxidative Biaryl Coupling Reactions Catalyzed by 1,5-Diazadecalin Metal Complexes: Efficient Formation of Chiral Functionalized BINOL Derivatives. *J. Org. Chem.* **2003**, *68* (14), 5500–5511.

(54) Irie, R.; Masutani, K.; Katsuki, T. Asymmetric Aerobic Oxidation Coupling of 2-Naphthol Derivatives Catalyzed by Photo-Activated Chiral (NO) Ru (II)-Salen Complex. *Synlett* **2000**, No. 10, 1433–1436.

(55) Lou, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. Novel Achiral Biphenol-Derived Diastereomeric Oxovanadium(IV) Complexes for Highly Enantioselective Oxidative Coupling of 2-Naphthols. *Angew. Chem. Int. Ed.* **2002**, *41* (23), 4532–4535.

(56) Meyers, A. I.; Lutomski, K. A. Enantioselective Synthesis of Binaphthyls via Nucleophilic Aromatic Substitution on Chiral Oxazolines. *J. Am. Chem. Soc.* **1982**, *104* (3), 879–881.

(57) Wilson, J. M.; Cram, D. J. Chiral Leaving Groups Induce Asymmetry in Syntheses of Binaphthyls in Nucleophilic Aromatic Substitution Reactions. *J. Am. Chem. Soc.* **1982**, *104* (3), 881–884.

(58) Suzuki, T.; Hotta, H.; Tetsutaro, H.; Miyano, S. An Efficient Asymmetric Synthesis of Atropisomeric 1,1'-Binaphtyls via Nucleophilic Aromatic Substitution Reaction. *Chem. Lett.* **1990**, *19* (5), 807–810.

(59) Baker, R. W.; Pocock, G. R.; Sargent, M. V.; Twiss (née Stanojevic), E. Directed Metalation/Ligand Coupling Approach to the Enantioselective Synthesis of 1,1′-Binaphthyls. *Tetrahedron: Asymmetry* **1993**, *4* (12), 2423–2426.

(60) Harada, T.; Mai, T.; Tuyet, T.; Oku, A. Asymmetric Desymmetrization of 2,2′,6,6′-Tetrahydroxybiphenyl through Annulation with Enantiomerically Pure Bis(Mesylate). *Org. Lett.* **2000**, *2* (9), 1319–1322.

(61) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. Catalytic Asymmetric Synthesis of Axially Chiral Biaryls by Palladium-Catalyzed Enantioposition-Selective Cross-Coupling. *J. Am. Chem. Soc.* **1995**, *117* (35), 9101–9102.

(62) Uozumi, Y.; Kitayama, K.; Hayashi, T. Regio- and Enantioselective Hydrosilylation of 1-Arylalkenes by Use of Palladium-MOP Catalyst. *Tetrahedron: Asymmetry* **1993**, *4* (12), 2419–2422.

(63) Murai, S.; Ohtaki, H.; Yamada, A.; Le Gendre, P.; Kakiuchi, F. Atropselective Alkylation of Biaryl Compounds by Means of Transition Metal-Catalyzed C–H/Olefin

Coupling. *Tetrahedron: Asymmetry* **2002**, *11* (13), 2647–2651.
(64) Gustafson, J. L.; Lim, D.; Miller, S. J. Dynamic Kinetic Resolution of Biaryl Asymmetric Bromination. *Science* **2010**, *328* (4), 1251–1255.
(65) Zhang, S.; Yao, Q. J.; Liao, G.; Li, X.; Li, H.; Chen, H. M.; Hong, X.; Shi, B. F. Enantioselective Synthesis of Atropisomers Featuring Pentatomic Heteroaromatics by Pd-Catalyzed C-H Alkynylation. *ACS Catal.* **2019**, *9* (3), 1956–1961.
(66) Penhoat, M.; Levacher, V.; Dupas, G. Novel Extension of Meyers' Methodology: Stereoselective Construction of Axially Chiral 7,5-Fused Bicyclic Lactams. *J. Org. Chem.* **2003**, *68* (24), 9517–9520.
(67) Shimada, T.; Kina, A.; Hayashi, T. A New Synthetic Route to Enantiomerically Pure Axially Chiral 2,2′-Bipyridine N,N′-Dioxides. Highly Efficient Catalysts for Asymmetric Allylation of Aldehydes with Allyl(Trichloro)Silanes. *J. Org. Chem.* **2003**, *68* (16), 6329–6337.
(68) Bringmann, G.; Breuning, M.; Tasler, S. The Lactone Concept: An Efficient Pathway to Axially Chiral Natural Products and Useful Reagents. *Synthesis.* **1999**, *5* (4), 525–558.
(69) Bringmann, G.; Gussregen, S.; Vitt, D.; Stowasser, R. The Atropisomer-Selective Ring Cleavage of Helically Distorted, Configuratively Unstable Biaryl Lactones with a Chiral Metallated N -Nucleophile - the Complete PM3 Mechanistic Course and Its Video Presentation. *J. Mol. Model.* **2004**, *4* (5), 165–175.
(70) Bringmann, G.; Vitt, D. Stereoselective Ring-Opening Reaction of Axially Prostereogenic Biaryl Lactones with Chiral Oxazaborolidines: An AMI Study of the Complete Mechanistic Course. *J. Org. Chem.* **1995**, *60* (23), 7674–7681.
(71) Nelson, T. D.; Meyers, A. I. The Asymmetric Ullmann Reaction III. Application of a First-Order Asymmetric Transformation to the Synthesis of C2-Symmetric Chiral, Non-Racemic Biaryls. *Tetrahedron Lett.* **1994**, *35* (20), 3259–3262.
(72) Nelson, T. D.; Meyers, A. I. The Synthesis of a Useful Chiral Biaryl Catalyst. An Oxazoline-Mediated Ullmann Reaction. *Tetrahedron Lett.* **1993**, *34* (19), 3061–3062.
(73) Yu, S.; Rabalakos, C.; Mitchell, W. D.; Wulff, W. D. New Synthesis of Vaulted Biaryl Ligands via the Snieckus Phenol Synthesis. *Org. Lett.* **2005**, *7* (3), 367–369.
(74) Tanaka, K. Transition-Metal-Catalyzed Enantioselective [2+2+2] Cycloadditions for the Synthesis of Axially Chiral Biaryls. *Chem. Asian J.* **2009**, *4* (4), 508–518.
(75) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H. J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. Cobalt(I)-Catalyzed Asymmetric [2+2+2] Cycloaddition of Alkynes and Nitriles: Synthesis of Enantiomerically Enriched Atropoisomers of 2-Arylpyridines. *Angew. Chem. Int. Ed.* **2004**, *43* (29), 3795–3797.
(76) Heller, B.; Gutnov, A.; Fischer, C.; Drexler, H. J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. Phosphorus-Bearing Axially Chiral Biaryls by Catalytic Asymmetric Cross-Cyclotrimerization and a First Application in Asymmetric Hydrosilylation. *Chem. Eur. J.* **2007**, *13* (4), 1117–1128.
(77) Shibata, T.; Tsuchikama, K. Ir-Catalyzed Almost Perfect Enantioselective Synthesis of Helical Polyaryls Based on an Axially-Chiral Sequence. *Chem. Commun.* **2005**, No. 48, 6017–6019.
(78) Shibata, T.; Yoshida, S.; Arai, Y.; Otsuka, M.; Endo, K. Iridium-Catalyzed Consecutive and Enantioselective [2+2+2] Cycloaddition of Tetraynes and Hexaynes for the Construction of an Axially Chiral Biaryl System. *Tetrahedron* **2008**, *64* (5), 821–830.
(79) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. Enantioselective Synthesis of Axially Chiral Biaryls through Rhodium-Catalyzed Complete Intermolecular Cross-Cyclotrimerization of Internal Alkynes. *Org. Lett.* **2005**, *7* (14), 3119–3121.
(80) Nishida, G.; Suzuki, N.; Naguchi, K.; Tanaka, K. Enantioselective Synthesis of Tetra-Ortho-Substituted Axially Chiral Biaryls through Rhodium-Catalyzed Double [2 + 2 + 2] Cycloaddition. *Org. Lett.* **2006**, *8* (16), 3489–3492.
(81) Bringmann, G.; Tasler, S.; Pfeifer, R. M.; Breuning, M. The Directed Synthesis of Axially Chiral Ligands, Reagents, Catalysts, and Natural Products through the "Lactone Methodology." *J. Organomet. Chem.* **2002**, *661* (1–2), 49–65.

(82) Harinantenaina, L.; Noma, Y.; Asakawa, Y. Penicillium Sclerotiorum Catalyzes the Conversion of Herbertenediol into Its Dimers: Mastigophorenes A and B. *Chem. Pharm. Bull.* **2005**, *53* (2), 256–257.

(83) Buter, J.; Heijnen, D.; Vila, C.; Hornillos, V.; Otten, E.; Giannerini, M.; Minnaard, A. J.; Feringa, B. L. Palladium-Catalyzed, Tert-Butyllithium-Mediated Dimerization of Aryl Halides and Its Application in the Atropselective Total Synthesis of Mastigophorene A. *Angew. Chem. Int. Ed.* **2016**, *55* (11), 3620–3624.

(84) Cao, T.; Kong, Y.; Luo, K.; Chen, L.; Zhu, S. Cascade Claisen Rearrangement: Rapid Synthesis of Polysubstituted Salicylaldehydes and Total Syntheses of Hemigossypol and Gossypol. *Angew. Chem. Int. Ed.* **2018**, *57* (28), 8702–8707.

(85) Li, L.; Liu, Y.; Wang, Q. Regioselective Oxidative Dehydrogenation under Nonenzymatic Conditions: A Synthetic Route to Gossypol. *Eur. J. Org. Chem.* **2013**, No. 35, 8014–8021.

(86) Meltzer, P. C.; Bickford, P. H.; Lambert, G. J. A Regioselective Route to Gossypol Analogues: The Synthesis of Gossypol and 5,5'-Didesisopropyl-5,5'-Diethylgossypol. *J. Org. Chem.* **1985**, *50* (17), 3121–3124.

(87) Müller, M.; Lamottke, K.; Steglich, W.; Busemann, S.; Reichert, M.; Bringmann, G.; Spiteller, P. Biosynthesis and Stereochemistry of Phlegmacin-Type Fungal Pigments. *Eur. J. Org. Chem.* **2004**, No. 23, 4850–4855.

(88) Chen, L.; Liu, T.; Duan, Y.; Lu, X.; Yang, Q. Microbial Secondary Metabolite, Phlegmacin B1, as a Novel Inhibitor of Insect Chitinolytic Enzymes. *J. Agric. Food Chem.* **2017**, *65* (19), 3851–3857.

(89) Kuroda, M.; Mimaki, Y.; Sakagami, H.; Sashida, Y. Bulbinelonesides A-E, Phenylanthraquinone Glycosides from the Roots of Bulbinella Floribunda. *J. Nat. Prod.* **2003**, *66* (6), 894–897.

(90) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111* (2), 563–

(91) Goossens, J. F.; Goossens, L.; Bailly, C. Hinokiflavone and Related C–O–C-Type Biflavonoids as Anti-Cancer Compounds: Properties and Mechanism of Action. *Nat. Products Bioprospect.* **2021**.

(92) Bringmann, G.; Gunther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag, Ed.; 2001.

(93) Koyama, K.; Natori, S.; Iitaka, Y. Absolute Configurations of Chaetochromin A and Related Bis(Naphtho-γ-Pyrone) Mold Metabolites. *Chem. Pharm. Bull.* **1987**, *35* (10), 4049–4055.

(94) He, Z.; Pulis, A. P.; Procter, D. J. The Interrupted Pummerer Reaction in a Sulfoxide-Catalyzed Oxidative Coupling of 2-Naphthols. *Angew. Chem. Int. Ed.* **2019**, *58* (23), 7813–7817.

(95) Kobayashi, T.; Ishiwari, F.; Fukushima, T.; Hanaya, K.; Sugai, T.; Higashibayashi, S. Analysis of Interconversion between Atropisomers of Chiral Substituted 9,9'-Bicarbazole. *Eur. J. Org. Chem.* **2021**, *2021* (3), 449–451.

(96) Mallick, S.; Maddala, S.; Kollimalayan, K.; Venkatakrishnan, P. Oxidative Coupling of Carbazoles: A Substituent-Governed Regioselectivity Profile. *J. Org. Chem.* **2019**, *84* (1), 73–93.

(97) Scaglioni, L.; Mazzini, S.; Mondelli, R.; Merlini, L.; Ragga, E.; Nasini, G. Conformational and Thermodynamical Study of Some Helical Perylenequinones. *J. Chem. Soc. Perkin Trans. 2* **2001**, *12*, 2276–2286.

(98) Weiss, U.; Nasini, G.; Merlini, L.; Goto, T.; Chakraborty, D.; Bhattacharyya, P.; Achenbach, H. *Pogress in the Chemistry of Organic Natural Products*; Springer-Verlag, Ed.; New York, 1987.

(99) Mulrooney, C. A.; Morgan, B. J.; Li, X.; Kozlowski, M. C. Perylenequinone Natural Products: Enantioselective Synthesis of the Oxidized Pentacyclic Core. *J. Org. Chem.* **2010**, *75* (1), 16–29.

(100) O'Brien, E. M.; Li, J.; Carroll, P. J.; Kozlowski, M. C. Synthesis of the Cores of Hypocrellin and Shiraiachrome: Diastereoselective 1,8-Diketone Aldol Cyclization. *J. Org. Chem.* **2010**, *75* (1), 69–73.

(101) RAO, K. V; CULLEN, W. P. Streptonigrin, an Antitumor Substance. I. Isolation and Characterization. *Antibiot. Annu. 7*, 950–953.

(102) Rao, K. V.; Biemann, K.; Woodward, R. B. The Structure of Streptonigrin. *J. Am. Chem. Soc.* **1963**, *85* (16), 2532–2533.

(103) Seupel, R.; Hemberger, Y.; Feineis, D.; Xu, M.; Seo, E. J.; Efferth, T.; Bringmann, G. Ancistrocyclinones A and B, Unprecedented Pentacyclic N, C-Coupled

Naphthylisoquinoline Alkaloids, from the Chinese Liana Ancistrocladus Tectorius. *Org. Biomol. Chem.* **2018**, *16* (9), 1581–1590.
(104) Seupel, R.; Hertlein-Amslinger, B.; Gulder, T.; Stawski, P.; Kaiser, M.; Brun, R.; Bringmann, G. Directed Synthesis of All Four Pure Stereoisomers of the N,C-Coupled Naphthylisoquinoline Alkaloid Ancistrocladinium A. *Org. Lett.* **2016**, *18* (24), 6508–6511.
(105) Huang, Z.; Lumb, J. P. Mimicking Oxidative Radical Cyclizations of Lignan Biosynthesis Using Redox-Neutral Photocatalysis. *Nat. Chem.* **2021**, *13* (1), 24–32.
(106) Laplante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. Revealing Atropisomer Axial Chirality in Drug Discovery. *Chem. Med. Chem.* **2011**, *6* (3), 505–513.
(107) Kim, J. H.; Scialli, A. R. Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. *Toxicol. Sci.* **2011**, *122* (1), 1–6.
(108) Clayden, J.; Moran, W. J.; Edwards, P. J.; Laplante, S. R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem. Int. Ed.* **2009**, *48* (35), 6398–6401.
(109) Bachollet, S. P. J. T.; Volz, D.; Fiser, B.; Münch, S.; Rönicke, F.; Carrillo, J.; Adams, H.; Schepers, U.; Gómez-Bengoa, E.; Bräse, S.; Harrity, J. P. A. A Modular Class of Fluorescent Difluoroboranes: Synthesis, Structure, Optical Properties, Theoretical Calculations and Applications for Biological Imaging. *Chem. Eur. J.* **2016**, *22* (35), 12430–12438.
(110) Sandford, C.; Aggarwal, V. K. Stereospecific Functionalizations and Transformations of Secondary and Tertiary Boronic Esters. *Chem. Commun.* **2017**, *53* (40), 5481–5494.
(111) Allais, C.; Grassot, J. M.; Rodriguez, J.; Constantieux, T. Metal-Free Multicomponent Syntheses of Pyridines. *Chem. Rev.* **2014**, *114* (21), 10829–10868.
(112) Joule, J.; Mills, K. *Heterocyclic Chemistry*, Fifth Ed.; Wiley, 2010.
(113) Varela, A.; Saa, C. Construction of Pyridine Rings by Metal-Mediated [2 + 2 + 2] Cycloaddition. *Chem. Rev.* **2003**, *103*, 3787–3802.
(114) Nakamura, I.; Yamamoto, Y. Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis. *Chem. Rev.* **2004**, *104* (5), 2127–2198.
(115) Zhang, F. G.; Chen, Z.; Tang, X.; Ma, J. A. Triazines: Syntheses and Inverse Electron-Demand Diels-Alder Reactions. *Chem. Rev.* **2021**, *121* (23), 14555–14593.
(116) Neunhoeffer, H.; Hans-Werner, F. Zur Chemie Der 1,2,4-Triazine I. Reaktion von 1,2,4-Triazinen Mit 1-Diathylaminopropin. *Tetrahedron Lett.* **1969**, *10* (37), 3151–3154.
(117) W. Dittmar, J. Sauer, A. S. (4+2)-Cycloadditionen Der 1,2,4-Triazine - Ein Neuer Weg Zu 4-H-Azepinen. *Tetrahedron Lett.* **1969**, No. 59, 5171–5174.
(118) Molander, G. A. Organotrifluoroborates: Another Branch of the Mighty Oak. *J. Org. Chem.* **2015**, *80* (16), 7837–7848.
(119) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Locatelli, M.; Melchiorre, P.; Sambri, L. Alcohols and Di-Tert-Butyl Dicarbonate: How the Nature of the Lewis Acid Catalyst May Address the Reaction to the Synthesis of Tert-Butyl Ethers. *J. Org. Chem.* **2006**, *71* (26), 9580–9588.
(120) Chen, H.; Tsalkova, T.; Chepurny, O. G.; Mei, F. C.; Holz, G. G.; Cheng, X.; Zhou, J. Identification and Characterization of Small Molecules as Potent and Specific EPAC2 Antagonists. *J. Med. Chem.* **2013**, *56* (3), 952–962.
(121) Xia, X. F.; Wang, N.; Zhang, L. L.; Song, X. R.; Liu, X. Y.; Liang, Y. M. Palladium(II)-Catalyzed Tandem Cyclization/C-H Functionalization of Alkynes for the Synthesis of Functionalized Indoles. *J. Org. Chem.* **2012**, *77* (20), 9163–9170.
(122) Kitamura, T.; Morita, K.; Nakamori, H.; Oyamada, J. Synthesis of [1]Benzothieno[3,2- b][1]Benzothiophene Derivatives via Successive Iodocyclization/Photocyclization of Alkynes. *J. Org. Chem.* **2019**, *84* (7), 4191–4199.
(123) Mehta, S.; Waldo, J. P.; Larock, R. C. Competition Studies in Alkyne Electrophilic Cyclization Reactions. *J. Org. Chem.* **2009**, *74* (3), 1141–1147.
(124) Lennox, A. J. J.; Lloyd-Jones, G. C. Organotrifluoroborate Hydrolysis: Boronic Acid Release Mechanism and an Acid-Base Paradox in Cross-Coupling. *J. Am. Chem. Soc.* **2012**, *134* (17), 7431–7441.
(125) Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S.

C. Asymmetric Synthesis of QUINAP via Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **2013**, *135*, 16829–16832.

(126) Ros, A.; Estepa, B.; Ramírez-López, P.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Dynamic Kinetic Cross-Coupling Strategy for the Asymmetric Synthesis of Axially Chiral Heterobiaryls. *J. Am. Chem. Soc.* **2013**, *135* (42), 15730–15733.

(127) Roscales, S.; Cs, A. G. How to Make C–N Bonds Using Boronic Acids and Their Derivatives without Transition Metals. *Chem. Soc. Rev*. **2020**, *49*, 5159–5177.

(128) Liu, X.; Zhu, Q.; Chen, D.; Wang, L.; Jin, L.; Liu, C. Synthetic Methods Aminoazanium of DABCO : An Amination Reagent for Alkyl and Aryl Pinacol Boronates. **2019**, 2745–2749.

(129) Chatterjee, N.; Arfeen, M.; Bharatam, P. V; Goswami, A. A Metal and Base-Free Chemoselective Primary Amination of Boronic Acids Using Cyanamidyl/Arylcyanamidyl Radical as Aminating Species: Synthesis and Mechanistic Studies by Density Functional Theory. *J. Org. Chem*. **2016**, *81* (12), 5120-5127.

(130) Voth, S.; Hollett, J. W.; Mccubbin, J. A. Transition-Metal-Free Access to Primary Anilines from Boronic Acids and a Common + NH 2 Equivalent. *J. Org. Chem*. **2015**, *80* (5), 2545-2553.

(131) Tao, C.; Cui, X.; Li, J.; Liu, A.; Liu, L.; Guo, Q. Copper-Catalyzed Synthesis of Aryl Azides and 1-Aryl-1 , 2 , 3-Triazoles from Boronic Acids. *Tetrahedron Lett*. **2007**, *48*, 3525–3529.

(132) Grimes, K. D.; Gupte, A.; Aldrich, C. C. Copper(II)-Catalyzed Conversion of Aryl/Heteroaryl Boronic Acids, Boronates, and Trifluoroborates into the Corresponding Azides: Substrate Scope and Limitations. *Synthesis.* **2010**, *9*, 1441–1448.

(133) Niu, L.; Yang, H.; Yang, D.; Fu, H. Functionalizations of Aryl C□H Bonds in 2-Arylpyridines via Sequential Borylation and Copper Catalysis. *Adv. Synth. Catal.* **2012**, *354* (11–12), 2211–2217.

(134) Partridge, B. M.; Hartwig, J. F. Sterically Controlled Iodination of Arenes via Iridium-Catalyzed C-H Borylation. *Org. Lett.* **2013**, *15* (1), 140–143.

(135) Harris, M. R.; Li, Q.; Lian, Y.; Xiao, J.; Londregan, A. T. Construction of 1-Heteroaryl-3-Azabicyclo[3.1.0]Hexanes by Sp3−sp2 Suzuki−Miyaura and Chan−Evans−Lam Coupling Reactions of Tertiary Trifluoroborate. *Org. Lett.* **2017**, *19* (9), 2450–2453.

(136) Rao, K.; Biemann, K.; Woodward, R. B. The Structure of Streptonigrin. *J. Am. Chem. Soc.* **1963**, *85*, 2532.

(137) Chiu, Y. Y. H.; Lipscomb, W. N. Molecular and Crystal Structure of Streptonigrin. *J. Am. Chem. Soc.* **1975**, *97* (9), 2525–2530.

(138) Dholakia, S.; Gillard, R. Chiroptical Properties of Streptonigrin and a Comment on Atropisomerism in Heterocyclic Chemistry. *Tetrahedron* **1981**, *37* (16), 2929–2933.

(139) Tennant, S.; Rickards, R. W. Determination of the Absolute Configuration of the Chiral Biaryl System in the Streptonigrin Antibiotics by Exciton Coupled Circular Dichroic Spectroscopy. *Tetrahedron* **1997**, *53* (44), 15101–15114.

(140) Harding, M. M.; Long, G. V.; Brown, C. L. Solution Conformation of the Antitumor Drug Streptonigrin. *J. Med. Chem.* **1993**, *36* (21), 3056–3060.

(141) Hajdu, J.; Armstrong, E. C. Interaction of Metal Ions with Streptonigrin. 1. Formation of Copper(II) and Zinc(II) Complexes of the Antitumor Antibiotic. *J. Am. Chem. Soc.* **1981**, *103* (1), 232–234.

(142) Bolzán, A. D.; Bianchi, M. S. Genotoxicity of Streptonigrin: A Review. *Mutat. Res. - Rev. Mutat. Res.* **2001**, *488* (1), 25–37.

(143) Loyola, A. C.; Dao, K.; Shang, R.; Zhang, L.; Dutta, P.; Fowler, C.; Li, J.; Li, W. X. Streptonigrin at Low Concentration Promotes Heterochromatin Formation. *Sci. Rep.* **2020**, *10* (1), 1–11.

(144) Rao, K. V. Interaction of Streptonigrin with Metals and with DNA. *J. Pharm. Sci.* **1979**, *68* (7), 853–856.

(145) Kendrick, D. Interaction of Metal Ions with Streptonigrin . 1 . Formation of Copper (II) and Zinc (II) Complexes of the Antitumor Antibiotic. **1981**, No. 1, 232–234.

(146) Dreyton, C. J.; Anderson, E. D.; Subramanian, V.; Boger, D. L.; Thompson, P. R. Insights into the Mechanism of Streptonigrin-Induced Protein Arginine Deiminase Inactivation. *Bioorganic Med. Chem.* **2014**, *22* (4), 1362–1369.

(147) Cone, R.; Hasan, S. K.; Lown, J. W.; Morgan, A. R. The Mechanism of the Degradation of DNA by Streptonigrin. *Can. J. Biochem.* **1976**, *54* (3), 219–223.

(148) Kong, D.; Zou, Y.; Zhang, Z.; Xu, F.; Brock, N. L.; Zhang, L.; Deng, Z.; Lin, S. Identification of (2S,3S)-β-Methyltryptophan as the Real Biosynthetic Intermediate of Antitumor Agent Streptonigrin. *Sci. Rep.* **2016**, *6*, 1–8.

(149) Gould, S. J.; Chang, C. C. Studies of Nitrogen Metabolism Using 13C NMR Spectroscopy. 1. Streptonigrin Biosynthesis. *J. Am. Chem. Soc.* **1978**, *100* (5), 1624–1626.

(150) Erickson, W. R.; Gould, S. J. Streptonigrin Biosynthesis. 8. Evidence for the Involvement of a New Shikimate Pathway Product and a New Route to Quinolines1. *J. Am. Chem. Soc.* **1987**, *109* (2), 620–621.

(151) Gerwick, W.; Gould, S.; Fonouni, H. The Biosynthesis of Streptonigrin from [1-13C]-D-Erythrose. *Tetrahedron Lett.* **1983**, *24* (49), 5445–5448.

(152) Gould, S. J.; Darling, D. S. Streptonigrin Biosynthesis. 2. The Isolation of β-Methyltryptophan and Its Intermediacy in the Streptonigrin Pathway. *Tetrahedron Lett.* **1978**, *19* (35), 3207–3210.

(153) Erickson, W. R.; Gould, S. J. Streptonigrin Biosynthesis. 7. Incorporation of Oxygen from 18O2: Evidence for an Oxidative O-Carboline Cleavage. *J. Am. Chem. Soc.* **1985**, *107* (20), 5831–5832.

(154) Xu, F.; Kong, D.; He, X.; Zhang, Z.; Han, M.; Xie, X.; Wang, P.; Cheng, H.; Tao, M.; Zhang, L.; Deng, Z.; Lin, S. Characterization of Streptonigrin Biosynthesis Reveals a Cryptic Carboxyl Methylation and an Unusual Oxidative Cleavage of a N-C Bond. *J. Am. Chem. Soc.* **2013**, *135* (5), 1739–1748.

(155) Qian, T.; Wo, J.; Zhang, Y.; Song, Q.; Feng, G.; Luo, R.; Lin, S.; Wu, G.; Chen, H. F. Crystal Structure of StnA for the Biosynthesis of Antitumor Drug Streptonigrin Reveals a Unique Substrate Binding Mode. *Sci. Rep.* **2017**, *7*, 1–13.

(156) Bringmann, G.; Reichert, Y.; Kane, V. V. The Total Synthesis of Streptonigrin and Related Antitumor Antibiotic Natural Products. *Tetrahedron* **2004**, *60* (16), 3539–3574.

(157) Kende, A.; Lorah, D.; Boatman, R. A New and Efficient Total Synthesis of Streptonigrin. *J. Am. Chem. Soc.* **1981**, *103* (5), 1271–1273.

(158) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T. T. Total Synthesis of the Antitumor Antibiotic Streptonigrin. *J. Am. Chem. Soc.* **1982**, *104* (2), 536–544.

(159) Donohoe, T. J.; Jones, C. R.; Kornahrens, A. F.; Barbosa, L. C. A.; Walport, L. J.; Tatton, M. R.; O'Hagan, M.; Rathi, A. H.; Baker, D. B. Total Synthesis of the Antitumor Antibiotic (±)-Streptonigrin: First- and Second-Generation Routes for de Novo Pyridine Formation Using Ring-Closing Metathesis. *J. Org. Chem.* **2013**, *78* (24), 12338–12350.

(160) Boger, D. L.; Panek, J. S. Formal Total Synthesis of Streptonigrin. *J. Org. Chem.* **1983**, *48*, 623–625.

(161) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T. T.; Weinreb, S. M. Total Synthesis of Streptonigrin. *J. Am. Chem. Soc.* **1980**, *102* (11), 3962–3964.

(162) Liao, T.; Nyberg, W.; Cheng, C. Synthesis of 7-Amino-6-Methoxy- 5,8-Quinolinedione. *Angew. Chem. Int. Ed.* **1967**, *6* (8), 1967.

(163) Kende, A. S.; Lorah, D. P.; Boatman, R. J. A New and Efficient Total Synthesis of Streptonigrin. *J. Am. Chem. Soc.* **1981**, *103* (5), 1271–1273.

(164) Donohoe, T. J.; Jones, C. R.; Barbosa, L. C. A. Total Synthesis of (±)-Streptonigrin: De Novo Construction of a Pentasubstituted Pyridine Using Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2011**, *133* (41), 16418–16421.

(165) Neunhoeffer, H.; Reichel, D.; Cullmann, B.; Rehn, I. Zur Chemie Der 1,2,4-Triazine, XIV. Synthese Und Reaktionen von 5-Chlor-1,2,4-Triazinen. *Liebigs Ann. der Chemie* **1990**, *1990* (7), 631–640.

(166) Roudesly, F.; Veiros, L. F.; Oble, J.; Poli, G. Pd-Catalyzed Direct C-H Alkenylation and Allylation of Azine N -Oxides. *Org. Lett.* **2018**, *20* (8), 2346–2350.

(167) Xu, F.; Li, Y.; Huang, X.; Fang, X.; Li, Z.; Jiang, H.; Qiao, J.; Chu, W.; Sun, Z. Hypervalent Iodine(III)-Mediated Regioselective Cyanation of Quinoline N-Oxides with Trimethylsilyl Cyanide. *Adv. Synth. Catal.* **2019**, *361* (3), 520–525.

(168) Sarmah, B. K.; Konwar, M.; Bhattacharyya, D.; Adhikari, P.; Das, A. Regioselective Cyanation of Six-Membered N-Heteroaromatic Compounds Under Metal-, Activator-, Base- and Solvent-Free Conditions. *Adv. Synth. Catal.* **2019**, *361* (24), 5616–5625.

(169) Elbert, B. L.; Farley, A. J. M.; Gorman, T. W.; Johnson, T. C.; Genicot, C.;

Lallemand, B.; Pasau, P.; Flasz, J.; Castro, J. L.; MacCoss, M.; Paton, R. S.; Schofield, C. J.; Smith, M. D.; Willis, M. C.; Dixon, D. J. C–H Cyanation of 6-Ring N-Containing Heteroaromatics. *Chem. - A Eur. J.* **2017**, *23* (59), 14733–14737.

(170) Daunis, J.; Djouai-Hifdi, L.; Pigière, C. A Study of the Tautomerism of 5-as-triazinones by Mass Spectrometry. *Org. Mass Spectrom.* **1981**, *16* (8), 347–350.

(171) Wang, J.; Li, Y. H.; Pan, S. C.; Li, M. F.; Du, W.; Yin, H.; Li, J. H. Efficient Phosphorus-Free Chlorination of Hydroxy Aza-Arenes and Their Application in One-Pot Pharmaceutical Synthesis. *Org. Process Res. Dev.* **2020**, *24* (2), 146–153.

(172) Konno, S.; Ohba, S.; Agata, M.; Aizawa, Y.; Sagi, M.; Yamanaka, H. Studies on As-Triazine Derivatives. VIII. Synthesis of 5-Substituted 1,2,4-Triazines. *Heterocycles* **1987**, *26* (12), 3259–3264.

(173) Romer, D. Synthesis of 2,3-Dichloroquinoxalines via Vilsmeier Reagent Chlorination. *J. Heterocycl. Chem.* **2009**, *46* (March), 317–319.

(174) Sun, Z.; Wang, H.; Wen, K.; Li, Y.; Fan, E. Solvent-Free or Low-Solvent Large-Scale Preparation of Chloropyrimidine and Analogues. *J. Org. Chem.* **2011**, *76* (10), 4149–4153.

(175) Whittaker, N. A New Synthesis and the Chemical Properties of 5-Aminopyridine. *J. Chem. Soc.* **1951**, 1565.

(176) Wu, J.; Zhou, J.; Shi, Y.; Zhu, J. PhPOCl2as a Potent Catalyst for Chlorination Reaction of Phenols with PCl5. *Synth. Commun.* **2016**, *46* (19), 1619–1624.

(177) Neunhoeffer, H.; Ohsumi, T. Synthesis of 1,2,4-Triazines-XIV. Regioselective Synthesis of Ethyl 1,2,4-Triazine-5-Carboxylates. *Tetrahedron* **1992**, *48* (25), 5227–5234.

(178) Vantourout, J. C.; Miras, H. N.; Isidro-Llobet, A.; Sproules, S.; Watson, A. J. B. Spectroscopic Studies of the Chan-Lam Amination: A Mechanism-Inspired Solution to Boronic Ester Reactivity. *J. Am. Chem. Soc.* **2017**, *139* (13), 4769–4779.

(179) Hünig, S.; Schaller, R. The Chemistry of Acyl Cyanides. *Angew. Chemie Int. Ed. English* **1982**, *21* (1), 36–49.

(180) Nicolaou, K. C.; Yin, J.; Mandal, D.; Erande, R. D.; Klahn, P.; Jin, M.; Aujay, M.; Sandoval, J.; Gavrilyuk, J.; Vourloumis, D. Total Synthesis and Biological Evaluation of Natural and Designed Tubulysins. *J. Am. Chem. Soc.* **2016**, *138* (5), 1698–1708.

(181) Boger, D. L.; Cassidy, K. C.; Nakahara, S. Total Synthesis of Streptonigrone. *J. Am. Chem. Soc.* **1993**, *115*, 10733–10741.

(182) Chan, B. K.; Ciufolini, M. A. Total Synthesis of Streptonigrone. *J. Org. Chem.* **2007**, *72* (22), 8489–8495.

(183) Bonne, D.; Rodriguez, J. A Bird's Eye View of Atropisomers Featuring a Five-Membered Ring. *European J. Org. Chem.* **2018**, *2018* (20), 2417–2431.

(184) Li, H.; Shi, B.-F.; Yao, Q.-J.; Zhang, S.; Li, X.; Hong, X.; Chen, H.-M.; Liao, G. Enantioselective Synthesis of Atropisomers Featuring Pentatomic Heteroaromatics by Pd-Catalyzed C–H Alkynylation. *ACS Catal.* **2019**, *9*, 1956–1961.

(185) Deng, H.; Konopelski, J. P. Aryllead(IV) Reagents in Synthesis: Formation of the C11 Quaternary Center of N-Methylwelwitindolinone C Isothiocyanate. *Org. Lett.* **2001**, *3* (19), 3001–3004.

(186) Zhou, N.; Shi, Q.; Xie, Z. Total Synthesis of Lycogarubin C and Lycogalic Acid A. *Chinese J. Org. Chem.* **2014**, *34* (6), 1104–1109.

(187) Pedras, M. S. C.; Jha, M. Concise Syntheses of the Cruciferous Phytoalexins Brassilexin, Sinalexin, Wasalexins, and Analogues: Expanding the Scope of the Vilsmeier Formylation. *J. Org. Chem.* **2005**, *70* (5), 1828–1834.

(188) Zhou, H. J.; Wang, J.; Yao, B.; Wong, S.; Djakovic, S.; Kumar, B.; Rice, J.; Valle, E.; Soriano, F.; Menon, M. K.; Madriaga, A.; Kiss Von Soly, S.; Kumar, A.; Parlati, F.; Yakes, F. M.; Shawver, L.; Le Moigne, R.; Anderson, D. J.; Rolfe, M.; Wustrow, D. Discovery of a First-in-Class, Potent, Selective, and Orally Bioavailable Inhibitor of the P97 AAA ATPase (CB-5083). *J. Med. Chem.* **2015**, *58* (24), 9480–9497.

(189) Bao, X.; Rodriguez, J.; Bonne, D. Enantioselective Synthesis of Atropisomers with Multiple Stereogenic Axes. *Angew. Chemie - Int. Ed.* **2020**, *59* (31), 12623–12634.

(190) Hayashi, T.; Hayashizaki, K.; Ito, Y. Asymmetric Synthesis of Axially Chiral 1,1′:5′,1″- and 1,1′:4′,1″-Ternaphthalenes by Asymmetric Cross-Coupling with a

Chiral Ferrocenylphosphine-Nickel Catalyst. *Tetrahedron Lett.* **1989**, *30* (2), 215–218.

(191) Nguyen, Q. H.; Guo, S. M.; Royal, T.; Baudoin, O.; Cramer, N. Intermolecular Palladium(0)-Catalyzed Atropo-Enantioselective C-H Arylation of Heteroarenes. *J. Am. Chem. Soc.* **2020**, *142* (5), 2161–2167.

(192) Amatore, M.; Aubert, C. Recent Advances in Stereoselective [2+2+2] Cycloadditions. *European J. Org. Chem.* **2015**, *2015* (2), 265–286.

(193) Ma, G.; Sibi, M. P. Catalytic Kinetic Resolution of Biaryl Compounds. *Chem. - A Eur. J.* **2015**, *21* (33), 11644–11657.

(194) Zhu, S.; Chen, Y. H.; Wang, Y. Bin; Yu, P.; Li, S. Y.; Xiang, S. H.; Wang, J. Q.; Xiao, J.; Tan, B. Organocatalytic Atroposelective Construction of Axially Chiral Arylquinones. *Nat. Commun.* **2019**, *10* (1), 1–10.

(195) He, X. L.; Zhao, H. R.; Song, X.; Jiang, B.; Du, W.; Chen, Y. C. Asymmetric Barton-Zard Reaction to Access 3-Pyrrole-Containing Axially Chiral Skeletons. *ACS Catal.* **2019**, *9* (5), 4374–4381.

(196) Gao, Q.; Wu, C.; Deng, S.; Li, L.; Liu, Z. S.; Hua, Y.; Ye, J.; Liu, C.; Cheng, H. G.; Cong, H.; Jiao, Y.; Zhou, Q. Catalytic Synthesis of Atropisomeric O-Terphenyls with 1,2-Diaxes via Axial-to-Axial Diastereoinduction. *J. Am. Chem. Soc.* **2021**, *143* (19), 7253–7260.

(197) Zhu, C.; Yoshimura, A.; Ji, L.; Wei, Y.; Nemykin, V. N.; Zhdankin, V. V. Design, Preparation, X-Ray Crystal Structure, and Reactivity of o-Alkoxyphenyliodonium Bis(Methoxycarbonyl)Methanide, a Highly Soluble Carbene Precursor. *Org. Lett.* **2012**, *14* (12), 3170–3173.

(198) Yue, D.; Yao, T.; Larock, R. C. Synthesis of 3-Iodoindoles by the Pd/Cu-Catalyzed Coupling of N,N-Dialkyl-2-Iodoanilines and Terminal Acetylenes, Followed by Electrophilic Cyclization. *J. Org. Chem.* **2006**, *71* (1), 62–69.

(199) Ratushnyy, M.; Parasram, M.; Wang, Y.; Gevorgyan, V. Palladium-Catalyzed Atom-Transfer Radical Cyclization at Remote Unactivated C(Sp3)−H Sites: Hydrogen-Atom Transfer of Hybrid Vinyl Palladium Radical Intermediates. *Angew. Chemie - Int. Ed.* **2018**, *57* (10), 2712–2715.

(200) Faizi, D. J.; Davis, A. J.; Meany, F. B.; Blum, S. A. Catalyst-Free Formal Thioboration to Synthesize Borylated Benzothiophenes and Dihydrothiophenes. *Angew. Chemie - Int. Ed.* **2016**, *55* (46), 14286–14290.

(201) Fürstner, A.; Davies, P. W.; Lehmann, C. W. Bidentate Ruthenium Vinylcarbene Catalysts Derived from Enyne Metathesis. *Organometallics* **2005**, *24* (16), 4065–4071.

(202) Yue, D.; Yao, T.; Larock, R. C. Synthesis of 2,3-Disubstituted Benzo[b]Furans by the Palladium-Catalyzed Coupling of o-Iodoanisoles and Terminal Alkynes, Followed by Electrophilic Cyclization. *J. Org. Chem.* **2005**, *70* (25), 10292–10296.

(203) Chiu, H. C.; See, X. Y.; Tonks, I. A. Dative Directing Group Effects in Ti-Catalyzed [2+2+1] Pyrrole Synthesis: Chemo- and Regioselective Alkyne Heterocoupling. *ACS Catal.* **2019**, *9* (1), 216–223.

(204) Tan, J. F.; Bormann, C. T.; Perrin, F. G.; Chadwick, F. M.; Severin, K.; Cramer, N. Divergent Synthesis of Densely Substituted Arenes and Pyridines via Cyclotrimerization Reactions of Alkynyl Triazenes. *J. Am. Chem. Soc.* **2019**, *141* (26), 10372–10383.

(205) Smela, M. P.; Hoye, T. R. A Traceless Tether Strategy for Achieving Formal Intermolecular Hexadehydro-Diels-Alder Reactions. *Org. Lett.* **2018**, *20* (17), 5502–5505.

(206) Sekerová, L.; Vyskočilová, E.; Červený, L.; Sedláček, J. A Novel Application of Terminal Alkynes as the Homogeneous Catalysts for Acetalization and Esterification. *Tetrahedron* **2019**, *75* (20), 2877–2882.

(207) Song, J. H.; Choi, P.; Lee, S. E.; Jeong, K. H.; Kim, T.; Kang, K. S.; Choi, Y. S.; Ham, J. Efficient and Rapid Regioselective One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from in Situ Generated Potassium Arylethynyltrifluoroborates through Sonogashira Reaction. *European J. Org. Chem.* **2013**, No. 28, 6249–6253.

(208) Boger, D. L.; Panek, J. S.; Duff, S. R. Inverse Electron Demand Diels-Alder Reactions of Heterocyclic Azadienes: Formal Total Synthesis of Streptonigrin. *J. Am. Chem. Soc.* **1985**, *107* (20), 5745–5754.

Appendix

^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR spectra, X-ray structures and HPLC chromatograms can be found in the appendix.