Copper-catalyzed synthesis of heterocycles *via* oxidative ring closure reactions of aromatic nitriles with diaryliodonium salts

PhD thesis

Klára Aradi

pharmaceutical engineer

Eötvös Loránd University, Doctoral School of Chemistry,
Synthetic Chemistry, Materials Science and Biomolecular Chemistry PhD program

Head of Doctoral School: Dr. György Inzelt
Full Professor

Head of Doctoral program: Dr. András Perczel
Full Professor

Supervisor: Dr. Zoltán Novák
Assistant Professor

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In memory of my Father

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List of abbrevations and symbols

Å	Ångström
Ac	acetyl
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
Ar	aryl
atm	atmosphere
$BF_3{\cdot}OEt_2$	boron trifluoride diethyl etherate
Bu	butyl
COOEt	ethoxycarbonyl
COOMe	methoxycarbonyl
$Cu(acac)_2$	copper(II) acetylacetonate
$Cu(OTf)_2$	copper triflate
DCE	dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIB	(dicaetoxyiodo)benzene
DIPA	diisopropylamine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DPE	1,1-diphenylethylene
dtbpy	2,6-di-*tert*-butylpyridine

EDG	electron donating group
ee	enantiometic excess
eq	equivalent
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
GC-MS	gas chromatography-mass spectrometry
GC-MS	gas chromatography flame ionization detector
IBX	2-iodobenzoic acid
KO^tBu	potassium-*tert* butoxide
L	ligand
LiO^tBu	litium-*tert* butoxide
m	*meta*
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
$Me(CN)_4Cu(OTf)$	tetrakis(acetonitrile)copper(I)hexafluorophosphate
MeCN	acetonitrile
MeOH	methanol
Mes	mesityl
MS	molecular sieve
MTBE	methyl *tert*-butyl ether

MW	microwave
NaOEt	sodium ethoxide
NaO^tBu	sodium-*tert* butoxide
NaOTf	sodium triflate
NHAc	acetylamino
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NUMABS	numerical absoption
o	*ortho*
OAc	acetoxy
OEt	ethoxy
OMe	methoxy
OTf	triflate
OTs	tosylate
p	*para*
PEG	polyethylene glycol
Ph	phenyl
PhMe	toluene
rt	room temperature
S_EAr	electrophilic aromatic substitution
S_N2	nucleophilic substitution
SXRD	single christal X-ray diffraction
T3P	propylphosphonic anhydride

^{t}Bu	tert-butyl
TC	thiophene-2-carboxylate
TEA	triethyl amine
TFE	trifluoroethanol
TfOH	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSOTf	trimethylsilyl triflate
TsOH	*para*-toluene sulfonic acid
α	Alpha
β	Beta
γ	Gamma
δ	Delta
λ	Lambda
π	Pi
θ	Theta
σ	Sigma

1. Introduction

In the last decades, the need for efficient and fast syntheses and functionalization of important condensed heterocycles such as indoles, quinolines, carbazoles and other derivatives has received great attention in organic chemistry. The presence of cheap and commercially available metals such as copper or iron enables the development of several coupling reactions *via* the formation of carbon-carbon or carbon-heteroatom bonds. With the utilization of hypervalent diaryliodonium salts in the presence of transition-metal catalysts several arylations, C-H arylation and cyclization reactions were developed in the last few years. In some cases, especially in arylation of carbon nucleophiles or heteroatoms, the reactions were able to realize in the absence of transition-metals.

This doctoral thesis aims to discuss the results achieved in the development of the copper-catalyzed synthesis of important condensed heterocycles, such as iminobenzoxazines, chromenoquinolines and indenoquinolines from different nitriles and diaryliodonium salts. In collaboration, the geometry of the chromenoquinoline frame was established by single crystal X-ray diffraction, furthermore intermolecular interactions were investigated from different homologue sequences.

2. Literature review

In the following five chapters, the literature of iminobenzoxazines and chromenoquinolines focusing on the synthetic methods for the construction of these two heterocyclic cores and on their biological activities (chapters 2.1-2.4) is aimed to be summarized. In section 2.5 the literatures of diaryliodonium salts are collected including their structural properties, reactivity, methods for their preparation and their applications in organic syntheses.

2. 1. Benzoxazines and their derivatives: structure and biological activity

Benzoxazine is an aromatic heterocyclic compound composed of a benzene and an oxazine ring, from which the latter is a six-membered ring with an oxygen and a nitrogen atom. There are several benzoxazine derivatives depending on the position of the oxygen and the nitrogen atoms in the ring, for example benzo[1,4]oxazine (**1a**) or benzo [1,3]oxazine (**1b**) are two out of them (**Figure 1**). Moreover, the oxygen atom can be replaced with other heteroatoms in the ring, for example the sulfur-containing derivatives are known as benzothiazines. One representative of this compound class is benzo[1,4]thiazine (**2**). Benzoxazinones are the oxidized form of benzoxazines equipped with a C=O double bond such as benzo[1,3]oxazine-4-one (**3**). Imino[1,3]- and [1,4]benzoxazines (**4a** and **4b**) can be derived from benzoxazinones by the replacement of the carbonyl group with an imino group. The functionalization of the NH group enables the opportunity of versatile syntheses.

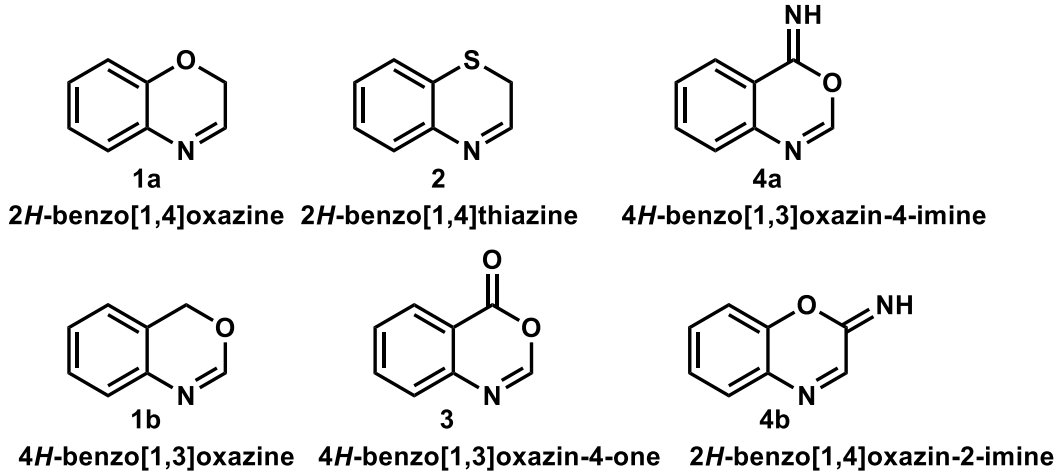


Figure 1. *General structure of benzoxazine derivatives*

Benzoxazines and their derivatives are synthetically useful compounds and are employed in organic synthesis for building natural products and designed synthetic compounds. They have been frequently utilized as suitable skeletons for the design of biologically active compounds.[1]. The versatility of the benzoxazine skeleton, in addition to its relative chemical simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds. Thanks to this fact, the number of publications related to the biological activity of this compound class has increased significantly in the last decade. Therefore, in this chapter some selected examples are only given as indicative examples and not exhaustive.

For example, several benzoxazine derivatives were found to show antimicrobial[2] and antimycobacterial[3] activity. Novel 6-chloro-2,4-diphenyl-3,4-dihydro-2*H*-1,3-benzoxazine[4] derivatives (**5**) were evaluated against *S. Aureus*, *E. Coli* and *C. Albicans*, while a series of 6-chloro-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones[5] **(6)** were synthesized and exhibited *in vitro* activity against *Mycobacterium tuberculosis, M. kansasii* and *M. avium* (**Figure 2a**). Some representatives of benzoxazines such as 6-bromo-2,2-dimethyl-benzo[1,4]thiazine-4-acetamide (**7**, **Figure 2b**) can act as potassium channel openers[6] as they have vasorelexant activity, whereas a number of benzoxazinones have enzyme inhibitor activity[7]. For example, 2-cyclohexyl-4*H*-benzo[1,3]oxazin-4-one (**8**, **Figure 2c**) showed inhibitor activity against C1r serine protease[8].

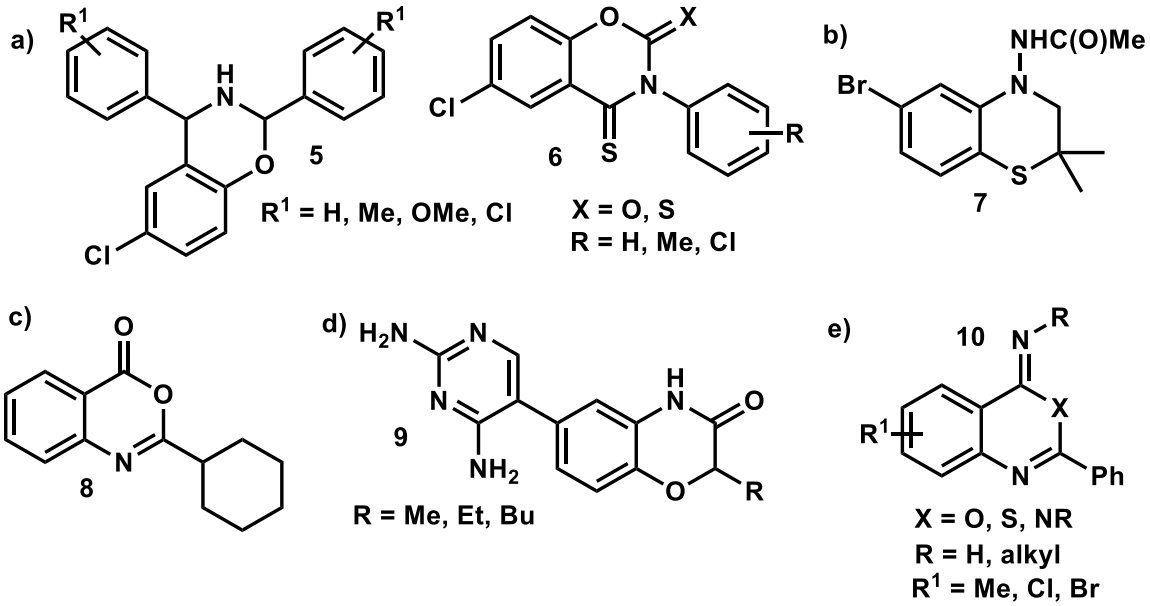


Figure 2. *Biologically active benzoxazine derivatives*

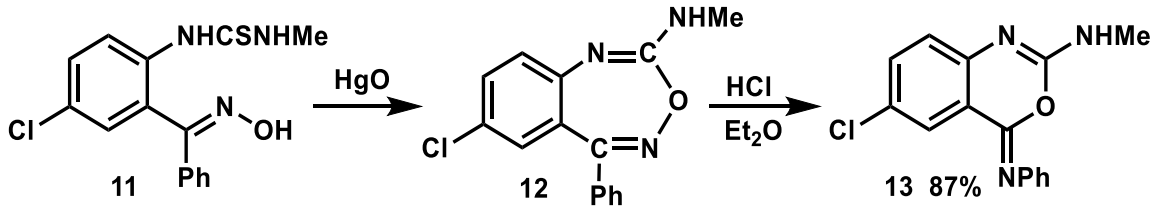
In case of some benzoxazine derivatives, receptor agonist[9] or antagonist[10] activity was also observed: a series of 6-(2, 4 diaminopyrimidinyl)-benz[1,4]oxazin-3-ones (**9**,

Figure 2d) were synthesized by Powell et al. and was found that compounds with a 2-methyl-2-aryl substitution pattern exhibit potent renin inhibition and good permeability-solubility and metabolic stability[11]. Additionally, some derivatives of iminobenzoxazines, iminobenzothiazines and iminoquinazolines can be used for controlling invertebrate pests[12] (**10, Figure 2e**).

2. 2. Synthesis of iminobenzoxazines

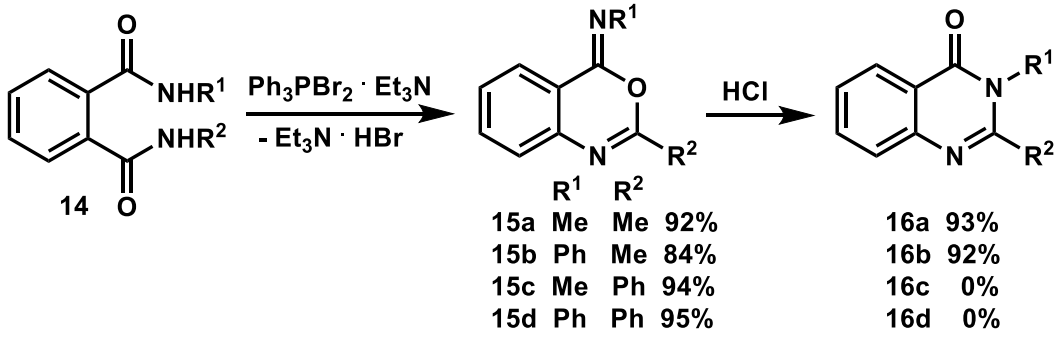
The compound class of benzoxazines has numerous derivatives, and some of them were already presented in Chapter 2. 1. Thanks to the large number of representatives, this chapter is limited to the preparation methods and syntheses for only iminobenzoxazines (1,3- and 1,4-derivatives).

The first preparation of imino[1,3]benzoxazines (**13**) was reported by Metlesics[13] et al. in 1967 during the synthesis of quinazolines and 1,4-benzodiazepines. In the presence of HgO the methylthiourea derivative **11** was converted to an oxadiazepine derivative (**12**), which was than treated with hydrochloric acid in ether to form the desired product (**13**) in 87% yield (**Scheme 1**).



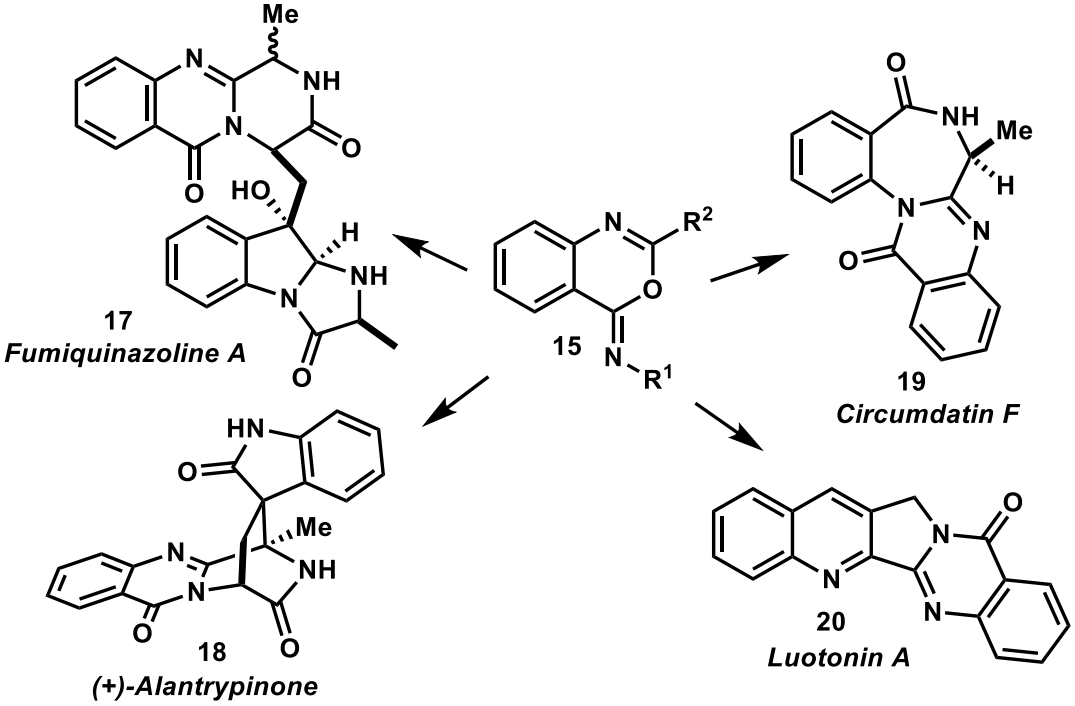
Scheme 1. *Preparation of imino[1,3]benzoxazines from oxadiazepines*

In 1989, the synthesis of 4-imino-4*H*-3,1-benzoxazines (**15**) was described by Mazurkiewicz[14] from *N*-acylanthranilamides (**14**) in the presence of Ph_3PBr_2 reagent. If 2-methyl-4-imino-4H-3,1-benzoxazines (**15a** and **15b)** were treated with hydrochloric acid, a rearrangement was occurred giving 4-quinazolones (**16a** and **16b**) in high yields. In contrast, the phenyl-substituted derivatives did not undergo any essential changes (**Scheme 2**). Similarly, iminobenzoxazine-quinazolone rearrangement was observed by Snider[15] and co-workers during the investigation of the total synthesis of Fumiquinazoline G reported previously by Ganesan[16] et al.



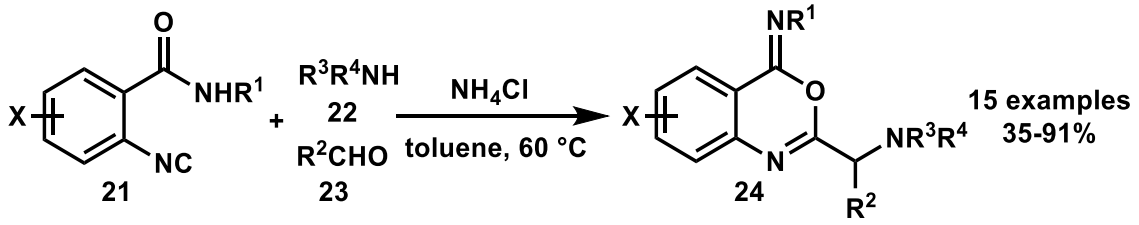
Scheme 2. *Synthesis and rearrangement of imino-3,1-benzoxazines*

In the following years, the total synthesis of further Fumiquinazoline[17] derivatives and other important alkaloids such as Alantrypinone[18] (**18**), Circumdatin[19] (**19**) or Luotonin[20] (**20**) *via* the formation of imino[1,3]benzoxazine intermediates (**15**) were also published by Snider, Hart, Bergman and Batey (**Scheme 3**).



Scheme 3. *Iminobenzoxazines: intermediates of the total synthesis of different alkaloids*

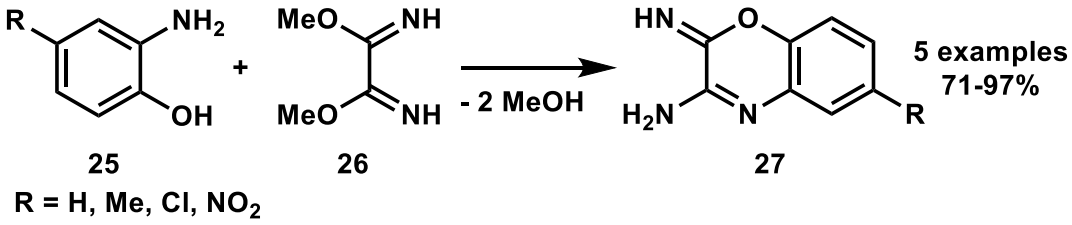
The three-component synthesis of 4-imino-4*H*-3,1-benzoxazines (**24**) was developed by Zhu[21] and co-workers in 2005. Heating a toluene solution of an aldehyde (**23**), an amine (**22**), and an isonitrile (**21**) in the presence of stoichiometric amount of ammonium chloride produced the title compound in good to excellent yields (**Scheme 4**).



Scheme 4. *Three-component synthesis of imino-1,3-benzoxazines*

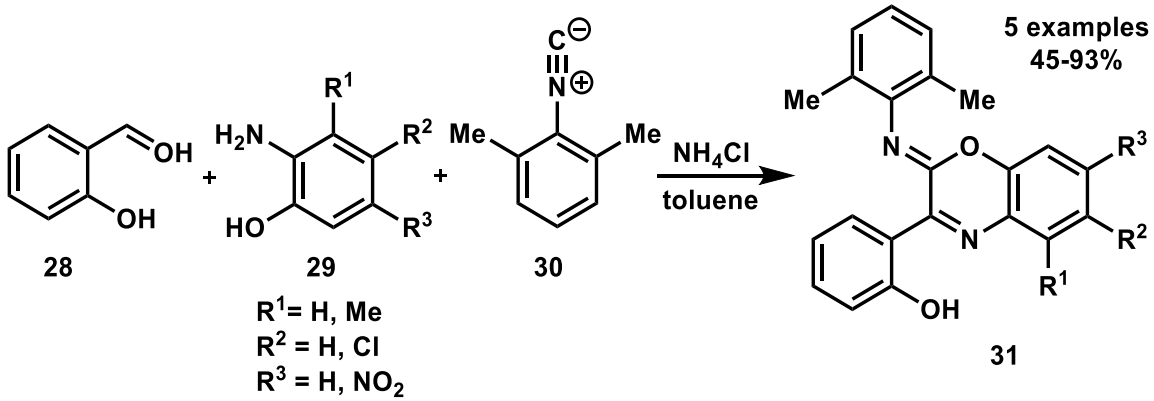
Recently, the microwave-assisted palladium-catalyzed synthesis of imino-1,3-benzoxazines was reported by Batra[22] et al. They also utilized isonitriles as starting materials which were reacted with 2-bromophenylureas in the presence of Pd-ligand and cesium carbonate base.

The first synthesis of imino-1,4-benzoxazines (**27**) was reported by Weidinger and Kranz[23] in 1964 by the condensation of *ortho*-aminophenols (**25**) with oxalyl bismethylimidate (**26**) under acidic conditions (**Scheme 5**).



Scheme 5. *Preparation of 2-imino-3-amino-1,4-benzoxazines*

In 2009, González[24] et al. developed a three-component synthesis for the construction of 2-imino-1,4-benzoxazine derivatives (**31**) from salicylaldehydes (**28**), *ortho*-aminophenols (**29**) and arylisocyanides (**30**) in toluene in the presence of ammonium-chloride (**Scheme 6**). The desired iminobenzoxazine derivatives could also be obtained by preparing the putative Schiff base intermediate followed by addition of the isonitrile, but in that case, more vigorous conditions were required.



Scheme 6. *Three-component synthesis of imino-1,4-benzoxazines*

Another approach for the synthesis of imino-1,4-benzoxazines with the utilization of *ortho*-aminophenols and isocyanides was published by Liu[25] and co-workers in 2013. Palladium chloride was used as a catalyst and the reactions were conducted in dioxane solvent. The applicability of the developed procedure was demonstrated on 28 examples in good to high yields.

2. 3. Chromenoquinolines and their derivatives: structure and biological activity

Chromenoquinolines are condensed heterocyclic compounds built from a chromene (**32**) and a quinoline core (**33**). Depending on the mode of the anellation between the basic and the prefix ring, the formed four-ring system can be chromeno[4,3]- or chromeno[3,4]quinolines. Two representatives, chromeno[4,3-*b*]quinoline (**34a**) and chromeno[3,4-*b*]quinoline (**35a**) are shown on **Figure 3**.

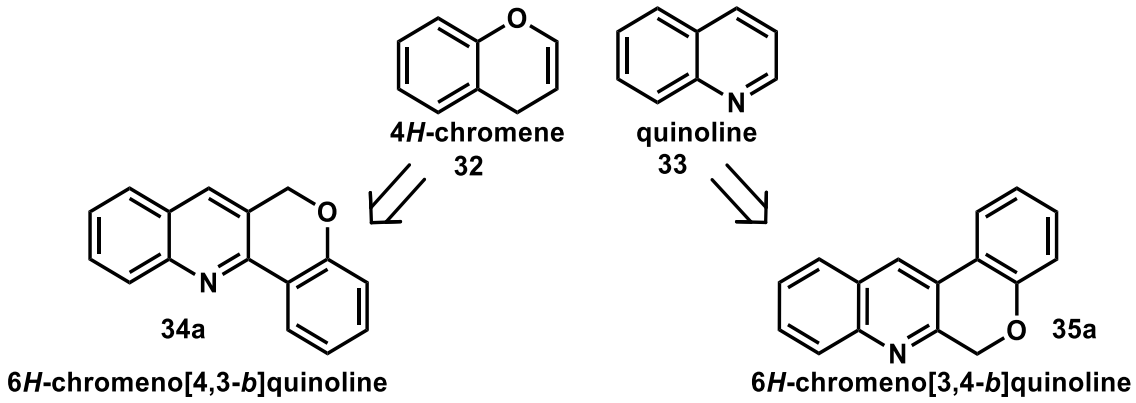
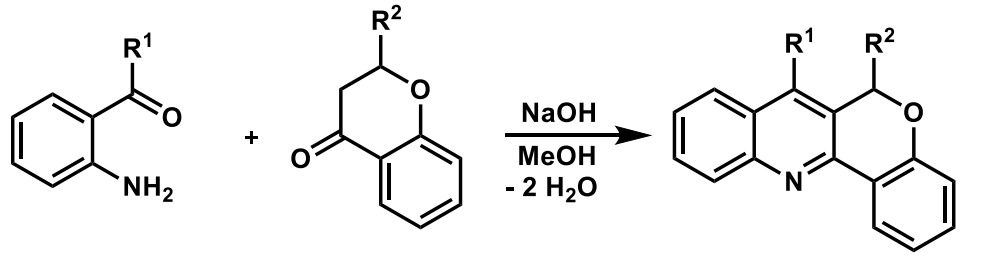


Figure 3. *Different chromenoquinoline derivaties built from chromene and quinoline ring*

Although, the number of publications according to the biological aspects of chromenoquinolines is not widespread as in the case of benzoxazine derivatives, their applications in medical chemistry have increased notably in the last decade. For example, 6*H*-chromeno[4,3-*b*]quinolines can act as estrogen receptor β–selective ligands[26] and they can be used also for bioimaging due to their fluorescent properties[27]. Moreover, the spiro analogues of benzothiazolylchromeno derivatives have shown cytotoxic activity[28] against MCF-7 (breast cancer) and HeLa (cervical cancer) cell lines.

2. 4. Synthesis of chromenoquinolines

In contrast to benzoxazines, the literatures according to the synthetic methods for the construction of chromenoquinoline core are more limited. However, the first synthesis of 6*H*-chromeno[4,3-*b*]quinoline (**34a**) was described nearly 80 years ago by Pfeiffer[29] in 1938 *via* the Friedländer[30] synthesis of *ortho*-aminobenzaldehyde (**36a**) and chromanone (**37a**) in methanol in the presence of sodium hydroxide (**Scheme 7**). The fluorescent property of the title compound in solution with green color was even then observed. In a similar way, the synthesis of other benzopyarano- and benzothiopyrano[4,3-*b*]quinoline derivatives including the preparation of 7-methyl-6*H*-chromeno[4,3-*b*]quinoline (**34b**) and 7-methyl-6-phyenyl-6*H*-chromeno[4,3-*b*]quinoline (**34c**) from *ortho*-aminoacetophenone (hydrochloric acid salt) (**36b**) and chroman-4-one derivatives (**37a**, **37b**) was published in 1965 by Kempter[31] et al. They also utilized methanol as a solvent and the title products were prepared in 77% and 78% yield after recrystallization.



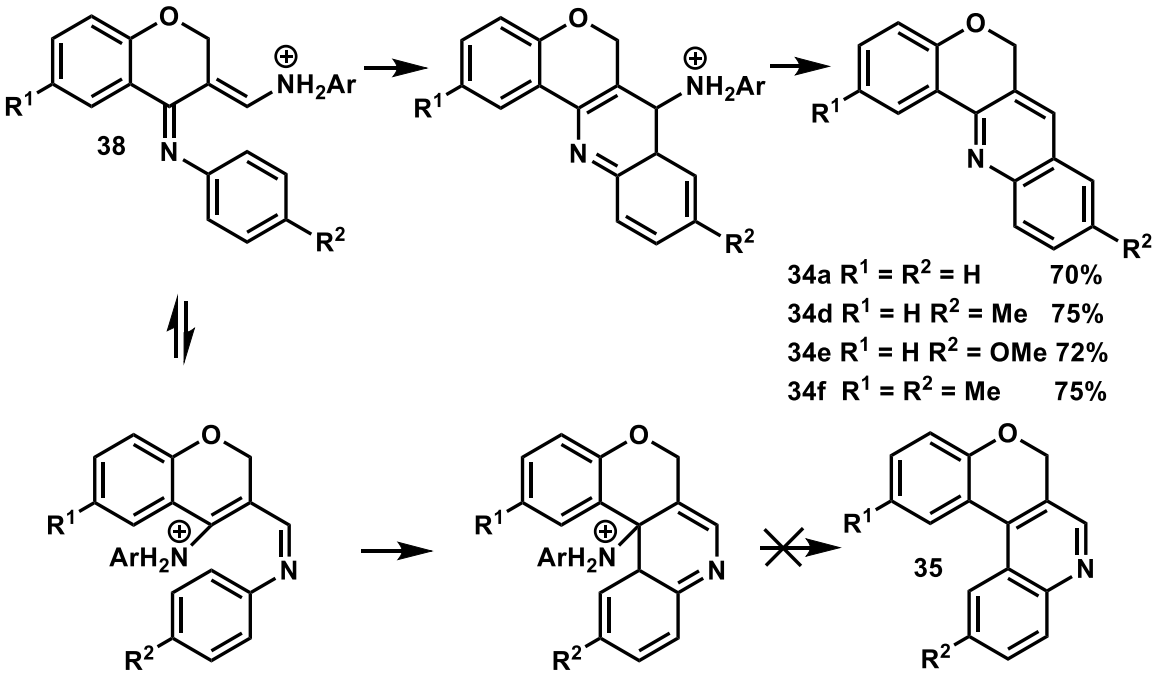
36a R^1 = H
36b R^1 = Me

37a R^2 = H
37b R^2 = Me

34a $R^1 = R^2$ = H 55%
34b R^1 = Me R^2 = H 77%
34c R^1 = Me R^2 = Ph 78%

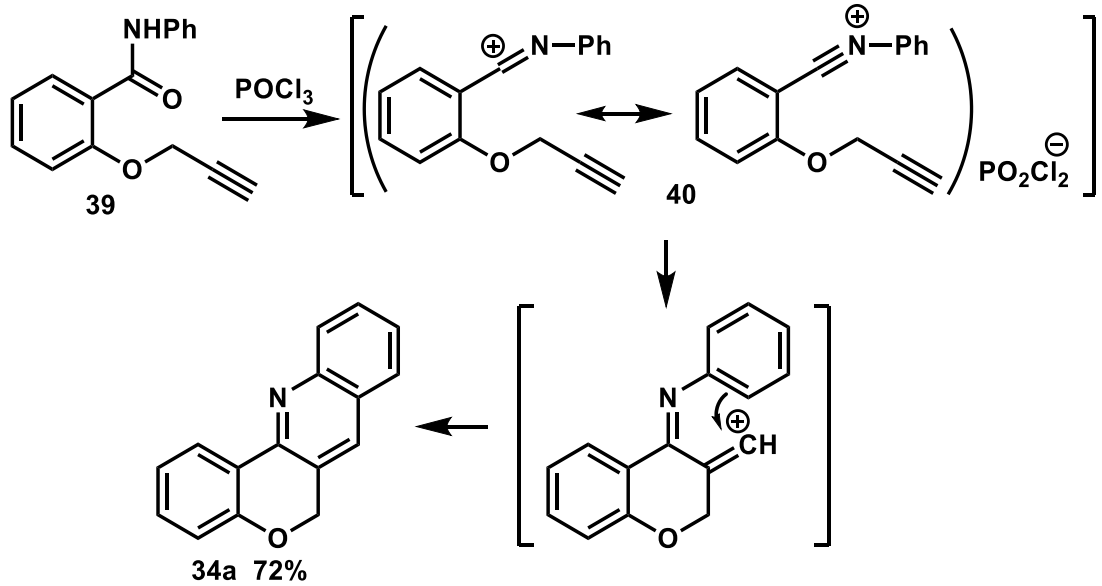
Scheme 7. *Synthesis of chromeno[4,3-b]quinoline derivatives via Friedländer synthesis*

In 1977, Balasubramanian[32] and co-workers reported a convenient route for the selective synthesis of chromeno[4,3-*b*]quinolines (**34a**, **34d-34f**) based on the thermal transformation of enaminoimines (**38**). According to their publication, the formation of the chromeno[3,4-*c*]quinoline core (**35**) was not observed in these type of reactions (**Scheme 8**).



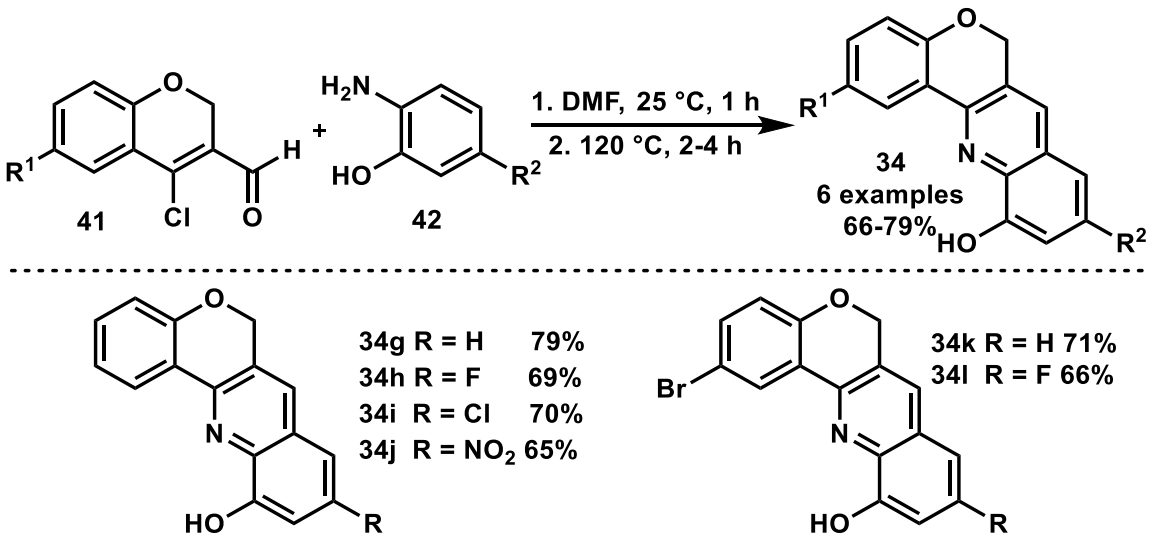
Scheme 8. *Thermal transformation of enaminoimines to chromenoquinolines*

In 1983, the same research group published the preparation of chromeno[4,3-*b*]quinolines by the photocyclization of chloroimines.[33] The photochemical transformation may proceed either through the intermediacy of enaminoimine or through the anilino-aldehyde derivative. In the same year, another synthesis was developed by Rougeot[34] et al. for the construction of chromeno[4,3-*b*]quinolines by heating propargyloxysalicylanilides (**39**) in the presence of phosphoryl chloride. The reaction is proposed to undergo *via* a nitrilium salt intermediate (**40**) (**Scheme 9**).



Scheme 9. *Synthesis of chromenoquinolines from propargyloxysalicylanilides with $POCl_3$*

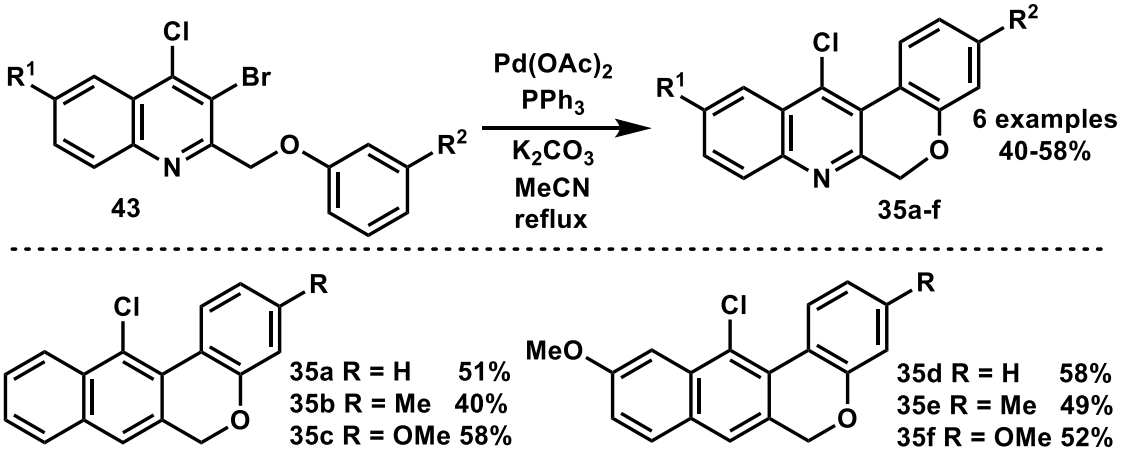
In 1999, Sabitha[35] reported the microwave-assisted, clay-catalyzed Friedländer[30] condensation of chromeno[4,3-*b*]quinolines. Propylphosphonic anhydride (T3P) can also catalyze the reaction, described later by Jida[36]. Nine years later, another approach for the synthesis of this compound class was realized by Bera[37] et al from β-chloroacroleins (**41**) and aminophenols (**42**) in dimethylformamide solvent (**Scheme 10**).



Scheme 10. *Chromeno[4,3-b]quinoline synthesis from β-chloroacroleins and aminophenols*

The preparation of chromenoquinolines *via* cyclization of differently substituted anilines or naphthylamine with *O*-propargylated salicylaldehydes using CuI/La(OTf)$_3$ as an efficient catalyst in refluxing acetonitrile was published by Nagarajan[38] and co-workers in 2010. The desired products were isolated in good and high yields.

One year later, the palladium-mediated intramolecular coupling reaction of 2-[(3-substituted-phenoxy)methyl]quinolines (**43**) for preparing chromeno[3,4-*b*]quinolines was explored by Jackson[39] et al. Potassium carbonate was utilized as a base and the reactions were conducted in acetonitrile, while the products (**35a-f**) were obtained in moderate yields (**Scheme 11**). The results of the cyclizations gave convincing evidence for an electrophilic aromatic substitution mechanism under standard Heck conditions.



Scheme 11. *Synthesis of chromeno[3,4-b]quinolines via Heck reaction*

2. 5. Diaryliodonium salts

In the last decades, hypervalent iodine compounds – the iodine atom contains more than eight electrons in the valence shell required for the octet rule - have received significant attention in organic syntheses[40] due to the fact that they are efficient reagents[41] for several organic reactions. Moreover, they can be employed as alternative oxidizing agents of various toxic heavy-metal-based oxidants such as mercury, arsenic, cadmium and nickel compounds. Amongst the hypervalent iodine compounds, iodine(III) and iodine(V) reagents are distinguished. The versatility of these λ^3- and λ^5-iodine reagents is becoming firmly established by the numerous transformations in which these reagents were involved. For example, 2-iodobenzoic acid (IBX) or Dess-Martin periodinane (DMP) are now routinely used in oxidative C-C couplings, oxidative cyclizations, oxidative rearrangements, oxidative deoximations, oxidative ring expansions and contractions, C-N bond formations and especially in oxidation of alcohols.[42]

In contrast, diaryliodine(III) reagents[43] can be utilized in reaction pathways which are similar to metal-catalyzed reactions. Owing to the highly electron-deficient nature of diaryliodonium salts at the iodine center and excellent leaving-group ability of the iodobenzene, they serve as versatile arylating agents with a variety of nucleophiles. Thus, as they are capable to transfer aryl group, their use enables the functionalization of different aromatic and heteroaromatic substrates. Moreover, they can also be used in sequential cyclizations for the synthesis of several important heterocyclic compounds.

2. 5. 1. Structural properties and reactivity

Diaryliodonium salts have been known for more than 100 years. They were described by Meyer[44] in 1894 as air- and moisture-stable compounds. Their structure consists of two aryl moieties connected to the iodine and a "counterion" X, being mainly halogen, triflate, tosylate or tetrafluoroborate (**Figure 4a**). The triflate and tetrafluoroborate salts have good solubility in many organic solvents, moreover, the week or non-existent nucleophilicity of these anions make these iodonium salts easily applicable in organic syntheses. In contrast, diaryliodonium salts with halide anions are generally sparingly soluble, thus, there are less applications according to diaryliodonium chlorides or bromides.

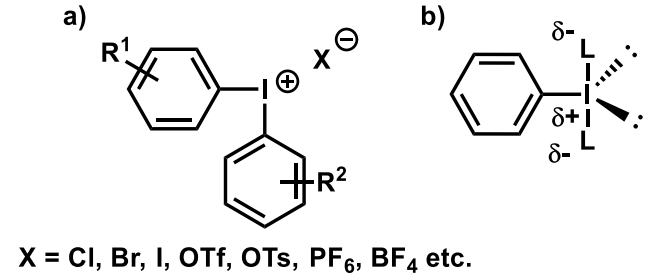
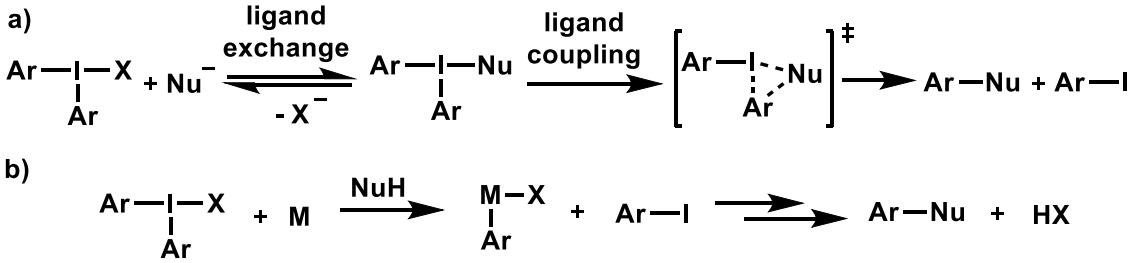


Figure 4. *a) General structure of diaryliodonium salts; b) T-shaped form determined by X-ray structure analysis*

According to the *lambda* (λ) convention, they are classified as λ^3-compounds,[45] where the iodine and two apical ligands (L) share a hypervalent, three-center four-electron (3c–4e) bond (**Figure 4b**). Hence, as it was mentioned previously, the electron configuration of the iodine in hypervalent iodine compounds is not conventional: instead of eight electrons, ten or twelve are located around the iodine center. The X-ray structures of these iodine(III) compounds show a T-shaped molecular geometry.[46] Thus, the Ar–I–Ar bond angle is close to 90°, which is believed to retain also in solution. The degree of dissociation to Ar_2I^+ and X^- in solution depends on both the solvent and the counterion[47]. For example, di-*p*-tolyliodonium tetrafluoroborate is much less dissociated in dichloromethane than the closely related bis(4-(*tert*-butyl)phenyl)iodonium hexafluorophosphate.

The reactivity of iodine(III) compounds is based on the electrophilic nature of the iodine, which is derived from the electron distribution in the 3c–4e bond. In reactions with Ar_2IX, one aryl group is transferred to the nucleophile, resulting diverse arylated compounds, while the other one is reductively eliminated as ArI. The high reactivity of

aryliodonium salts in these reactions is explained by the 'hyperleaving group ability' of the ArI group.[48] In metal-free reactions the nucleophile first attacks the electrophilic iodine of the diaryliodonium salt to give a T-shaped intermediate in a ligand exchange. In the subsequent step, the nucleophile and the equatorial aryl moiety are reductively eliminated in a ligand coupling, resulting ArNu and ArI (**Scheme 12a**).[49] Arylations under metal-catalyzed conditions are generally suggested to proceed by transfer of one aryl group to the metal to create a high oxidation state aryl metal complex (ArMX), followed by reductive elimination with the nucleophile (**Scheme 12b**).



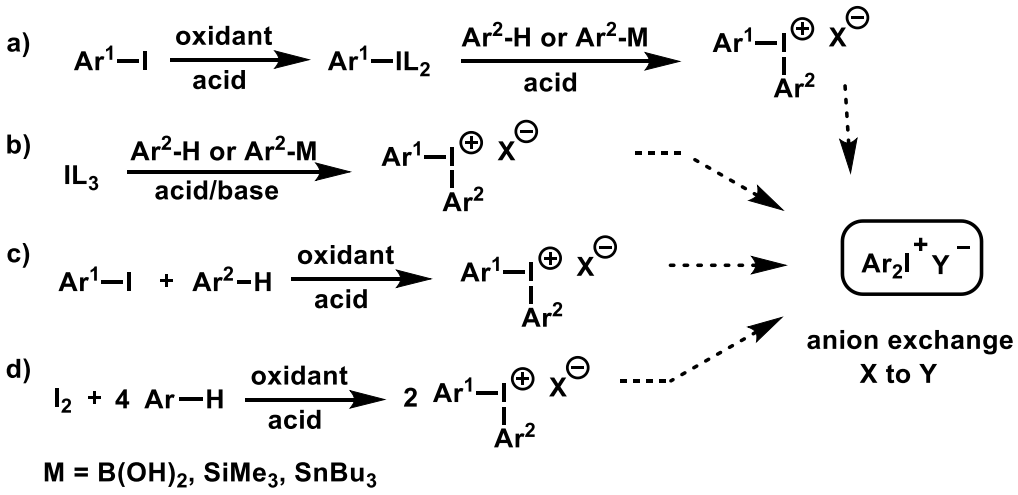
Scheme 12. *General mechanism for a) metal-free arylation; b) metal-catalyzed reaction*

The drawbacks of the application of diaryliodonium salts in organic synthesis are the formation of a stoichiometric amount of iodoarene in the reaction, and the selectivity of possible aryl transfers. With the utilization of symmetric diaryliodonium salts ($R^1 = R^2$, **Figure 4a**) selectivity problems can be solved in aryl-transfer reactions. However, this structural requirement may limit the scope of the transformations. Arylations with unsymmetric diaryliodonium salts ($Ar^1 \neq Ar^2$) are often desired, both because these salts are more easily synthesized, they enable the possibility of wide substrate scope and because an inexpensive 'dummy' aryl moiety is wasted as ArI. The most frequently used non-transferable 'dummy-group' for metal-catalyzed reactions is the mesityl group.

2. 5. 2. Synthetic strategies to diaryliodonium salts

Since the first synthesis of diaryliodonium salts was described by Meyer[44], a large variety of synthetic routes to diaryliodonium salts have been reported. Owing to the large number of publications, without exhaustive, only selected examples are given in this chapter focusing on the different synthetic strategies. Most of them are typically stepwised, with initial oxidation of an aryl iodide (Ar^1I) to iodine(III) (*preformed iodine (III) reagent*) and then ligand exchange with an arene (Ar^2H) or an organometallic reagent (Ar^2M) to obtain the diaryliodonium salt (**Scheme 13a**). In many cases a subsequent anion exchange step is necessary. To shorten the number of steps, *inorganic(III) iodine reagents*

can be employed (**Scheme 13b**). Recent progresses focus onto the development of *one-pot methods* to obtain the diaryliodonium salts directly from arenes and iodoarenes or molecular iodine (**Scheme 13c** and **13d**).

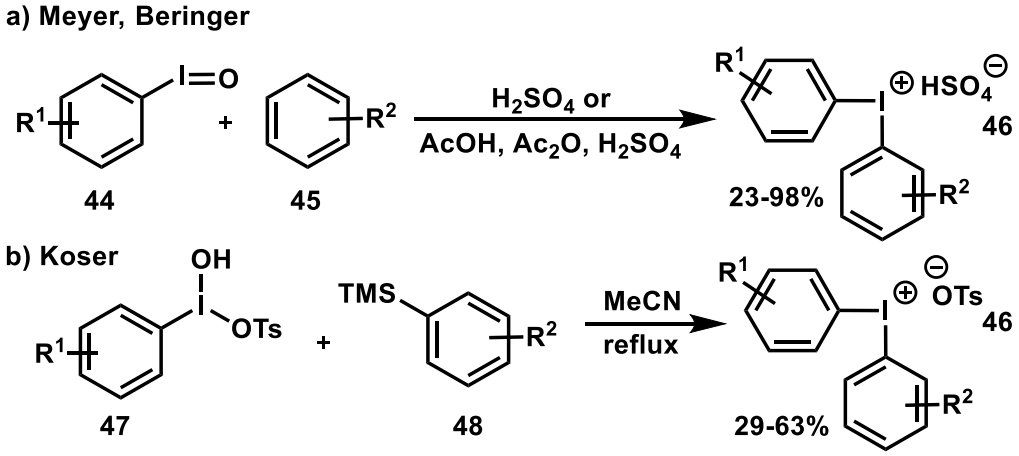


Scheme 13. *Synthetic strategies for preparing diaryliodonium salts*

The substitution of the arene (ArH) onto an iodine(III) intermediate undergoes *via* electrophilic aromatic substitution, which limits the number of possible products. In case of *o*/*p* directing substituents, mostly *para*-substituted diaryliodonium salts are formed, whereas *m*-directing substituents often lead to poor yields and byproduct formation. Thus, the aryl iodide should contain *o*/*m* substituents or lithiated arenes, arylboronic acids, stannanes, or silanes should be employed during the transformation.

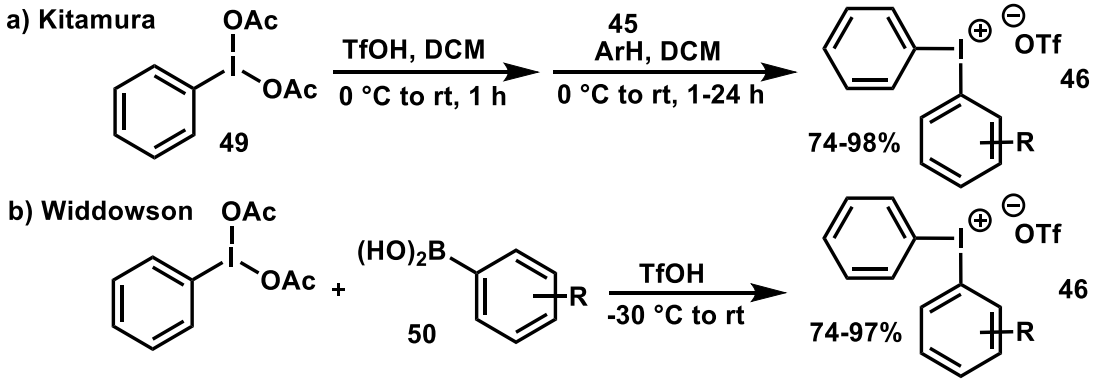
One of the most common synthetic routes to the access of diaryliodonium salts is generally performed with *preformed organic iodine(III) compounds* (**Scheme 13a**). The aryl iodide (Ar^1I) is converted into an aryliodine(III) compound (Ar^1IL_2) by its treatment with an inorganic oxidant under acidic conditions. Then the desired iodonium salt can be obtained after isolation of the aryliodine(III) followed by ligand exchange with an arene, an arylstannane or an arylsilane. The first synthesis of diaryliodonium salts reported previously by Meyer[44] was prepared from iodosylbenzene. In the 1950s Beringer[50,51] et al. published a large number of synthetic methods for the preparation of symmetric and unsymmetric diaryliodonium salts (**46**). In their transformations a wide range of hypervalent iodine(III) compounds were utilized such as iodosylarenes (**44**), (diacetoxyiodo)arenes and iodoxyarenes which were reacted with arenes (**45**) in the presence of different acids (**Scheme 14a**). The first regiospecific synthesis of diaryliodonium tosylates was discovered by Koser[52] and co-workers in 1980 by the reaction of hydroxy(tosyloxy)iodobenzene (**47**) (Koser's reagent) with arylsilanes (**48**)

under neutral conditions (**Scheme 14b**). Electron-rich thiophenes[53] were also suitable substrates of the developed method, but in that case the reaction was completed without the need of the trimethylsilyl (TMS) activating group.



Scheme 14. *Preparation of diaryliodonium salts from a) iodosylarene and b) Koser reagent*

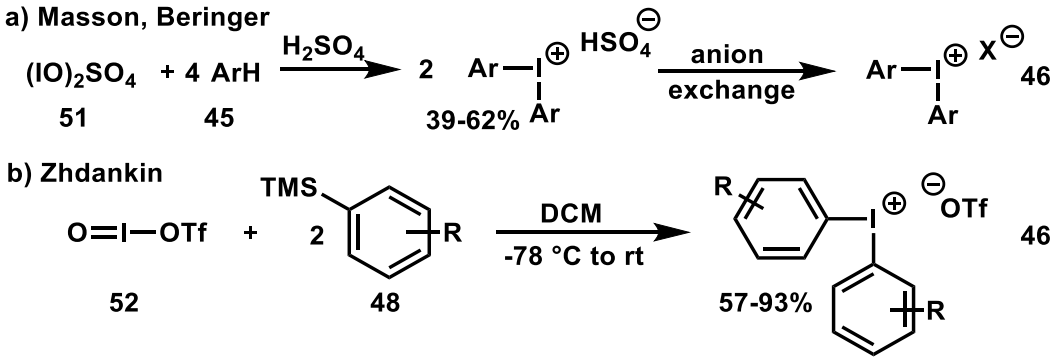
In 1994, Kitamura[54] et al developed the triflic acid-mediated synthesis of diaryliodonium salts with the utilization of (diacetoxyiodo)benzene (DIB) (**49**). In the first step of the reaction, [PhI(OAc)$_2$·2TfOH] is formed *in situ*, followed by the subsequent addition of electron-rich arenes to give the desired diaryliodonium triflates in good to high yields (**46**) (**Scheme 15a**). This method was further developed by Widdowson[55] and co-workers, who reacted DIB with arylboronic acids (**50**) in the presence of triflic acid, giving diaryliodonium triflates in 74-97% yields (**Scheme 15b**).



Scheme 15. *Synthesis of diaryliodonium triflates from diacetoxyiodobenzenes*

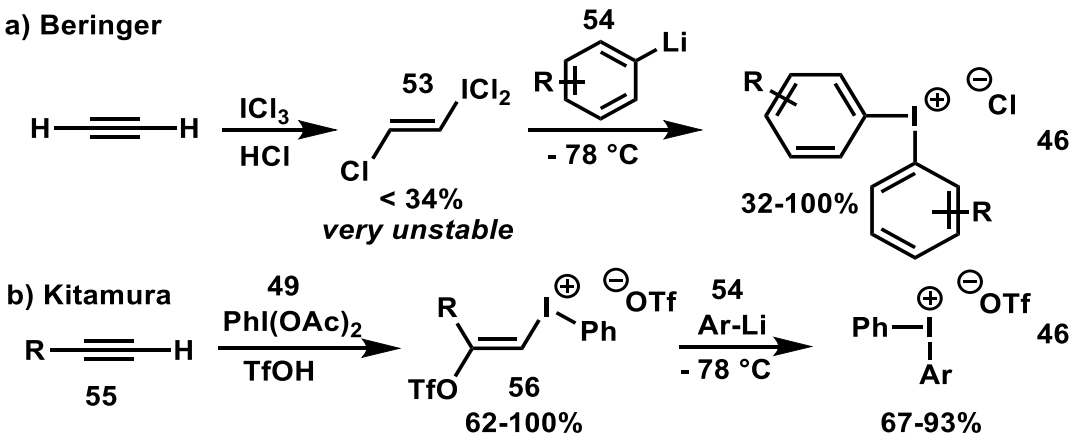
Another opportunity for the construction of diaryliodonium salts can be accomplished from *preformed inorganic hypervalent iodine reagents* (**Scheme 13b**). With this strategy, the synthesis of iodonium salts can be shortened, moreover, it is generally efficient in the synthesis of symmetric diaryliodonium salts. The disadvantage of this process is that the inorganic iodine reagents must be prepared beforehand and some of them are not storable. Masson[56] and Beringer[50] reported that arenes (**45**) could be

treated with iodic acid or iodosyl sulfate (**51**) to form diaryliodonium salts (**46**) in modarate yields (**Scheme 16a**). As described by Zhdankin[57], the desired products can also be synthesized in better yields utilizing iodosyl triflates (**52**) and arylsilanes (**48**) at low temperatures (**Scheme 16b**).



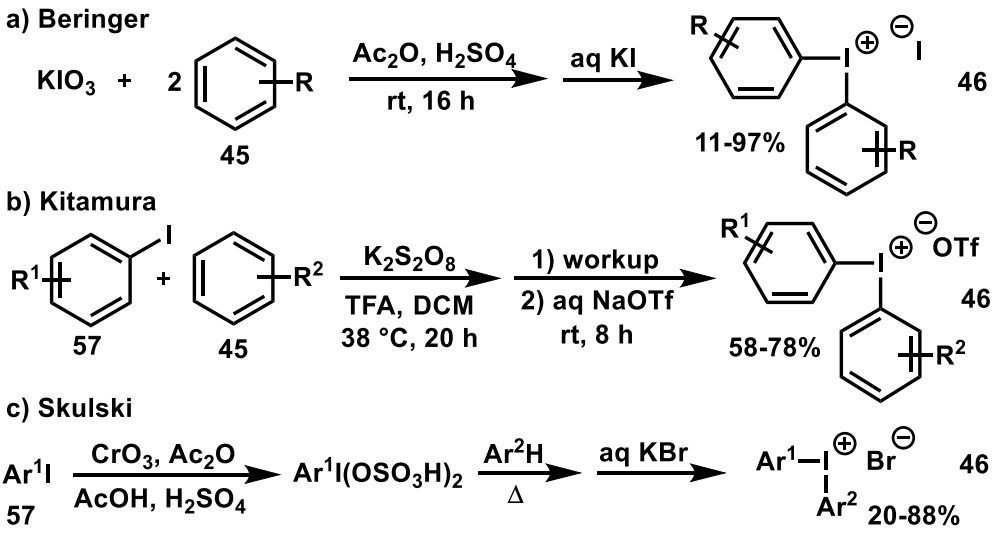
Scheme 16. *Preparation of diaryliodonium salts from a) iodosyl sulfate and b) iodosyl triflate*

In case of acid-sensitive substituents or heteroatoms that are prone to oxidation or protonation, the two strategies presented above cannot be employed. The utilization of *very reactive iodine(III) reagents* such as vinyl iodine(III) can solve this problem. As an advantage, applying them under strongly basic conditions such as in reactions with metallated arenes, both symmetric and unsymmetric diaryliodonium salts can be synthesized in a regiospecific manner. The drawbacks of this approach are that the unstable iodine(III) reagents are commercially not available and during their preparation strong bases should be used at low temperatures. In 1969, Beringer and Nathan[58] reported the application of highly unstable *trans*-chlorovinyliodoso dichloride (**53**) in the synthesis of diaryliodonium salts. In the presence of lithiated arenes (**54**) symmetric diaryliodonium salts could be obtained at low temperatures in moderate to good yields (**Scheme 17a**). In 1990, a variety of aryl(vinyl)iodonium triflates[59] (**56**) have been prepared by the reaction of (diacetoxy)iodoarenes (**49**) with alkynes (**55**) and utilized[60] for the synthesis of diaryliodonium salts treating them with lithiated arenes (**54**) (**Scheme 17b**).



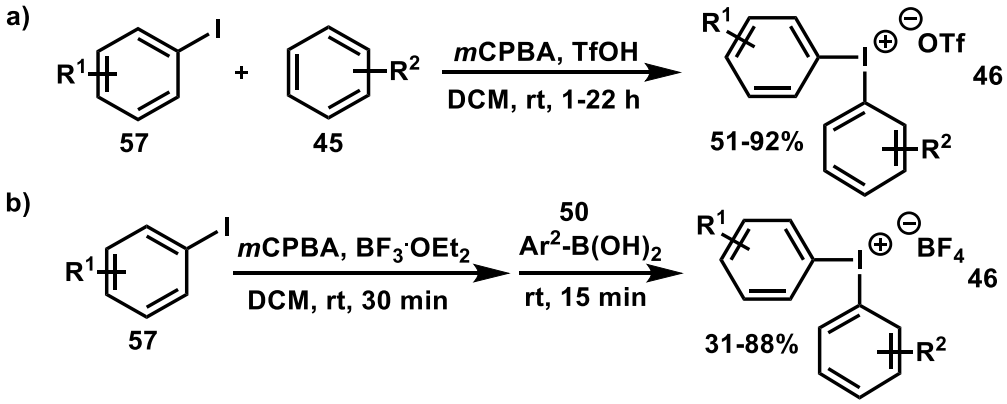
Scheme 17. *Synthesis of diaryliodonium salts from reactive iodine(III) reagents*

The most attractive ways to prepare diaryliodonium salts are the *one-pot syntheses* (**Scheme 13c and 13d**). Advantages include reduced reaction time and diverse substrate scope. To achieve a successful one-pot reaction, the arene should be carefully selected. For example, too electron deficient arenes cannot be employed in order to avoid the formation of byproducts. Due to the numerous publications according to this synthetic method, only selected examples are discussed in the followings. In 1953, Beringer[51] et al. reported that certain diaryliodonium salts (**46**) could be prepared directly from alkyl-substituted arenes (**45**) with the commercial oxidant potassium iodate (**Scheme 18a**). Three years later, Sandin[61] described that the preparation of cyclic diaryliodonium salts can also be realized with the utilization of peracetic acid. In the presence of potassium persulfate or barium peroxide the synthesis of acyclic diaryliodonium salts was reported by Beringer[51] in 1959. This method was further developed by Kitamura[62-64] et al. utilizing $K_2S_2O_8$ in various reaction conditions. For example, they synthesized diaryliodonium triflates from aryl iodides (**57**) and arenes (**45**) in the presence of potassium persulfate[62] and TFA followed by an anion exchange induced by NaOTf (**Scheme 18b**). Hence, these conditions were suitable for a direct synthesis of diaryliodonium triflates from iodine[63] and arenes (**45**) too. Moreover, the anion-exchange step was later avoided by adding triflic acid[64] to the reaction. The employment of chromium trioxide oxidant with the reagent combination acetic anhydride, acetic acid, and sulfuric acid under anhydrous conditions for the construction of diaryliodonium bromides was published by Skulski[65] and Kaźmierczak in 1995 (**Scheme 18c**). An elegant electrochemical synthesis of diaryliodonium salts was also reported by Pletcher[66] and Peacock in 2000.



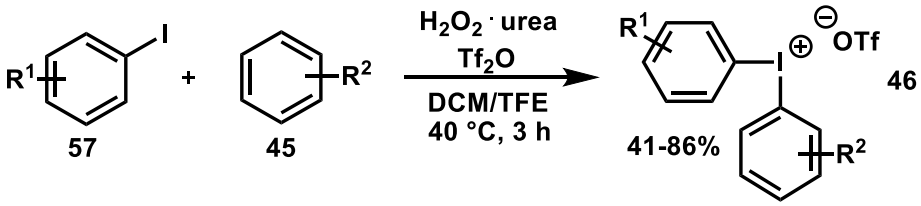
Scheme 18. *One-pot synthesis of diaryliodonium salts with a) KIO_3 b) $K_2S_2O_8$ and c) CrO_3*

Similar to Kitamura,[62-64] Olofsson and co-workers recently developed several syntheses for the preparation of diaryliodonium salts, but in their transformations *m*-chloroperbenzoic acid (*m*CPBA) was employed as an oxidizing agent. With their methodologies a wide range of diaryliodonium salts were able to prepare in short reaction times and in high yields without the need for excess reagents (**Scheme 19**). The reactions were performed in DCM, in combination with triflic acid (TfOH), toluenesulfonic acid (TsOH), or boron trifluoride etherate ($BF_3 \cdot OEt_2$), depending on the structure of the iodonium salt. The TfOH based method (**Scheme 19a**),[67] which applies aryl iodides (**57**) and arenes (**45**), is the most versatile, while the utilization of TsOH[68] is more suitable for the synthesis of electron-rich salts. Both of them could be extended to the synthesis of symmetric diaryliodonium salts directly from and arenes (**45**) and iodine.[67,68] The employment of $BF_3 \cdot OEt_2$ together with arylboronic acids[69] (**50**) allows a regiospecific synthesis of iodonium salts with otherwise inaccessible substitution patterns (**Scheme 19b)**. Gaunt[70] et al. modified the TfOH method (**Scheme 19a**) by using tetrafluoroboric acid instead of triflic acid. The obtained diaryliodonium tetrafluoroborates were converted into the corresponding triflates by treatment with TMSOTf.



Scheme 19. *Olofsson's one pot syntheses of diaryliodonium salts with mCPBA*

As reported by Olofsson[71] in 2009, the use of environmentally more benign urea-hydrogen peroxide in combination with triflic anhydride instead of *m*CPBA also serves as an efficient oxidation system delivering a wide range of diaryliodonium triflates in good yields from aryl iodides (**57**) and arenes (**45**) (**Scheme 20**).



Scheme 20. *Preparation of diaryliodonium salt with urea-hydrogen peroxide*

2. 5. 3. Application of diaryliodonium salts in organic syntheses

In the last decades, transformations including diaryliodonium salts have become an important and widespread research field of organic syntheses. Therefore, numerous applications have been developed such as metal-catalyzed cross-couplings, C–H activation, aryne generation or dearomatization of phenols. Recently, diaryliodonium salts have been recognized as efficient reagents in arylation reactions with a wide range of nucleophiles under both metal-free and metal-catalyzed conditions. In these kinds of transformations, diaryliodonium salts implement the aryl transfer, providing diverse arylated aromatic and heteroaromatic substrates. In the followings, we aim to resume the arylation reactions accomplished with the employment of diaryliodonium salts with nucleophilic systems (C-, O-, N- and S-nucleophiles) under both metal-free conditions and with the utilization of copper catalyst.

2. 5. 3. 1. Transition-metal free arylations of heteroatom and carbon nucleophiles

The application of diaryliodonium salts in the functionalization of carbon and heteroatoms opens new possibilities to access the target compounds. The report of Beringer[50] in 1953 can be considered as a pioneering study, in which he demonstrated that diaryliodonium bromides are useful reagents for the phenylation of versatile organic and inorganic bases including alkoxides, phenoxides, benzoates, nitrites, sulfonamides, amines, sulfites, sulfonates, and cyanides under relatively mild conditions. Hence, the publications according to this research field have been increasing significantly from the 1950s, therefore only assorted articles are presented in the followings.

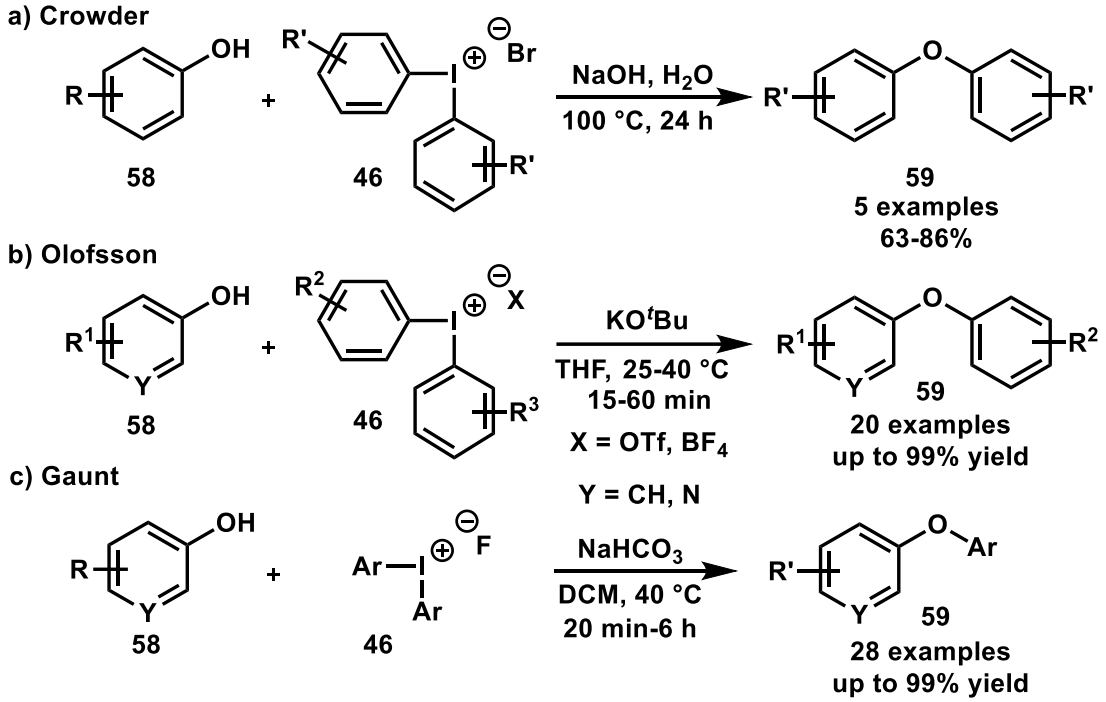
According to *arylation of oxygen nucleophiles*, we can find examples for the transition metal-catalyzed synthesis of aromatic, heteroaromatic and aliphatic alcohols too. In 1963, Crowder[72] reported the preparation of diaryl ethers by the S_N2-type reactions of phenols (**58**) in the presence of sodium hydroxide base in aqueous conditions (**Scheme 21a**). Diaryliodonium bromides (**46**) were employed as arylating agents and the reactions were carried out at 100°C. Electron-donating methyl or methoxy groups as well as electron-withdrawing carbonyl group were tolerated in the reaction providing the appropriate products (**59**) in 63-86% yields.

In the last few years, Olofsson and co-workers developed a few examples for metal-free O-arylations, for example in 2011 they published the preparation of diaryl ethers (**59**) from phenols (**58**) under mild conditions in short reaction times (compared to Crowder's work, 25-40 °C reaction temperature was employed in 15-60 min) and in good to high yields (**Scheme 21b**).[73] In the reaction potassium-*tert* butoxide was utilized as a base and the reactions were conducted in tetrahydrofurane. Sterically crowded, *ortho*-substituted phenol derivatives and heteroaromatic pyridines were also able to transform to the desired products (**59**).

Similar to Crowder, Olofsson also realized the metal-free synthesis of aryl ethers (**59**) in aqueous medium under mild conditions (instead of 100 °C lower temperature, 25-50 °C was applied). Both allylic, benzylic alcohols and phenols were active in the reaction providing the desired products in good to high yields.[74] The functionalization of phenol substrates worked with the best efficiency, the appropriate arylated products were isolated in up to 98% yield.

Very recently, Gaunt et al. also developed a mild and transition metal-free counter anion triggered electrophilic O-arylation strategy by using diaryliodonium fluorides.[75]

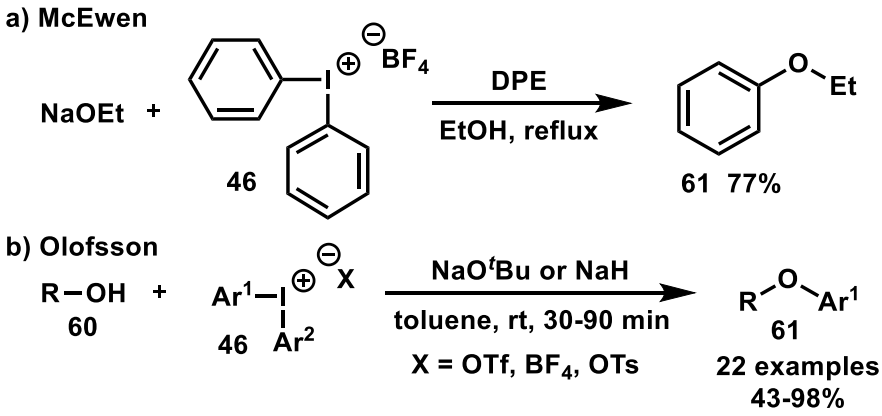
Sodium hydroxide base was used in dichloromethane solvent and a wide range of diaryl ethers (**59**) were synthesized in high yields (**Scheme 21c**). Beside the aromatic substrates, heteroaromatic compounds such as pyridine and quinoline derivatives were also able to functionalize. Not only phenols and pyridine derivatives, but compounds containing two nitrogen atoms such as 2-oxo-pyrimidines were also suitable substrates for O-arylations, as described by Karade[76] in 2014. The reactions were conducted in toluene in the presence of potassium carbonate base. The reaction was selective, while the two nitrogen atoms of the heteroaromatic ring did not change under the employed reaction conditions.



Scheme 21. *Preparation of diaryl ethers with a) NaOH b) KO^{t}Bu c) $NaHCO_3$ base*

According to the arylation of aliphatic alcohols, after the work of Beringer,[50] McEwen[77] reported an etherification reaction induced by sodium ethoxide and diphenyliodonium tetrafluoroborate (**Scheme 22a**) for the preparation of ethoxybenzene (**61**). With the utilization of 1,1-diphenylethylene (DPE) additive selectivity problems could be solved and only the desired O-arylated product was obtained and was isolated in 77% yield. In 2006, Fujita and Okuyama[78] described the solvolysis of diaryliodonium tetrafluoroborates occurred in alcohol solvent at elevated temperature (130 °C) in the absence of base. Only poor yields were achieved as both aryl groups of unsymmetrical diaryiodonium salts were transferred in the reaction. Another approach for the synthesis of alkyl-aryl ethers (**61**) from aliphatic alcohols (**60**) with diaryliodonium salts (**46**) was developed by Olofsson[79] in 2014. As a base, sodium *tert*-butoxide or sodium hydride was

utilized in toluene and the products were isolated in 43-98% yields (**Scheme 22b**). Amongst the alcohol derivatives, primary alcohols were the most efficient reaction partners providing the appropriate products in high yields. However, secondary, benzylic and allylic alcohols were also able to transform to the corresponding alkyl-aryl ether derivatives.



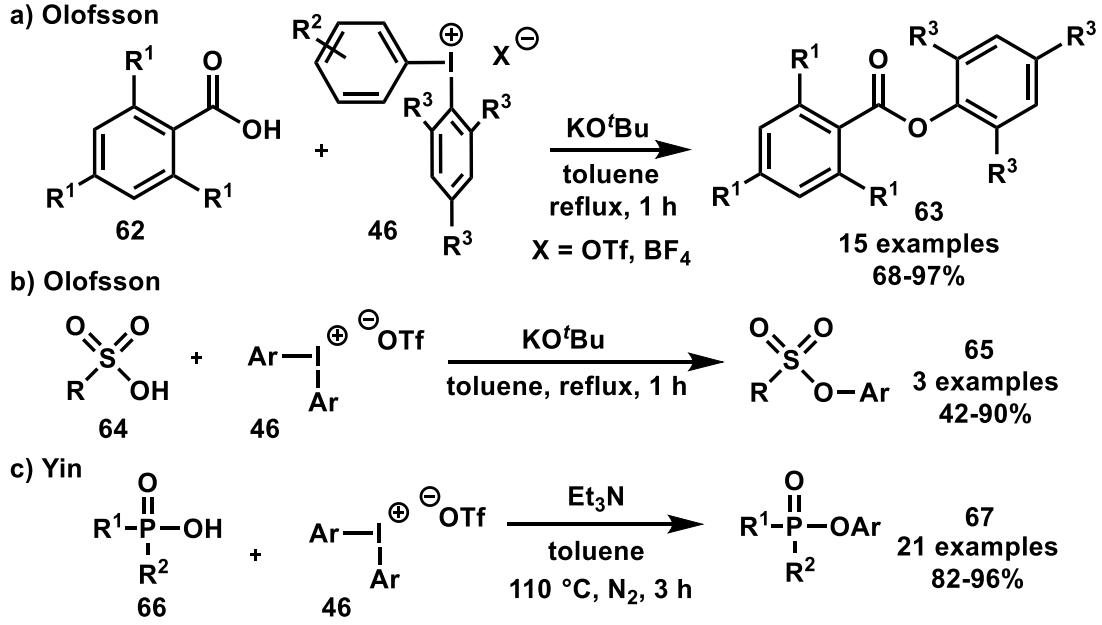
Scheme 22. *Synthesis of alkyl-aryl ethers with diaryliodonium salts*

In the presence of sodium hydride base Stuart[80] and co-workers reported another transition metal-free approach for the preparation of alkyl-aryl ethers (**61**) from aliphatic alcohols (**60**) and unsymmetric arylmesityliodonium bromides. In their reactions methyl *tert*-butyl ether (MTBE) was used as a solvent. Primary, secondary, tertiary, allylic, and benzylic aliphatic alcohols were all suitable substrates for the transformation obtaining the desired products in 44-83% yields. The applicability of the developed procedure was also employed in the synthesis of Pioglitazone, active ingredient of the antidiabetic Actos.

The arylation of acids with the employment of diaryliodonium salts were also discussed in the literature. For example, the preparation of aryl esters (**63**) from carboxylic acids (**62**) and diaryliodonium salts in the presence of potassium *tert*-butoxide in toluene solvent was realized by Olofsson[81] in 2011 (**Scheme 23a**). Aromatic as well as aliphatic substates were suitable for the transformation providing the corresponding products in good to high yields. With the utilization of *t*-BuOK base in toluene solvent, other acid derivatives such as sulfonic acids (**64**) were also suitable reaction partners for the iodonium salts and the desired arylsulfonates (**65**) were isolated in moderate to good yields (**Scheme 23b**).[82]

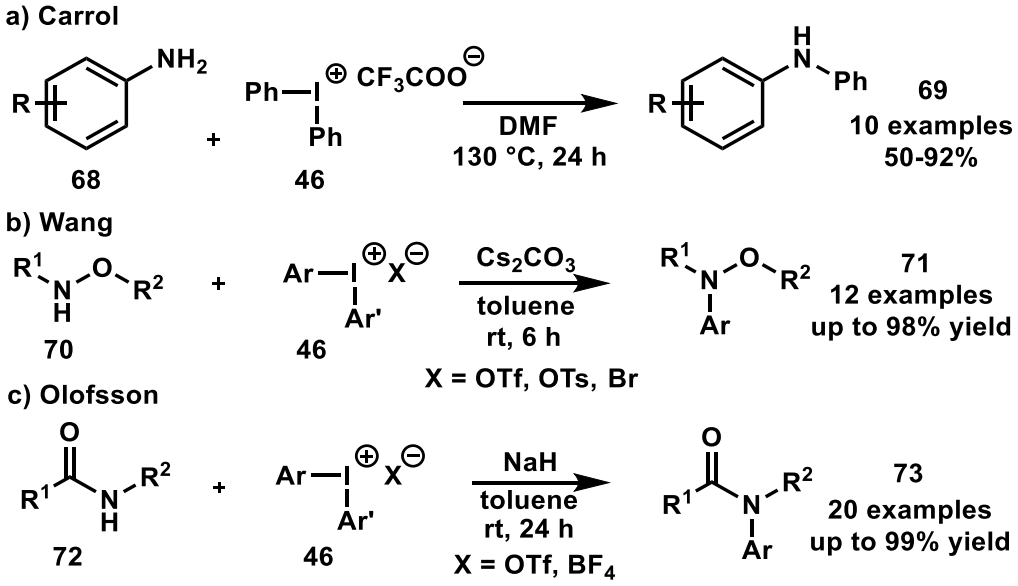
One year later, the microwave-assisted metal-free arylation of sulfinate salts for the construction of diaryl sulfones in was developed by Kumar and co-workers.[83] The reactions were performed in PEG-400 solvent at 50 °C and the appropriate products were synthesized in good to high yields. Beside the arylation of carboxylic and sulfonic acids,

the base-promoted arylation of phosphoric acid derivatives (**66**) with diaryliodonium triflates (**46**) was also realized and recently reported by Yin[84] et al. The reactions were performed in toluene solvent at its reflux temperature in the presence of triethylamine and the arylated phorphorus compounds (**67**) were obtained in 82-96% yields (**Scheme 23c**).



Scheme 23. *Arylation of acids with iodonium salts*

Besides the O-arylation reactions, the *arylation of nitrogen nucleophiles* in the absence of transition-metal catalysts was also demonstrated on numerous examples in the last few years. For example, in 2007, Carrol[85] and Wood published a transition-metal-free *N*-arylation for the preparation of diarylamines (**69**) using anilines (**68**) and diphenyliodonium trifluoroacetate in dimethylformamide at 130 °C (**Scheme 24a**). The appropriate products were isolated in 50-92% yields. Chen[86] and co-workers recently described the metal-free arylation of *ortho*-acylanilines for the construction of acridine derivatives. The reactions were accomplished in dichloroethane (DCE) also at elevated temperature and the condensed heteroaromatic compounds were obtained in good to high yields. Another approach was developed by Wang[87] et al. in 2014 for the *N*-arylation of hydroxylamines (**70**) with iodonium salts (**46**) in toluene solvent under mild conditions. The cesium-carbonate promoted direct arylation provided the corresponding products (**71**) in good to high yields (**Scheme 24b**).

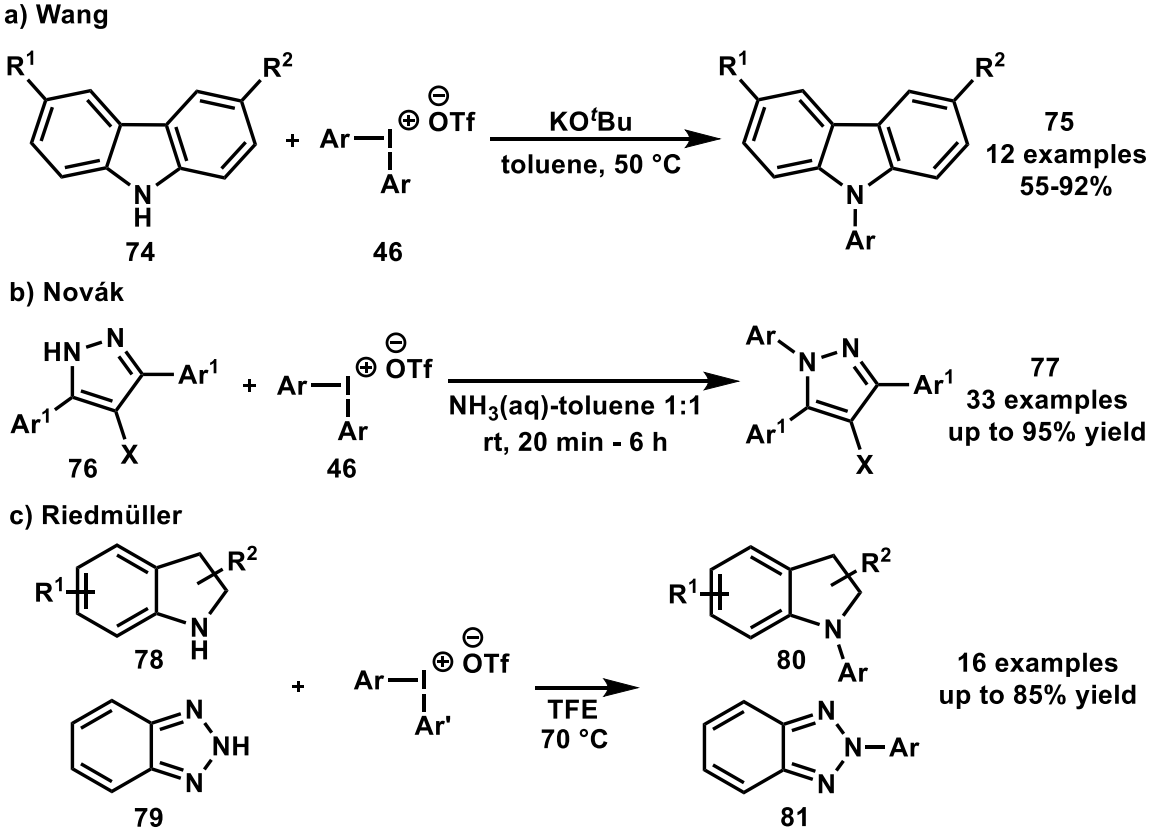


Scheme 24. *N-arylation of a) anilines b) hydroxylamines and c) acyclic amides*

One year later, the synthesis of α,β-unsaturated *N*-aryl ketonitrones from oximes and diaryliodonium salts *via* metal-free *N*-arylation process under mild conditions was described by Mo[88] and co-workers. Potassium hydroxide base was utilized as a base in carbon tetrachloride solvent at room temperature. Based on DFT calculations, the products were presumed to form *via* [1,3]-phenyl migration. The *N*-arylation of non-aromatic systems, such as alkyl amides was alsoable to realize in the presence of iodonium salts. Very recently, the sodium hydride-mediated *N*-arylation of secondary acyclic amides (**72**) using iodonium salts in toluene at room temperature was reported by Olofsson (**Scheme 24c**).[89] The desired arylated products (**73**) were isolated in high yields. Results of the substrate scope revealed that amides equipped with electron-donating groups provided the tertiary acyclic amides (**73**) in high yields, whereas in the case of the iodonium salts electron-deficient aryl groups were more efficiently transferred.

Amongst the *N*-arylation reactions, in the last decade, a few methodologies were developed focusing on *N*-functionalization of different heterocyclic compounds with diaryliodonium salts under metal-free conditions. As an example, the potassium *tert*-butoxide-mediated synthesis of *N*-arylated carbazoles (**75**) using diaryliodonium tirflates (**46**) in toluene was described by Han and Wang in 2012 (**Scheme 25a**).[90] The arylated heterocyclic compounds were isolated in 55-92% yields. Employing the same reaction conditions for the N-H functionalization of tetrahydrocarbazole derivatives, in that case of substrates C-arylation reaction occurred.

Very recently, the metal-free *N*-arylation of pyrazole derivatives (**76**) under mild conditions in short reaction times was also realized and published in our research group[91] employing a wide range of diaryliodonium salts. The reactions were conducted in aqueous ammonia-toluene 1:1 mixture at room temperature providing the arylated products (**77**) in up to 95% yield (**Scheme 25b**). Iodonium salts containing sterically more hindered and more electron-deficient aryl groups were the most suitable reagents in the transformation. In the same year, according to the *N*-functionalization of heterocyclic compounds, the synthesis of *N*-arylated indolines (**80**) and 2-arylated benzotriazoles (**81**) using diaryliodonium triflates was realized by Riedmüller[92] et al. The reactions were accomplished in trifluoroethanol (TFE) at higher temperature (70 °C) without the use of any additional additive affording the corresponding products in moderate to good yields (**Scheme 25c**).

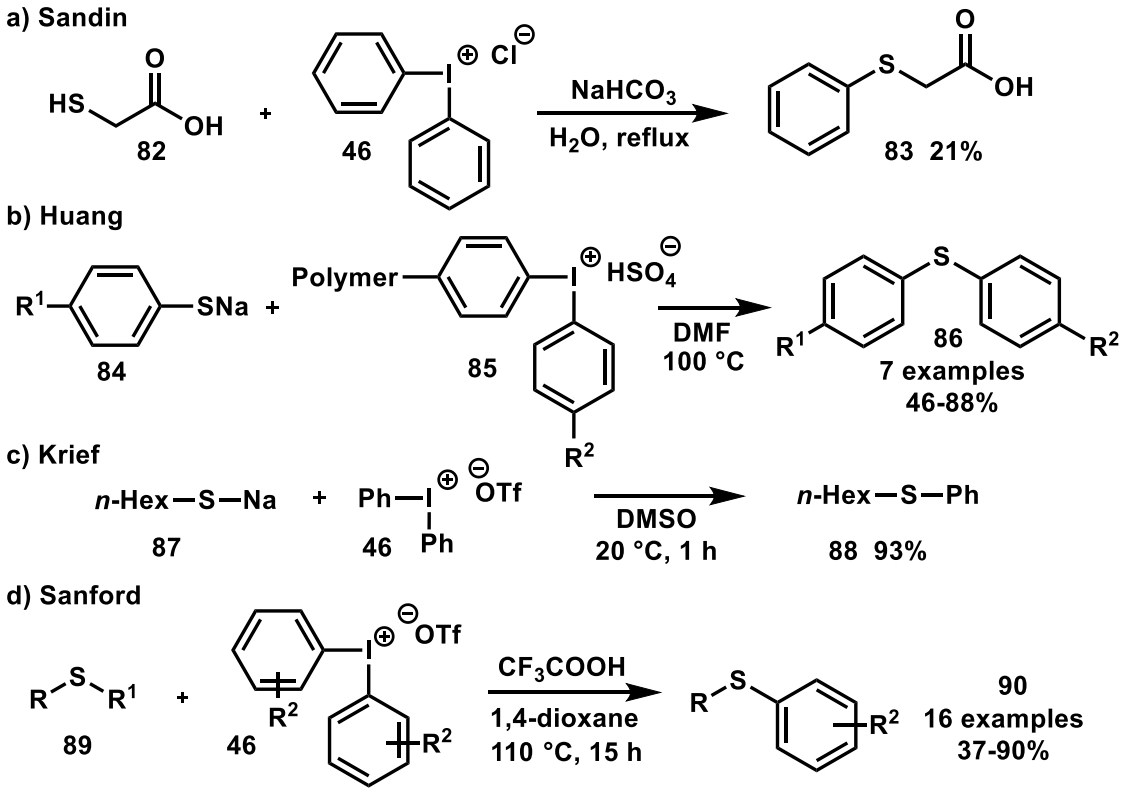


Scheme 25. *N-arylation of heterocycles with diaryliodonium triflates*

The *arylation of sulfur nucleophiles* with diaryliodonium salts in the absence of transition-metal catalysts has been known for 1947, when Sandin[93] reported the reaction of diphenyliodonium chloride (**46**) with thioglycolic acid (**82**), thiophenol and cysteine. However, *S*-phenylthioglycolic acid (**83**) was isolated in only 21% yield (**Scheme 26a**). In 2001, Huang[94] et al. published another S-arylation reaction for the synthesis of diaryl

sulfides (**86**) from benzenethiolates (**84**) utilizing polymeric diaryliodonium salts (**85**). The reactions were carried out in dimethylformamide solvent at 100 °C and the desired products were obtained in 46-88% yields (**Scheme 26b**). Beside the employment of aromatic thiolates in S-arylation reactions, the application of alkyl thiolate derivatives in these kinds of transformations was also achieved. In 2006, the S-arylation of *n*-hexyl thiolate (**87**) with diphenyliodonium triflate was attained by Krief[95] and co-workers in dimethylsulfoxide solvent at lower temperature. The reaction provided the arylated product (**88**) in 93% yield (**Scheme 26c**).

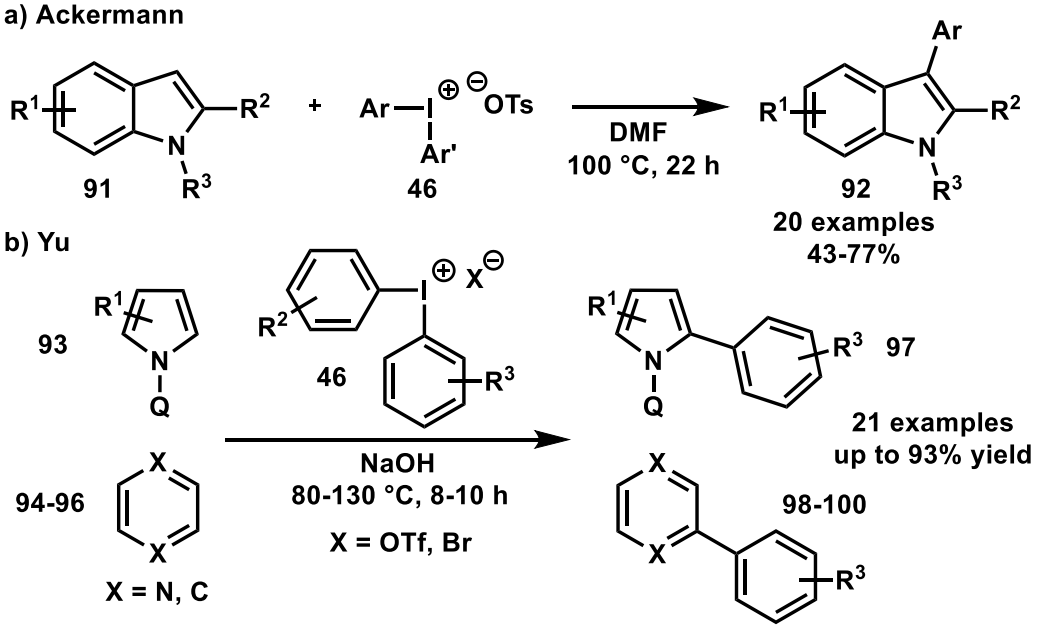
The typical disadvantages of the examples presented above are the relatively low yields or poor functional group tolerance. Amongst these transformations the work of Sandin presents the most synthesized S-arylated products, in which only 7 examples are given. The solution to these problems was achieved by Sanford[96] by the development of a novel metal free acid-mediated synthesis for the construction of diaryl and alkyl-aryl sulfides (**90**) from thiols and thioethers (**89**) with high functional group tolerance and good to excellent yields (**Scheme 26d**). In contrast with previous examples, the applicability of the developed reaction was demonstrated on 16 examples.



Scheme 26. *Arylation of sulfur nucleophiles with diaryliodonium salts*

The *arylation of carbon nucleophiles* using diaryliodonium salts in the absence of transition-metal catalysts was an underdeveloped research field of organic syntheses after the early work of Beringer[50]. However, in recent years, besides the arylation of heteroatom nucleophiles, this process has received considerable attention, thus, the arylation of several aromatic and heteroaromatic systems was achieved *via* C-arylation processes. In 2011, Ackermann[97] developed the metal-free C3-arylation of indoles (**91**) and pyrroles using diaryliodonium salts in dimethylformamide solvent at high temperature (100 °C). Without the use of any additives nitrogen-protected and free indole derivatives were also able to transform to the desired products (**92**) in moderate to good yields (**Scheme 27a**).

One year later, the C-arylation of different aromatic and heteroaromatic substrates including substituted pyrroles **(93)**, pyridine (**94**), pyrazine (**95**) and benzene derivatives (**96**) in the absence of transition-metal catalysts was published by Yu[98] et al. Sodium hydroxide was utilized as a base at elevated temperature (**Scheme 27b**). C-arylation of pyridine derivatives provided isomers, while in the case of pyridazine and benzene derivatives the corresponding arylated products (**97**-**100**) could be isolated selectively.



Scheme 27. *C-arylation of electron-rich heterocycles with diaryliodonium salts*

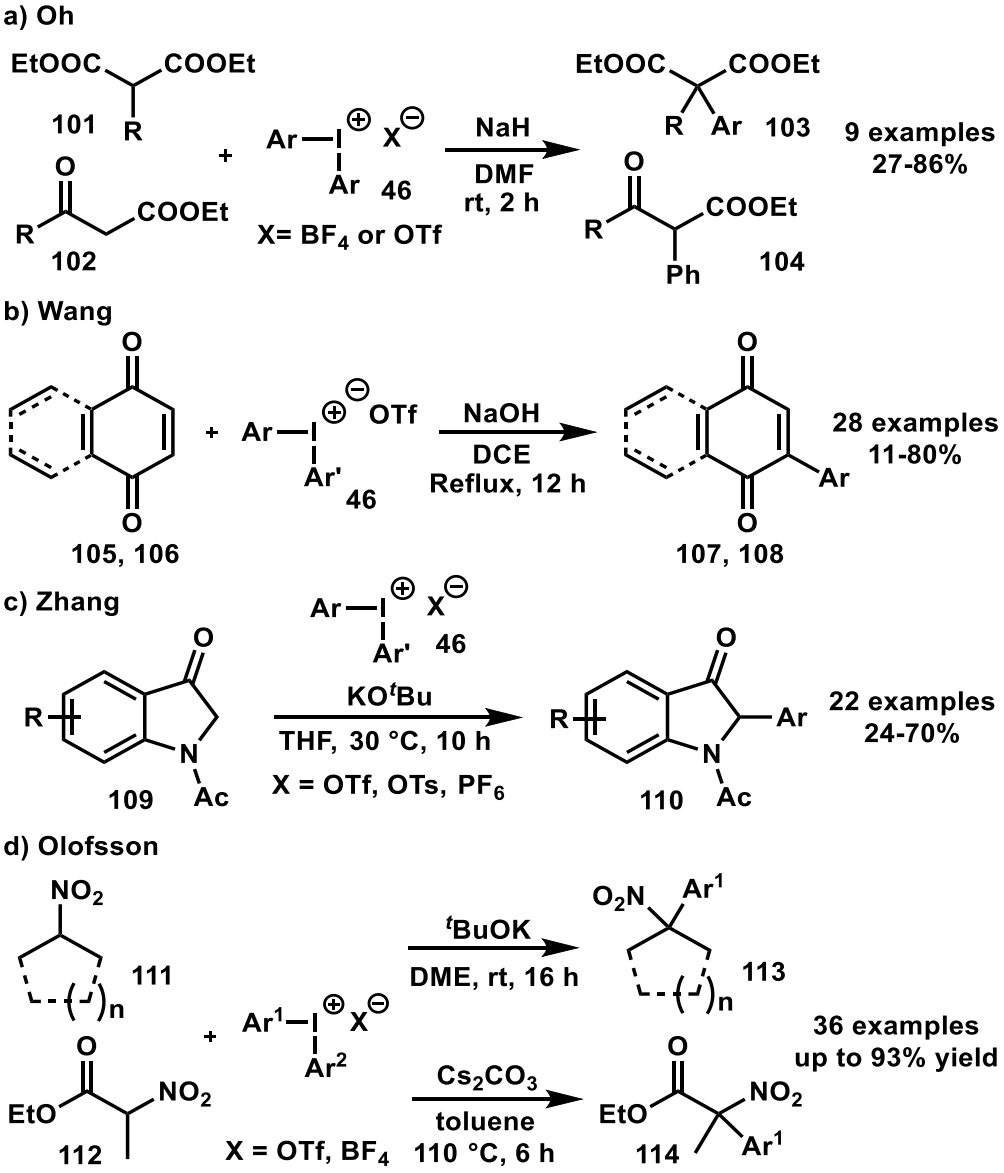
Besides the arylation of different heterocyclic cores, carbonyl compounds were also suitable substrates for these kinds of transformations. The metal-free arylation of silyl enol ethers for the construction of α-arylated carbonyl compounds was published by Koser[99] in 1991. The arylation with diaryliodonium salts took place at low temperature (-40 °C) in tetrahydrofuran solvent. The products were obtained in moderate to good yields

(20-88%). The metal-free arylation of other carbonyl compounds such as alkyl malonates (**101**) and alkyl β-keto esters (**102**) under mild conditions was also realized by Oh[100] et al. As a base, sodium hydride was utilized while the solvent of the transformation was dimethylformamide. The appropriate arylated products (**103** and **104**) were isolated in moderate to good yields (**Scheme 28a**). The reactions could be selectively accomplished with the employment of diaryliodonium salts containing trimethoxyphenyl 'dummy' group promoting the transfer of the less electron-deficient and less hindered aryl group. A similar approach was followed by Manetsch[101] for the C-arylation of β-ketocarboxylic acids in the presence of *t*-BuOK base in DMF. The synthesis of ELQ-300 was also realized with the developed method, an antimalarial compound currently in preclinical development phase. Olofsson[102] et al. published the first enantioselective transition-metal-free arylation of cyclohexanones with the utilization of Simpkin's base, which allows the generation of the nucleophilic enolate intermediate. The appropriate arylated products were isolated in 41-70% yields.

According to the arylation of cyclic carbonyl compounds, the C2-functionalization of quinones and naphthoquinones (**105** and **106**) was also achieved by Wang[103] and co-workers with diaryliodonium triflate reagents (**46**) and sodium hydroxide base in DCE at elevated temperature (**Scheme 28b**). In the presence of electron-donating groups, the reaction provided the desired arylated quinones (**107**) in good yields. However, electron-withdrawing groups had deleterious effects on the transformation and the expected products could be isolated only in lower yields. Other heterocyclic compounds such as indolines (**109**) were also suitable substrates for metal-free arylations.

Employing diaryliodonium salts with the combination of *t*-BuOK base in THF under mild conditions, Zhang[104] described a C2-arylation method for the construction of arylated indolinones (**110**). Various products were synthesized, although in moderate yields (**Scheme 28c**).

Not also carbonyl, but nitro compounds were also able to transform to the appropriate arylated derivatives. Very recently, Olofsson's group[105] reported the metal-free arylation of nitrocycloalkanes (**111**) and nitroesters (**112**) in the presence of potassium-tert butoxide or cesium carbonate bases in DME and toluene solvents. The applicability of the developed procedure was demonstrated on numerous examples and the products (**113** and **114**) could be isolated in up to 93% yields (**Scheme 28d**).



Scheme 28. *Metal-free arylation of carbonyl and nitro compounds with diaryliodonium salts*

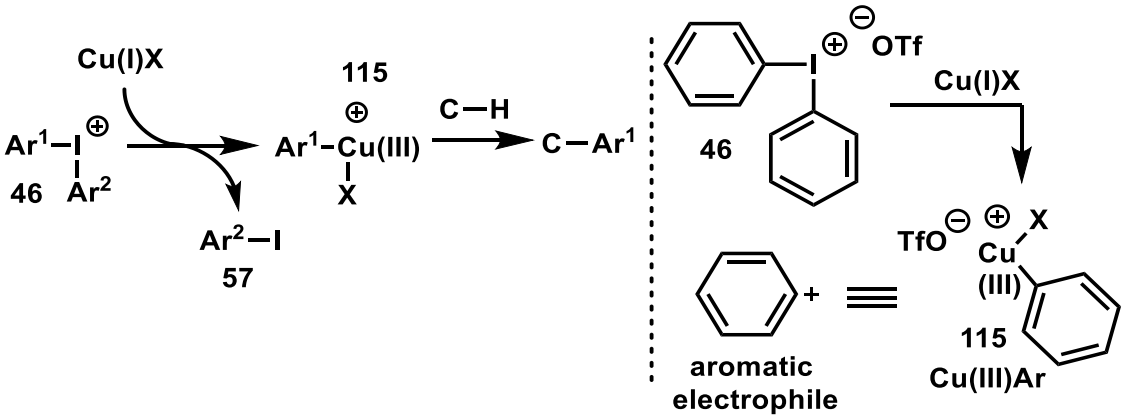
2. 5. 3. 2. Copper-catalyzed functionalization of aromatic and heteroaromatic molecules with diaryliodonium salts

The publications according to transition-metal-catalyzed arylations have been increasing noteworthy in the last decade. As our researches carried out during my PhD are involving copper-catalyzed transformations, thus, in the followings only those articles of the literatures are discussed, which were performed in the presence of copper catalyst.

2. 5. 3. 2. 1. Copper-catalyzed C-H arylations

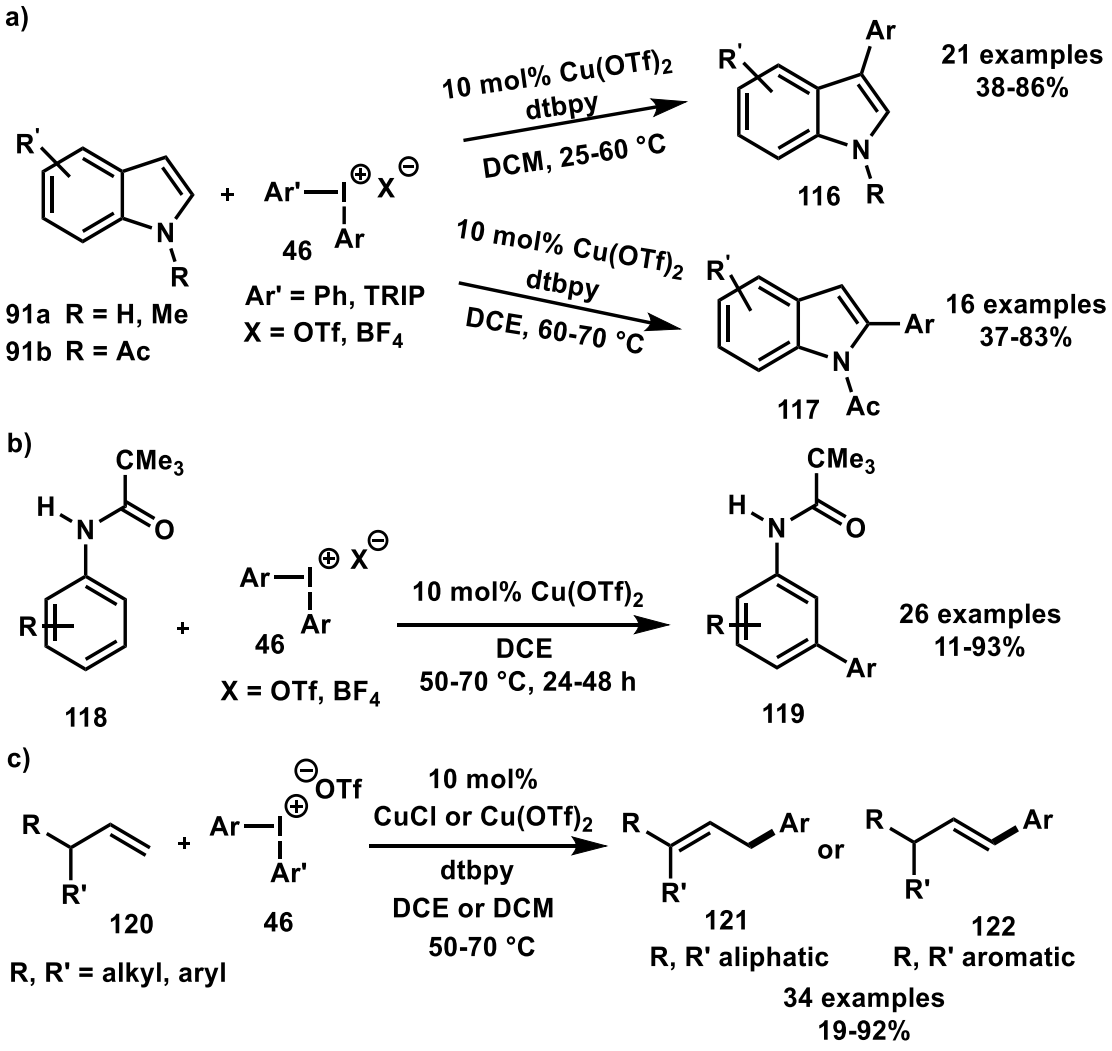
Functionalization of aromatic and heteroaromatic systems *via* copper-catalyzed C–H activation[106] is an important and intensively studied area of current organic chemistry. Diaryliodonium salts (**46**) are efficient reagents in these types of transformations due to the fact that their employment enables the introduction of aryl moiety into aromatic and heteroaromatic substrates.

According to the publications owing to this research field, Gaunt and co-workers marked an era in copper-catalyzed C-H arylations. They reported in 2008 that Cu(I) or Cu(II) catalysts could be oxidized in the presence of diaryliodine(III) reagent affording a highly electrophilic arylcopper(III) intermediate.[107] The generation of this aromatic electrophile equivalent species (**115**) allows the transfer of the aryl group, thereby enables the functionalization of aromatic C–H bonds *via* C–H arylation processes (**Scheme 29**).



Scheme 29. *The formation of Ar-Cu(III) intermediate and its employment in C-H arylations*

With the utilization of this strategy several arylations were described by Gaunt et al. For example, the selective arylation of indoles[107] at either the C3 or C2 position under mild conditions was realized using diaryliodonium triflates or tetrafluoroborates (**46**), copper triflate catalyst and 2,6-di-*tert*-butylpyridine base in DCM or DCE solvents (**Scheme 30a**). Unprotected and *N*-alkyl indole derivatives (**91a**) delivered the C3-arylated products (**116**), while *N*-acetylindoles (**91b**) afforded the C2 isomers in moderate to good yields (**117**).

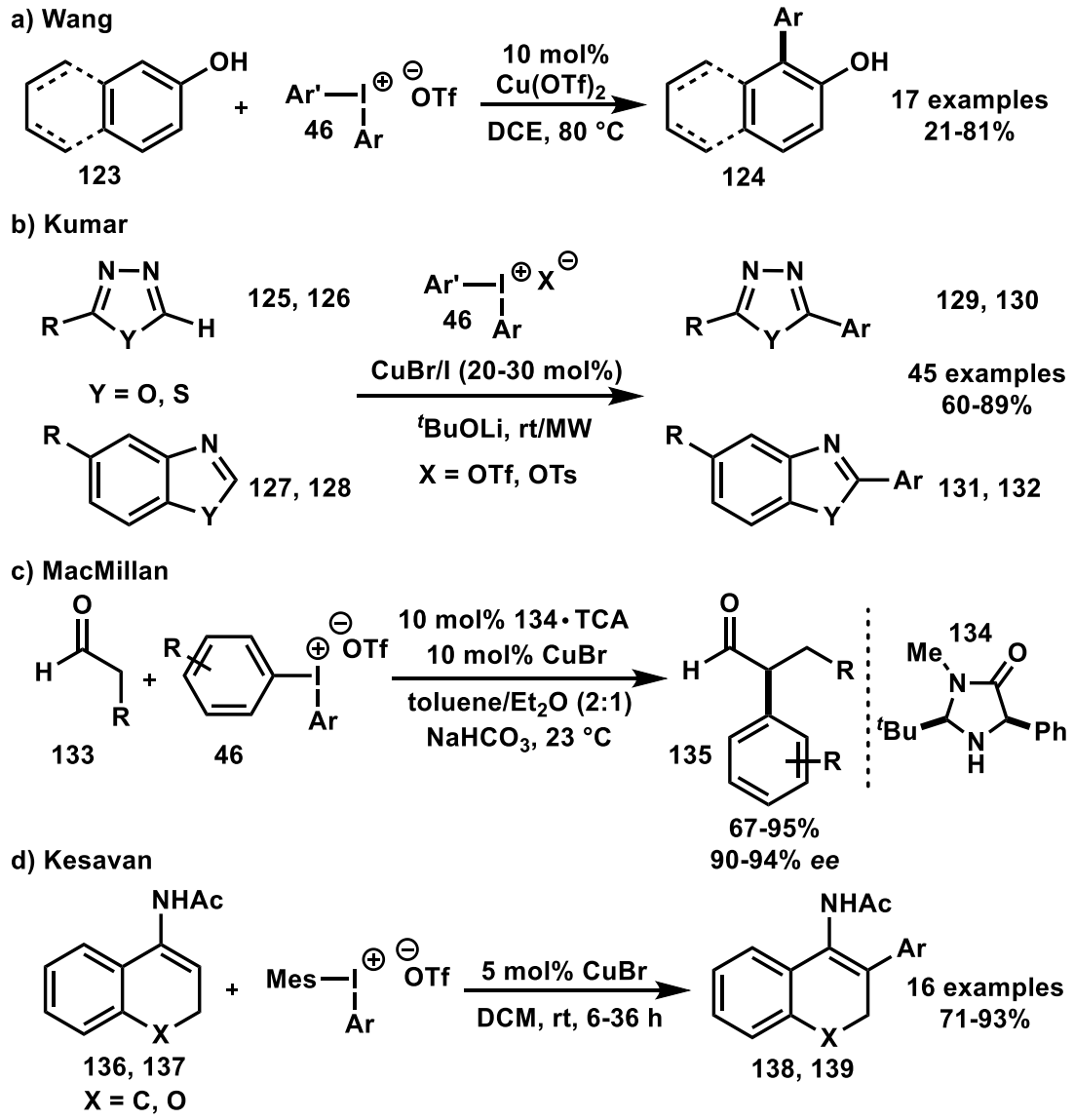


Scheme 30. *Gaunt's copper-catalyzed arylations with diaryliodonium salts*

This fact can be explained by the migration of the Cu(III)-aryl group from C3 to C2. In the case of *N*-acetylindoles, the carbonyl oxygen of the acetyl group can coordinate to the copper and may steer the Cu(III) species to the C2 position. One year later, the *meta*-selective arylation of pivalanilides[108] (**118**) utilizing diarylidonium salts was described by Gaunt et al. The reactions were performed in DCE and as a catalyst, copper triflate was employed (**Scheme 30b**). The corresponding *meta*-arylated products were obtained in 11-93% yields. According to the mechanism of the developed transformation, the reaction was proposed to undergo *via* the formation of a highly active arylcopper(III) intermediate. As an extension, the copper-catalyzed *meta*-selective direct arylation of α-aryl carbonyl compounds[109] was also reported by Gaunt and co-workers two years later. Moreover, an enantioselective α-arylation procedure of *N*-acyloxazolidinones[110] with copper(II)-bisoxazoline catalysts and diaryliodonium salts was also achieved in the same year. In 2012, the copper-catalyzed arylation of alkenes[111] (**120**) was demonstrated by

this research group. Diaryliodonium triflates, copper chloride or triflate and di-*tert*-butylpyridine base were employed in DCE or DCM solvents (**Scheme 30c**). Two alkene isomers (**121** and **122**) were formed and the selectivity was influenced by the structure of the starting alkene and the diaryliodonium salt. The developed method was demonstrated on numerous examples.

Beside the pioneering works of Gaunt, the C-H functionalization of aromatic and heteroaromatic cores using diaryliodonium salts was discussed by other research groups too. For example, Modha[112] and Greaney also developed a copper-catalyzed procedure for the arylation of indoles. In their methodology tandem C–H and N–H arylation occurred. Very recently, the copper-catalyzed selective *ortho*-arylation of 2-naphtol and phenol derivatives (**123**) with diaryliodonium triflates was reported by Wang[113] et al. Copper triflate was employed in DCE at 80 °C (**Scheme 31a**). Another C–H arylation approach for the construction of arylated 1,3-azoles (**129** and **130**) and benzoxazoles (**131** and **132**) was reported by Kumar[114] and co-workers in 2014. The reactions were accomplished with the utilization of copper bromide or iodide catalyst in dimethyl sulfoxide solvent at room temperature and a wide range of products were synthesized in good yields (**Scheme 31b)**. Similarly to the publications of Gaunt, [109-110] the α-arylation of carbonyl compounds was also accomplished by Stang and MacMillan. In 1997, Stang[115] reported the copper cyanide mediated arylation of cyclic ketones with diaryliodonium triflates. The disadvantages of this reaction are low yields and the need of equivalent amount of copper. The enantioselective α-arylation of aldehydes[116] (**133**) and silyl enol ethers[117] in the presence of catalytic amount of copper could be also achieved by MacMillan in 2011. In the first transformation, copper bromide was utilized in the presence of amine catalyst (**134**). The appropriate α-aryl aldehydes (**135**) were isolated in 67-95% yields and in high enantioselectivity (**Scheme 31c**). The C-arylation of cyclic enamide and naphthyl-acetamide substrates (**136** and **137**) was also demonstrated by Kesavan[118] et al. for the synthesis of β-aryl cyclic enamides (**138** and **139**) with the employment of copper bromide catalyst in DCM solvent (**Scheme 31d**). The appropriate products were obtained in 71-93% yields.



Scheme 31. *Copper-catalyzed arylation of a) phenole b) azole c) aldehyde and d) enamide derivatives*

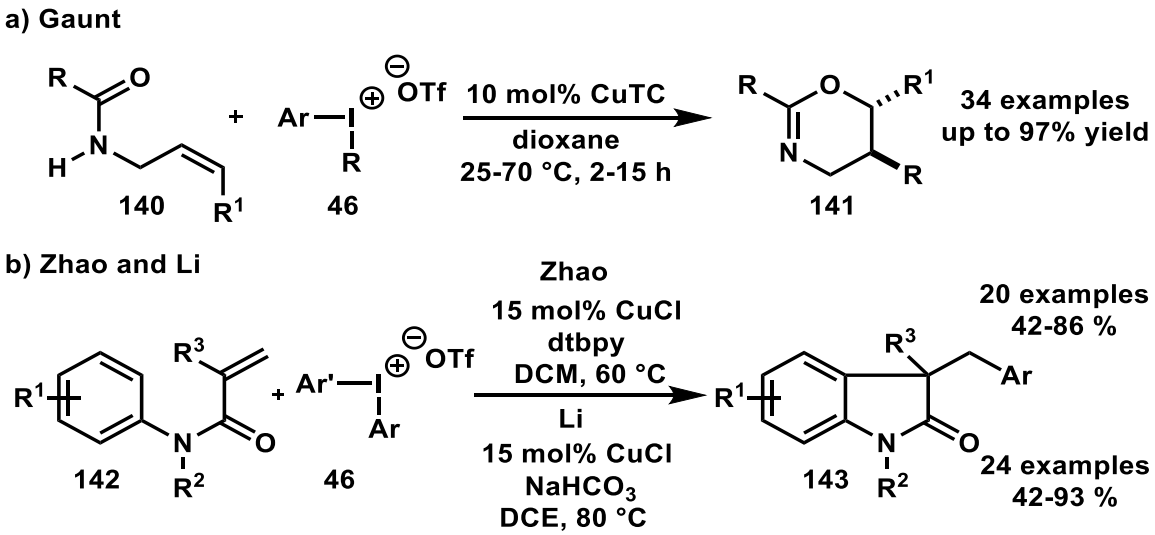
Another example for the synthesis of non-aromatic cyclic enamide derivatives was reported by Gillaizeau.[119] In this transformation, instead of copper bromide, copper triflate was employed as the catalyst in the same solvent (DCM) and di-*tert*-butylpyridine (dtbpy) base was also added to the reaction mixture.

2. 5. 3. 2. 2. Copper-catalyzed cyclizations of unsaturated compounds

With the functionalization of unsaturated systems such as electron-rich alkenes, alkynes and nitriles *via* copper-catalyzed arylation processes in the presence of iodonium salts diverse heterocyclic skeletons can be constructed. Due to this fact, the synthesis of several complex heterocyclic compounds was accomplished in the last few years. The mechanism of these kinds of transformations is presumed to involve the formation of a

highly active arylcopper(III) species. In the presence of this aromatic electrophile equivalent (**115**) activation of triple bonds or generation of carbocationic species from alkynes and nitriles can occur inducing different cyclization reactions.

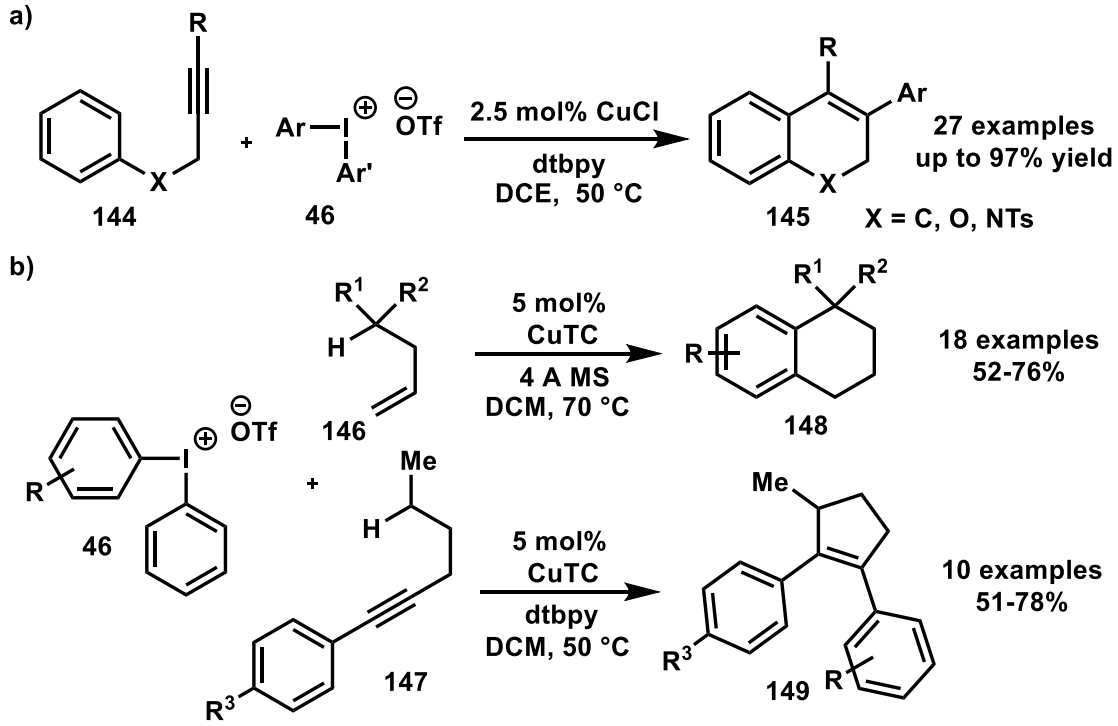
According to the ring closures of *alkene* derivatives, in 2013, Gaunt and co-workers reported the copper-catalyzed *endo*-selective oxyarylation and oxyvinylation of allylic amide substrates[120] (**140**) using diaryliodonium triflates (**46**) and CuTC (TC = thiophene-2-carboxylate) catalyst in dioxane solvent. The applicability of the developed transformation was demonstrated on numerous examples. A wide range of *endo*-oxazine products (**141**) were synthesized in up to 97% yield (**Scheme 32a**). The method was further developed and recently the catalytic both enantioselective and regiodivergent arylation of allylic amides was reported.[121] The arylation can be controlled by the electronic nature of the diaryliodonium salt enabling the preparation of nonracemic diaryloxazines or β,β-diaryl enamides. In 2013, two very similar approaches were published by Zhao[122] and Li[123] for the preparation of oxindoles (**143**) from acrylamides (**142**). The first transformation utilizes CuCl catalyst in combination with di-*tert*-butylpyridine (dtbpy) base in DCM at 60 °C, while in the second one inorganic $NaHCO_3$ base was employed with the same copper source in DCE solvent at 80 °C (**Scheme 32b**). The products were obtained in moderate to good yields (42-86% and 42-93% yields, respectively).



Scheme 32. *Copper-catalyzed arylation of different amides with diaryliodonium triflates*

Besides the alkynes, electron-rich *alkynes* were also suitable substrates for copper-catalyzed ring closures with diaryliodonium salts. In 2013, Gaunt et al. described the copper-catalyzed carboarylation of alkynes[124] (**144**) with diaryliodonium triflates (**46**) in

the presence of copper chloride catalyst and dtbpy base. The reactions were conducted in DCE at 50 °C and the desired tetrasubstituted alkenes (**145**) were isolated in up to 97% yield (**Scheme 33a**).

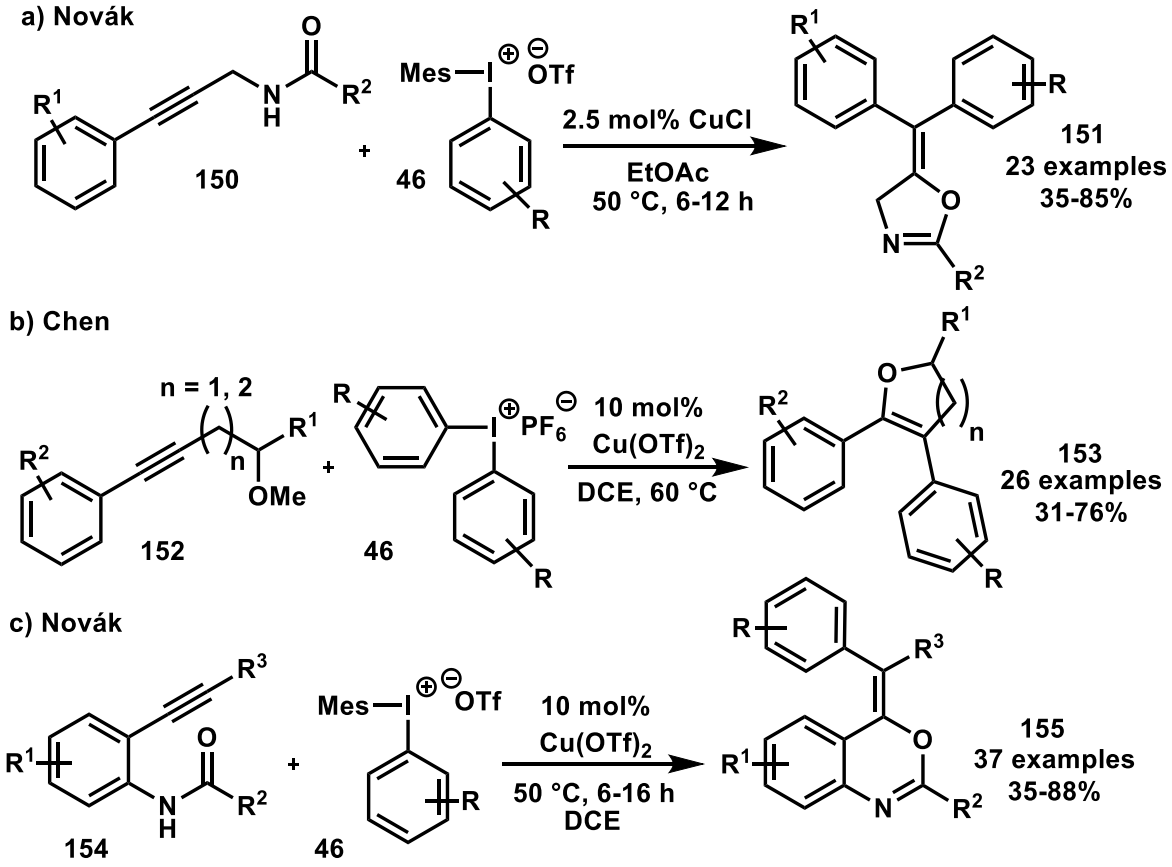


Scheme 33. *Gaunt's copper-catalyzed arylation-cyclization reactions of functionalized alkenes and alkynes*

One year later the developed methodology was extended to the synthesis of different carbocycles such as tetraline (**148**) and cyclopentene (**149**) derivatives.[125] Instead of CuCl CuTC was utilized as a copper source in DCE solvent (**Scheme 33b**). The corresponding cyclic products were obtained in moderate to good yields. Both reactions are supposed to undergo *via* the formation of arylcopper(III) species. A very similar arylcarbocyclization approach was published simultaneously by Chen et al. from alkyl alkynes for the construction of carbocycles and spirocycles.[126] Diaryliodonium hexafluorophosphates were utilized in the reaction as coupéing partners along with copper triflate catalyst in dichloroethane solvent. Moderate to good yields were achieved.

Copper-catalyzed transformations by the functionalization of electron rich substrates such as *alkynes* employing diaryliodonium salts were developed in our research group, too. In 2015, using this cyclization strategy the preparation of new oxazoline[127] derivatives (**151**) from propargyl amides (**150**) and arylmesitylidonium triflates (**46**) was achieved in our laboratory. Copper chloride was employed as copper source in ethyl acetate solvent at 50 °C. The products were obtained in 35-85% yields (**Scheme 34a**).

According to the mechanism, the reaction is presumed to involve a 5-*endo-dig* cyclization step *via* the formation of arylcopper(III) intermediate (**115**).

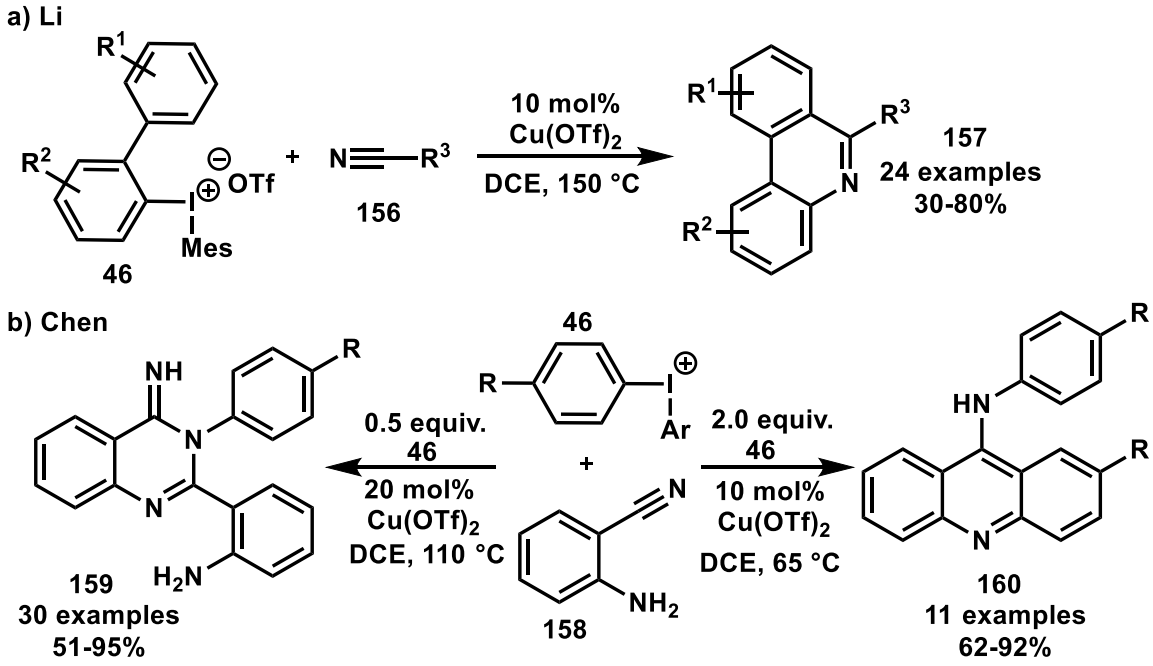


Scheme 34. *Copper-catalyzed ring closures of electron rich alkynes with diaryliodonium salts*

Recently, a very similar approach was realized and published by Chen and co-workers by the intramolecular aryl etherification of alkoxy-alkynes[128] (**152**) *via* C-O bond cleavage in the presence of diaryliodonium hexafluorophosphates. Copper triflate was used as a copper source in dichloroethane solvent at 60 °C, while the oxo-heterocyclic products (**153**) were prepared in moderate to good yields (**Scheme 34b**). According to the high reactivity of alkyne substrates observed in these kinds of arylation-ring closures, in 2013, a novel copper-catalyzed oxidative cyclization reaction was achieved in our laboratory for the synthesis of benzoxazine[129] derivatives (**155**) from 2-ethynylanilides (**154**). Similarly to the publication just presented this reaction also applies copper triflate in DCE. The desired products were isolated in 35-88% yields (**Scheme 34c**). The mechanism of the transformation is proposed to involve a *6-exo-dig* cyclization step.

In the last few years, some examples were also reported demonstrating the applicability of electron rich *nitriles* in copper-catalyzed oxidative arylation-cyclization reactions with diaryliodonium salts. For example, the copper triflate-mediated synthesis

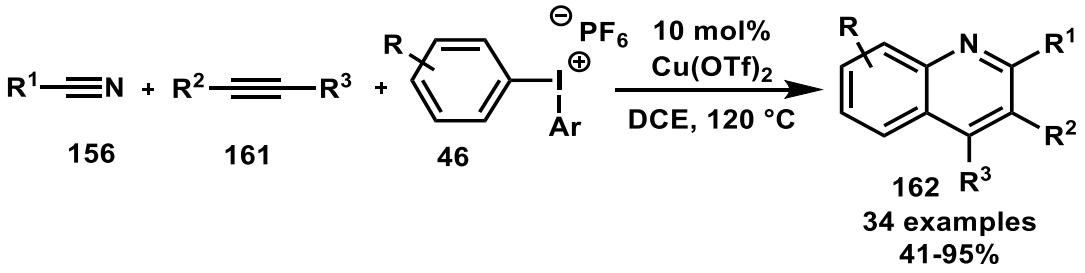
of phenanthridine[130] derivatives (**157**) *via* cascade annulation of diaryliodonium salts (**46**) and nitriles (**156**) was recently realized by Li et al. The reactions were performed in DCE at high temperature (150°C) and numerous products were prepared in 30-80% yields (**Scheme 35a**). According to the plausible mechanism of the transformation, the reaction is supposed to undergo *via* the formation of a highly active copper(III)-aryl intermediate (**115**), the same species which was assumed to generate when alkynes were employed as substrates in the copper-catalyzed arylation-ring closing reactions. Another approach for the construction of quinazolinimine[131] and acridine scaffolds (**158** and **159**) from diverse tandem cyclization reactions of *ortho*-cyanoanilines (**158**) and diaryliodonium salts (**46**) in the presence of copper triflate catalyst was reported by Chen and co-workers in 2014. The developed methodology provided the products in good to high yields (**Scheme 35b**). The formation of products **159** and **160** could be influenced by the amount of the iodonium salt. If 0.5 equivalent of diaryliodonium salt was added to the *ortho*-cyanoanilide, quinazolinimine (**159**) was formed during the reaction. In contrast, the employment of 2.0 equivalent of diaryliodonium salt afforded acridines (**160**).



Scheme 35. *Copper-catalyzed ring closures of electron rich nitriles with diaryliodonium salts*

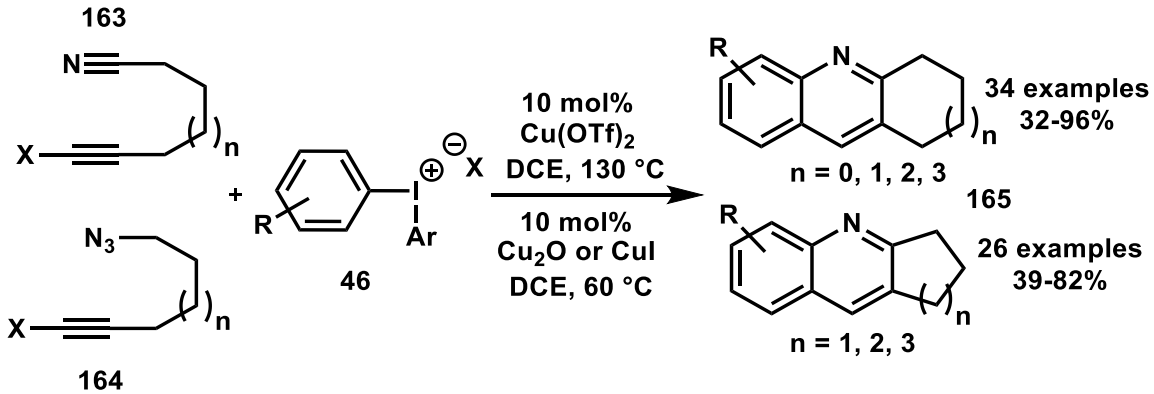
The publications presented above demonstrate the applicability of alkynes and nitriles in arylation-cyclization reactions induced by copper catalysts. However, the activation of a nitrile group in the presence of a carbon–carbon triple bond with copper catalyst and iodonium salt is also possible, as described by Chen et al. The employment of *alkynes and nitriles* altogether in oxidative arylation-cyclization reactions enables the

construction of various heterocyclic compounds. Utilizing this strategy, the synthesis of diverse heterocyclic skeletons such as quinolines[132], quinazolines,[133] dihydro-cyclopentaquinolines and tetrahydroacridines[134] were accomplished by Chen and co-workers in the last few years. In these reactions, copper triflate was utilized as a copper source in dichloroethane solvent with diaryliodonium hexafluorophosphates (**46**) and triflates. The synthesis of quinoline derivatives (**162**) was presented on numerous examples (34 products were prepared) and moderate to high yields were achieved (**Scheme 36**). The possible mechanism of these transformations was presumed to involve the formation of arylcopper(III) intermediate (**115**).



Scheme 36. *Copper-catalyzed arylation-cyclization reaction for the synthesis of quinolines*

These methods were further developed and were found that instead of nitriles[134] azydes can also be employed for the synthesis of polycyclic quinolines. Therefore, in 2014 Chen realized the tandem annulation of ω-azido-1-alkynes (**164**) with diaryliodonium salts (**46**) for the preparation of polycyclic quinolines.[135] The reaction utilizes copper(I) catalyst (CuI or Cu_2O) in DCE solvent at 60 °C. A wide range of products were synthesized and the desired polycyclic quinolines (**165**) (dihydrocyclopenta- and heptaquinolines, tetrahydroacridines) were obtained in moderate to high yields (**Scheme 37**).

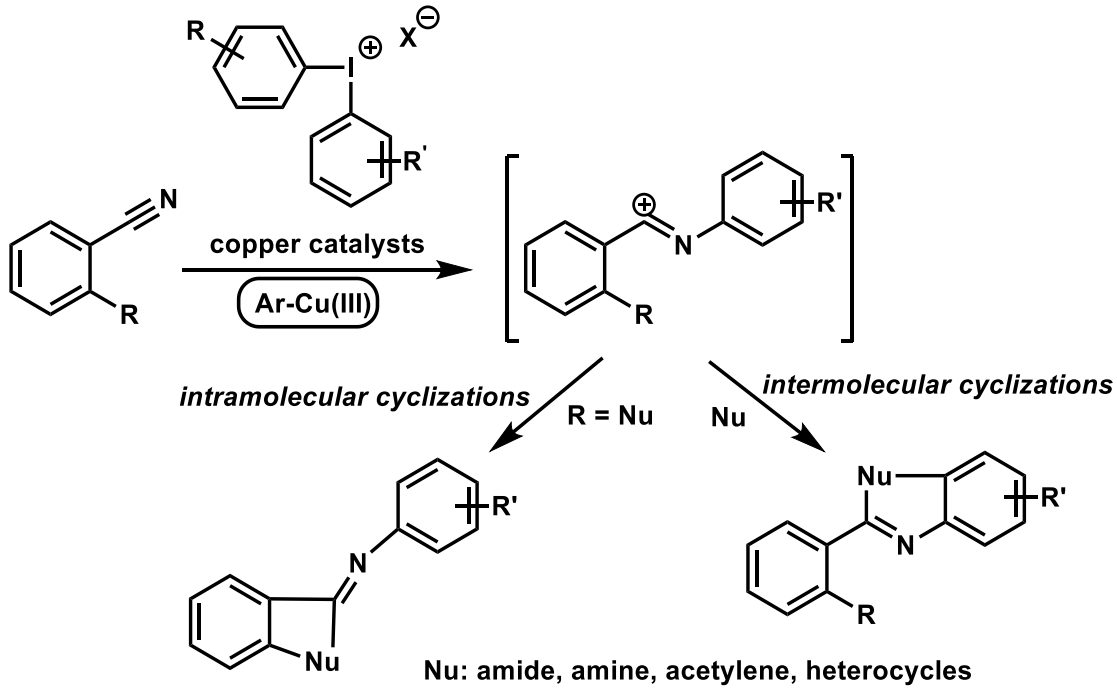


Scheme 37*. Chen's syntheses of polycyclic quinolines from cyano-alkynes and azido-alkynes*

3. Objectives

The goal of the presented PhD research is to develop novel copper-catalyzed transformations for the construction of condensed heterocyclic skeletons *via* arylation-ring closure procedures with the employment of diaryliodonium salts.

From electron rich substrates such as nitriles, in the presence of diaryliodonium salts and copper catalysts the formation of a highly active arylcopper(III) species can occur, described previously in the literature. This aromatic equivalent species is supposed to interact with the nitrile moiety affording an *N*-arylnitrilium intermediate, which enables the construction of diverse heterocylic compounds both in an intramolecular and in an intermolecular manner (**Scheme 38**).



Scheme 38. *Synthesis of heterocycles from nitriles and diaryliodonium salts via intramolecular and intermolecular cyclizations*

Our aim is to realize the construction of novel heterocyclic skeletons from diversely functionalized nitriles and diaryliodonium salts *via* intramolecular and intermolecular cyclizations. The outcome of the ring closures is investigated in the case of nitriles equipped with different nucleophilic functional groups and in the presence of nucleophilic reagents (amides, amines, acetylenes or heterocycles). The structure of the synthesized products is purposed to prove by NMR and by SXRD methods.

4. Results and discussion

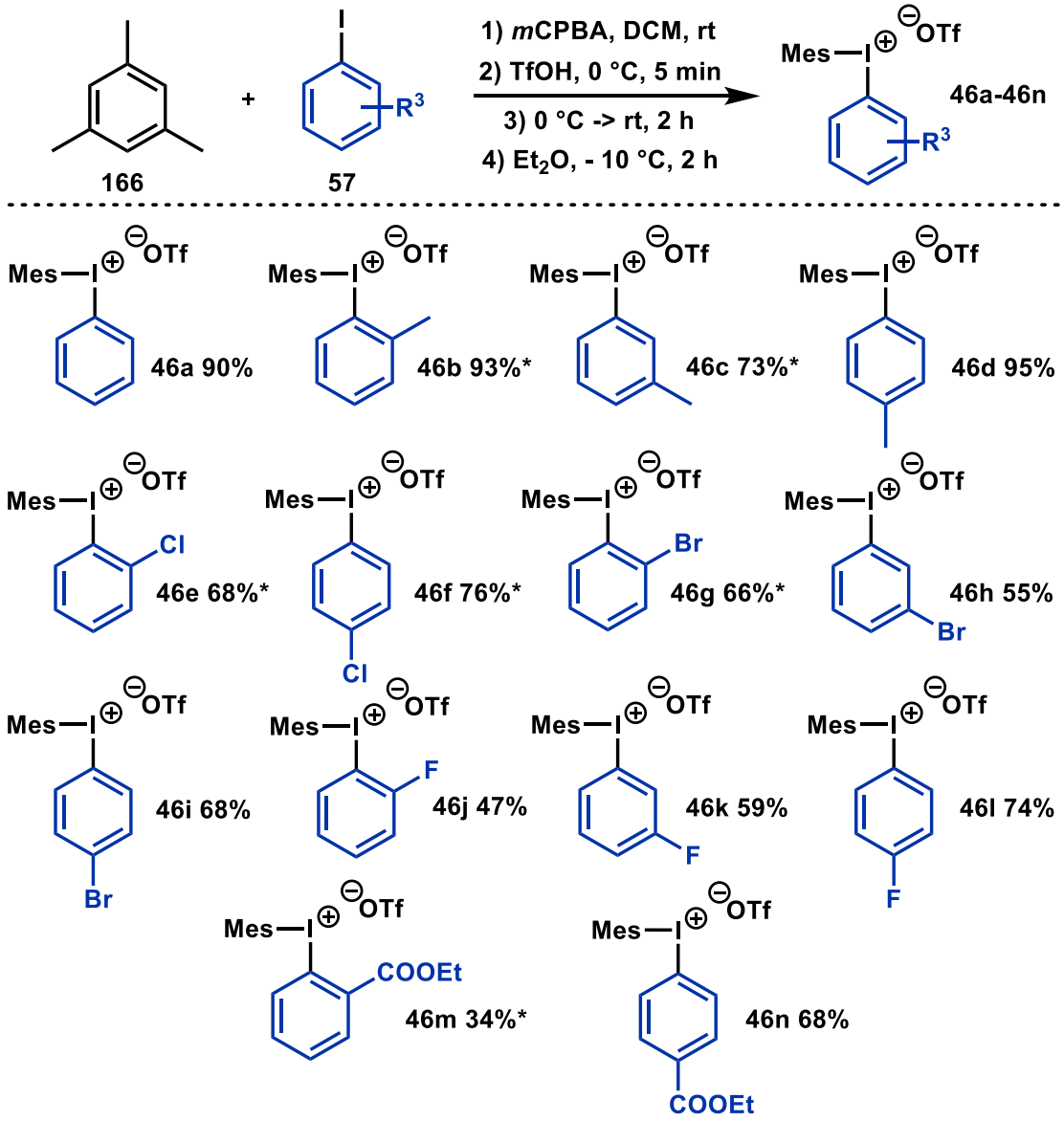
In the following sections, we aim to summarize our results achieved in copper-catalyzed functionalizations (especially cyclizations) of aromatic and heteroaromatic substrates with the employment of diaryliodonium salts. We successfully developed two copper-catalyzed oxidative arylation-ring closure strategies for the construction of iminobenzoxazine (Chapter 4.2) and chromenoquinoline (Section 4.3.2) frames utilizing arylmesityliodonium triflates (Chapter 4.1). Moreover, the geometry of the chromenoquinoline skeleton was established by single crystal X-ray diffraction, which initiated a collaboration providing further results in crystallographic researches (Section 4.4).

4. 1. Synthesis of diaryliodonium salts

As described in Chapter 2.5.2, several approaches were published for the preparation of diaryliodonium salts. Out of these synthetic strategies, in our researches the modified[129] one-pot method of Olofsson[67] was utilized for the synthesis of arylmesityliodonium triflates. Thus, the appropriate aryl iodides (**57**) were reacted with mesitylene (**166**) in the presence of *m*-chloroperbenzoic acid (*m*CPBA) oxidant in dichloromethane solvent. Then trifluoromethanesulfonic acid (triflic acid) was added to the reaction mixture to ensure the anion exchange and providing the desired arylmesityliodonium triflates (**46a**-**46n**) in 34-95% yields (**Scheme 39**). 14 examples were prepared with different electronical properties on the aromatic ring. Out of these reagents, some were prepared previously in our research group[129] and these salts were used in the ring closure reactions discussed in the following chapters (marked with asterisk), others were prepared during the work according to this doctoral thesis. Diaryliodonium triflates bearing both electron-donating and electron-withdrawing substituents in *ortho*, *meta* and *para* positions were synthesized to investigate the study of their influence on the ring closure reactions.

The first representative compound was the phenymesityliodonium derivative (**46a**), which was isolated in 90% yield. With the application of the synthetic procedure, further arylmesityliodonium triflates bearing electron-donating methyl group in the *ortho*, *meta* and *para* positions (**46b**, **46c** and **46d**) were prepared in 93%, 73% and 95%, respectively. Diaryliodonium salts containing halogens (Cl, Br, F) in the *ortho*, *meta* and

para positions (**46e-46l**) were also prepared in moderate to good yields (47-76%). Arylmesityliodonium salts bearing COOEt group in the *ortho* position (**46m**) could be isolated in only 34% yield. However, the *para*-ester derivative (**46n**) was synthesized in 68% isolated yield.



Scheme 39. *Prepared diaryliodonium salts in one-pot synthesis from mesitylene and aryl iodides (* these iodonium salt was prepared by other member of the research group)*

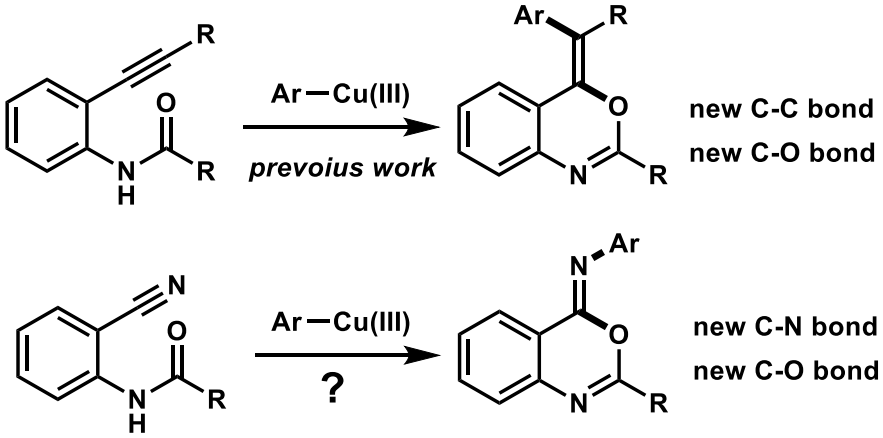
The synthesized arylmesityliodonium triflates were utilized in copper-catalyzed oxidative cyclizations for the construction of important heterocycles such as iminobenzoxazines and chromenoquinolines. These results will be discussed in the following chapters.

4. 2. Synthesis of iminobenzoxazines

4. 2. 1. Base of the developed methodology

The utilization of electron rich alkenes, alkynes or nitriles in the presence of copper catalyst and diaryliodonium salts enables the construction of diverse heterocyclic compounds *via* oxidative arylation processes.[120-135] Therefore, several approaches were achieved in the last few years for the synthesis of different heterocyclic skeletons such as quinolines, quinazolines or tetrahydroacridines.

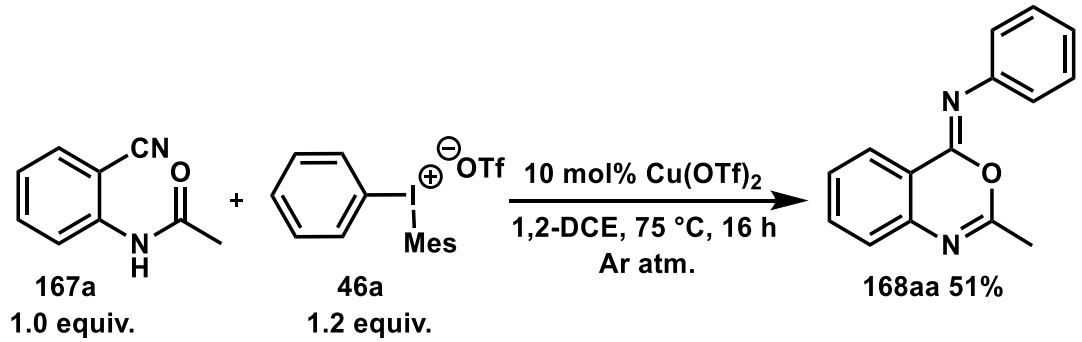
In 2013, a novel arylation-ring closure strategy was developed in our laboratory for the construction of benzoxazine derivatives[129] (**155**) from *ortho*-ethynylanilides (**154**) and diaryliodonium triflates (**46**) using the concept of aromatic electrophile generation *via* the intermediacy of Cu(III) species discussed previously by Gaunt et al.[107] Similarly to acetylene moiety, nitriles were also found to be suitable substrates for these kinds of transformations. Thus, we assumed that the replacement of the C≡C triple bond with a nitrile group in the *ortho* position to the amide moiety should provide iminobenzoxazines through a similar cyclization path (**Scheme 40**).



Scheme 40. *Arylation–ring closure strategies to benzoxazine derivatives via Ar-Cu(III)-mediated transformations*

For investigating our hypothesis, a test reaction was performed. *N*-(2-cyanophenyl)acetamide (**167a**) model substrate was reacted with phenylmesityliodonium triflate (**46a**) (1.2 equiv.) in the presence of 10 mol% copper triflate in dichloroethane solvent at 75 °C. We found that after 16 h reaction time total consumption of the cyanoanilide (**167a**) was reached, while the formation of a new product was observed, based on GC-MS measurement. After isolation of the appropriate product (**168aa**) in 51%

yield its structure was identified by ^{1}H and ^{13}C NMR measurement to be (Z)-2-methyl-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (**Scheme 41**).



Scheme 41. *Formation of iminobenzoxazine product by the reaction of cyanoacetanilide and mesitylphenyliodonium triflate*

After these results, for the examination of the transformation comprehensive optimization studies had to be done. The following chapters aim to present the broad optimization studies, the preparation of the different cyanoanilide derivatives, then their application in copper-catalyzed synthesis of iminobenzoxazines with arylmesityliodonium triflates.

4. 2. 2. Optimization of the reaction conditions and design of the substrate scope

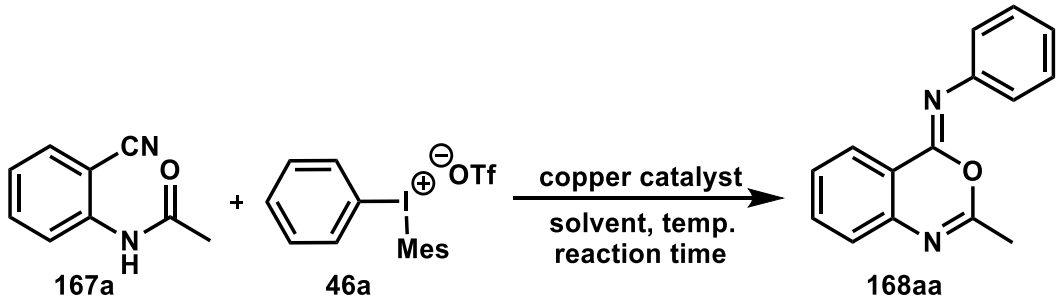
For the optimization of the reaction parameters, we chose *N*-(2-cyanophenyl)acetamide (**167a**) as the substrate which was prepared from 2-aminobenzonitrile (**169**) and acetic anhydride according to the modified procedure of Fagnou.[136] As the arylating agent, phenylmesityliodonium triflate (**46a**) was utilized (1.2 equiv).

As described above, when the reaction was performed at 75 °C in 1,2-DCE, full conversion was reached after 16 reaction time (**Table 1**, Entry 1). We attempted to implement the oxidative coupling reaction at lower *temperature*, but at 60 °C only 50% conversion could be reached in 12 h reaction time (Entry 2). Therefore, 75 °C temperature was utilized in the following experiments.

We also aimed to reduce the *reaction time* and we were pleased to observe that during the preparation of compound **168aa** full conversion could be reached in 2 h in DCE solvent in the presence of 10 mol% $Cu(OTf)_2$ catalyst (Entry 3). However, the utilization of other cyanoanilide derivatives for example benzamides in the ring closure

reactions required longer reaction times in order to reach total consumption of the starting materials.

We also aimed to reduce the *amount of copper catalyst* used in the reaction, but we found that after 2 h only 50% or 30% conversion could be reached utilizing 5 mol% or 2 mol% of $Cu(OTf)_2$. With the reduced amount of catalysts, full conversions could also be reached after 24 h and 6 h, respectively (Entries 4-8).



Entry	Catalyst	Amount of cat. (mol%)	Solvent	Temp. (°C)	Reaction time (h)	Conv. (%)
1	$Cu(OTf)_2$	10	1,2-DCE	75	16	100
2	$Cu(OTf)_2$	10	1,2-DCE	60	12	50
3	**$Cu(OTf)_2$**	**10**	**1,2-DCE**	**75**	**2**	**100**
4	$Cu(OTf)_2$	2	1,2-DCE	75	2	30
5	$Cu(OTf)_2$	2	1,2-DCE	75	6	68
6	$Cu(OTf)_2$	2	1,2-DCE	75	24	100
7	$Cu(OTf)_2$	5	1,2-DCE	75	2	50
8	$Cu(OTf)_2$	5	1,2-DCE	75	6	100
9	**$Cu(OTf)_2$**	**10**	**EtOAc**	**75**	**2**	**100**
10	$Cu(OTf)_2$	10	DCM	75	2	100
11	$Cu(OTf)_2$	10	$CHCl_3$	75	2	52
12	$Cu(OTf)_2$	10	$CHCl_3$	75	6	100
13	$Cu(OTf)_2$	10	THF	75	2	100
14	$Cu(OTf)_2$	10	MeOH	75	8	56
15	$Cu(OTf)_2$	10	DMF	75	8	9
16	$Cu(OTf)_2$	10	toluene	75	8	100*
17	CuCl	10	EtOAc	75	2	100
18	CuBr	10	EtOAc	75	2	100
19	CuI	10	EtOAc	75	2	35
20	CuI	10	EtOAc	75	6	100
21	$Me(CN)_4Cu(OTf)$	10	EtOAc	75	2	100
22	CuO	10	EtOAc	75	2	5
23	CuO	10	EtOAc	75	6	18
24	$CuSO_4$	10	EtOAc	75	2	16
25	$CuSO_4$	10	EtOAc	75	6	16
26	$Cu(acac)_2$	10	EtOAc	75	2	16
27	$Cu(acac)_2$	10	EtOAc	75	6	100

* product mixture was formed

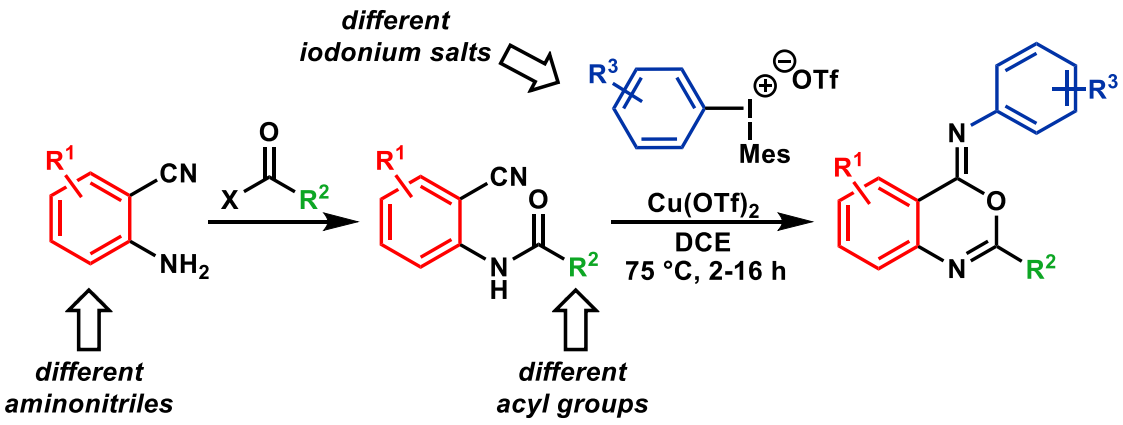
Table 1. *Optimization studies for the ring closure of* ***167a***

Examination of the effect of *solvent* on the reaction conversion showed that the reaction is slow in DMF or MeOH (9%and 56% conversions after 8 h reaction time, respectively) and provides a complex reaction mixture in toluene. The employment of $CHCl_3$ solvent resulted full conversion in 6 h. In contrast, full conversion could be reached in 2 h, when the reaction was conducted in THF, DCM, EtOAc or DCE solvents (Entries 9-16).

Comparison of the activity of different *copper catalysts* revealed that both copper(I) and copper (II) sources, such as CuCl, CuBr, $(MeCN)_4CuOTf$ and $Cu(OTf)_2$ are suitable catalysts for the transformation, whilst in the presence of CuI, CuO, $CuSO_4$ or $Cu(acac)_2$ only poor conversions was reached in 2 h reaction time. However, in the case of CuI and $Cu(acac)_2$ 100% conversion could be observed after 8 h, while no particular effect of the longer reaction time was noticed on the conversion values in case of CuO and $CuSO_4$ (Entries 17–27).

According to the *amount of phenylmesityliodonium triflate*, there is no need for the addition of larger excess of the reagent than 1.2 equivalents to reach full conversion in the reaction after 2 h.

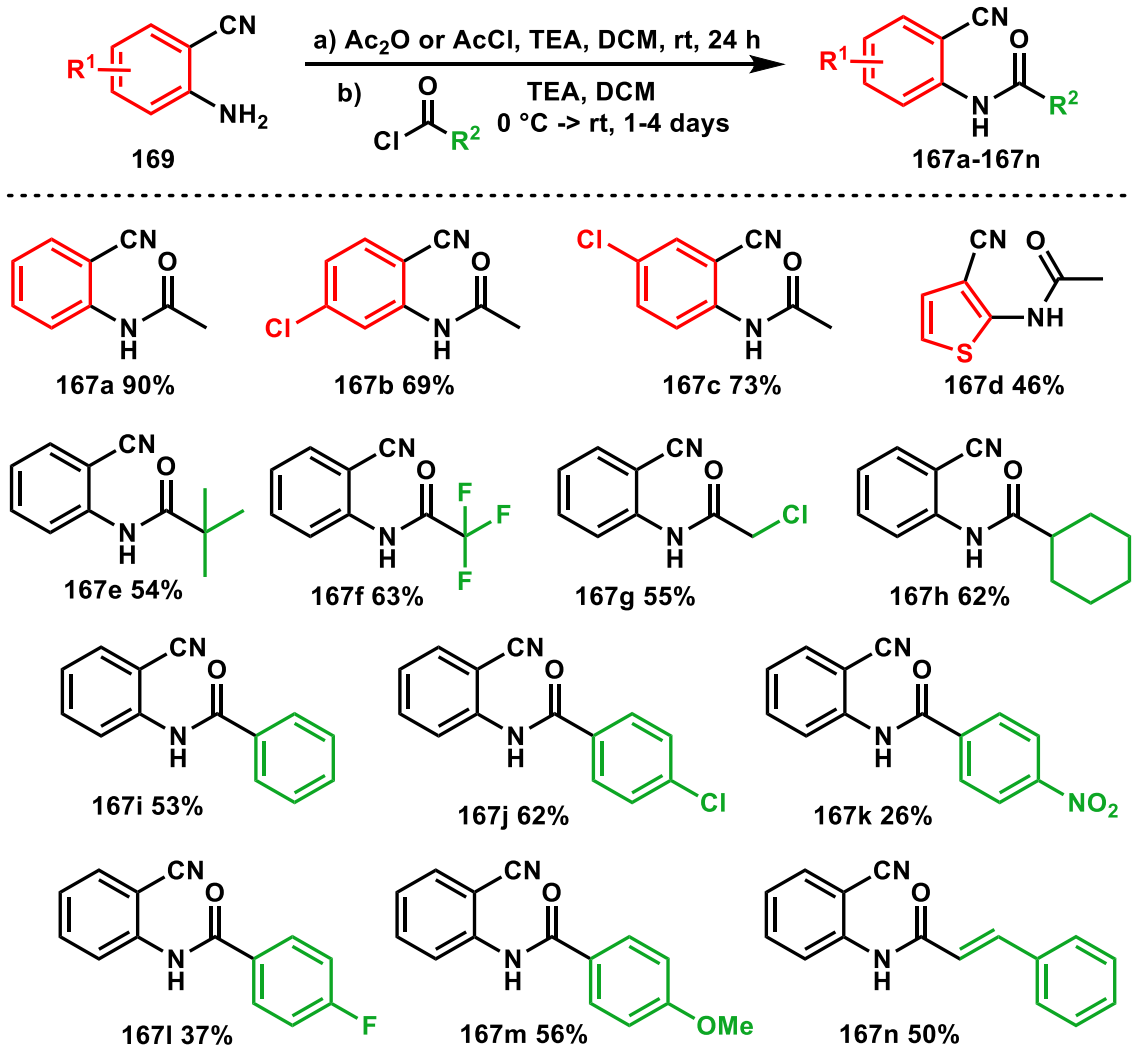
With the optimal conditions in hand, we designed the scope of the developed methodology. The desired iminobenzoxazine skeleton can be modified in three ways. First of all, different aminonitriles can be prepared and used in the reactions. Moreover, the scope of the obtainable products can be extended with the utilization of different acyl chlorides or anhydrides for the synthesis of the amide compounds. Thereby, beside the cyanoanilide **167a** other amide compounds (for example thiophene or cyclic β-acetylaminoacrylonitrile derivatives) could be synthesized. Finally, further iminobenzoxazines can be obtained with the application of substituted arylmesityliodonium triflates in the ring closing reactions (**Scheme 42**).



Scheme 42. *Designed substrate scope of iminobenzoxazines*

4. 2. 3. Synthesis of the amide substrates

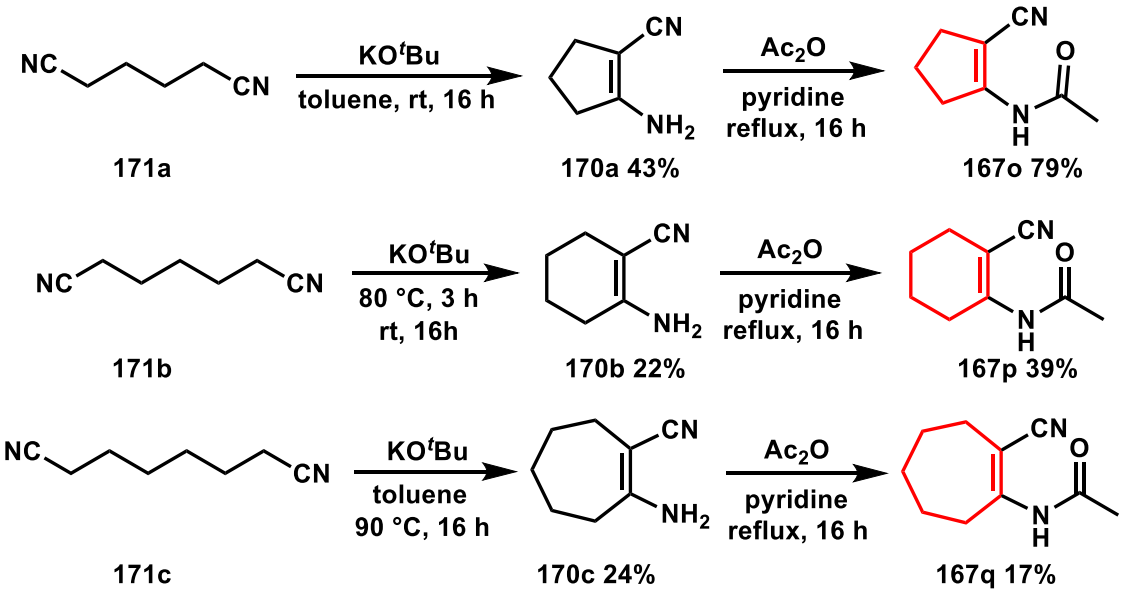
The desired *N*-(2-cyanophenyl)amide[136,137] derivatives were prepared according to the modified procedure of Fagnou and Zhdankin. Aromatic and heteroaromatic acetamide derivatives were synthesized from 2-aminobenzonitrile and 2-aminothiophene-3-carbonitrile in the presence of acetic anhydride or acetyl chloride and TEA base in DCM at rt (**Scheme 43**). Cyanophenyl acetamide (**167a**) was synthesized in 90% yield. Substrates bearing chloro substituents (**167b** and **167c**) were obtained in 69% and 73% yields after recrystallization. Heteroaromatic thiophene derivative (**167d**) was isolated in moderate yield (46%). 2-aminobenzonitrile (**169**) was also reacted with different acyl chlorides under the same reaction conditions to prepare further amide derivatives (**167e**-**167n**). Alkyl-substituted anilides (**167e**-**167g**) were obtained in 54%, 63% and 55% yields, respectively.



Scheme 43. *Synthesis of different N-(2-cyanoaryl)amide derivatives*

Cyclohexanecarboxamide derivative (**167h**) was isolated in 62% after recrystallization from ethanol. Furthermore, different benzamides (**167i**-**167m**) equipped with both electron-donating and electron-withdrawing substituents were also synthesized with the employed method. Moreover, cinnamamide derivative (**167n**) was prepared in 50% yield after recrystallization from ethanol then from toluene.

We also aimed to explore the applicability of non-aromatic systems in the ring closure reaction. Thus, we prepared non aromatic cyclic β-acetylaminoacrylonitriles (**167o**, **167p** and **167q**) from the appropriate β-enaminonitriles (**170a**-**170c**), which were synthesized from the corresponding dinitriles (**171a**-**171c**) in Ziegler-Thorpe ring closing reaction in the presence of potassium *tert*-butoxide base according to the modified procedure of Ma et al.[138] The desired cyclic amides (**167o**-**167q**) were obtained in various yields (79%, 39% and 17% yields, respectively) after acylation of the corresponding enaminonitrile substrates with acetic anhydride in pyridine solvent at its reflux temperature (**Scheme 44**).



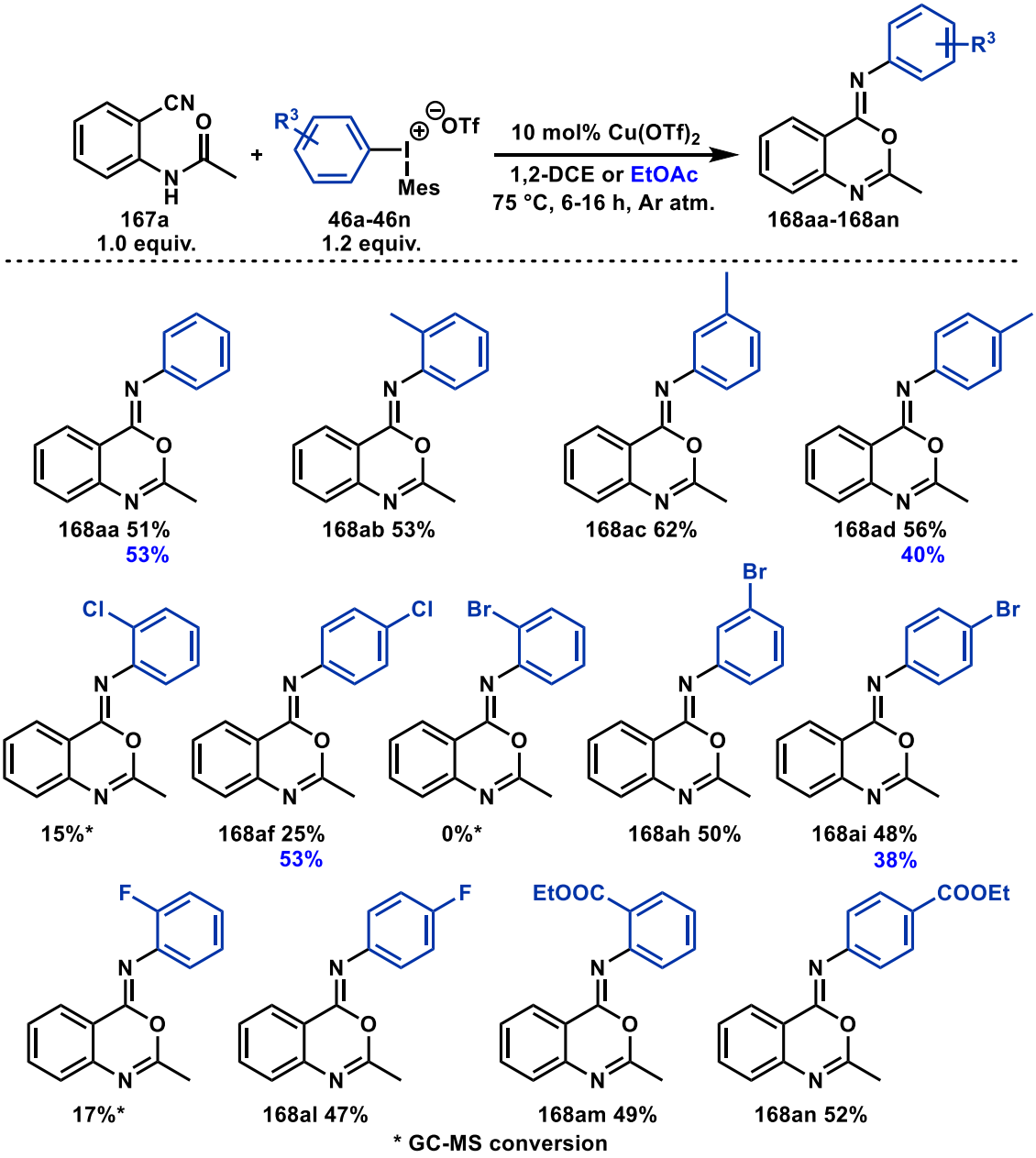
Scheme 44. *Synthesis of cyclic β-acetylaminoacrylonitriles*

4. 2. 4. Copper-catalyzed ring closure of *ortho*-cyanoanilides and arylmesityliodonium triflates

After preparing the amide substrates and diaryliodonium salts as arylating agents we aimed to explore the scope and limitations of the developed methodology.

First, we reacted *N*-(2-cyanophenyl)acetamide (**167a**) with phenylmesityliodonium triflate (**46a**) using 10 mol% of $Cu(OTf)_2$ catalyst in DCE 75 °C.

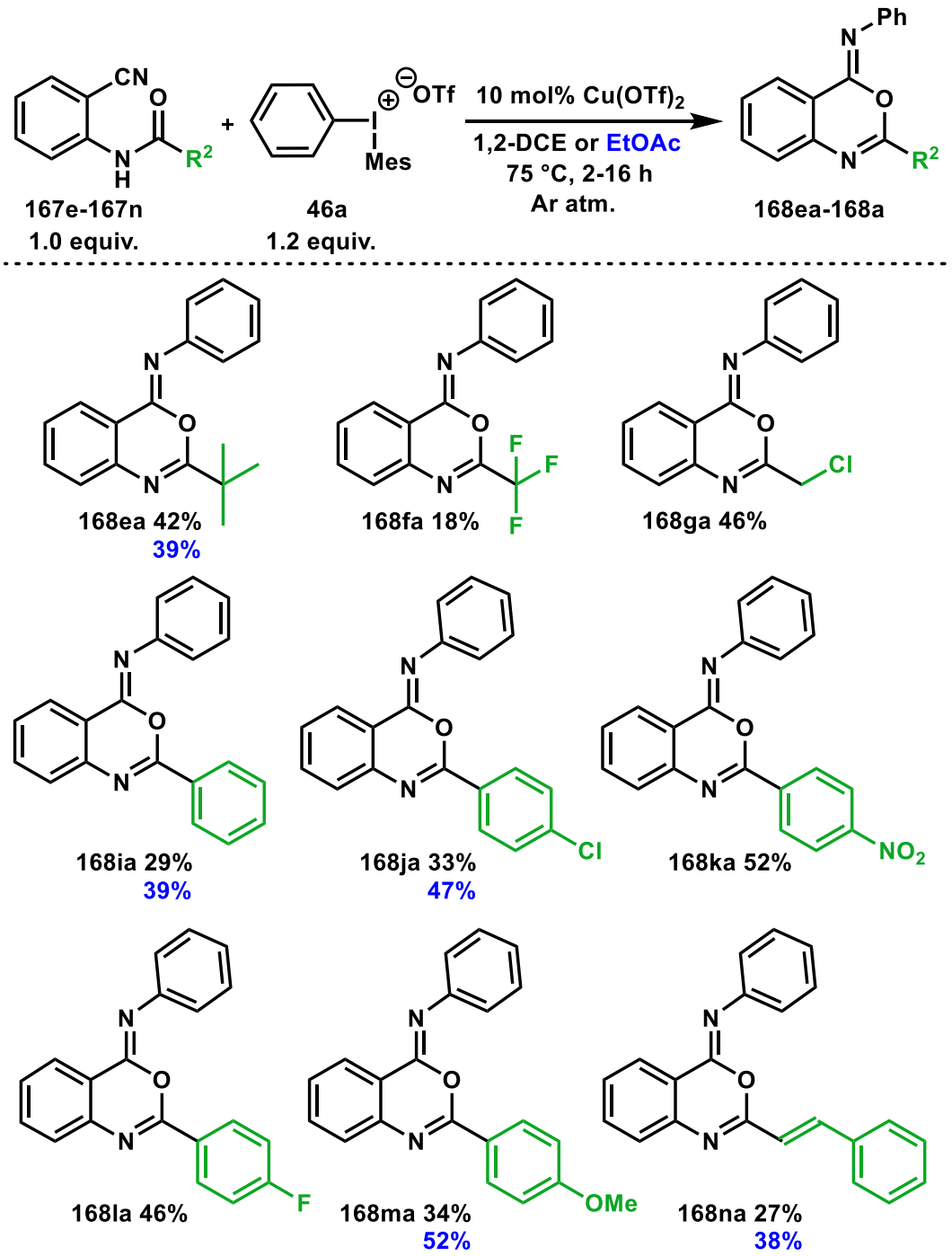
In some cases, the appropriate products were isolated from EtOAc solvent too. Compound **168aa** was synthesized in 51% (53% in EtOAc) after the workup. Then, testing the different arylmesityliodonium salts in the ring closure, we found that in the presence of methyl substituent in the *ortho*, *meta* and *para* position of the phenyl group of the iodonium salt the desired products (**168ab**, **168ac** and **168ad**) could be obtained in 53%, 62% and 56% (40% in EtOAc) yields, respectively (**Scheme 45**). Utilizing iodonium salts containing halogen atom (F, Cl or Br) *ortho* to the iodine, the ring closing reaction was retarded and the desired compounds were detected only with GC-MS (15%, 0% and 17% conversions, respectively). This fact can be explained by electronical and sterical properties. Comparing our results to similar copper-catalyzed oxidative arylation-cyclization reactions of the literature,[120-135] we can conclude, that fewer examples are given in which the corresponding products are synthesized with the employment of 2-haloaryliodonium salts, mainly from sterically not hindered substrates. However, in most cases, similar cyclization reactions were realized in the presence of 3- or 4-haloaryliodonium salts. According to our results, when the reaction was attempted with diaryliodonium salts equipped with halogens in the *meta* and *para* positions, the appropriate iminobenzoxazines (**168af**-**168al**) were isolated in 25% (53% in EtOAc), 50%, 48% (38% in EtOAc) and 47% yields. The employment of arymesityliodonium salts bearing a COOEt group in the *ortho* and *para* positions of the aromatic ring provided the desired products (**168am** and **168an**) with the similar efficiency (49% and 52% yields). The activity of 2-ethoxycarbonylphenyl(mesityl)iodonium triflate in the ring closing reaction is quite unexpective compared to the results of 2-haloaryliodonium salts. A probable explanation for this fact is that the carbonyl part of the COOEt group is able to form a six-membered stable complex coordinating to the copper, while in the presence of halogens the formation of this complex is not possible. However, the activity of *ortho*-methyl substituted diaryliodonium salt in the cyclization reaction can be explained by the electron-donating ability of the methyl group, which can thereby stabilize the forming carbocationic species (for details of the mechanism, see **Scheme 48**).



Scheme 45. *Ring closure with different arylmesityliodonium triflates*

After investigating the applicability of different arylmesityliodonium triflates, we studied the reactivity of different amides in the developed oxidative coupling (**Scheme 46**). The reaction of alkyl substituted amides (**167e**, **167f** and 1**67g)** with phenylmesityliodonium triflate (**46a**) provided the desired iminobenzoxazine derivatives (**168ea**, **168fa** and **168ga**) in 42% (39% in EtOAc), 18% and 46% yields. In contrast, when cyclohexane derivative (**167h**) was utilized, instead of the corresponding iminobenzoxazine the formation of by-products was observed. In the case of aromatic anilide derivative (**167i**), the appropriate product (**168ia**) was obtained in 29% (39% in EtOAc). When the reaction was attempted with aromatic amides bearing EWG or EDG

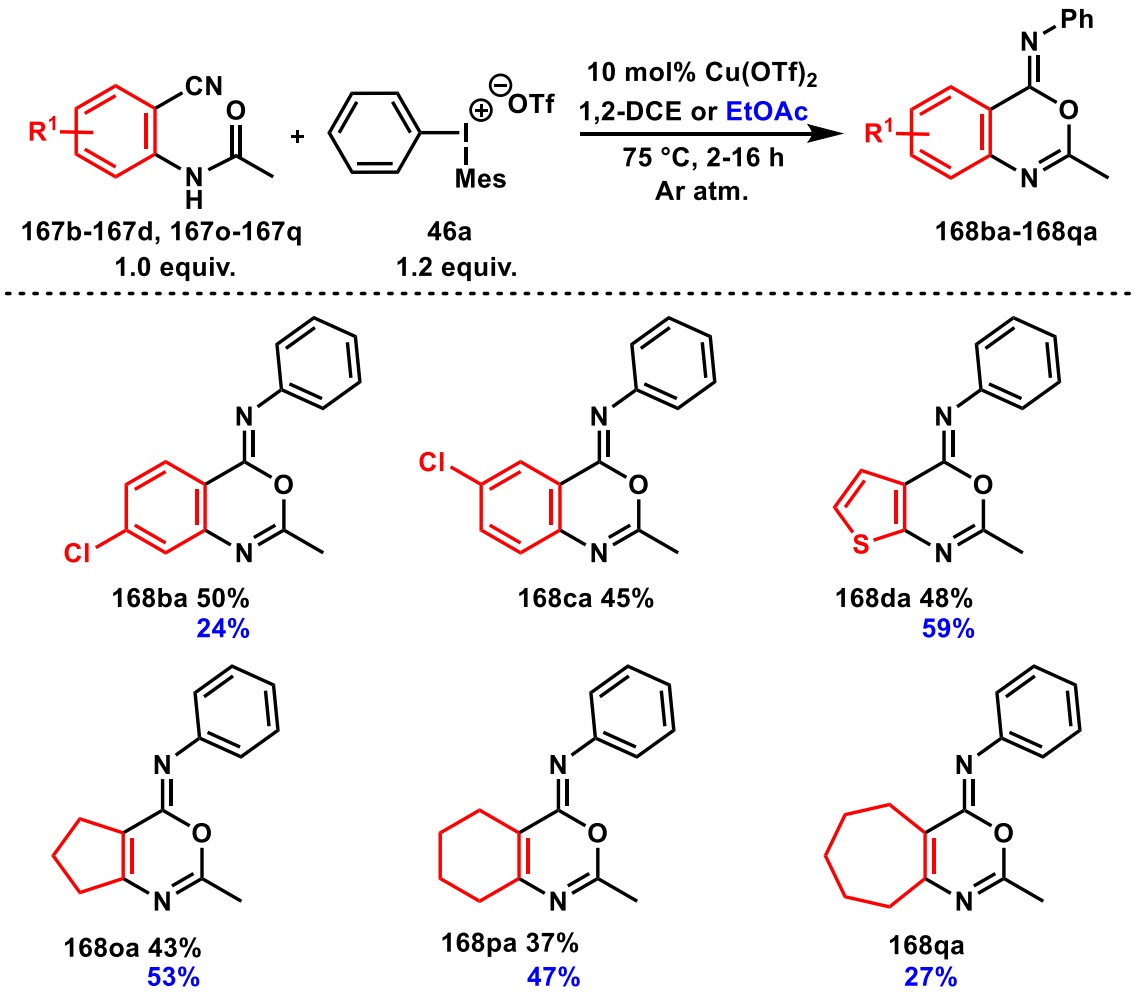
groups (**167j**, **167k**, **167l** and **167m**) in the *para* position, iminobenzoxazines (**168ja-168ma**) were isolated in 33% (47% in EtOAc), 52%, 46% and 34% (52% in EtOAc) yields, respectively. Reaction of conjugated amide (**167n**) with phenylmesityliodonium triflate (**46a**) afforded the desired product (**168na**) in 27% (38% in EtOAc) yield. Thus, in the case of the chloro (**168ja**) and methoxy derivatives (**168ma**) with the ulilization of EtOAc solvent instead of DCE the isolated yields of the appropriate products could be increased in about 15%.



Scheme 46. *Synthesis of iminobenzoxazines from different ortho-cyanoanilides*

In the case of **168ka**, the structure was investigated and the Z conformation (iminophenyl moiety) was proved by Dr. Tamás Gáti (Servier Research Centre) as no interaction was observed between the phenyl group connected to the imino part and the phenyl group of the benzoxazine core (based on NOE measurements).

Finally, the applicability of the developed ring closing reaction was demonstrated on amide substrates bearing chloro substituents on the anilide moiety (**167b**, **167c**), with a thiophene derivative (**167d**) and with non-aromatic unsaturated systems (**167o**, **167p** and **167q**) too (**Scheme 47**). The presence of halogens on the aromatic ring of the anilide was well-tolerated both in *meta* and *para* positions, and the desired products (**168ba** and **168ca**) were obtained in 50% (24% in EtOAc) and 45% yields. Reacting *N*-(3-cyanothiophen-2-yl)acetamide (**167d**) with phenylmesityliodonium triflate (**46a**) afforded the desired sulfur containing heteroaromatic system **168da** in 48% (59% in EtOAc) yield.



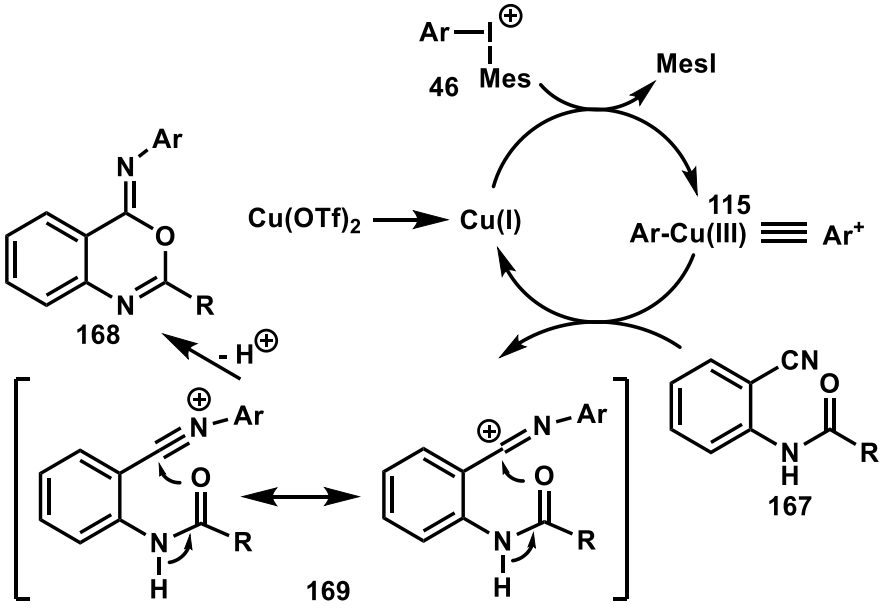
Scheme 47. *Preparation of iminobenzoxazines from different ortho-cyanoanilides*

Utilization of non-aromatic cyclic β-acetylaminoacrylonitriles (**167o**, **167p** and **167q**) also provided the appropriate products. The condensed iminooxazine systems containing cyclopentene, cyclohexene and cycloheptene rings (**168oa**, **168pa** and **168qa**) were obtained in 43% (53% in EtOAc), 37% (47% in EtOAc) and 27% yields, respectively. Based on these results, the employment of EtOAc instead of DCE resulted in approximately a 10% improvement of isolated yields in the case of iminobenzoxazine derivatives **168da**, **168oa** and **168pa**.

Results of the substrate scope study showed that both DCE and EtOAc are suitable solvents of the transformation. Based on the literature of similar arylation reactions, unsymmetric diaryliodonium salts are often reported to be less reactive in these kinds of transformations compared to the symmetric salts. Therefore, in two cases, we repeated the ring closures with the employment of symmetric diaryliodonium salts in order to improve the yields. When bis(*para*-chlorophenyl)iodonium triflate was utilized instead of phenymesityliodonium triflate (**46a**) in EtOAc solvent, the appropriate product (**168af**) was obtained with similar efficiency (47% vs. 53%). As another example, when the ring closing reaction was performed with symmetrical diphenyliodonium triflate instead of phenylmesityliodonium triflate (**46a**) **168aa** was obtained in 43% yield. Hence, the utilization of symmetric iodonium salts did not provided better isolated yields. Based on TLC analysis of the reaction mixture we suppose that the desired products are sensitive and are able to decompose during the work-up procedure. In accordance with our assumption, GC-MS analysis of the reaction mixture revealed fewer side products. The only identified side product was 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one, which could be formed via hydrolytic cleavage of the imine.

Beside the synthetic studies and applications, we also proposed a possible mechanism (**Scheme 48**) for the copper-catalyzed arylation-ring closure reaction, which is supposed to undergo *via* the formation of arylcopper(III) intermediate, presumed similarly in these kinds of transformations. According to similar copper-catalyzed cyclizations of the literature,[132-134] we assume, that the reaction starts with the formation of the Cu(I) species from $Cu(OTf)_2$ by reduction[107] or disproportion[139], discussed in previous reports. However, both Cu(I) and Cu(II) sources were able to initiate the oxidative coupling providing the corresponding iminobenzoxazine products. Thus, the presence of Cu(I) catalyst or *in situ* generated Cu(I) catalyst from the appropriate Cu(II) source is needed to the transformation. According to the following step, diaryliodonium salt (**46**) can oxidize the resulted Cu(I) species generating the Ar-Cu(III) intermediate

(**115**) and mesityliodide eliminated in the reaction. We suppose that the highly electrophilic Cu(III) species - which can be interpreted as an aryl cation equivalent - interacts with the nitrile function of compound **167** resulting the formation of a cationic species (**169**) and Cu(I). The formed *N*-arylnitrilium intermediate **169** readily undergoes cyclization with the participation of the amide group *via* nucleophilic attack of the carbonyl oxygen providing the iminobenzoxazine product (**168**).



Scheme 48. *Proposed mechanism of the developed arylation-ring closure*

4. 3. Activation of nitrile and acetylene moiety – route to condensed quinoline derivatives

The previous section involves the synthesis of iminobenzoxazines *via* nitrile activation with the utilization of arylmesityliodonium triflates and copper catalysts. In the following chapters we discuss the results achieved by the activation of nitrile moiety in the presence of acetylene function.

4. 3. 1. Synthesis of indeno[2,1-*b*]quinoline derivative

As reported previously, Chen et al. developed the synthesis of different heterocyclic compounds such as quinoline derivatives with the employment of diaryliodonium salts in the presence of alkynes and acetylenes (see Scheme 37).[132]

On the basis of these transformations, we aimed to develop novel ring closure reactions for the construction of condensed heterocyclic systems from substrates which

contain those functional groups together. To realize this approach, we designed a bifunctional substrate (**171**) containing both nitrile and acetylene moiety, which enables the activation of nitrile functional group in the presence of C≡C triple bond *via* copper-catalyzed oxidative arylation-cyclization path with diaryliodonium salts affording the indenoquinoline frame (**Figure 5**). The desired condensed heterocyclic compound (**172**) can be synthesized starting from 2-(2-iodophenyl)acetonitrile (**170**) which can be transformed to the bifunctional substrate (**171**) *via* Sonogashira coupling reaction. We supposed that in the presence of copper catalysts and diaryliodonium salts a ring closure occurred, providing indenoquinoline derivative (**172)**.

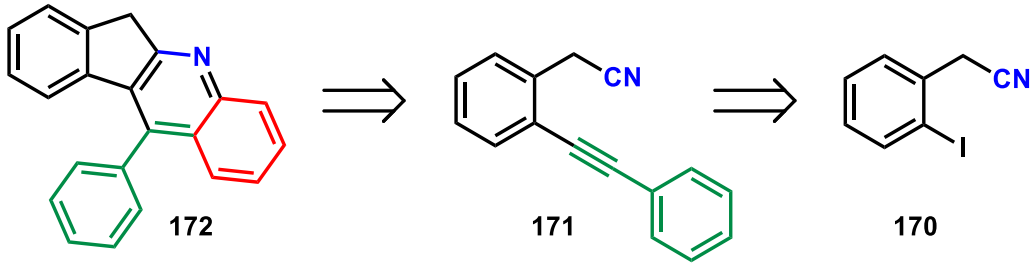
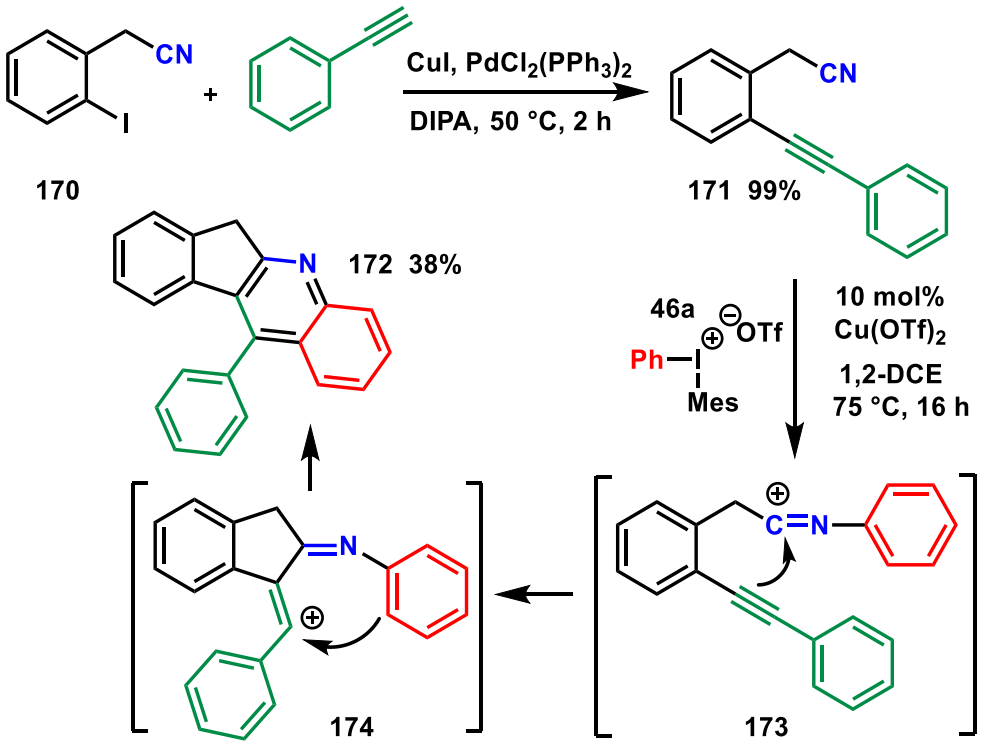


Figure 5. *Retrosynthetic path to the designed indenoquinoline derivative*

For testing our hypothesis, first we prepared the required alkynyl substrate (**171**) for the study. To achieve this 2-(2-iodophenyl)acetonitrile (**170**) was reacted with phenylacetylene in diisopropylamine (DIPA) solvent in the presence of catalytic amount of copper iodide and $PdCl_2(PPh_3)_2$ palladium catalysts according to the modified procedure of Kotschy.[140] The appropriate product (**171**) was isolated in quantitative yield (**Scheme 49**). Next, bifunctional substrate **171** was reacted with phenylmesityiodonium triflate (**46a**). Copper triflate was used as a copper source and the reaction was conducted in dichloroethane at 75 °C (the employed reaction condition was based on results achieved according to iminobenzoxazines). Based on GC-MS measurements, we found that the reaction mixture is supposed to contain the assumed indeno[2,1-*b*]quinoline. After isolation of the product **172** in 38% yield, its structure was proved by ^{1}H and ^{13}C NMR measurements. According to our plausible mechanism, we suppose that in the first step, the phenyl group of the iodonium salt interacts with the nitrile group providing a carbocationic species (**173**), which can easily form intermediate **174** by a cyclization step. The formation of the desired indeno[2,1-*b*]quinoline product (**172**) is presumed to occur *via* an electrophilic aromatic substitution (S_EAr) type intramolecular cyclization.



Scheme 49. *Synthesis of indeno[2,1-b]quinoline derivative via copper catalyzed arylation-ring closure reaction*

At the same time, simultaneously with our researches, Chen et al. reported the construction of the same skeleton in 83% isolated yield, and demonstrated the applicability of this synthetic strategy for the construction of the desired heterocyclic frame.[134] Followed by the publication of Chen, we designed another bifunctional substrate to develop novel ring closure reactions for the construction of further condensed heterocyclic molecules.

4. 3. 2. Synthesis of chromenoquinoline derivatives

Similar to bifunctional substrate **171**, we designed two further molecules (**177a**, **181**) containing both nitrile and acetylene functional groups. In the presence of copper catalysts and diaryliodonium salts these substrates are supposed to be able to afford chromeno[4,3-*b*]- and chromeno[3,4-*b*]quinoline derivatives *via* copper-catalyzed oxidative arylation-cyclization path. The desired chromenoquinoline frames (**178aa** and **182**) can be synthesized starting from 2-hydroxybenzonitrile (**175a**) and 2-iodophenol (**178**) by O-alkylation followed by a Sonogashira coupling then a diaryliodonium salt-mediated copper-catalyzed ring closure reaction (**Figure 6**).

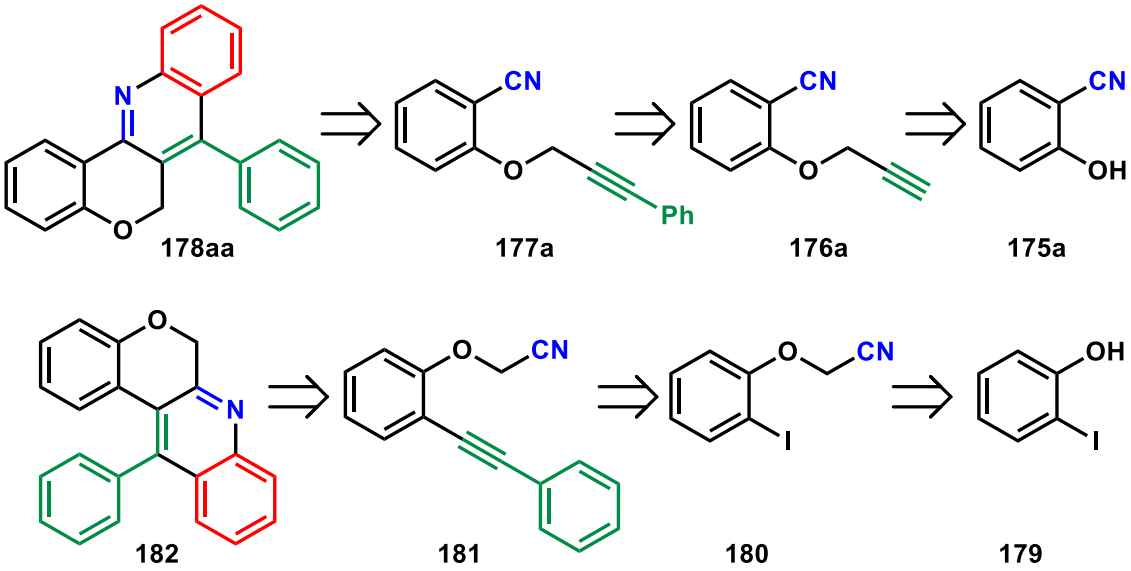
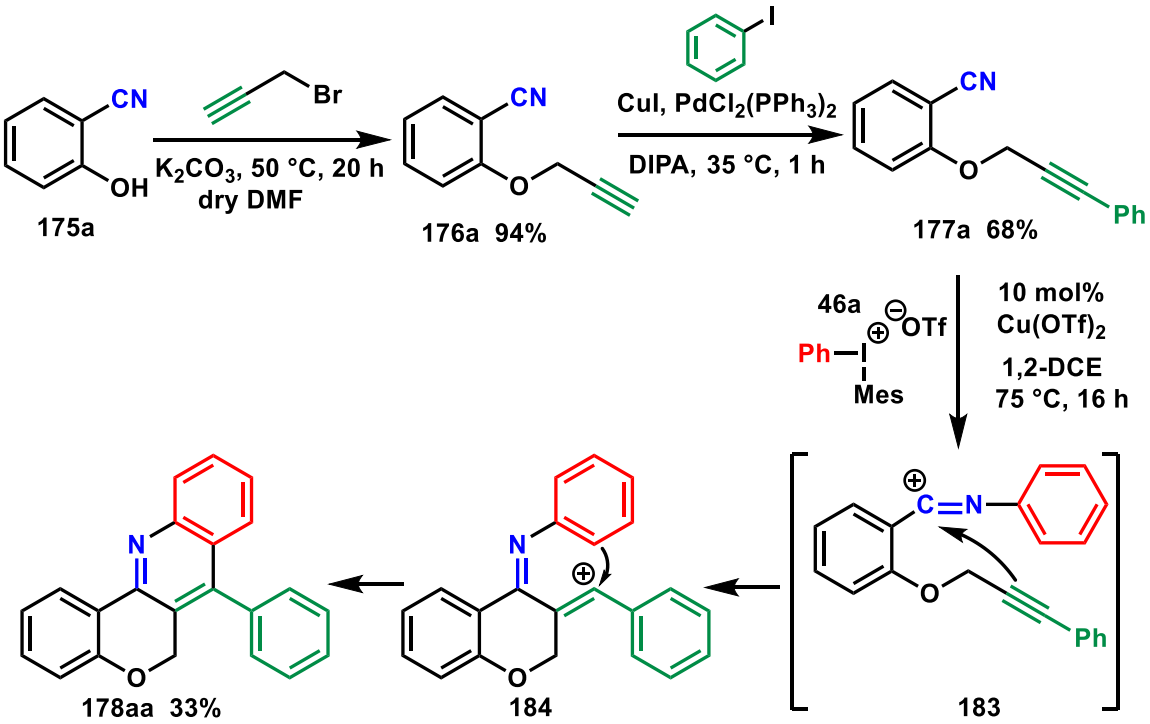


Figure 6. *Retrosynthetic path to the designed chromenoquinoline derivatives*

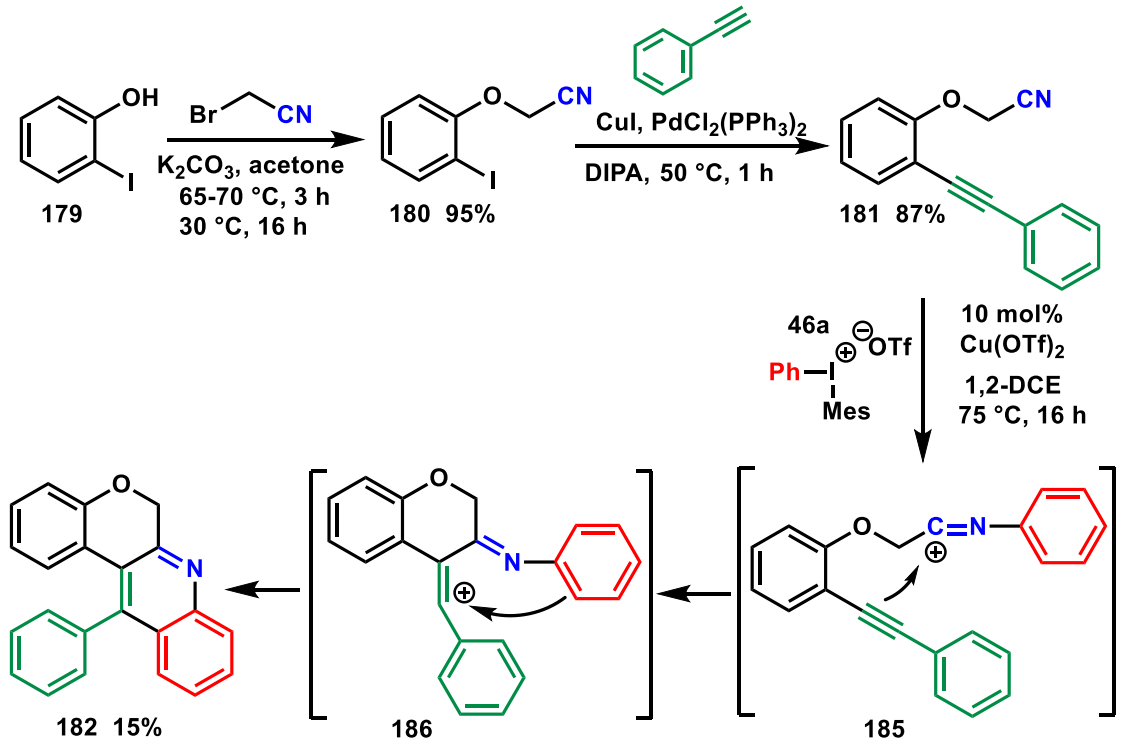
To realize this approach and test the applicability of our hypothesis, we synthesized the bifunctional substrates **177a** and **181**. Substrate **177a** was prepared in the reaction of 2-hydroxybenzonitrile (**175a**) and propargyl bromide in the presence of potassium carbonate base in dimethylformamide solvent at 50 °C. The O-alkylated product (**176a**) was isolated in 90% yield (**Scheme 50**). In the following step, a Sonogashira coupling was performed on the propargylic moiety with iodobenzene under the typical $PdCl_2(PPh_3)_2$-CuI Sonogashira reaction conditions. The appropriate coupling product (**177a**) was obtained in 68% yield after the workup. Next, bifunctional substrate **177a** was reacted with phenylmesityiodonium triflate (**46a**) in the presence of copper triflate catalyst in dichloroethane at 75 °C (according to previous test reaction conditions). Based on GC-MS measurements, we found that the reaction mixture is likely contains the assumed chromeno[4,3-*b*]quinoline. After isolation of the product **178aa** in 33% yield, its structure was proved by ^{1}H and ^{13}C NMR measurements. According to our plausible mechanism discussed later in details, we suppose that in the first step, the phenyl group of the iodonium salt forms a highly electrophilic Ar-Cu(III) species which interacts with the nitrile moiety generating a carbocationic intermediate (**183**), which can induce two consecutive cyclizations affording the appropriate product (**178aa**).



Scheme 50. *Synthesis of chromeno[4,3-b]quinoline via copper catalyzed arylation-ring closure reaction*

The other target molecule, quinoline (**182**) was also prepared according to the retrosynthetic path presented above. 2-iodophenol (**179**) was transformed to compound **180** in high yield by O-alkylation in the presence of 2-bromoacetonitrile (introduction of the nitrile moiety), then Sonogashira coupling was performed employing phenylacetylene (**Scheme 51**). The appropriate bifunctional substrate (**181**) was isolated in 87% yield. Next, the prepared substrate **181** was reacted with phenylmesityliodonium salt (**46a**) under the catalytic conditions applied previously. Although, the desired chromeno[3,4-*b*]quinoline product (**182**) was isolated from the reaction mixture, it was obtained only in 15% yield. We assume that the formation of the appropriate product undergoes *via* the generation of two carbocationic intermediates (**185** and **186**).

Whereas during the preparation of chromenoquinoline derivatives better isolated yield was achieved in the case of chromeno[4,3-*b*]quinoline derivative (**178aa**), our following researches focused on the synthesis of the corresponding compound. After broad optimization studies and the preparation of the appropriate starting materials, we studied the applicability of the developed cyclization for the construction of several chromeno[4,3-*b*]quinoline representatives.



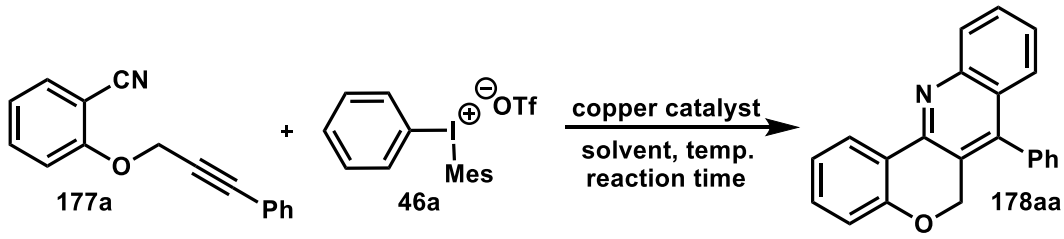
Scheme 51. *Synthesis of chromeno[3,4-b]quinoline via copper catalyzed arylation-ring closure reaction*

4. 3. 3. Optimization studies and design of the substrate scope

For the optimization of the reaction parameters we chose 2-(prop-2-yn-1-yloxy)benzonitrile (**177a**) as the substrate and phenylmesityliodonium triflate (**46a**) as the arylating agent.

As described above, when the reaction was performed at 75 °C in 1,2-DCE, full conversion was reached after 16 hours reaction time (**Table 2**, entry 1). We repeated the reaction in EtOAc and we were pleased to observe total consumption of **177a** within 1 h, while instead of $Cu(OTf)_2$ CuCl was utilized (entry 2). We attempted to implement the oxidative coupling reaction at lower *temperature*, but at 50 °C and 60 °C only 8% and 10% conversions could be reached in EtOAc after 1 h (entries 3-4). Therefore, 75 °C temperature and EtOAc solvent was utilized in the following experiments.

Examining the effect of the *solvent* on the conversion revealed that the reaction is slow in DMF, Et_2O, DCM, THF, PhMe, DCE (5%, 5%, 19%, 29%, 35%, 41% conversions after 1 h, respectively) and no reaction occurs in MeOH (entries 5-11). However, in case of PhMe and DCE full conversion could be reached after 3 h, while after the same reaction time the other solvents (MeOH, DMF, Et_2O, DCM, THF) provided 0%, 5%, 20%, 89%, 39% conversions, respectively (entries 12-18).



Entry	Catalyst	Amount of cat. (mol%)	Solvent	Temp. (°C)	Reaction time (h)	Conv. (%)
1	$Cu(OTf)_2$	10	1,2-DCE	75	16	100
2	**CuCl**	**10**	**EtOAc**	**75**	**1**	**100**
3	CuCl	10	EtOAc	50	1	8
4	CuCl	10	EtOAc	60	1	10
5	CuCl	10	MeOH	75	1	0
6	CuCl	10	DMF	75	1	5
7	CuCl	10	Et_2O	75	1	5
8	CuCl	10	DCM	75	1	19
9	CuCl	10	THF	75	1	29
10	CuCl	10	PhMe	75	1	35
11	CuCl	10	1,2-DCE	75	1	41
12	CuCl	10	MeOH	75	3	0
13	CuCl	10	DMF	75	3	5
14	CuCl	10	Et_2O	75	3	20
15	CuCl	10	DCM	75	3	89
16	CuCl	10	THF	75	3	39
17	CuCl	10	PhMe	75	3	100
18	CuCl	10	1,2-DCE	75	3	100
19	CuBr	10	EtOAc	75	1	100
20	CuI	10	EtOAc	75	1	0
21	CuO	10	EtOAc	75	1	0
22	$Cu(OTf)_2$	10	EtOAc	75	1	3
23	$CuSO_4$	10	EtOAc	75	1	10
24	$Cu(acac)_2$	10	EtOAc	75	1	12
25	$Me(CN)_4Cu(OTf)$	10	EtOAc	75	1	40
26	-	10	EtOAc	75	1	0
27	$Cu(OTf)_2$	10	EtOAc	75	3	100
28	$Cu(acac)_2$	10	EtOAc	75	3	100
29	$Me(CN)_4Cu(OTf)$	10	EtOAc	75	3	100
30	CuI	10	EtOAc	75	3	18
31	CuI	10	EtOAc	75	18	100
32	CuCl	5	EtOAc	75	1	34
33	CuCl	2.5	EtOAc	75	1	18
34	CuCl	5	EtOAc	75	3	100
35	CuCl	2.5	EtOAc	75	3	100

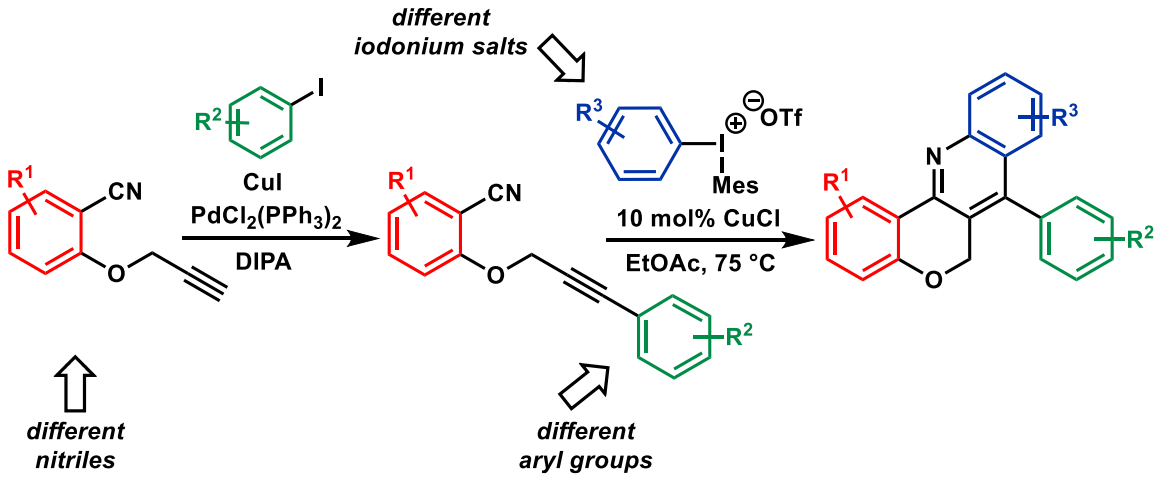
Table 2. *Optimization studies for the ring closure of* ***177a***

Comparing the activity of different *copper sources* in the ring closing reaction revealed that both CuCl and CuBr are suitable catalysts for the transformation (entries 2, 19) as total consumtption of **177a** could be achieved within 1 h reaction time. Utilization of CuI or CuO showed that no reaction occurs in 1 h (entries 20-21), while the reaction was slow when $Cu(OTf)_2$, $CuSO_4$, $Cu(acac)_2$, or $(MeCN)_4Cu(OTf)$ were utilized as a copper source (entries 22-25). However, in the case of $Cu(acac)_2$ or $(MeCN)_4Cu(OTf)$ full conversion could be observed after 3 h, while 14% conversion was reached when CuI was employed as a catalyst. Otherwise, the utilization of CuI catalyst gave full conversion after 18 h (entries 27-31). We also performed the reaction without copper source and we found that no reaction was observed in the absence of catalyst (entry 26).

We also aimed to reduce the *amount of copper catalyst* used in the reaction, but we got only 34% or 18% conversion after 1 h in the presence of 5 mol% or 2.5 mol% of CuCl (entries 32-33). Otherwise, 3 h reaction time in both cases afforded the complete consumption of compound **177a** (entries 34-35). Nevertheless, we utilized 10 mol% of CuCl to achieve the key transformation in shorter reaction times.

According to the *amount of phenylmesityliodonium triflate*, based on the applied quantity used in the synthesis of iminobenzoxazines, we utilized 1.2 equivalents of iodonium salt.

With the optimal conditions in hand, we aimed to extend the developed methodology for the construction of diverse chromenoquinoline derivatives. To realize this approach, the synthesis of various O-propargylic *ortho*-cyanophenol derivatives was necessary. Beside the 2-arylpropynyloxybenzonitrile (**177a**) other bifunctional substrates can be prepared utilizing different cyanophenols in the propargylation step. Moreover, the diversity of the substrates can be extended with the employment of different aryl iodides in the Sonogashira coupling of the propargylic moiety. Finally, the prepared internal alkynes were ready for the copper catalyzed ring closure reaction achieved in the presence of versatile diaryliodonium salts to access the desired chromenoquinolines (**Scheme 52**).

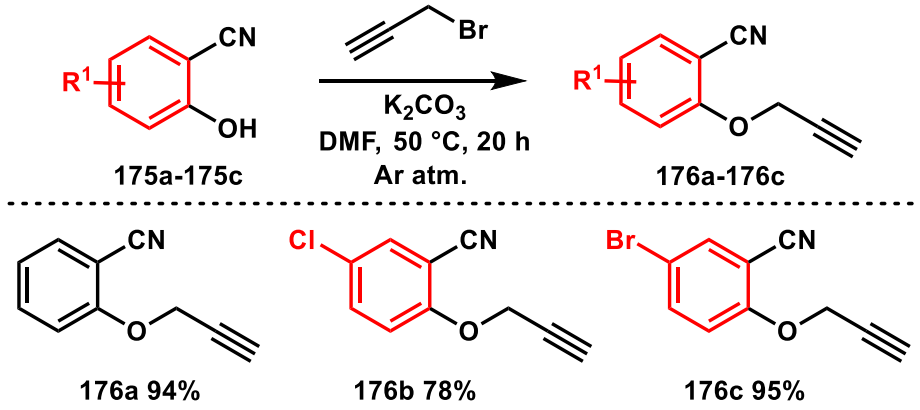


Scheme 52. *Designed substrate scope of chromenoquinolines*

4. 3. 4. Synthesis of the arylpropynyloxybenzonitrile bifunctional substrates

The synthesis of the desired arylpropynyloxybenzonitrile derivatives was accomplished from 2-hydroxybenzonitrile derivatives in a two-step procedure. First of all, 2-(prop-2-yn-1-yloxy)benzonitrile derivatives were synthesized from the appropriate 2-hydroxybenzonitrile derivatives and propargyl bromide according to the procedure of Lingam.[141]

The propargylation of 2-hydroxybenzonitrile (**175a**) afforded the appropriate product (**176a**) in high yield (**Scheme 53**). Furthermore, 2-(prop-2-yn-1-yloxy)benzonitrile derivatives bearing chloro and bromo substituents (**176b** and **176c**) on the nitrile moiety were also prepared from the appropriate cyanophenoles (**175b** and **175c**) in 78% and 95% yields.

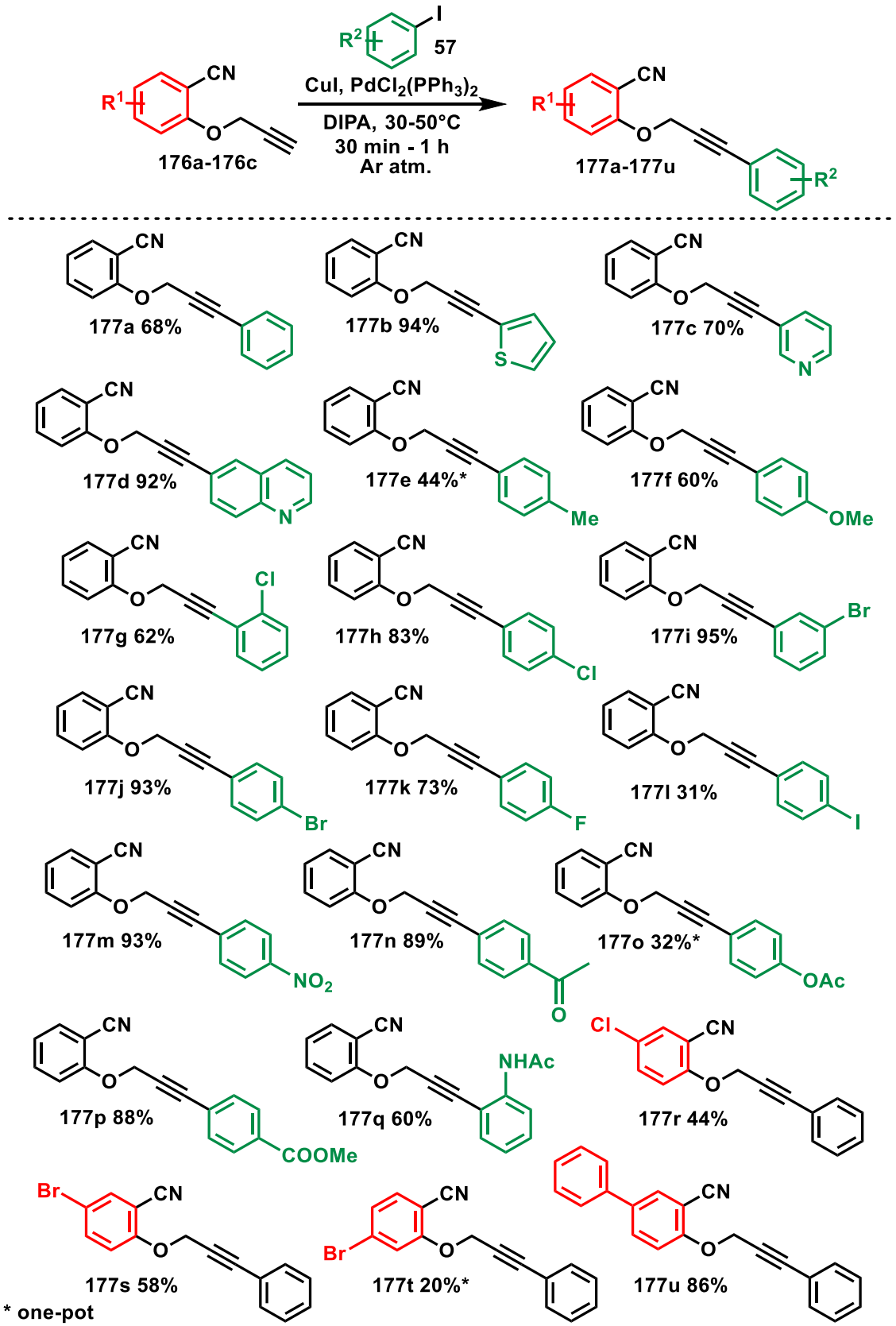


Scheme 53. *Propargylation of hydroxybenzonitrile derivatives*

In the next step, the propargylated compounds were reacted with aryl iodides (**57**) in the presence of copper and palladium catalyst *via* Sonogashira coupling. Aromatic and

heteroaromatic substrates such as thiophene, pyridine and quinoline derivative (**177a-177d**) were obtained in 68%, 94%, 70% and 72% yields, respectively (**Scheme 54**). Arylpropynyloxybenzontiriles equipped with electron-donating groups such as methyl (**177e**) or methoxy (**177f**) group were isolated in 44% and 60%. Compound **177e** was prepared in a one-pot synthesis from 2-hydroxybenzonitrile (**175a).** The propargylated compound (**176a**) was not isolated from the mixture, but palladium and copper catalysts, DIPA base and 4-iodotoluene were added to the reaction mixture when the propargylation reaction completed. After the Sonogashira reaction **177e** was isolated in 44% yield (for two steps). Bifunctional substrates bearing chloro, bromo, fluoro and iodo substituents (**177g-177l**) in the *ortho*, *meta* or *para* position to the aryl group were also synthesized in good to high yields. Arylpropynyloxybenzontiriles equipped with electron-withdrawing groups such as nitro (**177m**), keto (**177n**), acetoxy (**177o**) or ester (**177p**) group were obtained in high yields (88-93%) except compound **177o**, which was prepared in only 32% yield in a one-pot procedure from **175a**. Compound **177q** bearing an amido group *ortho* to the aryl group was also synthesized in 60% yield. The reactivity study of this substrate in the key transformation was conceptually important in establishing the proposed mechanism of the transformation, discussed later in details.

The Sonogashira reaction of propargylated compounds **176b** and **176c** with iodobenzene provided the appropriate products (**177r**, **177s** and **177t**) in moderate to good yields. Bromo-substituted arylpropynyloxy derivative **177t** was prepared in a one-pot synthesis from compound **175a** without the isolation of the corresponding propargylated compound. Moreover, we also synthesized a bifunctional substrate (**177u**) equipped with a phenyl group on the nitrile moiety. The preparation of this compound was accomplished by the Suzuki reaction of compound **177s** with phenylboronic acid, resulting the appropriate product (**177u**) in 86% isolated yield.

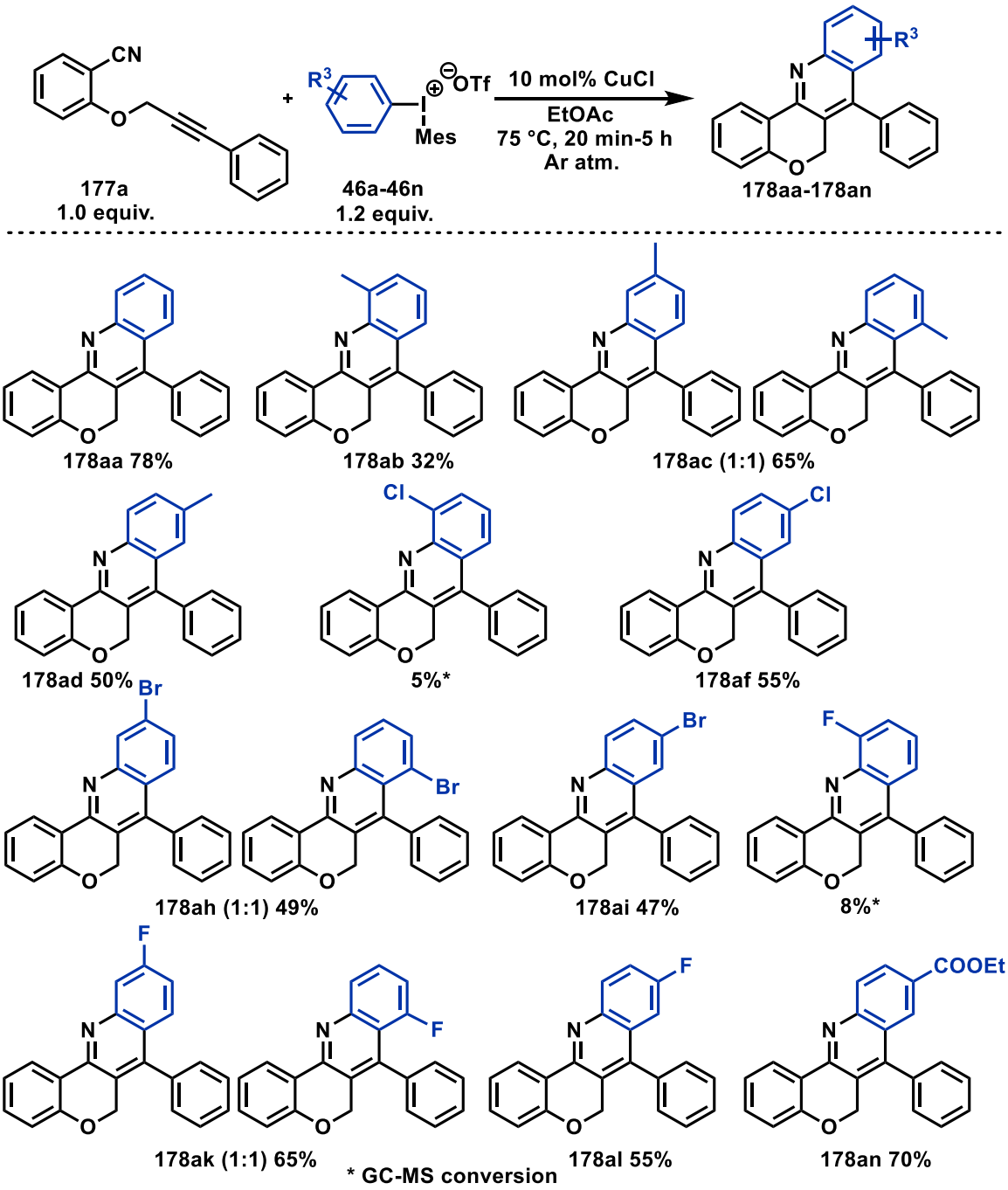


Scheme 54. *Synthesis of bifunctional substrates via Sonogashira coupling*

4. 3. 5. Synthesis of chromeno[4,3-*b*]quinolines

In order to explore the scope and limitations of the developed methodology, we reacted the prepared arylpropynyloxybenzonitrile substrates (**177a**-**177u**) with arymesityliodonium salts (**46a**-**46n**) under the optimized reaction conditions (10 mol% of CuCl in EtOAc at 75 °C).

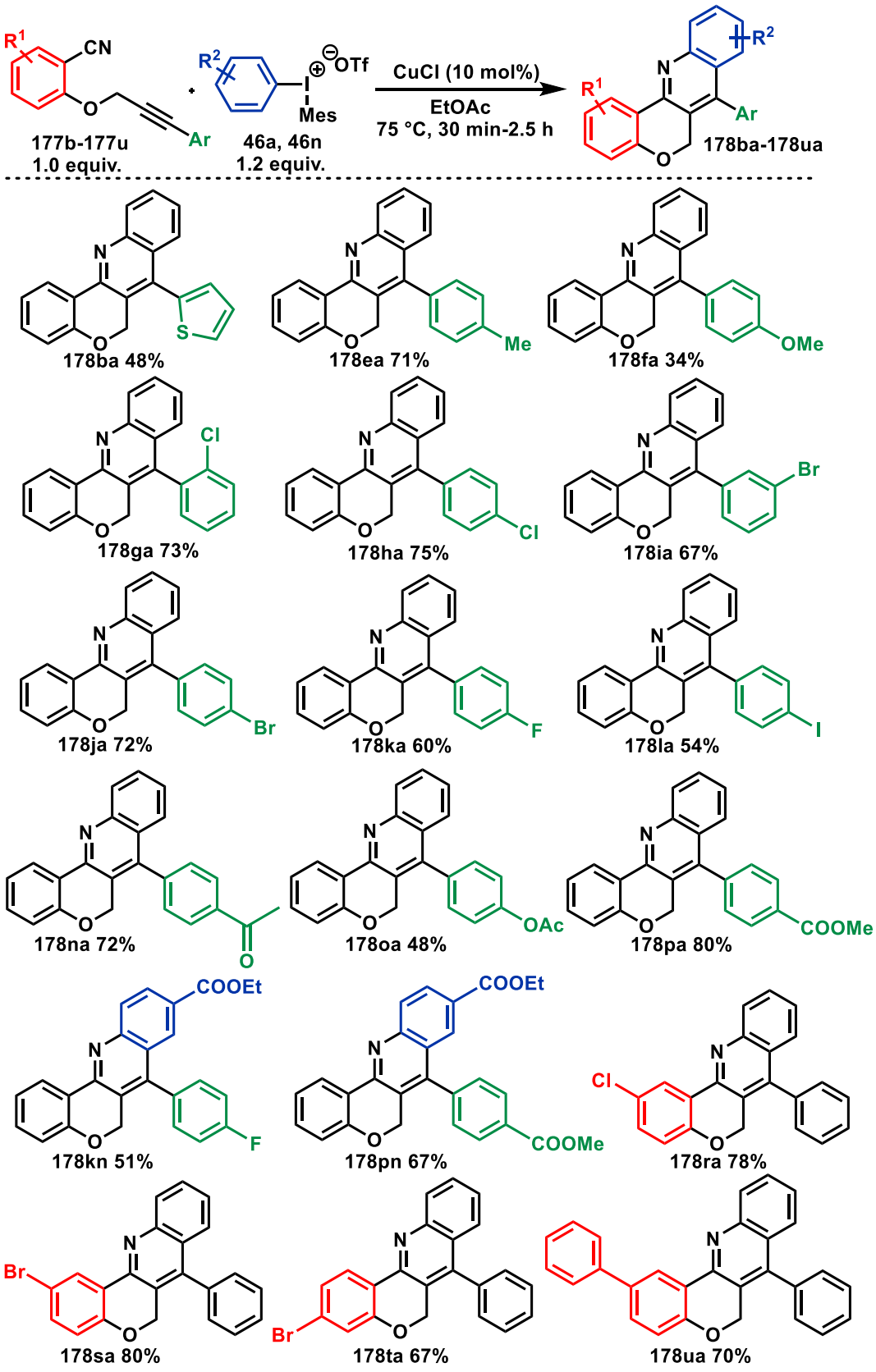
First, we reacted 2-((3-phenylprop-2-yn-1-yl)oxy)benzonitrile (**177a**) with phenylmesityliodonium triflate (**46a**) in the presence of 10 mol% CuCl catalyst and we were pleased to observe that **178aa** was obtained in 78% yield (33% isolated yield could be reached before the optimization studies) (**Scheme 55**). When arylmesityliodonium triflate containing methyl group *ortho* to the iodine was utilized, the reaction was slower (5 h reaction time was needed) and the desired product (**178ab**) was isolated only in 32% yield. In contrast, when a methyl substituent was present in the *meta* or *para* positions of the phenyl group of the iodonium salt, the reaction was fast, and the desired chromenoquinolines (**178ac** and **178ad**) were synthesized in 65% and 50% yields, respectively. When the aryl group of the iodonium salt was equipped with a halogen atom (F, Cl, or Br) *ortho* to the iodine, the ring closure reaction was retarded and the appropriate compounds were detected only with GC−MS (5−8% GC−MS conversion). The same deactivating effect was observed similar to the synthesis of iminobenzoxazines. When diaryliodonium salts containing halogens in the *meta* or *para* positions were employed in the copper-catalyzed cyclization, **177a** was transformed to the corresponding chromenoquinoline derivatives (**178af**−**178al**) in 47−65% yield. Amongst the functionalized arylmesityliodonium salts diaryliodonium triflate bearing a *para* COOEt group worked with the best efficiency and provided the desired product (**178an**) in 70% yield. When *meta* substituted iodonium salts were applied in the reaction, chromenoquinolines **178ac**, **178ah**, and **178ak** were obtained as 1:1 mixtures of possible regioisomers. This case can be explained by the last step of the transformation, in which - according to our plausible mechanism - an aromatic electrophilic substitution occures (for details of the mechanism, see **Scheme 59**).



***Scheme 55**. Synthesis of chromenoquinolines with different arylmesityliodonium triflates*

Next, we examined the scope of the developed transformation by studying the reactivity of different nitriles bearing versatile arylpropargyl function (**177b**-**177u**) in the ring closure reaction (**Scheme 56**). Two more examples (**178kn** and **178pn**) are given where the cyclization is performed with 4-ethoxycarbonyl-phenylmesityliodonium triflate (**46n**).In the case of nitriles equipped with heteroaromatic ring such as thiophene, pyridine or quinoline ring (**177b**-**177d**) only substrate **177b** afforded the appropriate chromenoquinoline derivative (**3ba**) in 48% yield, while the quinoline (**177c**) and

pyridine (**177d**) derivatives were not able to transform to the corresponding products (not shown).

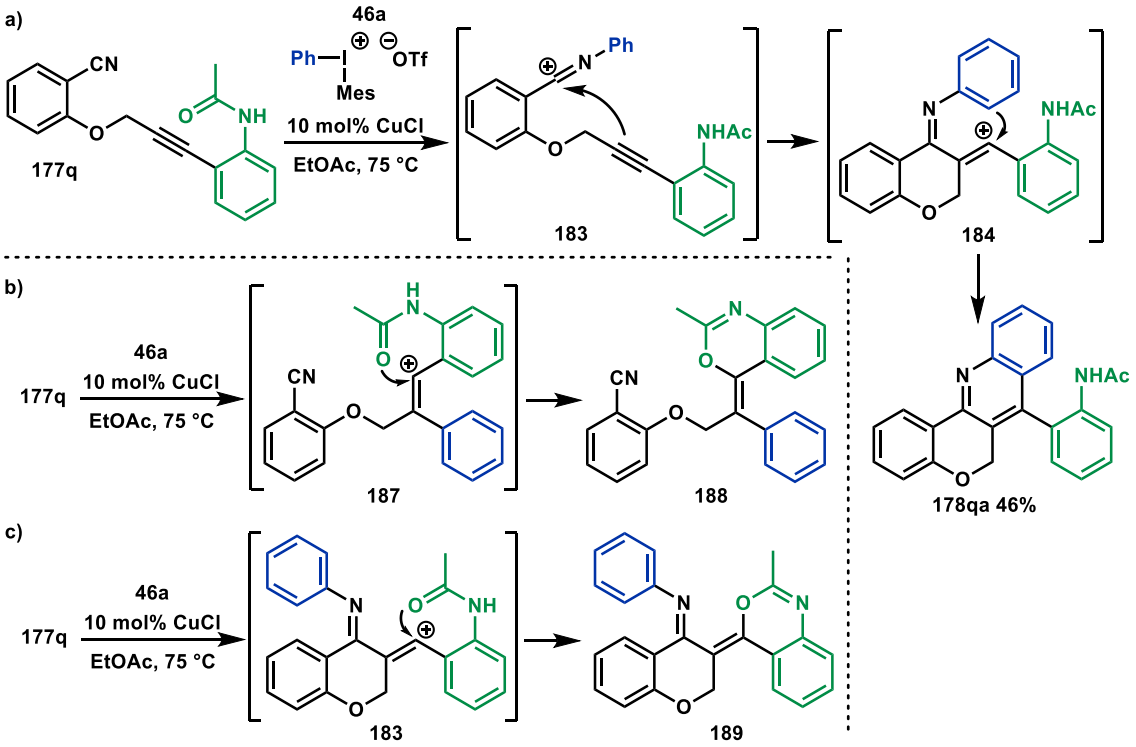


Scheme 56. *Synthesis of chromenoquinolines with different nitriles*

When the reaction was attempted with nitrile derivative bearing electron donating methyl group (**177e**) in the *para* position, the desired chromenoquinoline derivative (**178ea**) was isolated in 71%. In the case of strong electron donating methoxy group in the *para* position (**177f**), the appropriate product (**178fa**) was isolated in lower yield (34%). The presence of halogens (**177g**−**177l**) on the aromatic ring of the aryl iodide was well-tolerated in the *ortho*, *meta*, and *para* positions, and the corresponding products (**178ga**−**178la**) were obtained in 54−75% yield. In the case of nitriles bearing electron-withdrawing groups such as nitro (**177m**), keto (**177n**) or acetoxy groups (**177o**) in the *para* position, substrates **177n** and **177o** afforded the desired chromenoquinoline derivatives (**177na** and **177oa**) in 72% and 48% yields. However, the reaction of the substrate containing strong electron withdrawing nitro group (**177m)** with phenylmesityliodonium triflate (**46a**) did not result the appropriate chromenoquinoline derivative, by-product was formed (based on ^{1}H NMR measurements). Nevertheless, the presence of an ester group on the aromatic ring of the arylpropynyloxy-benzonitrile derivative (**177p**) was well-tolerated and we could isolate the corresponding product (**178pa**) in good yield (80%). When substrate **177k** and **177p** were reacted with the para-ester derivative (**46n**) of the iodonium salt, the ring closure reaction provided the appropriate products (**178kn** and **178pn**) in 51% and 67% yields.

Finally, the cyclization was also demonstrated on nitrile substrates bearing halogen (Cl, Br) and phenyl substituents (**177r**−**177u**) on the hydroxybenzonitrile moiety. When the aromatic ring of the nitrile contained halogens (**177r**, **177s**, and **177t**) the appropriate chloro (**178ra**) and bromo (**178sa** and **178ta**) substituted chromenoquinolines were obtained in 78%, 80% and 67% yields, respectively. The presence of phenyl group (**177u**) on the nitrile was also well-tolerated and was active in the ring closure reaction affording the desired product (**178ua**) in 70% yield.

The reactivity of the substrate containing amide group in the *ortho* position of the aromatic ring (**177q**) was conceptually important in establishing a plausible mechanism for the developed transformation comparing the reactivity of the acetylene and the nitrile groups toward the highly electrophilic arylcopper(III) species (**Scheme 57**).

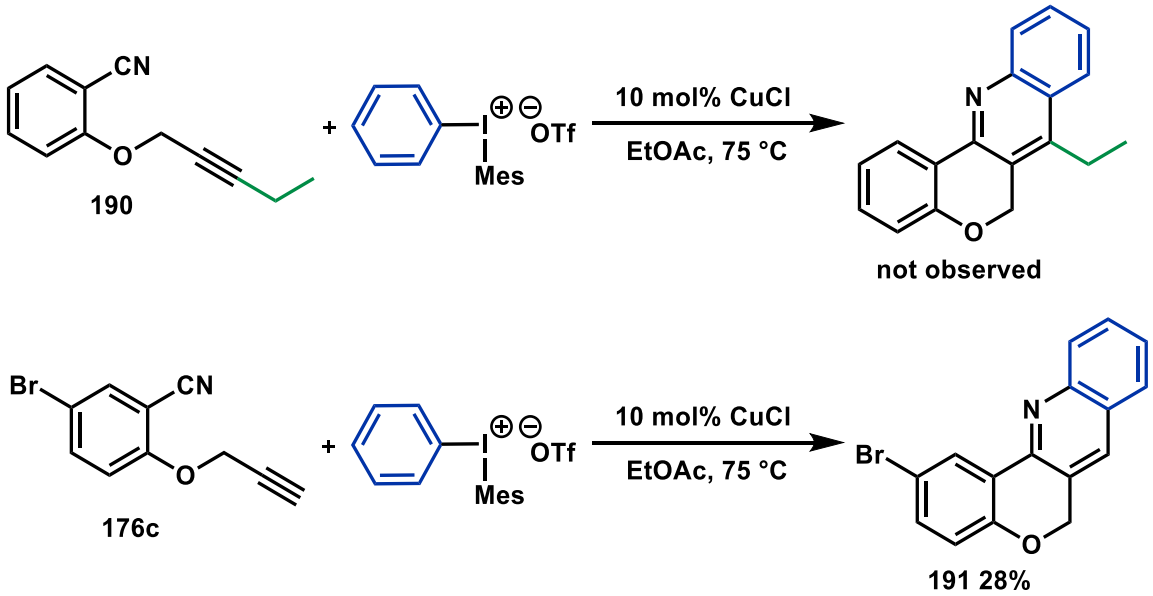


Scheme 57. *Ring closure of acetamido substrate* ***177q***

The *ortho* ethynyl anilide motif could undergo cyclization in which the amide moiety is involved, while alkyne functional group is activated by the diaryliodonium salt (**Scheme 57b**), affording benzoxazines (**188**) *via* intermediate **187** as we demonstrated earlier (synthesis of benzoxazine derivatives from 2-ethynylanilides).[129] The *N*-aryliminium ion formation *via* nitrile activation (**Scheme 57a** and **Scheme 57c**) could provide quinolines (**178qa**) or condensed benzoxazines (**189**). The latter could be formed if the generation of the arylnitrilium intermediate (**183**) is followed by a cyclization involved the amido and the alkyne functions. In contrast, if the ring closure occurs with the contribution of the *N*-aryliminium ion and the acetylene moiety, while the amido group is retained, quinoline derivative **178qa** could be produced. The reaction of substrate **177q** with phenylmesityliodonium triflate (**46a**) obtained the appropriate chromenoquinoline product (**178qa**) in 46% yield. While we were not able to detect the formation of any other by-products (by GC-MS), we can conclude that the nitrile function has preferential reactivity over the alkyne moiety. The electrophilic substitution of the assumed vinyl cation intermediate by the aromatic ring is preferable to attack by the amide part.

We also aimed to investigate the reactivity of benzonitriles equipped with alkylpropargyl substituent instead of arylpropargyl moiety (**177a-177u**). The corresponding ethyl-substituted compound (**190**) was prepared from 2-

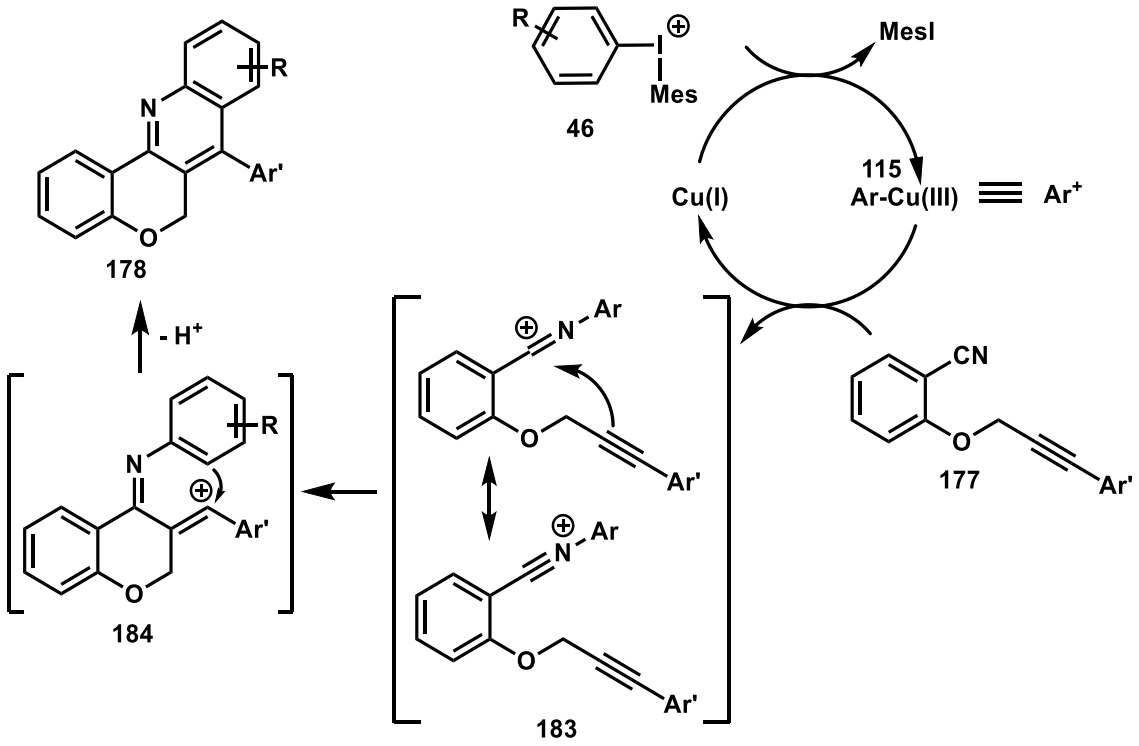
hydroxybenzonitrile (**175a**) and 1-bromopent-2-yne according to the procedure of Lu et al.[142] Furthermore, we examined the reaction of substrate **176c** with phenylmesityliodonium triflate (**46**), comparing the reactivity of terminal alkynes to internal acetylenes in the copper-catalyzed ring closing reaction (**Scheme 58**). In the case of compound **190** accomplishing the reaction in the presence of phenylmesityliodonium triflate (**46**) and CuCl, we were not able to detect the formation of the appropriate chromenoquinoline product (by GC-MS). However, the utilization of substrate **176c** in the ring closing reaction afforded the corresponding chromenoquinoline derivative (**191**) in 28% yield. Thereby, we can conclude that terminal alkynes are also suitable substrates for this transformation, although, compared to most of the chromenoquinoline derivatives (**178a-178q**) lower isolated yield could be reached for compound **191** after the ring closing reaction. In contrast, the presence of electron donating ethyl group instead of aryl substituents hindered the arylation-cyclization reaction.



Scheme 58. *Copper-catalyzed reaction of substrates **190** and **176c** with phenylmesityliodonium triflate*

Based on the results according especially to the reactivity of substrates **177q**, **190** and **176c**, we also report our plausible mechanism for the transformation, which is presumed to begin with the formation of arylcopper(III) species (**115**) from copper catalyst and diaryliodonium salt (**46a**) (**Scheme 59**). In the following step, the formed copper(III) intermediate interacts with the nitrile function (**177**) generating a cationic species (**183**) and Cu(I). Then, the acetylene moiety can readily attack the arylnitrilium intermediate **183** in an intramolecular fashion, resulting the formation of intermediate **184** containing a chromene ring with an *exo* vinyl cation. Finally, this intermediate (**184**) can

undergo an intramolecular cyclization *via* electrophilic aromatic substitution, affording the chromenoquinoline product (**178**).



Scheme 59. *Proposed mechanism of the developed arylation-ring closure*

According to the substrate scope, when strong electron-donating methoxy-substituted chromenoquinoline derivative (**178fa**) was synthesized, only 34% isolated yield could be reached, while the reaction of the substrate containing strong electron-withdrawing nitro group (**177m)** with phenylmesityliodonium triflate (**46a**) did not result the appropriate chromenoquinoline derivative. This fact is in accordance with our proposed mechanism. The formation of intermediate **184** from **183** *via* nucleophile attack is influenced by electronical properties of the arylpropargyl moiety and the nitrilium cation. The presence of electron-donating group on the arylpropargyl moiety enhances the nucleophilic character of the acetylene, while the occurence of electron-withdrawing substituents on the aromatic ring connected to the nitrilium cation is favorable, related to the nucleophilic attack. These two opposite facts both contribute to the cyclization, thus, the presence of too electron-donating or electron-withdrawing substituents retard or hinder the cyclization.

Furthermore, the structure of the chromenoquinoline frame was established by single-crystal X-ray diffraction measurements, discussed in details in the following chapter.

4. 4. Single crystal X-ray diffraction mesurements of chromeno[4,3-*b*]quinolines

In a collaboration with the Chemical Crystallography Research Group (Research Centre for Natural Sciences of the Hungarian Academy of Sciences), the conformation of the chromenoquinoline frame was established by single crystal X-ray diffraction in the case of compound **178aa**.

The chromeno (A and B) and quinolino moieties (C and D) of **178aa** are nearly coplanar, their angle is 8.63(6)^{o} owing to the saturated ring B, where O5 is -0.222(1) Å, while C6 is 0.239(2)Å out of the plane of the hetero ring (**Figure 7**).[143] The phenyl ring (E) is almost perpendicular to the quinoline moiety (C and D) having the angle of 85.13(8)^{o}. The crystal structure (**Figure 8**) (triclinic crystal system, space group P-*1*) of **178aa** is stabilized by a weak C18-H18…O5 interaction (**Figure 9**, **Table 3**). There are C-H…π intermolecular interactions (**Figure 10**) between a phenyl hydrogen and a chromeno moiety (C17-H17…A, 2-X,1-Y,-Z) on one side, and on the opposite side of the phenyl ring from a phenyl hydrogen to a quinoline moiety (C15-H15…D, 2-X,-Y,-Z) of another neighboring molecule. Because of the presence of the almost perpendicular phenyl group there are no close π…π contacts in the crystal lattice, the shortest distance between the aromatic rings is 4.2082(12)Å. For crystal data and details of the structure refinement, as well as the results of the structural analyses, see **Table 3** and **Table S5** in Chapter 7.14.

The packing coefficient of **178aa** is 69.0%, there is no residual solvent accessible void in the crystal.[144]

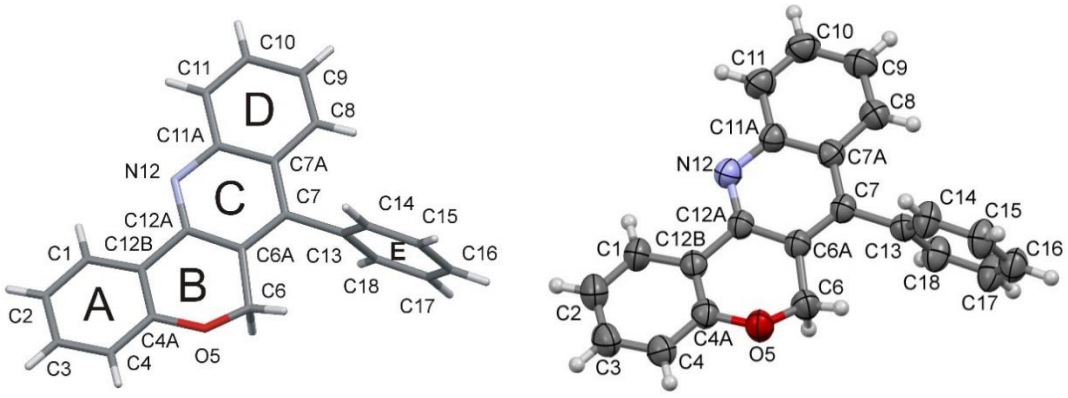


Figure 7. *Molecular structure with ring indications and ORTEP representation of compound* ***178aa*** *at 50% probability level of displacement ellipsoids*

Functional group	**178aa** -	**178ea** CH_3	**178ka** F	**178ha** Cl	**178ja** Br	**178la** I
	C…A distance [Å] and angles (º) of C-H…A interactions					
C14-H14…N12			3.415(2)	3.3849(18)	3.444(3)	
			163	160	163	
C15-H15…F19			3.492(2)			
			162			
C17-H17…N12						3.407(4)
						159
C18-H18…N12			3.451(2)	3.3439(19)		
			140	134		
C18-H18…O5	3.521(2)	3.522(2)				
	148	148				
	distances [Å] and angles (º) of C-H…Cg (π-Ring) interactions					
C9-H9… Cg(E)		3.744(2)				
		148				
C6-H6A… Cg(D)			3.7420(17)			
			156			
C6-H6B… Cg(D)				3.7004(16)	3.822(3)	
				154	149	
C10-H10… Cg(E)			3.6655(17)	3.6313(16)		
			132	137		
C15-H15… Cg(D)	3.641(3)	3.699(3)				
	146	141				
C17-H17… Cg(A)	3.706(2)	3.721(2)				
	153	143				
	distances [Å] Cg(I)…Cg(J) ring interactions					
Cg(A)…Cg(A)						3.871(2)
Cg(C)…Cg(C)			3.8816(8)	3.8285(8)	3.8791(13)	3.7465(14)
Cg(C)…Cg(C)			3.9661(8)	3.7551(8)	3.8423(13)	
Cg(C)…Cg(D)			3.9615(9)	3.7103(8)	3.8135(14)	
	distances [Å] and angles (º) of halogen-halogen interactions					
I19…I19						3.777
						140.11

Table 3. *Comparison of the intermolecular interactions in the crystals*

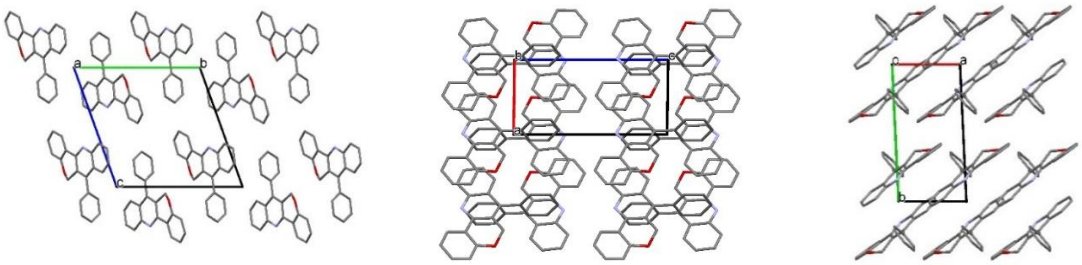


Figure 8. *The crystal packing of* ***178aa*** *viewed along the a, b and c crystallographic axes, respectively (hydrogen atoms are omitted for clarity)*

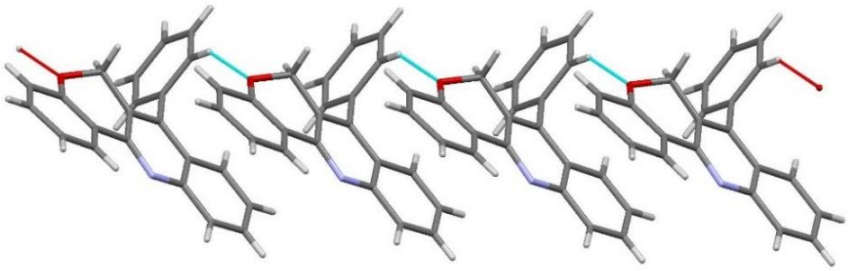


Figure 9. *The weak C18-H18…O5 interaction in the crystallographic a direction in* ***178aa***

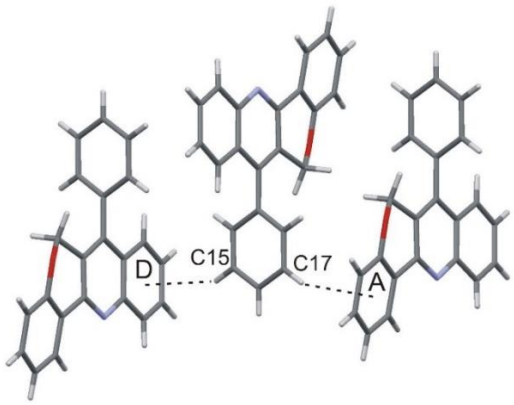


Figure 10. *The weak C-H…π (C15-H15…D and C17-H17…A) interactions in the crystallographic b direction in* ***178aa***

Having the results of the SXRD measurement of compound **178aa,** numerous homologue series of derivatives were included in the structural investigation in order to perform and investigate the steric and electrostatic fine tuning of the system. We defined five series (**Figure 11**): EDG-EWG series (green), halogen derivatives 1 and 2 (blue and red), ester series (purple) and methyl sequence (orange). We aimed to compare the changes occurred in the conformation and the crystal structure (considering the intermolecular interactions) by the modification of the atoms or functional groups in the corresponding derivatives of homologue series. The evaluation of the methyl derivative (**178ea**) and the halogen series 1 (blue, **178ha**-**178la**) were completed until now.

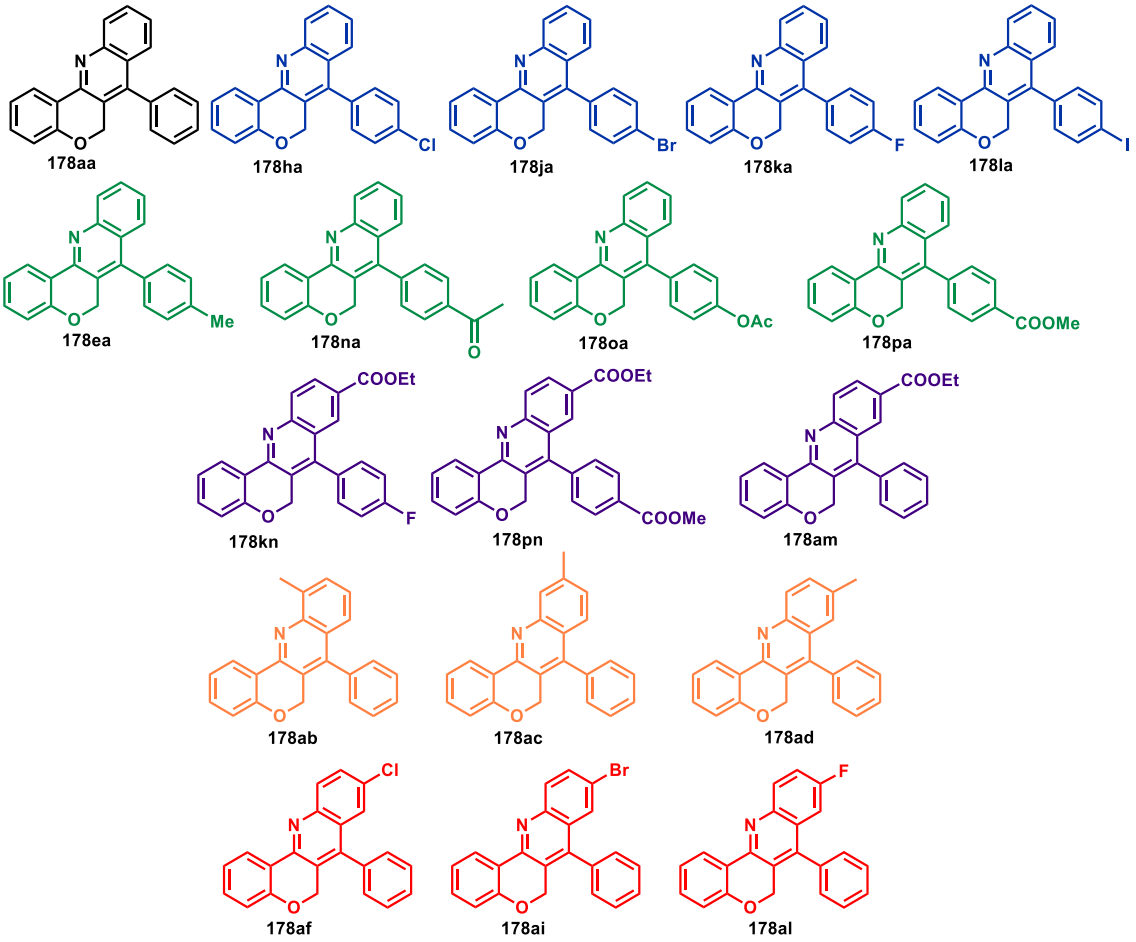


Figure 11. *The synthesized homologous series*

In the molecular structure of the methyl derivative (**178ea**), similarly to **178aa**, the chromeno (A and B) and quinolino moieties (C and D) are nearly in the same plane, their angle is 7.44(6)^{o} owing to the saturated ring B, where O5 is -0.221(1)Å, while C6 is 0.258(2)Å out of the plane of the hetero ring (**Figure 12**). The phenyl ring spings somewhat more from the perpendicular position to the quinoline group 76.19(10)^{o} in **178ea** than in **178aa**.

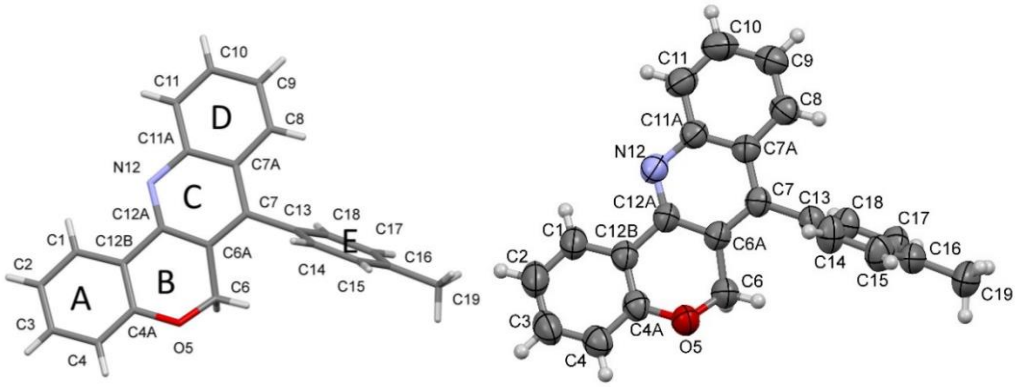


Figure 12. *Molecular structure with ring indications and ORTEP representation of* ***178ea*** *at 50% probability level of displacement ellipsoids*

In accordance with **178aa,** the crystal structure of **178ea** (**Figure 13**) (triclinic crystal, space group P-*1*), is also stabilized by a weak C18-H18…O5 interaction (**Figure 14**, **Table 3**). Isostructurally, there are C-H…π intermolecular interactions in **178ea** between a phenyl hydrogen and a chromeno moiety (C17-H17…A) on one side, and on the opposite side of the phenyl ring from a phenyl hydrogen to a quinoline moiety (C15-H15…D) of another neighboring molecule. Because of the presence of the close to perpendicular phenyl group there are no close π…π contacts in the crystal lattice, the shortest distance between the aromatic rings is 4.0954(12)Å in case of rings A and C.

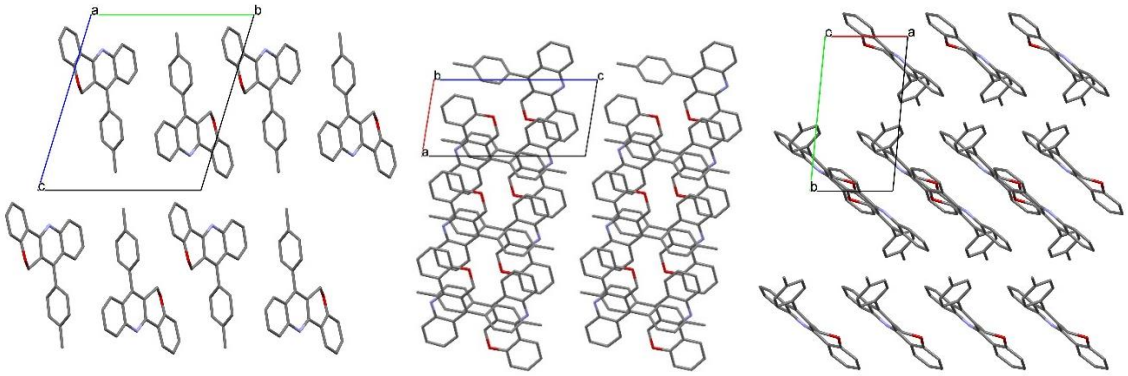
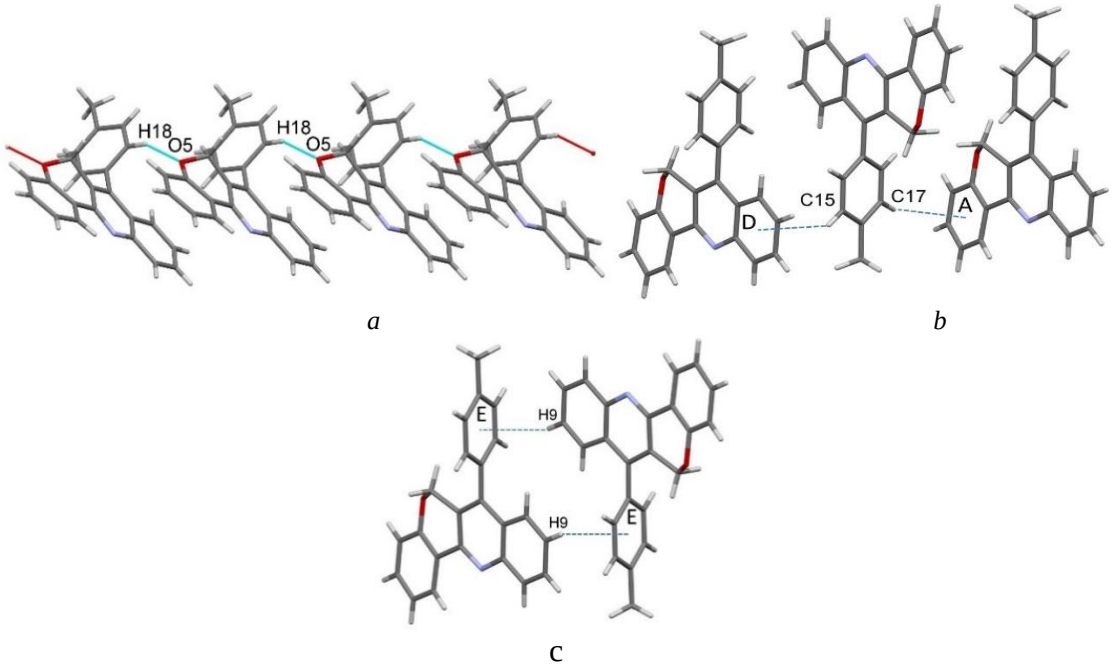


Figure 13. *The crystal packing of* ***178ea*** *viewed from the a, b and c crystallographic axes*



a *b*

c

Figure 14. *Week C18-H18…O5 interactions (a left), the weak C-H…π (C15-H15…D and C17-H17…A and C9-H9…E) interactions (b right and c) in* ***178ea*** *crystals*

The molecular structure of the fluoro derivative (**178ka**) from the halogen series 1 showed that the chromeno (A and B) and quinolino moieties (C and D) are slightly

bended, their angle is 15.86(5)^o owing to the saturated ring B, where O5 is -0.209(1) Å, while C6 is 0.272(2)Å out of the plane of the hetero ring (**Figure 15**). The phenyl ring turns with an angle of 64.12(6)^o to the quinoline group.

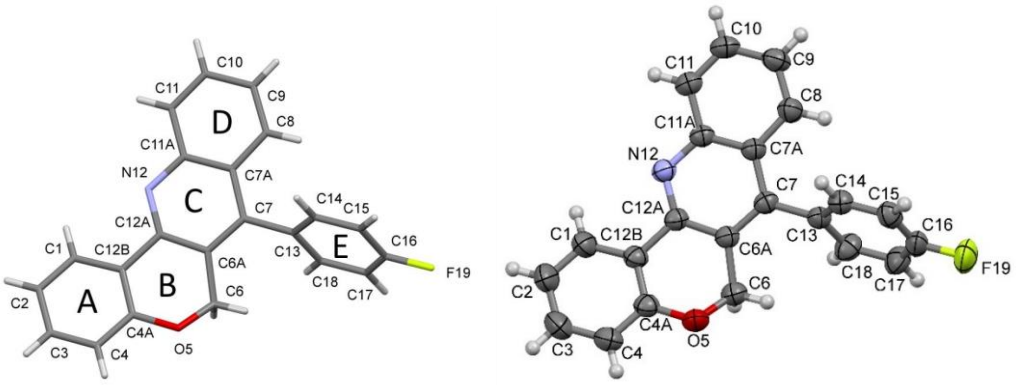


Figure 15. *Molecular structure with ring indications and ORTEP representation of* ***178ka*** *at 50% probability level of displacement ellipsoids*

The crystal structure of **178ka** (the only monoclynic crystal in the series, space group $P2_1/c$) (**Figure 16**), is stabilized by weak C14-H14…N12 and C18-H18…N12 interactions and a halogen-hydrogen interaction between C15-H15…F19 (**Figure 17**, **Table 3**). A dimer is formed around an inversion centre by weak C-H…π intermolecular interaction via C6-H6A…D at both sides. Another C-H…π interaction, C10-H10…E, forms a chain of the dimers in the crystallographic *a* dimension. The C-C and C-D rings of the nerby quinolino moieties get close to form week π…π interactions (< 4.0 Å).

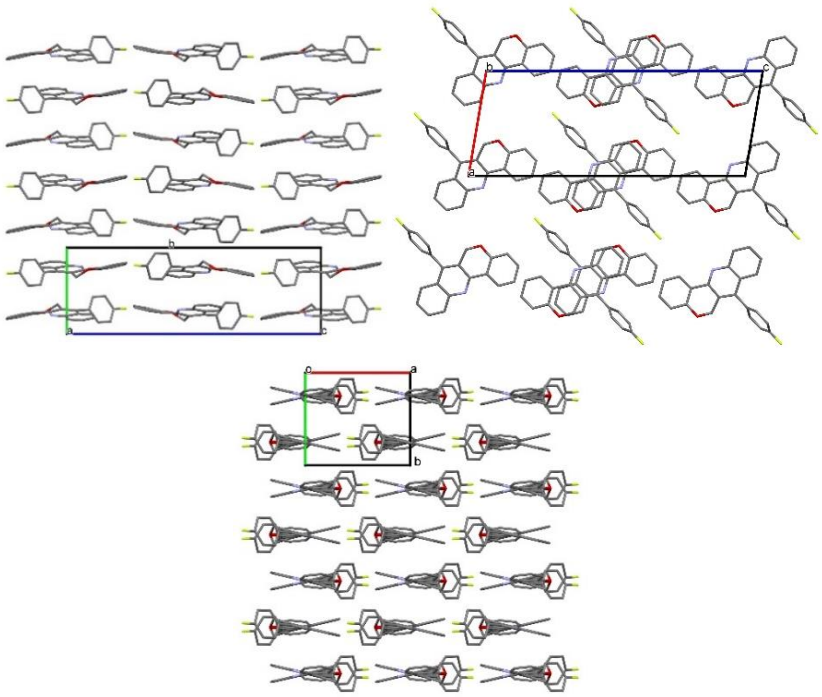


Figure 16. *The crystal packing of* ***178ka*** *viewed from the a, b and c crystallographic axes*

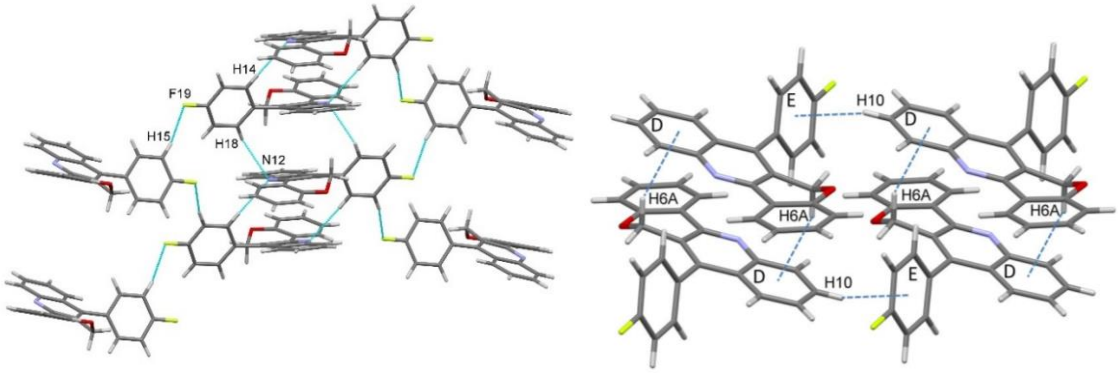


Figure 17. *Week intermolecular interactions in* ***178ka*** *crystals including C-H…N and C-H…F interactions (left). The weak C-H…π (C6-H6A…D and C10-H10…E) interactions in the crystallographic ab plane in 178ka (right)*

Investigation of the molecular structure of chloro derivative (**178ha**) showed that the chromeno (A and B) and quinolino moieties (C and D) are slightly bended, their angle is 14.15(4)^{o} owing to the saturated ring B, where O5 is -0.235(1) Å, while C6 is 0.272(1)Å out of the plane of the hetero ring (**Figure 18**). The phenyl ring turns with an angle of 59.85(6)^{o} to the quinoline group.

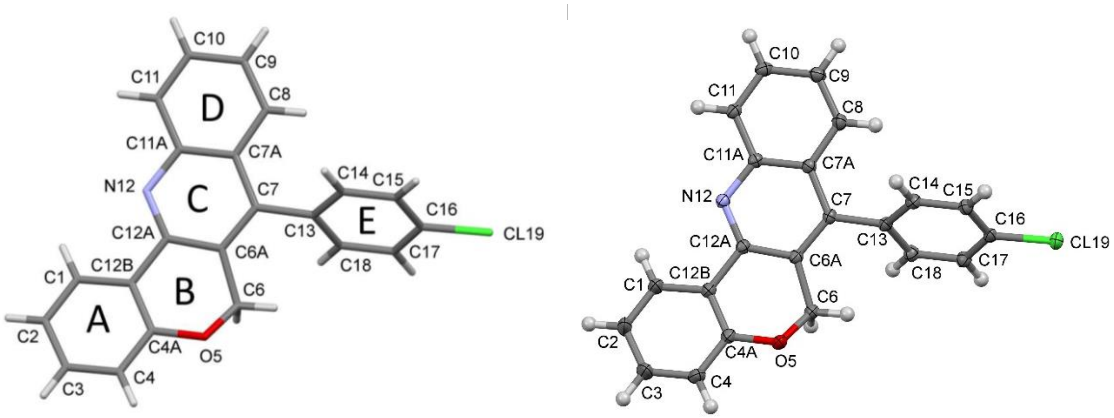


Figure 18. *Molecular structure with ring indications and ORTEP representation of* ***178ha*** *at 50% probability level of displacement ellipsoids*

The crystal structure of **178ha** (triclinic crystal system, space group *P*-1) (**Figure 19**) is stabilized by weak C14-H14…N12 and C18-H18…N12 interactions (**Figure 20**, **Table 3**) like in **178ka**. A C-H…π intermolecular interaction between two molecules via C6-H6A…D, *vica versa*, originates a dimer and another C-H…π by C10-H10…E expand the connection in the crystallographic dimension *a*. The C-C and C-D rings of the nerby quinolino moieties get close to form week π…π interactions (< 4.0 Å).

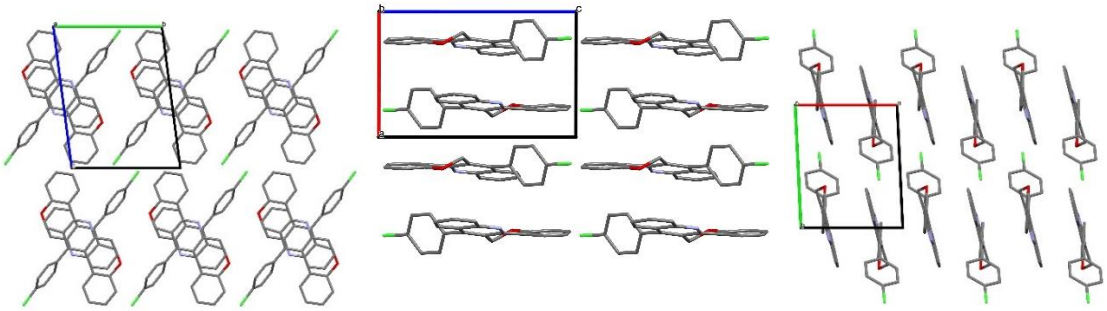


Figure 19. *The crystal packing of* ***178ha*** *viewed from the a, b and c crystallographic axes*

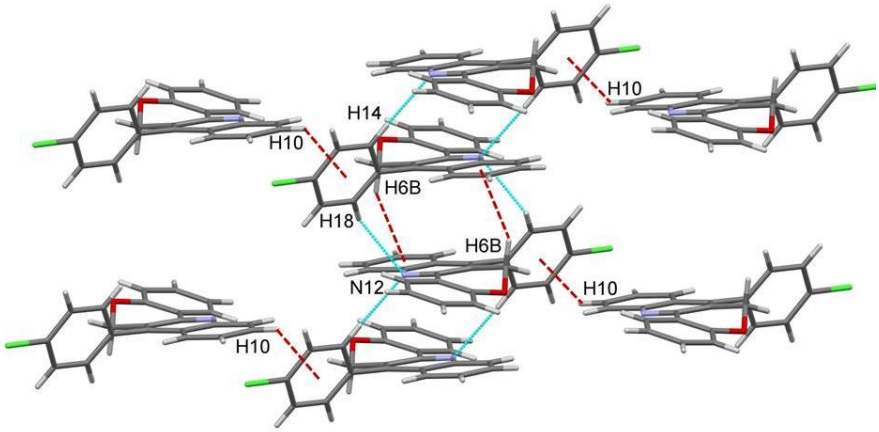


Figure 20. *Week intermolecular interactions in* ***178ha*** *crystals including C-H…N in the crystallographic a axis and C-H…π (C6-H6B…D and C10-H10…E) interactions in the crystallographic b axis*

Examining the molecular structure of the bromo derivative (**178ja**), we found that the chromeno (A and B) and quinolino moieties (C and D) are slightly bended, their angle is 14.01(8)^{o} owing to the saturated ring B, where O5 is -0.226(2)Å, while C6 is 0.259(3)Å out of the plane of the hetero ring (**Figure 21**). The phenyl ring turns with an angle of 62.72(12)^{o} to the quinoline group.

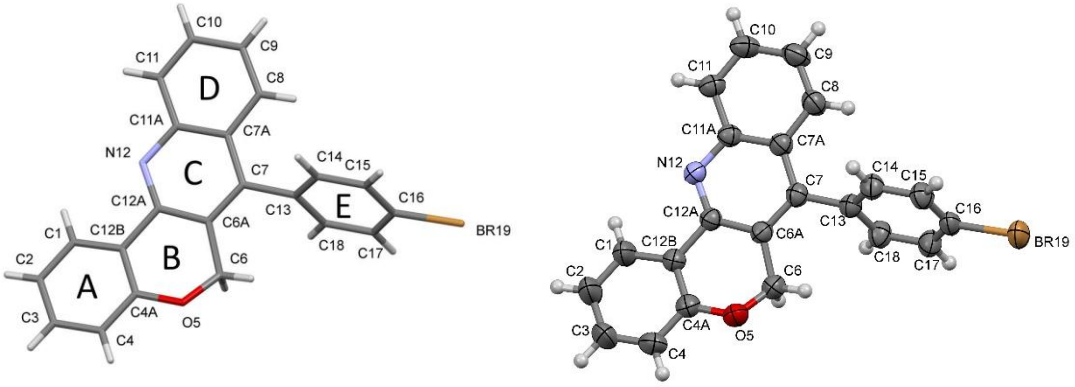


Figure 21. *Molecular structure with ring indications and ORTEP representation of* ***178ja*** *at 50% probability level of displacement ellipsoids*

The crystal structure of **178ja** (triclinic crystal system, space group *P*-1) (**Figure 22**) is stabilized by weak C14-H14…N12 and C18-H18…N12 interactions (**Figure 23**, **Table 3**) like in **178ka**. A dimer is formed around an inversion centre by weak C-H…π intermolecular interaction via C6-H6A…D at both sides. Another C-H…π interaction, C10-H10…E, forms a chain of the dimers in the crystallographic *a* dimension. The C-C and C-D rings of the nerby quinolino moieties get close to form week π…π interactions (< 4.0 Å).

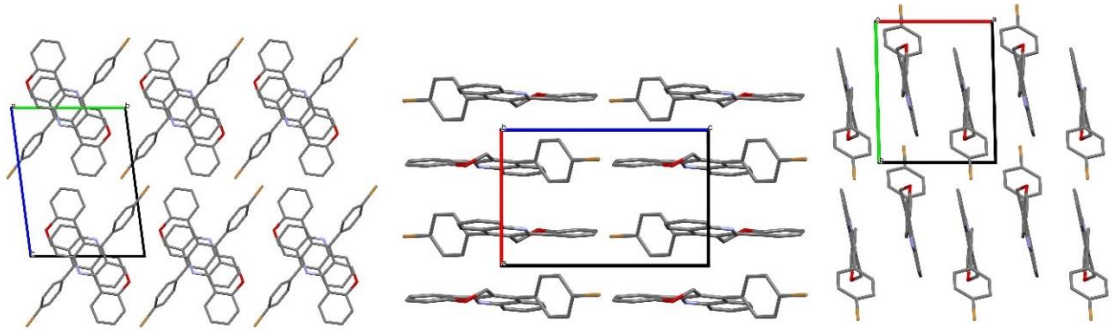


Figure 22. *The crystal packing of* ***178ja*** *viewed from the a, b and c crystallographic axes*

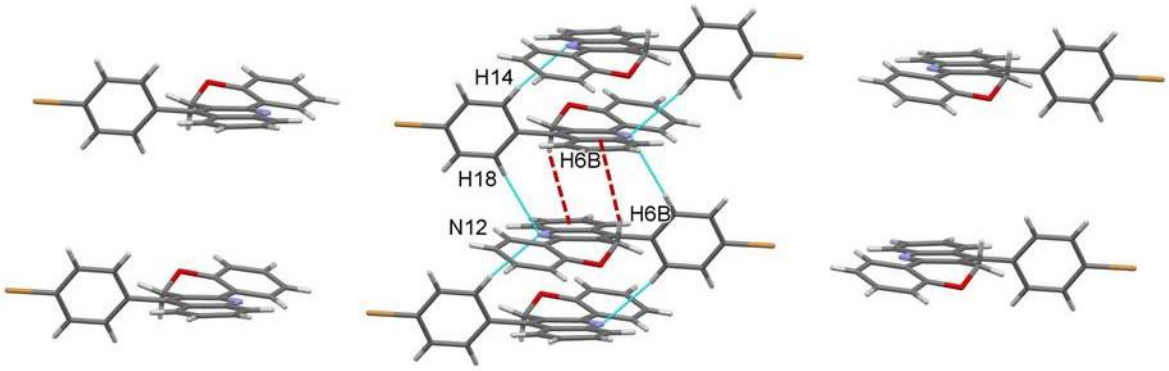


Figure 23. *Week intermolecular interactions in* ***178ja*** *crystals including C-H…N in the crystallographic a axis and C-H…π (C6-H6B…D) interactions in the crystallographic b axis*

Molecular structure of the iodo derivative (**178la**) was examined and was determined that the chromeno (A and B) and quinolino moieties (C and D) are slightly bended, their angle is 17.18(9)^{o} owing to the saturated ring B, where O5 is -0.245(3)Å, while C6 is 0.266(4)Å out of the plane of the hetero ring (**Figure 24**). The phenyl ring turns with an angle of 63.34(12)^{o} to the quinoline group.

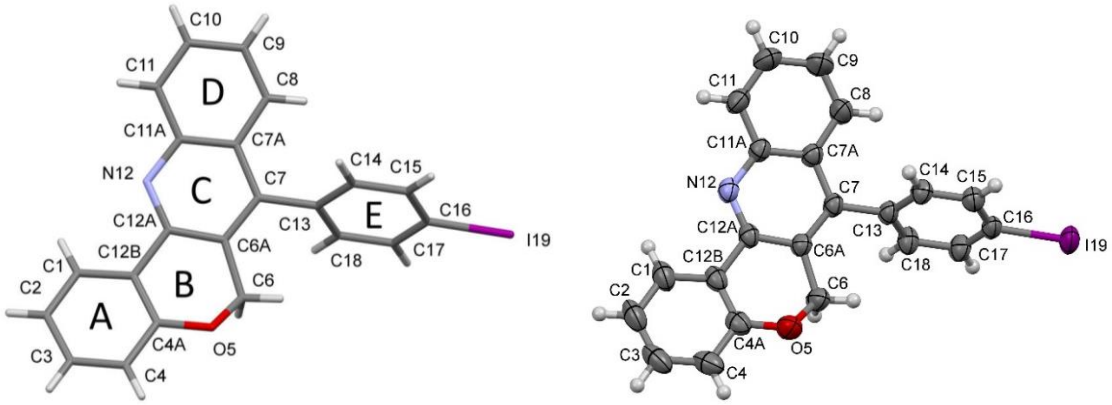


Figure 24. *Molecular structure with ring indications and ORTEP representation of* ***178la*** *at 50% probability level of displacement ellipsoids*

Owing to the iodo substituent the crystal structure of **178la** differs the most from the F, Cl and Br derivatives. The crystal structure of **178la** (triclinic crystal system remains, space group *P*-1) (**Figure 25**) is stabilized by weak C17-H17…N12 interactions (**Figure 26**, **Table 3**). C-H…π intermolecular interaction could not be detected. The shortest distance between nerby quinolino moieties allow a week π…π interactions (< 4.0 Å) between the C-C and A-A rings. Halogen-halogen interaction between I19…I19 could be found.

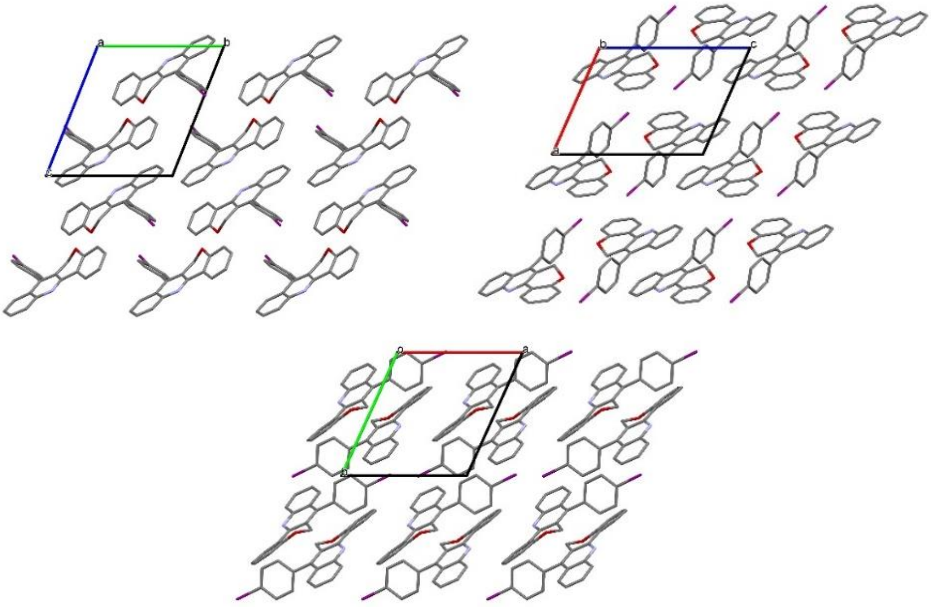


Figure 25. *The crystal packing of* ***178la*** *viewed from the a, b and c crystallographic axes*

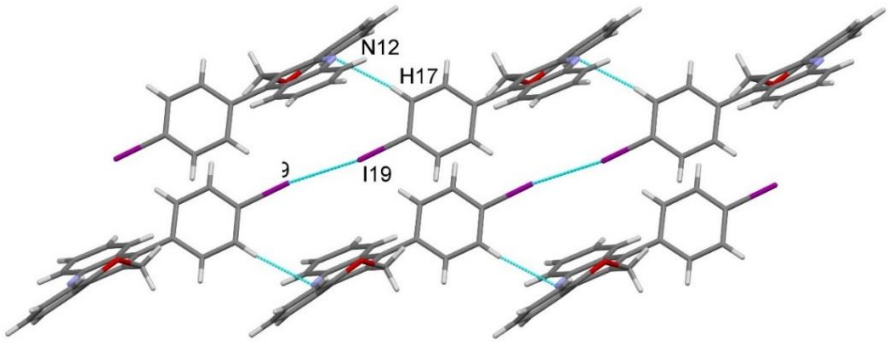


Figure 26. *Week intermolecular interactions in* ***178la*** *crystals*

Conformational comparison of the corresponding molecules showed strong similarities for **178aa** and its methyl derivative (**178ea**). In both cases the chromeno (AB) and quinolino (CD) moieties are not far to be in the same plane, the angle between the AB and CD rings are 8.63(6)^{o} and 7.44(6)^{o}, respectively (**Figure 27** and **Table 4**).

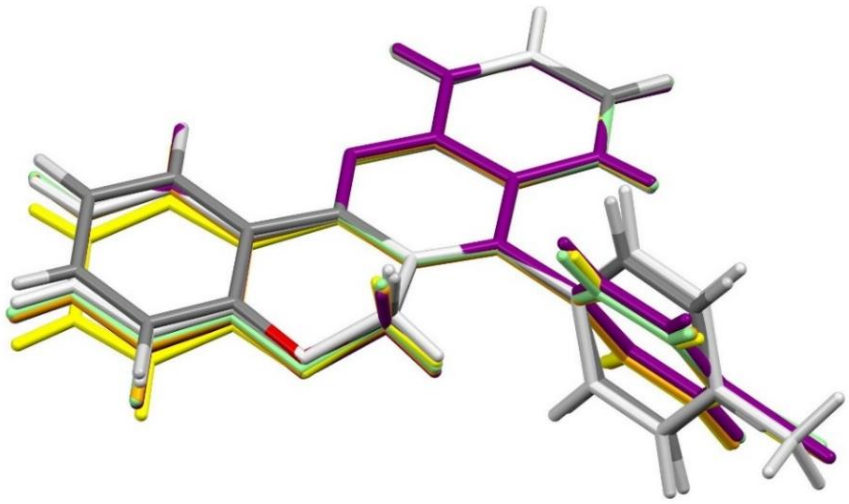


Figure 27. *Conformational comparison between* ***178aa*** *(coloured by element),* ***178ea*** *(white),* ***178ka*** *(yellow),* ***178ha*** *(green),* ***178ja*** *(orange) and* ***178la*** *(purple) structures*

	178aa	**178ea**	**178ka**	**178ha**	**178ja**	**178la**
	-	**Me**	**F**	**Cl**	**Br**	**I**
AB – CD	8.63(6)	7.44(6)	15.86(5)	14.15(4)	14.01(8)	17.18(9)
C – E	+85.13(8)	+76.19(10)	-63.45(7)	-59.85(6)	-62.72(12)	-63.34(12)
A –D	11.95(10)	8.75(10)	18.83(8)	17.24(8)	17.34(15)	21.21(16)
A – CD	12.17(8)	10.12(9)	19.15(7)	17.32(7)	17.15(14)	20.07(13)

Table 4. *Angles between different ring planes (^{o})*

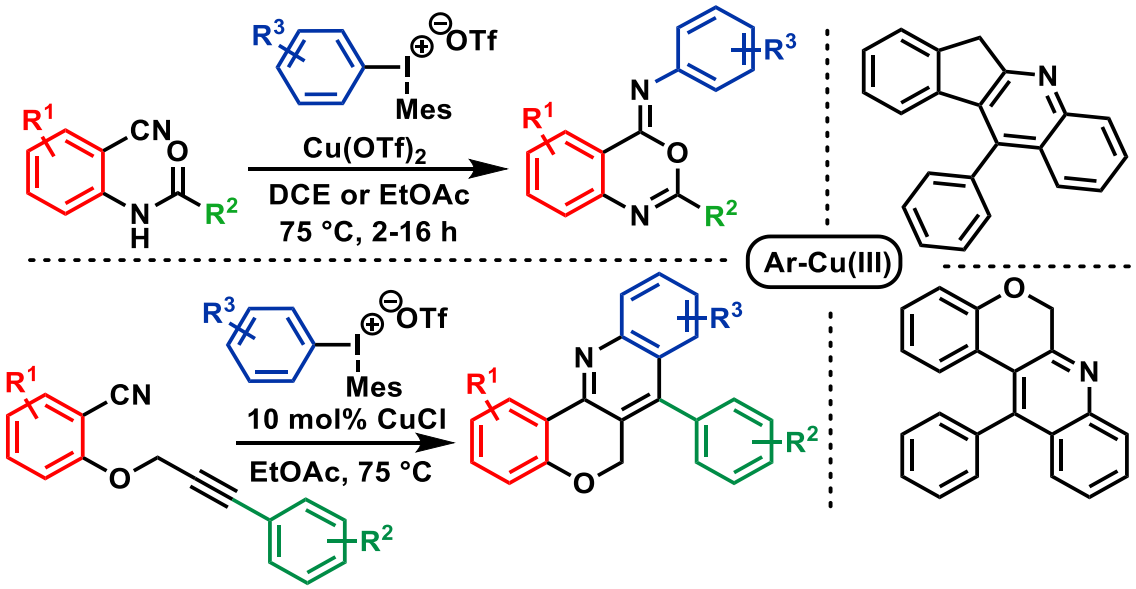
In the non- and the methyl-substituted compounds (**178aa** and **178ea**) the angle between the two most distant rings A-D are below 12º. The angle between the phenyl ring (E) and the ring C is almost perpendicular 86.88(9)º, which means that it turns 4.87 and 13.81 degrees from the perpendicular plane. However, the halogen derivatives are much more bended, as far as the chromeno and quinolino moieties are concerned. Greater turning of the ring systems can be found for the fluoro (**178ka**) and iodo (**178la**), and less for the chloro (**178ha**) and bromo (**178ja**) derivatives. In all four cases the phenyl ring (E) turns to the opposite site in comparing with the **178aa** and its methyl derivative (**178ea**), and are around 30 degrees.

Comparing the *crystal structures* (**Table S5**) considering the *intermolecular interactions* (**Table 3**), we can affirm that amongst the investigated structures chromenoquinoline **178aa** and its methyl derivative (**178ea**) are very similar, in both cases the crystal structure is stabilized by a weak C18-H18…O5 interaction. However, investigation of the halogen series showed that the chloro (**178ha**) and bromo (**178ja**) derivatives are isostructural, the main stabilizing interactions are C14-H14...N12 and C18-H18…N12. In the case of the fluoro derivative (**178ka**), beside the C-H…N interactions, the crystal structure is further strengthened by the C15-H15…F19 interaction. Finally, in the case of the iodo derivative (**178la**), beside the C17-H17…N12 interaction, halogen-halogen interaction between I19…I19 is also found.

5. Summary

The present thesis aims to demonstrate the development of novel arylation-ring closure reactions based on electrophilic Ar-Cu(III) activation of triple bonds such as nitriles and alkynes.

Thus, we successfully realized the copper-catalyzed synthesis of iminobenzoxazines (**168**) from *ortho*-cyanoanilides (**167**) and arylmesityliodonium triflates (**46**). Copper triflate was utilized as a catalyst and the reactions were conducted in DCE or EtOAc solvent at 75 °C. 25 derivatives were prepared in 18-62% yields. According to our plausible mechanism, the overall transformation includes a *6-exo-dig* cyclization which is accompanied by the formation of new C–O and C–N bonds.



Scheme 60. *Copper-catalyzed synthesis of iminobenzoxazines and quinoline derivatives*

Furthermore, we developed synthetic routes for the construction of condensed quinoline frames such as indeno[2,1-*b*]quinolines (**172**) and chromenoquinolines (**178**, **182**) *via* nitrile activation in the presence of acetylene function with the employment of arylmesityliodonium triflates. The transformations are supposed to undergo *via* the formation of arylcopper(III) intermediate (**115**). The applicability of the synthetic tool to the access of chromeno[4,3-*b*]quinolines (**178**) was demonstrated on 28 examples. The reactions were performed in EtOAc at 75 °C with the employment of CuCl as a copper source, and the desired products were isolated in 32-80% yields.

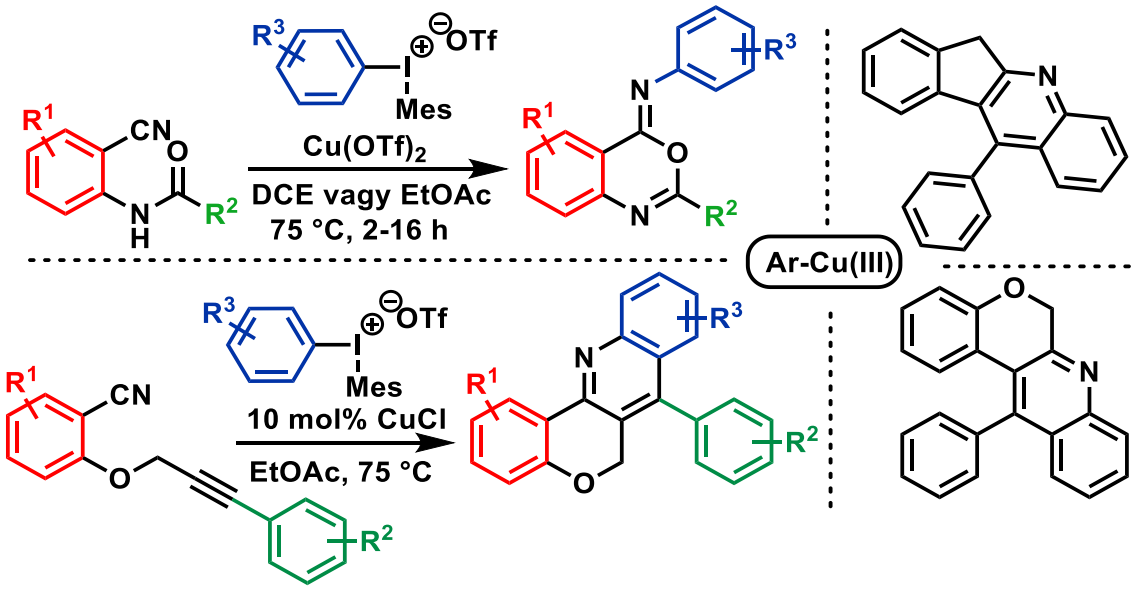
The structure of the chromeno[4,3-*b*]quinoline frame was established by single crystal X-ray diffraction for compound **178aa**. Investigations of the methyl analogue and the halogen homologue substituted series revealed strong similarities in the conformation

of **178aa** and the methyl (**178ea**) derivative, as well as the comparison of the crystal structures of the halogen derivatives proved that the chloro (**178ha**) and bromo (**178ja**) derivatives are isostructural.

6. Összefoglalás

Doktori munkám során olyan újszerű, arilezési-gyűrűzárási reakciók kerültek kidolgozásra, amelyek hármas kötést tartalmazó vegyületek, pl. nitrilek és acetilének elektrofil Ar-Cu(III) aktiválásán alapulnak.

Így, sikeresen valósítottuk meg iminobenzoxazinok (**168**) rézkatalizált szintézisét *orto*-cianoanildekből (**167**) és aril-mezitil-jodónium triflátokból (**46**). Réz-triflát katalizátort alkalmaztunk és a reakciókat DCE illetve EtOAc oldószerekben végeztük el 75 °C-on. 25 származékot állítottunk elő 18-62%-os termelésekkel. Feltételezett mechanizmus szerint az átalakítás egy *6-exo-dig* ciklizációs lépésen megy keresztül, mely által új C-O és C-N kötések alakulnak ki.



60. ábra *Iminobenzoxazinok és kinolinszármazékok rézkatalizált szintézise*

Új szintetikus utakat dolgoztunk ki kondenzált kinolin vázas vegyületek felépítésére, indeno[2,1-*b*]kinolinokat (**172**) és krométokinolinokat (**178**, **182**) állítottunk elő acetilén funkció jelenlétében történő nitril aktiváláson keresztül aril-mezitil-jodónium triflátok alkalmazásával. Feltételezéseink szerint az átalakítások aril-réz(III) intermedieren (**115**) keresztül mennek végbe. A krométo[4,3-*b*]kinolinok (**178**) szintézisét 28 példán mutattuk be, a kívánt termékeket 32-80%-os termelésekkel izoláltuk. A reakciókat EtOAc oldószerben, 75 °C-on kiviteleztük CuCl alkalmazásával.

A krométokinolin váz szerkezetét a **178aa** vegyületre egykristály röntgendiffrakciós módszerrel határoztuk meg. Ezentúl, a metil analóg és a halogénes homológ sor vizsgálatával megállapítottuk, hogy a **178aa** vegyület és a metilszármazék (**178ea**) térszerkezete erős hasonlóságot mutat, míg a halogénszármazékok

kristályszerkezetét összehasonlítva azt kaptuk, hogy a klór (**178ha**) és a brómszármazékok (**178ja**) izostrukturálisak.

7. Appendix - Experimental data

7. 1. General information

Ring closure reaction of substrates **167a**-**167q** and **177a**-**177u** with the appropriate iodonium salt (**2a**-**2n**) were performed under argon atmosphere. All solvents used were distilled using standard methods. Ethyl acetate was distilled from calcium hydride. All other chemicals were used as received without further purification.

All reactions were monitored by TLC using Merck DC pre coated TLC plates with 0.25 mm Kieselgel 60 F254. Visualization was performed with a 254 nm UV lamp. *m*CPBA was dried under high vacuum at room temperature and was stored under argon. Unless otherwise noted, all reagents were ordered and used without further purification. ^{1}H-NMR and ^{13}C-NMR spectras were recorded on a Bruker Avance-250 spectrometer operating at 250 MHz and 62.5 MHz using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are given in ppm relative to TMS for $CDCl_3$, or the residual solvent peak of DMSO as internal standards. Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectras were recorded on Bruker Alpha spectrometer on a single-reflection diamond ATR spectrometer as solids or thin films. In the IR spectras only the strongest/structurally most important peaks (n, cm^{-1}) are listed. HRMS data for new compounds were obtained using a Waters Q-TOF Premier high resolution mass spectrometer. Melting points were recorded on Buchi 501 apparatus and are reported uncorrected.

7. 2. Synthesis and analytical data of arylmesityliodonium triflates

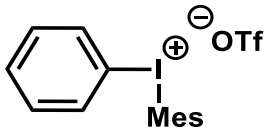
Arylmesityliodonium triflates (**46a**–**46n**) were synthesized in a one-pot procedure from the appropriate iodoarene (**57**) and mesitylene (**166**) according to the modified procedure[129] of Olofsson.[67]

General procedure for the one-pot synthesis of aryl-mesityliodonium triflates

m-Chloroperbenzoic acid (65% active oxidant, 1.32 g, 5.00 mmol) and the appropriate iodoarene (4.50 mmol) were dissolved in dichloromethane (20 mL). Mesitylene (696 μL, 5.00 mmol) was added, and the solution was cooled to 0 °C. Trifluoromethanesulfonic acid (825 mg, 486 μL, 5.50 mmol) was added dropwise in 5 min, and the resulting reaction mixture was allowed to warm to room temperature over 2 h. The volatile components were removed under reduced pressure, and the resulting material was suspended in

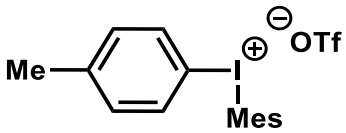
diethyl ether (40 mL). The suspension was stored at -20 °C for 2 h. The resulting crystals were filtered off and were washed with ether to give the appropriate arylmesityliodonium triflate as a solid, which was dried at 100 °C under vacuum.

Mesityl(phenyl)iodonium Trifluoromethanesulfonate (46a)



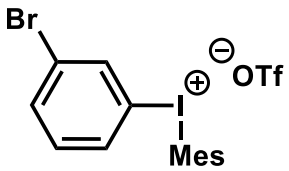
Prepared according to the general procedure from iodobenzene. The product was obtained as a white solid (1.91 g, 4.04 mmol, 90%). M. p. 147-148°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.99 (d, 2H, *J* = 7.7 Hz), 7.64 (t, 1H, *J* = 7.3 Hz), 7.50 (t, 2H, *J* = 7.4 Hz), 7.22 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 143.1, 141.5, 134.5, 131.8, 131.7, 129.7, 122.5, 114.5, 26.2, 20.5; IR ν_{max}/cm^{-1} (solid): 1443, 1246, 1157, 1025, 856, 742, 632, 572, 515, 454; HRMS m/z [M-OTf]$^{+}$ Calculated for $C_{15}H_{16}I$: 323.0291; found 323.0289.

4-Metylphenyl(mesityl)iodonium Trifluoromethanesulfonate (46d)



Prepared according to the general procedure from 4-iodotoluene. The product was obtained as a white solid (2.07 g, 4.26 mmol, 95%). M. p. 183-184 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.88 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.2 Hz), 7.20 (s, 2H), 2.60 (s, 6H), 2.32 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 142.9, 142.2, 141.4, 134.5, 132.4, 129.7, 122.7, 110.8, 26.2, 20.7, 20.4; IR ν_{max}/cm^{-1} (solid): 1452, 1246, 1157, 1024, 804, 632, 481; HRMS m/z [M-OTf]$^{+}$ Calculated for $C_{16}H_{18}I$: 337.0448; found 337.0444.

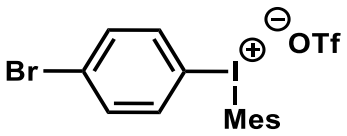
3-Bromophenyl(mesityl)iodonium Trifluoromethanesulfonate (46h)



Prepared according to the general procedure from 3-bromoiodobenzene. The product was obtained as an off-white solid (1.35 g, 2.45 mmol, 55%). M. p. 167-168 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.18 (dd, 1H, *J* = 7.9 and 1.4 Hz), 7.95 (dd, 1H, *J* = 7.9 and 1.4 Hz), 7.59 (td, 1H, *J* = 7.9 and 1.4 Hz), 7.47 (td, 1H, *J* = 7.9 and 1.4 Hz), 7.22 (s, 2H) 2.62

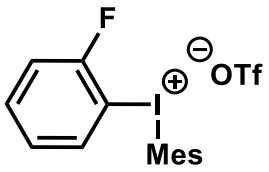
(s, 6H), 2.29 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 143.2, 141.8, 139.0, 134.1, 130.4, 130.0, 126.5, 119.4, 26.3, 20.4; IR ν_{max}/cm^{-1} (solid): 1442, 1276, 1241, 1160, 1025, 757, 631, 516; HRMS m/z [M-OTf]$^+$ Calculated for $C_{15}H_{15}BrI$: 400.9396; found 400.9386.

4-Bromophenyl(mesityl)iodonium Trifluoromethanesulfonate (46i)



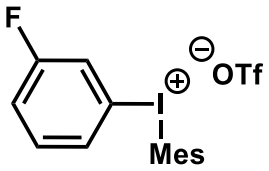
Prepared according to the general procedure from 4-bromoiodobenzene. The product was obtained as a white solid (1.69 g, 3.07 mmol, 68%). M. p. 179-180 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.90 (d, 2H, J = 8.5 Hz), 7.70 (d, 2H, J = 8.5 Hz), 7.22 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 143.2, 141.5, 136.3, 134.6, 129.8, 125.7, 122.7, 113.0, 26.2, 20.5; IR ν_{max}/cm^{-1} (solid): 1473, 1245, 1232, 1024, 807, 631, 518, 475; HRMS m/z [M-OTf]$^+$ Calculated for $C_{15}H_{15}BrI$: 400.9396; found: 400.9399.

2-Fluorophenyl(mesityl)iodonium Trifluoromethanesulfonate (46j)



Prepared according to the general procedure from 2-fluoroiodobenzene. The product was obtained as an off-white solid (1.04 g, 2.12 mmol, 47%). M. p. 161-162 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.27 (m, 1H), 7.72 (m, 1H), 7.56 (td, 1H, J = 8.8 Hz and 1.3 Hz), 7.35 (td, 1H, J = 7.9 Hz and 1.3 Hz), 7.20 (s, 2H), 2.62 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 143.2, 141.5, 137.4, 135.3 (d, J = 8.3 Hz), 129.8, 127.5 (d, J = 2.6 Hz), 122.7, 117.3, 116.9, 101.6, 101.3, 26.0, 20.4; IR ν_{max}/cm^{-1} (solid): 1476, 1279, 1236, 1161, 1027, 770, 635, 515; HRMS m/z [M-OTf]$^+$ Calculated for $C_{15}H_{15}FI$: 341.0197; found: 341.0194.

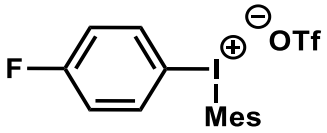
3-Fluorophenyl(mesityl)iodonium Trifluoromethanesulfonate (46k)



Prepared according to the general procedure from 3-fluoroiodobenzene. The product was obtained as an off-white solid (1.31 g, 2.67 mmol, 59%). M. p. 177-178 °C; ^{1}H NMR

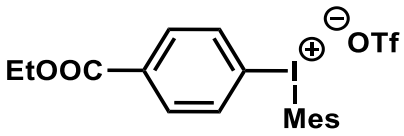
(250 MHz, DMSO-d_6) δ 7.97 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.53 (t, J = 9.6 Hz, 2H), 7.22 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 143.70, 142.05, 133.87, 133.75, 130.94, 130.90, 130.19, 123.05, 122.17, 121.77, 119.67, 119.33, 114.16, 26.65, 20.83; IR ν_{max}/cm^{-1} (solid): 2045, 1592, 1582, 1471, 1286, 1239, 1225, 1168, 1025, 839, 735, 668; HRMS m/z [M-OTf]$^+$ Calculated for $C_{15}H_{15}FI$: 341.0197; found: 341.0217.

4-Fluorophenyl(mesityl)iodonium Trifluoromethanesulfonate (46l)



Prepared according to the general procedure from 4-fluoroiodobenzene. The product was obtained as an off-white solid (1.63 g, 3.33 mmol, 74%). M. p. 178-179 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.37 (t, 2H, J = 8.7 Hz), 7.22 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 143.1, 141.5, 137.4, 137.2, 129.7, 119.4, 119.0, 26.2, 20.5; IR ν_{max}/cm^{-1} (solid): 1575, 1483, 1224, 1168, 1024, 849, 632, 508; HRMS m/z [M-OTf]$^+$ Calculated for $C_{15}H_{15}FI$: 341.0197; found: 341.0195.

4-(Ethoxycarbonyl)phenyl(mesityl)iodonium trifluoromethanesulfonate (46n)



Prepared according to the general procedure from ethyl 4-iodobenzoate with the exception that 3-chloroperoxybenzoic acid, mesitylene and the aryl iodide were stirred together at room temperature for 4 hours before the addition of the trifluoromethanesulfonic acid. The product was obtained as a white solid (1.159 g, 47%). M. p. 174-175 °C; ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.09 (d, 2H, J = 8.4 Hz), 7.99 (d, 2H, J = 8.4 Hz), 7.24 (s, 2H), 4.31 (q, 2H, J = 6.9 Hz), 2.59 (s, 2H), 2.30 (s, 1H), 1.29 (t, 3H, J = 7.0 Hz); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 164.5, 143.4, 141.7, 134.7, 132.7, 131.9, 129.9, 122.6, 119.3, 61.4, 26.3, 20.5, 14.0; IR ν_{max}/cm^{-1} (solid): 1723, 1584, 1458, 1395, 1272, 1238, 1161, 1103, 1025, 849, 753, 634, 516; HRMS m/z [M-OTf]$^+$ Calculated for $C_{18}H_{20}IO_2$: 395.0502; found: 395.0504.

7. 3. Optimization studies of the ring closure of compounds 167a and 46a: implementation of the experiments

General procedure for the optimization reactions

N-(2-cyanophenyl)acetamide (**167a**) (20.0 mg, 0.125 mmol), phenylmesityliodonium triflate (**46a**) (70.9 mg, 0.150 mmol, 1.2 equiv.) and copper catalyst (0.013 mmol, 10 mol%) were added to a 4 ml vial then the system was charged with argon. Solvent 250 μl) was added under argon atmosphere then the reaction mixture was stirred at 75°C for the appropriate time.

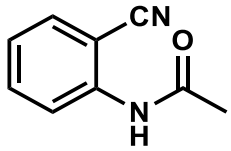
7. 4. Synthesis and analytical data of 2-cyanoanilides

N-(2-cyanophenyl)acetamides were synthesized from 2-aminobenzonitrile derivative and the appropriate acyl chloride or anhydride according to the modified procedure of Fagnou.[136]

General procedure for the synthesis of *N*-(2-cyanophenyl)acetamides

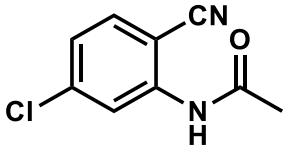
2-aminobenzonitrile (1.00 g, 8.47 mmol) was added to a 100 ml round bottom flask fitted with a rubber septum then the system was charged with argon. Dichloromethane (25 ml) was added under argon atmosphere then acetic anhydride (1.30 g, 12.7 mmol, 1.20 ml) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was washed with saturated sodium hydrogen carbonate solution (3 x 20 ml), with brine (2 x 20 ml), dried over anhydrous sodium sulfate, filtered and evaporated to yield white or yellow solids.

***N*-(2-cyanophenyl)acetamide (167a)**



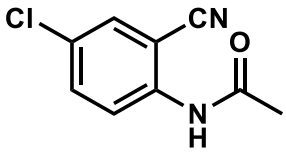
Prepared according to the general procedure from 2-aminobenzonitrile and acetic anhydride. After evaporation of the solvent under reduced pressure the product was afforded as a white solid (1.21 g, 7.59 mmol, 90%). R_f = 0.45 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.8 Hz, 1H), 7.71 (br s, 1H), 7.57 – 7.44 (m, 2H), 7.10 (t, *J* = 7.9 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 169.1, 140.9, 134.6, 132.7, 124.5, 121.9, 116.8, 102.4, 25.0; IR ν_{max}/cm^{-1} (solid): 3322, 2229, 1710, 1579, 1523, 1445, 1372,1293, 1252, 1229, 751, 634, 599, 575, 535, 495, 475.

***N*-(5-chloro-2-cyanophenyl)acetamide (167b)**



Prepared according to the general procedure from 2-amino-4-chlorobenzonitrile (1.00g, 6.55 mmol) and acetic anhydride (2.00 g, 19.66 mmol, 1.86 ml). The reaction mixture was stirred at room temperature for 3 days. The product was obtained as a yellow solid (880 mg, 4.54 mmol, 69%). R_f = 0.35 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.30 (br s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 1.9 Hz, 1H), 7.39 (dd, J = 8.4, 2.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 169.4, 142.0, 138.6, 135.1, 125.8, 125.0, 116.5, 105.4, 23.7; IR ν_{max}/cm^{-1} (solid): 3332, 2918, 2849, 2224, 1702, 1598, 1567, 1520, 1410, 1251, 1219, 887, 822, 655, 609, 596, 527514, 424.

***N*-(4-chloro-2-cyanophenyl)acetamide (167c)**



Prepared according to the general procedure from 2-amino-4-chlorobenzonitrile (250 mg, 1.64 mmol) and acetic anhydride (251 mg, 2.46 mmol, 232 µl) in 8 ml dichloromethane. The reaction mixture was stirred at room temperature for 4 days. The product was obtained as a white solid (234 mg, 1.21 mmol, 73%). R_f = 0.30 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, DMSO- d_6): δ 10.24 (s, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.8, 2.2 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 169.2, 139.7, 134.2, 132.8, 129.5, 127.2, 116.0, 108.7, 23.5; IR ν_{max}/cm^{-1} (solid): 3340, 2228, 1698, 1583, 1516, 1288, 833, 646, 574, 489, 437.

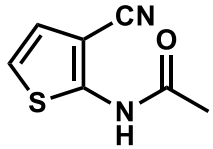
N-(2-cyanophenyl)amides were synthesized from 2-aminobenzonitrile and the appropriate acyl chloride or anhydride according to the modified procedure of Zhdankin.[137]

General procedure for the synthesis of *N*-(2-cyanophenyl)amides

2-aminobenzonitrile (1.00 g; 8.47 mmol) and triethylamine (9.73-19.1 mmol, 1.15-2.25 equiv.) were dissolved in 50-80 ml dichloromethane and cooled to 0°C. A solution of acyl chloride (9.73-19.1 mmol, 1.15-2.25 eq.) and dichloromethane (7 ml) was added dropwise then the resulted mixture was stirred at room temperature for the appropriate

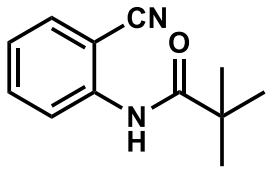
time. After that the pH of the reaction mixture was adjusted to 7-8 with saturated sodium hydrogen carbonate solution, the separated organic layer was washed with distilled water (3 x 50 ml) and with brine (2 x 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification of the crude product afforded the appropriate amides as white or yellow solids.

N-(3-cyanothiophen-2-yl)acetamide (167d)



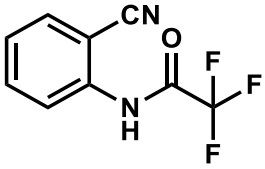
Prepared according to the general procedure from 2-aminothiophene-3-carbonitrile (261 mg, 2.10 mmol), triethylamine (319 mg, 3.15 mmol, 440 µl, 1.50 equiv.) and acetyl chloride (247 mg, 3.15 mmol, 224 µl, 1.50 equiv.) in 12 ml dichloromethane. The reaction mixture was stirred at room temperature for 18 h. The product was obtained as a yellow crystalline solid after recrystallization from ethanol (161 mg, 0.970 mmol, 46%). R_f = 0.40 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, DMSO-d_6): δ 11.66 (s, 1H), 7.11 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 168.7, 149.8, 125.0, 119.0, 115.2, 92.1, 22.7; IR ν_{max}/cm^{-1} (solid): 3269, 2217, 1692, 1545, 1496, 1363, 1280, 1238, 730, 720, 685, 670, 638, 593, 535, 486.

***N*-(2-cyanophenyl)pivalamide (167e)**



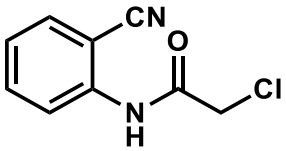
Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (985 mg, 9.73 mmol, 1.36 ml, 1.15 equiv.) and pivaloyl chloride (1.17 g, 9.73 mmol, 1.20 ml) in 80 ml dichloromethane. The reaction mixture was stirred at room temperature for 2 days. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid. (925 mg, 4.58 mmol, 54%). R_f = 0.60 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.36 (d, J = 8.5 Hz, 1H), 7.90 (br s, 1H), 7.51 (t, J = 7.4 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 177.3, 141.2, 134.6, 132.3, 124.3, 121.4, 116.8, 102.4, 40.6, 27.8; IR ν_{max}/cm^{-1} (solid): 3329, 2973, 2229, 1666, 1509, 1447, 1296, 1163, 755, 613.

***N*-(2-cyanophenyl)-2,2,2-trifluoroacetamide (167f)**



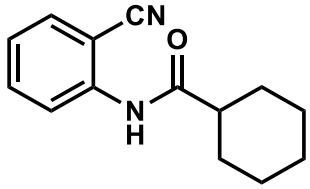
2-aminobenzonitrile (1.00 g; 8.47 mmol) was dissolved in 45 ml dichloromethane then 2,2,2-trifluoroacetic anhydride (2.13 g; 10.2 mmol; 1.43 ml) was added dropwise. The reaction mixture was stirred at room temperature overnight. After that the pH of the reaction mixture was adjusted to 7-8 with saturated sodium hydrogen carbonate, the separated organic layer was washed with distilled water (1 x 50 ml) and with brine (1 x 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. The product was obtained as a white crystalline solid after recrystallization from toluene (1.15 g, 5.37 mmol, 63%). R_f = 0.40 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): 8.38 (br s, 1H), 8.22 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 6.2 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 156.6, 156.0, 155.4, 154.8, 137.6, 134.8, 133.2, 127.0, 123.0, 118.0, 115.8, 113.5, 104.9; IR ν_{max}/cm^{-1} (solid): 3263, 2229, 1714, 1546, 1286, 1251, 1203, 1156, 1094, 917, 763, 716, 653, 494.

2-Chloro-*N*-(2-cyanophenyl)acetamide (167g)



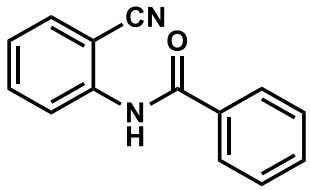
Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (1.07 g, 10.6 mmol, 1.48 ml, 1.25 equiv.) and chloroacetyl chloride (1.20 g, 10.6 mmol, 842 µl, 1.25 equiv.) in 50 ml dichloromethane. The reaction mixture was stirred at room temperature for 2 days. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid. (909 mg, 4.69 mmol, 55%). R_f = 0.30 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.79 (br s, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 7.57 –7.52 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 4.18 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.8, 139.6, 134.6, 132.8, 125.5, 121.6, 116.2, 103.3, 43.3; IR ν_{max}/cm^{-1} (solid): 3313, 2229, 1698, 1604, 1535, 1446, 1402, 1250, 766, 619, 495.

***N*-(2-cyanophenyl)cyclohexanecarboxamide (167h)**



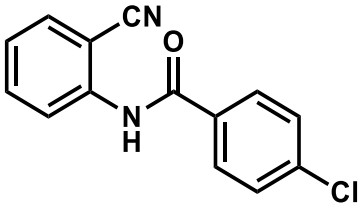
Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (1.29 g, 12.7 mmol, 1.77 ml, 1.50 equiv.) and cyclohexanecarbonyl chloride (1.86 g, 12.7 mmol, 1.71 ml, 1.50 equiv.) in 50 ml dichloromethane. The reaction mixture was stirred at room temperature for 2 days. The product was obtained as a white crystalline solid after recrystallization from ethanol (1.20 g, 5.26 mmol, 62%). R_f = 0.60 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.33 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.50 (s, 2H), 7.08 (s, 1H), 2.27 (s, 1H), 2.09 – 0.96 (m 10H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 175.0, 141.1, 134.6, 132.5, 124.3, 121.7, 116.9, 102.3, 46.8, 29.9, 25.9; IR ν_{max}/cm^{-1} (solid): 3294, 2925, 2852, 2230, 1664, 1602, 1511, 1492, 1447, 1437, 1250, 1198, 955, 776, 759, 671, 489.

***N*-(2-cyanophenyl)benzamide (167i)**



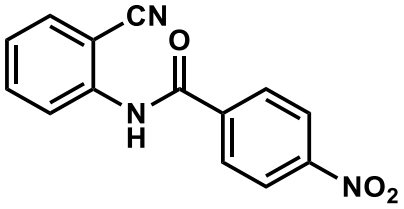
Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (1.29 g, 12.7 mmol, 1.77 ml, 1.50 equiv.) and benzoyl chloride (1.78 g, 12.7 mmol, 1.47 ml, 1.50 equiv.) in 80 ml dichloromethane. The reaction mixture was stirred at room temperature for 2 days. Recrystallization of the crude product from ethanol gave a white solid (992 mg, 4.47 mmol, 53%). R_f = 0.35 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.49 (d, *J* = 8.3 Hz, 1H), 8.36 (br s, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.59 – 7.41 (m, 5H), 7.13 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.9, 141.0, 134.7, 134.1, 133.0, 132.6, 129.5, 127.6, 124.7, 121.7, 116.8, 102.7; IR ν_{max}/cm^{-1} (solid): 3285, 2231, 1649, 1601, 1508, 1481, 1436, 1310, 1286, 1261, 1245, 794, 708, 686, 675, 488.

4-Chloro-*N*-(2-cyanophenyl)benzamide (167j)



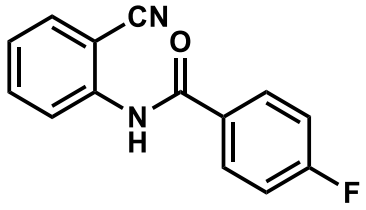
Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (1.29 g, 12.7 mmol, 1.77 ml, 1.50 equiv.) and 4-chlorobenzoyl chloride (2.22 g, 12.7 mmol, 1.63 ml, 1.50 equiv.) in 50 ml dichloromethane. The reaction mixture was stirred at room temperature for 24 h. The product was obtained as a white solid after recrystallization from ethanol (1.34 g, 5.23 mmol, 62%). R_f = 0.45 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.46 (d, *J* = 7.3 Hz, 1H), 8.29 (s, 1H), 7.90 (dd, *J* = 48.9, 6.6 Hz, 4H), 7.68 – 7.28 (m, 4H), 7.17 (d, *J* = 6.5 Hz, 1H).^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.8, 161.7, 141.8, 140.8, 139.5, 134.8, 132.6, 132.3, 129.8, 129.1, 127.4, 124.9, 121.7, 116.8, 102.8; IR ν_{max}/cm^{-1} (solid): 3282, 2223, 1653, 1590, 1579, 1523, 1485, 1445, 1307, 1091, 1007, 855, 754, 649, 622, 537, 500, 483, 470.

***N*-(2-cyanophenyl)-4-nitrobenzamide (167k)**



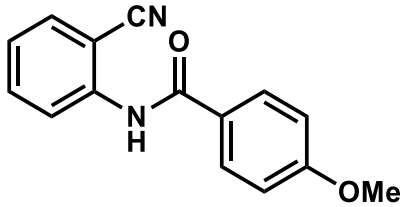
Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (1.93 g, 19.0 mmol, 2.66 ml, 2.25 equiv.) and 4-nitrobenzoyl chloride (3.53 g, 19.0 mmol, 2.25 equiv.) in 50 ml dichloromethane. The reaction mixture was stirred at room temperature for 2 days. Purification of the crude product by column chromatography on silica gel then recrystallization from 2-propanol afforded a yellow solid (223 mg, 0.835 mmol, 26%). R_f = 0.30 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, DMSO-*d6*): δ 10.97 (br s, 1H), 8.26-7.60 (m, 8H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.8, 149.9, 140.9, 139.4, 135.4, 134.5, 131.2, 130.5, 130.3, 124.2, 124.1, 111.8; IR ν_{max}/cm^{-1} (solid): 3113, 2232, 1676, 1524, 1334, 1316, 1228, 1143, 1109, 911, 859, 847, 765, 718, 702, 439.

***N*-(2-cyanophenyl)-4-fluorobenzamide (167l)**



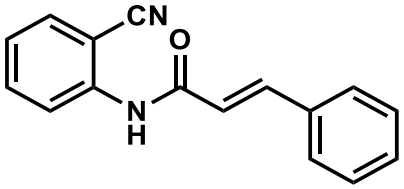
Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (1.93 g, 19.0 mmol, 2.66 ml, 2.25 equiv.) and 4-fluorobenzoyl chloride (3.02 g, 19.0 mmol, 2.25 ml, 2.25 equiv.) in 50 ml dichloromethane. The reaction mixture was stirred at room temperature for 24 h. The product was obtained as a white crystalline solid after recrystallization from ethanol then from toluene (368 mg, 1.53 mmol, 37%). R_f = 0.50 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.07 – 7.42 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-*d6*): δ 166.7, 164.9, 140.6, 134.2, 133.5, 131.0, 130.9, 130.3, 127.2, 126.8, 117.3, 116.1, 115.8, 109.7; IR ν_{max}/cm^{-1} (solid): 3278, 2225, 1652, 1601, 1579, 1525, 1504, 1444, 1310, 1296, 1224, 762, 620, 501.

***N*-(2-cyanophenyl)-4-methoxybenzamide (167m)**



Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g; 8.47 mmol), triethylamine (1.93 g, 19.0 mmol, 2.66 ml, 2.25 equiv.) and 4-methoxybenzoyl chloride (3.25 g, 19.0 mmol, 2.58 ml, 2.25 equiv.) in 50 ml dichloromethane. The reaction mixture was stirred at room temperature for 2 days. The product was obtained as a white crystalline solid after recrystallization from ethanol (1.19 g, 4.72 mmol, 56%). R_f = 0.80 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.50 (d, *J* = 8.3 Hz, 1H), 8.28 (br s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.55 (t, *J* = 8.2 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.3, 163.5, 141.3, 134.7, 132.5, 129.6, 126.2, 124.4, 121.4, 117.0, 114.7, 102.3, 55.9; IR ν_{max}/cm^{-1} (solid): 3277, 2227, 1649, 1605, 1579, 1525, 1508, 1444, 1302, 1251, 1176, 1022, 840, 762, 623, 503.

***N*-(2-cyanophenyl)cinnamamide (167n)**

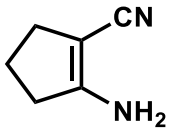


Prepared according to the general procedure from 2-aminobenzonitrile (1.00 g, 8.47 mmol), triethylamine (1.29 g, 12.7 mmol, 1.77 ml, 1.50 equiv.) and cinnamoyl chloride (2.12 g, 12.7 mmol, 1.50 equiv.) in 50 ml dichloromethane. The reaction mixture was stirred at room temperature for 24 h. The product was obtained as a white crystalline solid after recrystallization from ethanol then from toluene (550 mg, 2.22 mmol, 50%). R_f = 0.50 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.57 (d, *J* = 7.7 Hz, 1H), 7.94 (s, 1H), 7.81 (d, *J* = 15.0 Hz, 1H), 7.60 (d, *J* = 6.5 Hz, 4H), 7.41 (s, 3H), 7.26 – 7.08 (m, 1H), 6.67 (d, *J* = 15.3 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.6, 144.5, 141.2, 134.7, 134.6, 132.8, 130.9, 129.4, 128.6, 124.5, 121.8, 120.3, 117.0, 102.2; IR ν_{max}/cm^{-1} (solid): 3341, 2226, 1686, 1634, 1583, 1531, 1448, 1290, 1155, 976, 763, 710, 620, 550, 483.

7. 5. Synthesis and analytical data of cyclic β-enaminonitriles

β-enaminonitriles were synthesized from the appropriate dinitrile and potassium *tert*-butoxide according to the modified procedure of Ma et al.[138]

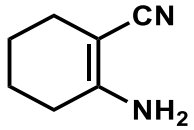
2-aminocyclopent-1-ene-1-carbonitrile (170a)



A mixture of powdered ^{t}BuOK (3.36 g; 30.0 mmol) and adiponitrile (2.70 g, 25.0 mmol, 2.84 ml) in toluene (40 ml) was stirred at room temperature overnight. Solvent was removed under reduced pressure, than distilled water was added to the reaction mixture and the product was extracted with dichloromethane (4 x 40 ml), the combined organics were washed with brine (1 x 100 ml), dried over anhydrous sodium sulfate, filtered and evaporated. The residual yellow solid was recrystallized from MeOH to give 2-aminocyclopent-1-ene-1-carbonitrile as a white solid (1.15 g; 10.6 mmol; 43%). R_f = 0.30 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.54 (s, 1H), 2.44 (s, 2H), 1.86

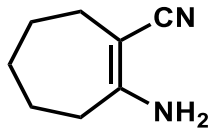
(s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=163.0, 119.5, 74.5, 34.6, 31.6, 22.4; IR ν_{max}/cm^{-1} (solid): 3434, 3346, 2947, 2172, 1636, 1604, 1401, 1209, 1147, 887, 492, 468, 448.

2-amino-1-cyclohexene-1-carbonitrile (170b)



A mixture of powdered ^{t}BuOK (6.73 g; 60.0 mmol) and pimelonitrile (6.11 g; 50.0 mmol; 6.43 ml) was kept at 80 °C for 3 h then at room temperature overnight. Distilled water was added to the reaction mixture and the product was extracted with ether (3 x 40 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. The residual yellow solid was recrystallized from MeOH to give 2-amino-1-cyclohexene-1-carbonitrile as a white solid (1.32 g; 10.8 mmol; 22%). R_f = 0.40 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.28 (s, 2H), 2.12 (s, 4H), 1.59 (s, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 156.7, 121.3, 74.3, 28.5, 24.6, 22.4, 22.0; IR ν_{max}/cm^{-1} (solid): 3421, 3348, 3232, 2179, 1640, 1604, 1410, 490, 457.

2-aminocyclohept-1-ene-1-carbonitrile (170c)



A mixture of powdered ^{t}BuOK (3.36 g; 60.0 mmol) and 1,6-dicyanohexane (3.41 g, 25.0 mmol, 3.57 ml) in toluene (40 ml) was stirred at 100°C for 2 days. Solvent was removed under reduced pressure, than distilled water was added to the reaction mixture and the product was extracted with dichloromethane (4 x 40 ml), the combined organics were washed with brine (1 x 100 ml), dried over anhydrous sodium sulfate, filtered and evaporated. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (825 mg, 6.07 mmol, 24%). The obtained product (not totally pure) was brought into the next step (acylation) without further purification. R_f = 0.74 (hexane-ethyl acetate, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.50 (s, 2H), 2.74-2.08 (m, 6H), 1.91 – 1.32 (m, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.6, 122.8, 120.0, 76.0, 35.7, 32.1, 28.9, 28.4, 28.2, 25.7, 25.4, 17.4, IR ν_{max}/cm^{-1} (solid): 3464, 3360, 2925, 2852, 2246, 2173, 1634, 1596, 1448, 1192.

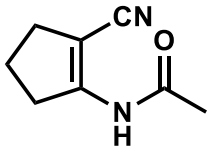
7. 6. Synthesis and analytical data of cyclic β-acetylaminoacrylonitriles

β-acetylaminoacrylonitriles were synthesized from the appropriate cyclic β-enaminonitrile and acetic anhydride according to the modified procedure of Ma et al.[138]

General procedure for the synthesis of β-acetylaminoacrylonitriles

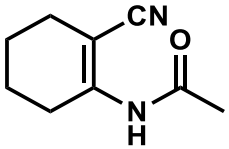
To a solution of cyclic-β-enaminonitrile (4.09 mmol) in pyridine (5 ml), acetic anhydride (8.19 mmol, 2.0 eq.) was added. The reaction mixture was heated at reflux for 16 h and cooled to room temperature. It was then poured onto 2 molar hydrochloric acid solution and extracted with chloroform (5 x 10 ml). The combined organics were washed with distilled water (2 x 50 ml), with brine (1 x 50 ml), dried over anhydrous sodium sulfate, filtered and evaporated. Purification of the crude product by column chromatography on silica gel afforded the product as a solid.

***N*-(2-cyanocyclopent-1-en-1-yl)acetamide (167o)**



Prepared according to the general procedure from 2-aminocyclopent-1-ene-1-carbonitrile (**170a**) (811 mg, 7.50 mmol) and acetic anhydride (1.53 g, 15.0 mmol, 1.42 ml). Purification of the crude product by column chromatography on silica gel afforded the product as a grey solid (884 mg, 5.90 mmol, 79%). R_f = 0.60 (hexane-ethyl acetate, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.54 (s, 1H), 3.26 – 2.88 (m, 2H), 2.54 – 2.36 (m, 2H), 2.06 (s, 3H), 1.99 – 1.83 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 169.0, 157.5, 117.0, 87.5, 34.1, 30.5, 24.3, 22.5; IR ν_{max}/cm^{-1} (solid): 3276, 2202, 1713, 1631, 1510, 1367, 1230, 1203, 995, 740, 604, 522, 467.

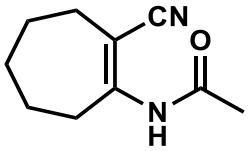
***N*-(2-cyanocyclohex-1-en-1-yl)acetamide (167p)**



Prepared according to the general procedure from 2-amino-1-cyclohexene-1-carbonitrile (**170b**) (500 mg, 4.09 mmol) and acetic anhydride (836 mg, 8.19 mmol, 774 μl). Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (260 mg, 1.59 mmol, 39%). R_f = 0.30 (hexane-ethyl acetate, 3:2).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.61 (s, 1H), 2.73 (s, 2H), 2.21 (s, 2H), 2.05 (s, 3H), 1.60 (s, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.8, 152.2, 118.4, 91.4, 28.1, 26.0, 24.9, 21.8, 21.4; IR ν_{max}/cm^{-1} (solid): 3230, 3148, 2932, 2210, 1667, 1520, 1440, 1422, 1366, 1281, 1267, 1229, 1032, 756, 583, 430.

***N*-(2-cyanocyclohept-1-en-1-yl)acetamide (167q)**



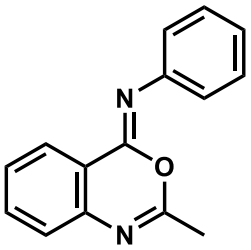
Prepared according to the general procedure from 2-aminocyclohept-1-ene-1-carbonitrile (**170c**) (732 mg, 5.38 mmol) and acetic anhydride (1.10 g, 10.8 mmol, 1016 μl). Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (160 mg, 0.899 mmol, 17%). M. p. 112-114 °C. R_f = 0.35 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$): 7.75 (s, 1H), 2.82 – 2.56 (m, 2H), 2.39 – 2.23 (m, 3H), 2.05 (s, 3H), 1.78 – 1.40 (m, 5H).^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.6, 158.8, 119.3, 99.7, 32.1, 32.0, 29.7, 26.6, 24.8, 24.6. IR ν_{max}/cm^{-1} (solid): 3223, 2997, 2932, 2919, 2852, 2203, 1657, 1627, 1517, 1445, 1366, 1350, 1289, 1275, 1264, 1044, 998, 880, 725, 692, 665, 610.

7. 7. Synthesis and analitical data of imino-1,3-benzoxazines

General procedure for the synthesis of (Z)-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)anilines

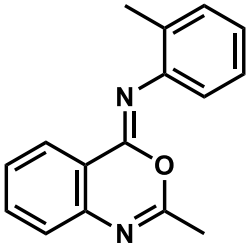
N-(2-cyanophenyl)acetamide (**167a**) (80.1 mg, 0.500 mmol), diaryl iodonium salt (0.600 mmol, 1.2 equiv.) and copper(II)triflate (18.08 mg; 0.050 mmol, 10 mol%) were added to a 4 ml vial then the system was charged with argon. Solvent (1,2-dichloroethane or ethyl acetate, 1000 μl) was added under argon atmosphere then the reaction mixture was stirred at 75°C for the appropriate time. Saturated sodium hydrogen carbonate solution (10 ml) was added to the mixture, the aqueous layer was extracted with dichloromethane (4 x 10 ml) the combined organics were dried over anhydrous sodium sulfate, filtered and evaporated. Purification of the crude products by column chromatography on silica gel afforded the products as solids.

(Z)-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168aa)



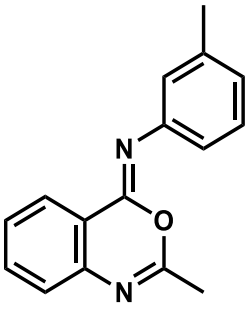
Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and phenyl(mesityl) iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 2 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (60.0 mg, 0.254 mmol, 51%). M. p. 142-145 °C. R_f = 0.30 (hexane-ethyl acetate, 3:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.78 – 7.55 (m, 2H), 7.55 – 7.28 (m, 4H), 7.19 (d, *J* = 6.8 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.6, 154.6, 147.9, 138.2, 135.0, 130.4, 129.7, 128.4, 127.5, 127.2, 127.0, 121.2, 24.8; IR ν_{max}/cm^{-1} (solid): 2923, 1676, 1606, 1585, 1572, 1470, 1265, 1116, 760, 692, 659, 622, 507.

(Z)-2-methyl-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168ab)



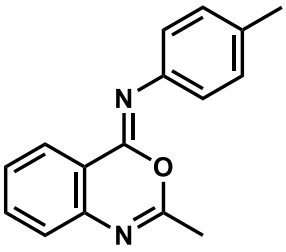
Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and 2-methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**46b**) (292 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (66.5 mg, 0.266 mmol, 53%). M. p. 115-117 °C. R_f = 0.35 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.82 – 7.60 (m, 2H), 7.53 – 7.28 (m, 4H), 7.15 (d, *J* = 6.2 Hz, 1H), 2.17 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.0, 154.7, 148.1, 137.2, 135.7, 135.0, 131.9, 130.0, 128.3, 128.0, 127.5, 127.2, 127.0, 121.1, 24.2, 17.8; IR ν_{max}/cm^{-1} (solid): 2921, 1673, 1607, 1597, 1567, 1468, 1325, 1279, 1269, 1123, 776, 759, 720, 702, 657, 624, 458; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{15}N_2O$: 251.1179; found 251.1175.

(Z)-3-methyl-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168ac)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and 3-methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**46c**) (292 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (77.0 mg, 0.308 mmol, 62%). M. p. 96-98 °C. R_f = 0.25 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.9 Hz, 1H), 7.89 – 7.57 (m, 2H), 7.44 (dd, *J* = 11.8, 7.7 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.7, 154.7, 147.9, 140.5, 138.1, 134.9, 130.5, 130.2, 128.9, 127.4, 127.1, 127.0, 125.3, 121.2, 24.7, 21.7; IR ν_{max}/cm^{-1} (solid): 2923, 2249, 1673, 1596, 1584, 1567, 1471, 1376, 1340, 1320, 1278, 726, 694, 659, 646, 630, 444; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{15}N_2O$: 251.1179; found 251.1180.

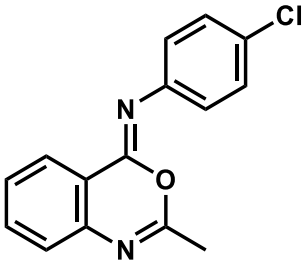
(Z)-4-methyl-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168ad)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and 4-methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**46d**) (292 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (70.5 mg, 0.282 mmol, 56%). M. p. 145-146 °C. R_f = 0.30 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.7 Hz, 1H), 7.88 – 7.68 (m, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.7, 154.9, 147.9, 139.7, 135.5, 134.9, 131.0, 128.1, 127.4, 127.1, 126.9, 121.2, 24.8, 21.6; IR ν_{max}/cm^{-1} (solid): 2922, 1680, 1605, 1589, 1566, 1512, 1468, 1342,

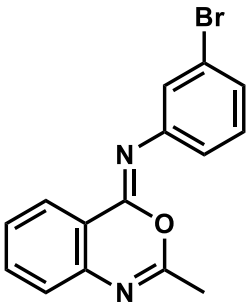
1321, 1267, 1109, 817, 776, 697, 615, 520; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{15}N_2O$: 251.1179; found 251.1180.

(Z)-4-chloro-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168af)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and (4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate (**46f**) (304 mg, 0.600 mmol) for 4 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (71.5 mg, 0.265 mmol, 53%). M. p. 153-155 °C. R_f = 0.28 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.18 (d, *J* = 7.4 Hz, 1H), 7.81 – 7.67 (m, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.45 – 7.33 (m, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.5, 154.1, 147.7, 136.6, 135.7, 135.1, 130.6, 129.9, 127.4, 127.2, 127.1, 121.0, 24.8; IR ν_{max}/cm^{-1} (solid): 3094, 1685, 1602, 1590, 1571, 1466, 1343, 1330, 1268, 1110, 1087, 1036, 864, 827, 764, 695, 629, 513, 444; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{12}ClN_2O$: 271.0633; found 271.0629.

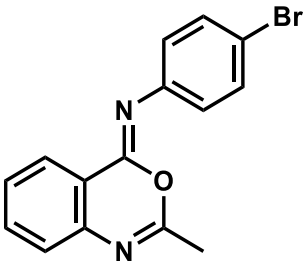
(Z)-3-bromo-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168ah)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and 3-bromophenyl(mesityl)iodonium trifluoromethanesulfonate (**46h**) (331 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (78.0 mg, 0.248 mmol, 50%). M. p. 124-126 °C. R_f = 0.22 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.74 – 7.63 (m, 1H), 7.62 – 7.52 (m, 2H), 7.43 – 7.36 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.10 (m, 1H), 2.17 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.4, 154.0, 147.7, 139.3, 135.2, 133.0, 131.7, 131.6, 128.4, 127.4, 127.4, 127.23, 127.22,

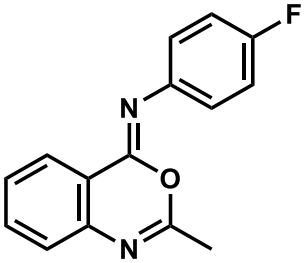
123.7, 120.9, 24.7; IR ν_{max}/cm^{-1} (solid): 3612, 2923, 1665, 1604, 1569, 1340, 1327, 1273, 1254, 765, 691, 420; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{12}BrN_2O$: 315.0128; found 315.0124.

(Z)-4-bromo-*N*-(2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168ai)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and 4-bromophenyl(mesityl)iodonium trifluoromethanesulfonate (**2i**) (331 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (76.0 mg, 0.242 mmol, 48%). M. p. 166-168 °C. R_f = 0.24 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.62 – 7.52 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.11 – 7.01 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.4, 154.0, 147.7, 137.1, 135.1, 133.7, 130.2, 127.4, 127.23, 127.17, 123.8, 121.0, 24.7; IR ν_{max}/cm^{-1} (solid): 2923, 1678, 1601, 1572, 1491, 1467, 1343, 1267, 1015, 822, 763, 692, 626, 508; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{12}BrN_2O$: 315.0128; found 315.0124.

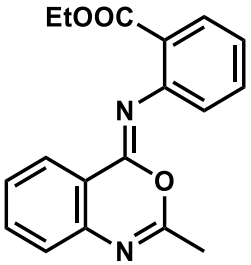
(Z)-*N*-(4*H*-benzo[*d*][1,3]oxazin-4-ylidene)-4-fluoroaniline (168al)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and 4-fluorophenyl(mesityl)iodonium trifluoromethanesulfonate (**46l**) (294 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a brown solid (60.0 mg, 0.236 mmol, 47%). M. p. 128-130 °C. R_f = 0.30 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.73 – 7.62 (m, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.43 – 7.30 (m, 1H), 7.16 (d, *J* = 6.0 Hz, 4H), 2.15 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.1, 162.7, 161.1, 154.4, 147.7, 135.1, 134.0, 130.4, 130.2, 127.4, 127.2, 121.0, 117.6, 117.3, 24.7; IR

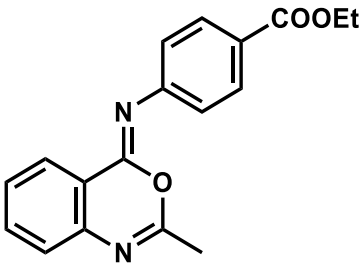
ν_{max}/cm^{-1} (solid): 3051, 2923, 1675, 1609, 1592, 1505, 1469, 1269, 1208, 849, 765, 693, 649, 612, 524, 507; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{12}FN_2O$: 255.0928; found 255.0924.

(Z)-ethyl-2-(4*H*-benzo[*d*][1,3]oxazin-4-ylideneamino)benzoate (168am)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and (2-(ethoxycarbonyl)phenyl)(mesityl)iodonium trifluoromethanesulfonate (**46m**) (326 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a brown solid (75.5 mg, 0.245 mmol, 49%). M. p. 120-122 °C. R_f = 0.40 (hexane-ethyl acetate, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.6 Hz, 1H), 7.72 – 7.58 (m, 2H), 7.52 (td, *J* = 7.7, 1.2 Hz, 1H), 7.44 – 7.30 (m, 1H), 7.23 (dd, *J* = 7.7, 1.0 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.12 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.9, 162.7, 154.6, 147.9, 138.2, 135.0, 134.3, 132.9, 130.2, 130.0, 128.8, 127.3, 127.1, 126.9, 121.1, 61.9, 24.3, 14.0; IR ν_{max}/cm^{-1} (solid): 2985, 1711, 1678, 1607, 1594, 1569, 1470, 1291, 1258, 1119, 1084, 1018, 780, 756, 696, 622, 515; HRMS m/z $[M+H]^+$ Calculated for $C_{18}H_{17}N_2O_3$: 309.1234; found 309.1231.

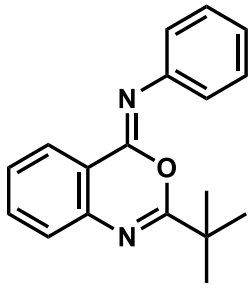
(Z)-ethyl-4-(4*H*-benzo[*d*][1,3]oxazin-4-ylideneamino)benzoate (168an)



Prepared according to the general procedure from *N*-(2-cyanophenyl)acetamide (**167a**) and (4-(ethoxycarbonyl)phenyl)(mesityl)iodonium trifluoromethanesulfonate (**46n**) (326 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as an orange solid (80.0 mg, 0.260 mmol, 52%). M. p. 166-168 °C. R_f = 0.40 (hexane-ethyl acetate, 5:3). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.4 Hz,

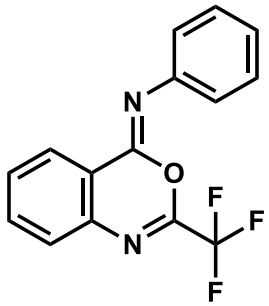
1H), 7.28 (d, *J* = 8.2 Hz, 1H), 4.33 (q, *J* = 14.1, 7.0 Hz, 2H), 2.14 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.9, 162.4, 153.7, 147.8, 142.1, 135.1, 131.9, 131.7, 128.7, 127.4, 127.3, 127.2, 121.0, 61.8, 24.7, 14.7 ; IR ν_{max}/cm^{-1} (solid): 2923, 1709, 1689, 1590, 1569, 1344, 1268, 1104, 1019, 770, 699, 662, 627, 505; HRMS m/z $[M+H]^+$ Calculated for $C_{18}H_{17}N_2O_3$: 309.1234; found 309.1232.

(Z)-2-(tert-butyl)-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168ea)



Prepared according to the general procedure from *N*-(2-cyanophenyl)pivalamide (**167e**) (101 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 6 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (58.3 mg, 0.210 mmol, 42%). M. p. 56-57 °C. R_f = 0.40 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.42 – 7.19 (m, 5H), 7.05 (d, *J* = 8.2 Hz, 3H), 1.14 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.3, 147.1, 146.1, 143.1, 133.9, 129.0, 128.3, 126.9, 126.6, 124.3, 122.8, 119.6, 38.3, 28.0, IR ν_{max}/cm^{-1} (solid): 2974, 2932, 1664, 1635, 1606, 1490, 1463, 1197, 1114, 1052, 1017, 773, 744, 696, 671, 582; HRMS m/z $[M+H]^+$ Calculated for $C_{18}H_{19}N_2O$: 279.1492; found 279.1492.

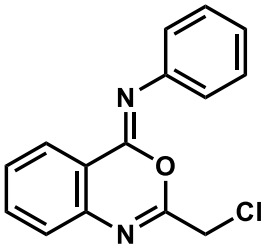
(Z)-*N*-phenyl-2-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazin-4-imine (168fa)



Prepared according to the general procedure from *N*-(2-cyanophenyl)-2,2,2-trifluoroacetamide (**167f**) (107 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 12 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (27.0 mg, 0.093 mmol, 18%). M. p. 70-71 °C. R_f = 0.60 (hexane-ethyl acetate, 10:1). ^{1}H

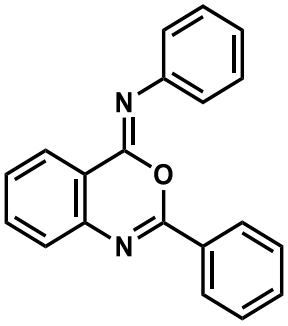
NMR (250 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.1 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.40 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.02 (m, *J* = 20.1, 6.8 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 143.8, 142.4, 140.4, 134.4, 131.1, 129.3, 128.1, 127.5, 125.7, 123.5, 121.1; IR ν_{max}/cm^{-1} (solid): 1690, 1216, 1152, 1112, 1037, 1004, 945, 903, 773, 748, 725, 695, 664, 564, 502; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{10}F_3N_2O$: 291.07; found .

(Z)-2-(chloromethyl)-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168ga)



Prepared according to the general procedure from 2-chloro-*N*-(2-cyanophenyl)acetamide (**167g**) (97.0 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 6 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (62.0 mg, 0.230 mmol, 46%). M. p. 150-151 °C. R_f = 0.25 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.21 (d, *J* = 6.4 Hz, 1H), 7.71 (s, 2H), 7.48 (s, 4H), 7.29 (s, 2H), 4.19 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.5, 151.9, 147.4, 136.3, 135.2, 130.3, 129.1, 128.4, 128.1, 127.6, 121.7, 44.0; IR ν_{max}/cm^{-1} (solid): 2922, 1682, 1602, 1587, 1568, 1471, 1278, 1256, 1085, 1072, 1012, 779, 762, 752, 691, 639, 608, 506; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{12}ClN_2O$: 271.0633; found 271.0629.

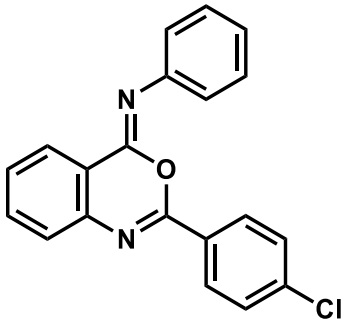
(Z)-*N*-(2-phenyl-4H-benzo[*d*][1,3]oxazin-4-ylidene)aniline (168ia)



Prepared according to the general procedure from *N*-(2-cyanophenyl)benzamide (**167i**) (111 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 6 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (58.0 mg, 0.195 mmol, 39%). M. p. 120-121 °C. R_f = 0.35 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.22 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.00 – 7.81 (m, 2H), 7.63 – 7.50 (m, 1H), 7.50

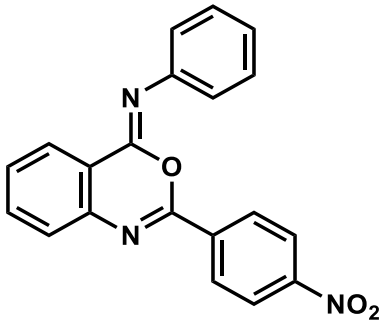
– 7.24 (m, 7H), 7.23 – 7.06 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.3, 146.5, 146.0, 143.4, 134.1, 132.5, 131.1, 129.3, 129.0, 128.6, 128.3, 127.2, 126.9, 124.6, 122.8, 119.9; IR ν_{max}/cm^{-1} (solid): 3057, 2921, 1679, 1625, 1594, 1573, 1463, 1248, 1197, 1064, 1044, 1026, 1016, 775, 766, 737, 688, 669, 583, 556, 539.

(Z)-2-(4-chlorophenyl)-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168ja)



Prepared according to the general procedure from 4-chloro-*N*-(2-cyanophenyl)benzamide (**167j**) (128 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 6 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (78,0 mg, 0.235 mmol, 47%). M. p. 158-160 °C. R_f = 0.35 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.28 (d, *J* = 6.6 Hz, 1H), 7.91 (d, *J* = 7.1 Hz, 2H), 7.61 (d, *J* = 6.5 Hz, 1H), 7.57 – 7.29 (m, 6H), 7.23 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 154.4, 149.7, 146.2, 145.9, 143.2, 138.9, 134.2, 129.5, 129.3, 128.8, 128.3, 127.2, 127.0, 124.7, 122.7, 119.8; IR ν_{max}/cm^{-1} (solid): 3057, 3016, 1681, 1621, 1591, 1568, 1485, 1475, 1463, 1252, 1086, 1069, 1047, 847, 777, 745, 718, 693, 668, 540, 464; HRMS m/z $[M+H]^+$ Calculated for $C_{20}H_{14}ClN_2O$: 333.0789; found 333.0781.

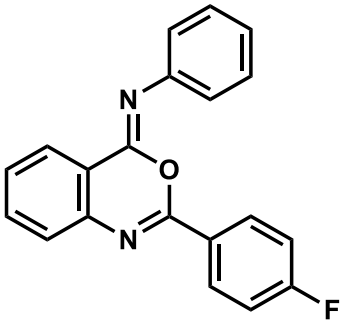
(Z)-2-(4-nitrophenyl)-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168ka)



Prepared according to the general procedure from *N*-(2-cyanophenyl)-4-nitrobenzamide (**167k**) (134 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 8 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (90,0 mg, 0.262 mmol,

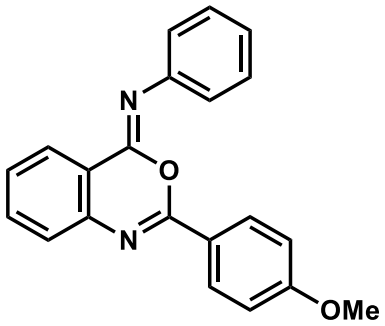
52%). M. p. 220-222 °C. R_f = 0.40 (hexane-ethyl acetate, 10:1). ^{1}H NMR (500 MHz, DMSO): δ 8.35 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO): δ 153.4, 149.9, 145.6, 145.4, 142.5, 136.7, 134.8, 129.8, 129.4, 129.1, 127.4, 126.6, 124.8, 124.5, 122.8, 119.8; IR ν_{max}/cm^{-1} (solid): 2917, 1678, 1592, 1519, 1486, 1345, 1315, 1252, 1236, 1071, 1047, 1011, 863, 845, 776, 743, 709, 698, 668, 537; HRMS m/z [M+H]$^+$ Calculated for $C_{20}H_{14}N_3O_3$: 334.1030; found 334.1024.

(Z)-2-(4-fluorophenyl)-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168la)



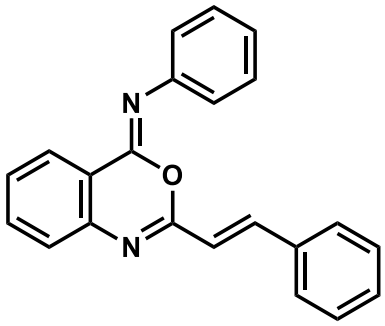
Prepared according to the general procedure from *N*-(2-cyanophenyl)-4-fluorobenzamide (**167l**) (120 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 10 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid. (73,0 mg, 0,231 mmol, 46%). M. p. 136-138 °C. R_f = 0.35 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.29 (d, *J* = 7.4 Hz, 1H), 8.00 (t, *J* = 5.6 Hz, 2H), 7.75 – 7.58 (m, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 3H), 7.23 (d, *J* = 6.7 Hz, 3H), 7.08 (t, *J* = 8.2 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 154.4, 146.3, 146.0, 143.3, 134.2, 130.7, 130.5, 129.3, 128.6, 127.1, 126.9, 124.7, 122.6, 119.7, 116.4, 116.0; IR ν_{max}/cm^{-1} (solid): 3032, 2922, 1681, 1623, 1591, 1576, 1505, 1485, 1474, 1251, 1236, 1222, 1198, 1151, 1068, 1052, 1014, 849, 771, 734, 692, 668, 539, 520; HRMS m/z [M+H]$^+$ Calculated for $C_{20}H_{14}FN_2O$: 317.1085; found 317.1082.

(Z)-2-(4-methoxyphenyl)-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168ma)



Prepared according to the general procedure from *N*-(2-cyanophenyl)-4-methoxybenzamide (**167m**) (126 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 7 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid. (85,2 mg, 0,260 mmol, 52%). M. p. 158-160 °C. R_f = 0.30 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 6.7 Hz, 1H), 7.43 – 7.21 (m, *J* = 16.6, 7.8 Hz, 4H), 7.22 – 6.99 (m, 3H), 6.76 (d, *J* = 7.5 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.2, 155.3, 146.7, 146.2, 143.75, 134.1, 130.2, 129.2, 128.3, 128.0, 126.9, 124.5, 123.4, 122.8, 119.6, 114.4, 55.8; IR ν_{max}/cm^{-1} (solid): 3058, 2933, 1668, 1619, 1593, 1568, 1509, 1486, 1465, 1420, 1245, 1168, 1118, 1069, 1050, 1028, 1016, 764, 736, 693, 670, 542; HRMS m/z $[M+H]^+$ Calculated for $C_{21}H_{17}N_2O_2$: 329.1285; found 329.1082.

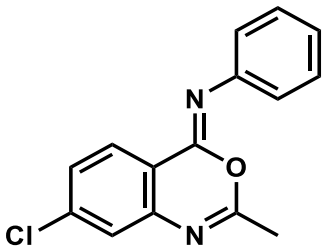
(Z)-*N*-phenyl-2-((E)-styryl)-4*H*-benzo[*d*][1,3]oxazin-4-imine (168na)



Prepared according to the general procedure from *N*-(2-cyanophenyl)cinnamamide (**167n**) (124 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 4 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid. (61,2 mg, 0,189 mmol, 38%). M. p. 105-107 °C. R_f = 0.32 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.03 (m, 13H), 6.51 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.7, 146.3, 146.0, 143.6,

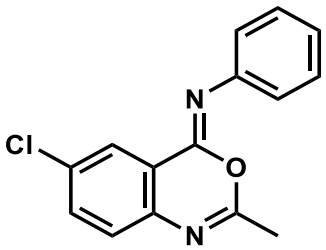
141.4, 135.1, 134.1, 130.5, 129.3, 129.2, 128.6, 128.3, 126.96, 126.95, 124.7, 123.0, 119.9, 119.5; IR ν_{max}/cm^{-1} (solid): 3023, 2922, 1665, 1632, 1590, 1570, 1487, 1463, 1446, 1247, 1196, 1051, 1021, 984, 971, 769, 752, 687, 667, 481; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{17}N_2O$: 325.1335; found 325.1331.

(Z)-7-chloro-2-methyl-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168ba)



Prepared according to the general procedure from *N*-(5-chloro-2-cyanophenyl)acetamide (**167b**) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 8 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid. (67.5 mg, 0.250 mmol, 50%). M. p. 153-155 °C. R_f = 0.30 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.1 Hz, 1H), 7.59 (d, *J* = 30.8 Hz, 4H), 7.39 (d, *J* = 6.0 Hz, 1H), 7.26 (s, 2H), 2.23 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.0, 156.0, 148.9, 141.1, 137.9, 130.5, 129.8, 128.9, 128.3, 127.6, 126.8, 119.7, 24.9; IR ν_{max}/cm^{-1} (solid): 2922, 1679, 1601, 1583, 1561, 1429, 1376, 1342, 1317, 1270, 1070, 896, 874, 830, 776, 761, 699, 689, 680, 586; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{12}ClN_2O$: 271.0633; found 271.0633.

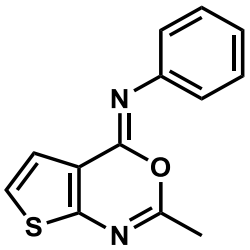
(Z)-6-chloro-2-methyl-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-imine (168ca)



Prepared according to the general procedure from *N*-(4-chloro-2-cyanophenyl)acetamide (**167c**) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 8 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid. (66.5 mg, 0.246 mmol, 45%). M. p. 162-164 °C. R_f = 0.30 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ: 8.11 (s, 1H), 7.78 – 7.33 (m, 5H), 7.18 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 161.6, 155.0, 146.4, 137.9, 135.3, 132.7, 130.5, 129.9, 128.91, 128.3, 126.7, 122.2, 24.8; IR ν_{max}/cm^{-1}

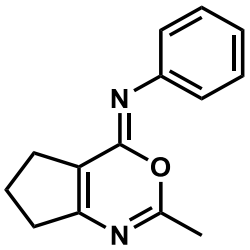
(solid): 2922, 1688, 1587, 1566, 1470, 1340, 1313, 1269, 821, 765, 718, 697, 684, 640, 538; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{12}ClN_2O$: 271.0633; found 271.0634.

(Z)-2-methyl-*N*-phenyl-4*H*-thieno[2,3-*d*][1,3]oxazin-4-imine (168da)



Prepared according to the general procedure from *N*-(3-cyanothiophen-2-yl)acetamide (**167d**) (83.1 mg, 0.500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 3 h.Purification of the crude product by column chromatography on silica gel afforded the products as a yellow oil (71.0 mg, 0.293 mmol, 59%). R_f = 0.30 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.65 – 7.48 (m, 3H), 7.44 (d, *J* = 5.8 Hz, 1H), 7.32 – 7.21 (m, 2H), 7.18 (d, *J* = 5.8 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.9, 159.1, 155.3, 137.9, 130.5, 129.8, 128.3, 123.0, 122.9, 24.6; IR ν_{max}/cm^{-1} (solid): 3083, 2924, 1674, 1553, 1513, 1489, 1417, 1286, 1256, 737, 697, 626; HRMS m/z $[M+H]^+$ Calculated for $C_{13}H_{11}N_2OS$: 243.0587; found 243.0586.

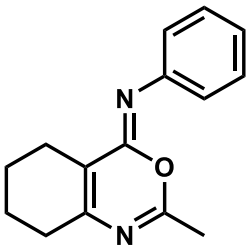
(Z)-2-methyl-*N*-phenyl-6,7-dihydrocyclopenta[*d*][1,3]oxazin-4(5*H*)-imine (168oa)



Prepared according to the general procedure from *N*-(2-cyanocyclopent-1-en-1-yl)acetamide (**167o**) (75,1 mg; 0,500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 3 h. Purification of the crude product by column chromatography on silica gel afforded the product as a brown solid. (60,2 mg, 0,266 mmol, 53%). M. p. 124-126 °C. R_f = 0.28 (hexane-ethyl acetate, 1:4). ^{1}H NMR (250 MHz, $CDCl_3$): ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.55 – 7.29 (m, 3H), 7.11 (d, *J* = 6.8 Hz, 2H), 2.94 – 2.61 (m, 4H), 2.07 (s, 3H), 2.00 (dd, *J* = 15.2, 7.6 Hz, 2H);^{13}C NMR (62.5 MHz, $CDCl_3$): δ=168.1, 161.2, 159.1, 138.2, 130.3, 129.6, 128.0, 123.0, 35.4, 28.2, 24.6, 21.6; IR ν_{max}/cm^{-1} (solid): 2923, 1687, 1517, 1493, 1430, 1367, 1258, 1092, 766,

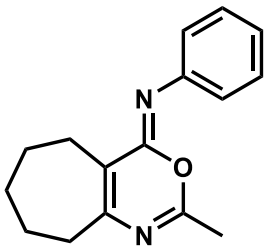
758, 724, 696, 648, 500; HRMS m/z $[M+H]^+$ Calculated for $C_{14}H_{15}N_2O$: 227.1179; found 227.1174.

(Z)-2-methyl-*N*-phenyl-5,6,7,8-tetrahydro-4*H*-benzo[*d*][1,3]oxazin-4-imine (168pa)



Prepared according to the general procedure from *N*-(2-cyanocyclohex-1-en-1-yl)acetamide (**167p**) (82,1 mg; 0,500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 3 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid. (56.7 mg, 0,236 mmol, 47%). M. p. 142-144 °C. R_f = 0.35 (hexane-ethyl acetate, 1:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.56 – 7.28 (m, 3H), 7.11 (d, *J* = 7.4 Hz, 2H), 2.70 – 2.50 (m, 2H), 2.49 – 2.34 (m, 2H), 2.05 (s, 3H), 1.86 – 1.55 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.0, 159.5, 155.4, 138.1, 130.3, 129.5, 128.0, 120.3, 31.9, 24.1, 22.7, 22.6, 22.2; IR ν_{max}/cm^{-1} (solid): 2926, 1660, 1603, 1536, 1486, 1431, 1377, 1359, 1262, 1237, 1196, 1135, 768, 754, 693, 502; HRMS m/z $[M+H]^+$ Calculated for $C_{15}H_{17}N_2O$: 241.1335; found 241.1338.

(Z)-2-methyl-*N*-phenyl-6,7,8,9-tetrahydrocyclohepta[*d*][1,3]oxazin-4(5*H*)-imine (168qa)

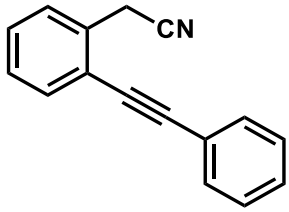


Prepared according to the general procedure from *N*-(2-cyanocyclohept-1-en-1-yl)acetamide (**167q**) (127 mg; 0,500 mmol) and mesityl(phenyl)iodonium triflouromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 4 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (348.0 mg, 0,134 mmol, 27%). M. p. 90-92 °C. R_f = 0.28 (hexane-ethyl acetate, 1:21). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.12 (s, 1H), 2.72 (s, 1H), 2.04 (s, 1H), 1.90 – 1.38 (m, 2H).; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.5, 163.3, 155.5, 138.5, 130.3, 129.5,

127.9, 124.8, 38.6, 32.7, 26.8, 25.7, 24.9, 24.2.; IR ν_{max}/cm^{-1} (solid): 2921, 2851, 1655, 1600, 1592, 1539, 1487, 1437, 1398, 1381, 1361, 1254, 1104, 958, 789, 751, 694, 506.

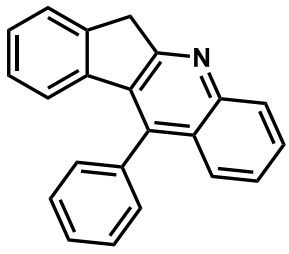
7. 8. Synthesis and analytical data of indeno[2,1-*b*]quinoline derivative 172

2-(2-(phenylethynyl)phenyl)acetonitrile (171)



Prepared by Sonogashira reaction from 2-iodophenylacetonitrile (**170**) and phenylacetylene according to the modified procedure of Kotschy.[140] 2-iodophenylacetonitrile (500 mg, 2.06 mmol), $PdCl_2(PPh_3)_2$ (43.5 mg, 0.060 mmol, 3 mol%) and copper(I)iodide (11.8 mg, 0.060 mmol, 3 mol%) were added to a 50 ml round bottom flask fitted with a rubber septum then the system was charged with argon. DIPA (20 ml) was added under argon atmosphere then phenylacetylene (315 mg, 3.09 mmol, 339 µl) was added dropwise. The resulted mixture was stirred at 50 °C for 2 h. The reaction mixure was diluted with dichloromethane (20 ml) and distilled water (20 ml), neutralized with 2 M HCl solution, extracted with dichloromethane (4 x 20 ml). The combined organics were washed with distilled water (1 x 50 ml), with brine (1 x 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification of the crude product by column chromatography on silica gel afforded the product as a brown oil (445 mg, 2.05 mmol, 99%); R_f = 0.30 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.67 – 7.48 (m, 4H), 7.46 – 7.30 (m, 5H), 3.98 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 132.8, 132.1, 132.0, 129.4, 129.3, 128.9, 128.6, 123.2, 122.9, 117.8, 96.1, 86.4, 23.2.

11-phenyl-6*H*-indeno[2,1-*b*]quinoline (172)



Prepared according to the synthesis of imino-1,3-benzoxazines from 2-(2-(phenylethynyl)phenyl)acetonitrile (**171**) (109 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (55.0 mg, 0.188 mmol, 38%); R_f = 0.20 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.39 (m, 6H), 7.31 (t, *J* = 6.6 Hz, 3H), 7.22 – 7.12 (m, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 4.10 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.9, 147.4, 142.3, 141.2, 139.5, 136.7, 130.9, 129.6, 129.5, 129.2, 129.1, 128.9, 128.4, 127.7, 127.4, 126.6, 126.3, 125.6, 124.1, 39.1.

7. 9. Optimization studies of the ring closure of compounds 177a and 46a: implementation of the experiments

General procedure for the optimization reactions

2-((3-phenylprop-2-yn-1-yl)oxy)benzonitrile (**177a**) (44.3 mg, 0.125 mmol), phenylmesityliodonium triflate (**46a**) (70.9 mg, 0.150 mmol, 1.2 equiv.) and copper catalyst (0.013 mmol, 10 mol%) were added to a 4 ml vial then the system was charged with argon. Solvent 250 μl) was added under argon atmosphere then the reaction mixture was stirred at 75°C for the appropriate time.

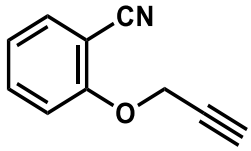
7. 10. Synthesis and analitical data of 2-(Prop-2-yn-1-yloxy)benzonitriles

General procedure for the synthesis of 2-(prop-2-yn-1-yloxy)benzonitriles

2-(Prop-2-yn-1-yloxy)benzonitriles were synthesized from the appropriate 2-hydroxybenzonitrile derivatives and propargyl bromide according to the procedure of Lingam.[141] 2-hydroxybenzonitrile (1.12 g; 10.0 mmol) and potassium carbonate (2.76 g; 20.0 mmol) were added to a 100 ml round botton flask fitted with a rubber septum then the system was charged with argon. Dimethyl formamide (60 ml) was added under argon atmosphere then propargyl bromide (80% toluene solution) (1.93 g; 13.0 mmol; 1.45 ml) was added dropwise. After that the mixture was stirred at 50 °C for 16 h. Dichloromethane (50 ml) and distilled water (50 ml) were added to the reaction mixture, the aqueous phase was extracted with dichloromethane (3 x 50 ml), the combined organics were washed

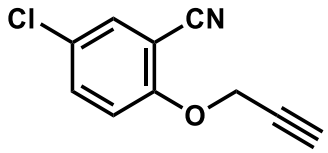
with saturated LiCl solution (5 x 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. The crude residue was purified by column chromatography.

2-(Prop-2-yn-1-yloxy)benzonitrile (176a)



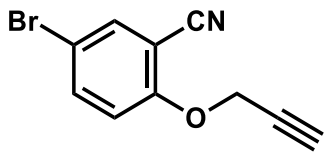
Prepared according to the general procedure from 2-hydroxybenzonitrile (**175a**). Purification of the crude product by column chromatography on silica gel afforded the product as a white crystalline solid (1.48 g, 9.42 mmol, 94%). M. p. 77-78 °C; R_f = 0.35 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.49 (dd, *J* = 10.1, 4.0 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 2.3 Hz, 1H), 2.50 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 159.4, 134.6, 134.3, 122.1, 116.6, 113.4, 102.9, 78.0, 77.6, 56.9; IR ν_{max}/cm^{-1} (solid): 2941, 2573, 2237, 1600, 1490, 1454, 1290, 1233, 1017, 740.

5-Chloro-2-(prop-2-yn-1-yloxy)benzonitrile (176b)



Prepared according to the general procedure from 5-chloro-2-hydroxybenzonitrile (500 mg, 3.27 mmol). Purification of the crude product by column chromatography on silica gel afforded the product as a white crystalline solid (488 mg, 2.56 mmol, 78%). M. p. 125-126 °C; R_f = 0.60 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 1H), 4.82 (d, *J* = 1.9 Hz, 2H), 2.59 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.1, 134.6, 133.5, 127.0, 115.2, 114.8, 104.3, 77.7, 77.1, 57.3; IR ν_{max}/cm^{-1} (solid): 2930, 1488, 1285, 1266, 1234, 1135, 1018; HRMS m/z [M-H] Calculated for $C_{10}H_5NOCl$: 190.0060; found 190.0069.

5-Bromo-2-(prop-2-yn-1-yloxy)benzonitrile (176c)



Prepared according to the general procedure from 5-bromo-2-hydroxybenzonitrile (1.00 g, 5.05 mmol). Purification of the crude product by column chromatography on silica gel afforded the product as a white crystalline solid (1.13 g, 4.81 mmol, 95%). M. p. 128-129

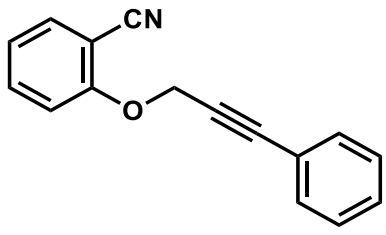
°C; R_f = 0.32 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66 – 7.52 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 1H), 4.76 (d, *J* = 2.4 Hz, 2H), 2.52 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.5, 137.4, 136.4, 115.10, 115.07, 113.7, 104.7, 77.8, 77.1, 57.2; IR ν_{max}/cm^{-1} (solid): 2957, 1486, 1286, 1235, 1132, 1016; HRMS m/z [M-H] Calculated for $C_{10}H_5NOBr$: 233.9554; found 233.9565.

7. 11. Synthesis and analitical data of Arylpropynyloxybenzonitriles

General procedure for the synthesis of arylpropynyloxy-benzonitriles

Arylpropynyloxy-benzonitriles were synthesized by Sonogashira reaction from the appropriate 2-(prop-2-yn-1-yloxy)benzonitrile derivative (**176a**-**176c**) and aryl iodide according to the modified procedure of Kotschy.[140] 2-(prop-2-ynyloxy)benzonitrile (390 mg, 2.48 mmol), $PdCl_2(PPh_3)_2$ (43.5 mg, 0.060 mmol, 3 mol%) and copper(I)iodide (11.8 mg, 0.060 mmol, 3 mol%) were added to a 50 ml round bottom flask fitted with a rubber septum then the system was charged with argon. DIPA (20 ml) was added under argon atmosphere then the iodobenzene (422 mg, 2.07 mmol, 231 μl) was added dropwise. If the iodoarene was solid, it was added with the copper and palladium sources before the addition of DIPA. The resulted mixture was stirred at 30-45 °C for the appropriate time. The reaction mixure was diluted with dichloromethane (20 ml) and distilled water (20 ml), neutralized with 2 M HCl solution, extracted with dichloromethane (4 x 20 ml). The combined organics were washed with distilled water (1 x 50 ml), with brine (1 x 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. The crude residue was purified by column chromatography.

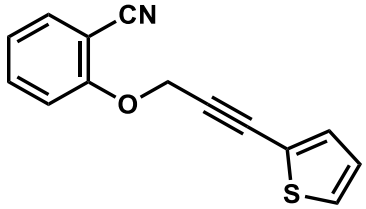
2-(3-Phenylprop-2-ynyloxy)benzonitrile (177a)



Prepared according to the general procedure from 2-(prop-2-yn-1-yloxy)benzonitrile (**176a**) and iodobenzene (422 mg, 2.07 mmol, 231 μl) at 40-45°C for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (327 mg, 1.40 mmol, 68%). M. p. 64-65 °C; R_f = 0.42 (hexane-ethyl acetate, 5:1).

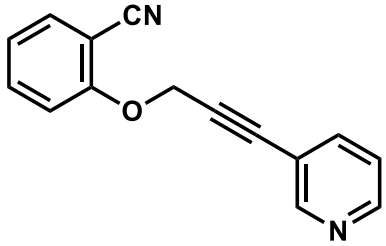
^{1}H NMR (250 MHz,$CDCl_3$) δ 7.65 – 7.51 (m, 2H), 7.48 – 7.39 (m, 2H), 7.37 – 7.26 (m, 3H), 7.26 – 7.18 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.06 (s, 2H);^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.7, 134.6, 134.3, 132.2, 129.4, 128.8, 122.2, 121.9, 116.8, 113.5, 102.9, 88.7, 82.9, 57.8; IR ν_{max}/cm^{-1} (solid): 2973, 2232, 1597, 1492, 1454, 1289, 1231, 1015, 758, 737, 694.

2-((3-(Thiophen-2-yl)prop-2-yn-1-yl)oxy)benzonitrile (177b)



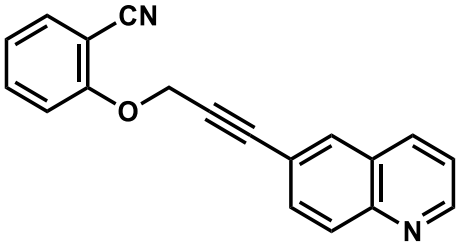
Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 2-iodothiophene (434 mg, 228 µl, 2.07 mmol) for 40 min at 30-35°C. Purification of the crude product by column chromatography on silica gel afforded the product as a browny solid (465 mg, 1.95 mmol, 94%). M. p. 79-80 °C; R_f = 0.45 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 – 7.42 (m, 2H), 7.19 (d, *J* = 5.2 Hz, 1H), 7.17 – 7.06 (m, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.88 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.97 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.6, 134.6, 134.3, 133.6, 128.5, 127.5, 122.0, 116.7, 113.4, 102.9, 86.9, 82.1, 57.8; IR ν_{max}/cm^{-1} (solid): 2234, 1597, 1491, 1455, 1290, 1231, 1196, 1167, 1113, 1004, 849, 701.

2-((3-(pyridin-3-yl)prop-2-yn-1-yl)oxy)benzonitrile (177c)



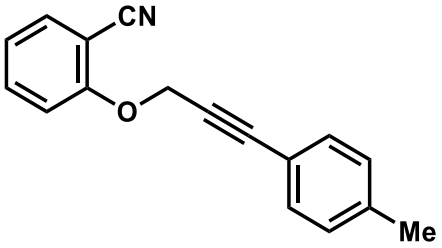
Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 3-iodopyridine (424 mg, 2.07 mmol) for 20 min at 30 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a light brown solid (340 mg, 1.45 mmol, 70%). R_f = 0.40 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ= 8.53 (d, *J* = 23.7 Hz, 2H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.45 (m, 2H), 7.20 (t, *J* = 6.3 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 5.00 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 159.50, 152.45, 149.35, 139.45, 134.62, 134.35, 123.58, 122.11, 116.57, 113.31, 102.97, 86.46, 85.23, 57.54.

2-((3-(quinolin-6-yl)prop-2-yn-1-yl)oxy)benzonitrile (177d)



Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 6-iodoquinoline (527 mg, 2.07 mmol). Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (538 mg, 1.90 mmol, 92%). R_f = 0.35 (hexane-ethyl acetate, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ= 8.89 (d, 1H, *J* = 2.5 Hz), 8.14 – 7.98 (m, 2H), 7.89 (d, 1H), 7.65 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.44 – 7.34 (m, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 5.09 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 159.65, 151.63, 148.13, 136.24, 134.62, 134.32, 132.29, 132.14, 130.02, 128.19, 122.26, 121.99, 120.44, 116.67, 113.38, 102.94, 88.21, 84.11, 57.73.

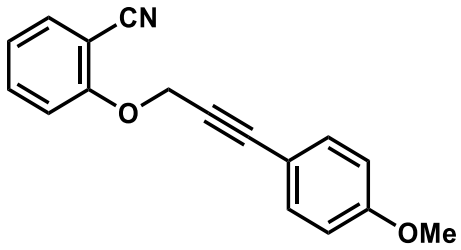
2-((3-(p-Tolyl)prop-2-yn-1-yl)oxy)benzonitrile (177e)



Prepared in a one-pot synthesis. 2-hydroxybenzonitrile (**175a**) (834 mg; 7.00 mmol) and potassium carbonate (1.94 g; 14.0 mmol) were added to a 100 ml round botton flask fitted with a rubber septum then the system was charged with argon. Dimethyl formamide (35 ml) was added under argon atmosphere then propargyl bromide (80% toluene solution) (1.35 g; 9.10 mmol; 1.02 ml) was added dropwise then the mixture was stirred at 50 °C for 16 h. After that $PdCl_2(PPh_3)_2$ (123 mg; 0.175 mmol; 3 mol%) and copper(I)iodide (33.3 mg; 0.175 mmol; 3 mol%) dissolved in diisopropylamine (3 ml) were added under argom atmosphere to the reaction mixture then 4-iodotoluene (1.27 g; 5.83 mmol) dissolved in diisopropylamine (1.5 ml) was added dropwise under argom atmosphere. The resulted mixture was stirred at 40-45 °C for 3 h. The workup is according to the steps written in the general procedure. Purification of the crude product by column chromatography on silica gel afforded the product as a light brown solid (637 mg, 2.58 mmol, 44% for the two steps). M. p. 37-38 °C; R_f = 0.32 (hexane-ethyl acetate, 7:1). ^{1}H

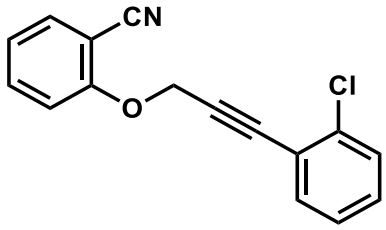
NMR (250 MHz, $CDCl_3$) δ 7.64 – 7.51 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 5.03 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.8, 139.6, 134.6, 134.2, 132.1, 129.5, 121.8, 119.1, 116.8, 113.5, 102.8, 88.9, 82.3, 57.8, 21.9; IR ν_{max}/cm^{-1} (solid): 2231, 1597, 1508, 1492, 1453, 1371, 1291, 1230, 1169, 1110, 1011, 820.

2-((3-(4-Methoxyphenyl)prop-2-yn-1-yl)oxy)benzonitrile (177f)



Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 4-iodoanisole (484 mg, 2.07 mmol). for 45 min at 45 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a reddish-brown solid (325 mg, 1.24 mmol, 60%). M. p. 58-59 °C; R_f = 0.32 (hexane-ethyl acetate, 4:1).^1H NMR (250 MHz, $CDCl_3$) δ 7.56 – 7.37 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.9 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 4.92 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 160.5, 159.8, 134.6, 134.2, 133.8, 121.8, 116.8, 114.4, 114.2, 113.5, 102.8, 88.8, 81.6, 57.9, 55.7; IR ν_{max}/cm^{-1} (solid): 2232, 1605, 1510, 1492, 1291, 1249, 1231, 1175, 1034, 834; HRMS m/z $[M+H]^+$ Calculated for $C_{17}H_{14}NO_2$: 264.1025; found 264.1023.

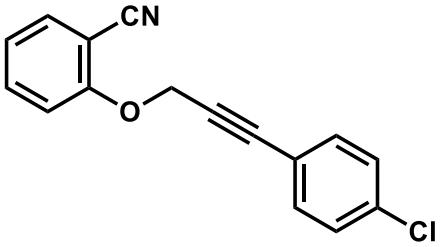
2-((3-(2-Chlorophenyl)prop-2-yn-1-yl)oxy)benzonitrile (177g)



Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 2-chloroiodobenzene (493 mg, 253 µl, 2.07 mmol) for 30 min at 40 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (344 mg, 1.29 mmol, 62%). M. p. 82-83 °C; R_f = 0.30 (hexane-ethyl acetate, 4:1). ^1H NMR (250 MHz, $CDCl_3$) δ 7.48 (t, *J* = 7.3 Hz, 2H), 7.37 – 7.06 (m, 5H), 6.96 (t, *J* = 7.5 Hz, 1H), 5.01 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.6, 136.6, 134.6, 134.2, 134.0, 130.5, 129.7, 126.9, 122.2, 122.0, 116.7, 113.7, 102.9, 88.0, 85.5, 57.7; IR ν_{max}/cm^{-}

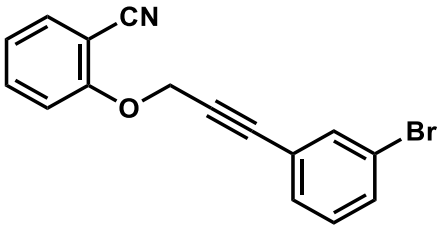
[1] (solid): 2232, 1600, 1492, 1475, 1455, 1290, 1231, 1015, 759, 739; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{11}NOCl$: 268.0524; found 268.0529.

2-((3-(4-Chlorophenyl)prop-2-yn-1-yl)oxy)benzonitrile (177h)



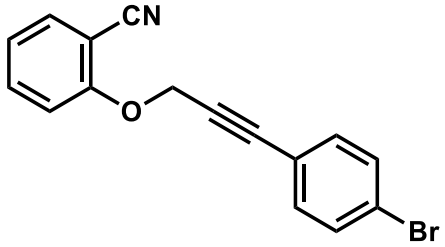
Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 4-chloroiodobenzene (493 mg, 2.07 mmol) for 30 min at 40 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (460 mg, 1.72 mmol, 83%). M. p. 128-129 °C; R_f = 0.62 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (t, *J* = 8.0 Hz, 2H), 7.22 (q, *J* = 8.6 Hz, 4H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.6, 135.5, 134.6, 134.3, 133.4, 129.1, 122.0, 120.7, 116.7, 113.4, 102.9, 87.6, 83.9, 57.7; IR ν_{max}/cm^{-1} (solid): 2923, 2232, 1597, 1487, 1453, 1290, 1231, 1014, 827, 753; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{11}NOCl$: 268.0529; found 268.0528.

2-((3-(3-Bromophenyl)prop-2-yn-1-yl)oxy)benzonitrile (177i)



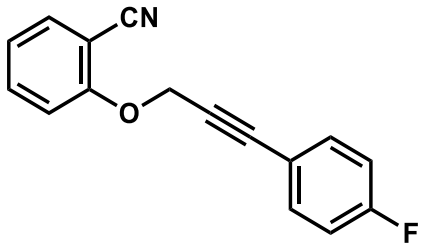
Prepared according to the general procedure 2-(prop-2-ynyloxy)benzonitrile (**176a**) and from 3-bromoiodobenzene (585 mg, 264 µl, 2.07 mmol) for 30 min at 35 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (614 mg, 1.97 mmol, 95%). M. p. 58-59 °C; R_f = 0.40 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66 – 7.52 (m, 3H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.25 – 7.13 (m, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 5.04 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.6, 134.9, 134.6, 134.3, 132.5, 130.8, 130.2, 124.1, 122.5, 122.0, 116.6, 113.3, 102.9, 87.1, 84.2, 57.6; IR ν_{max}/cm^{-1} (solid): 2236, 1600, 1558, 1490, 1474, 1455, 1289, 1231, 1019, 786, 739, 683; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{11}NOBr$: 312.0024; found 312.0028.

2-((3-(4-Bromophenyl)prop-2-yn-1-yl)oxy)benzonitrile (177j)



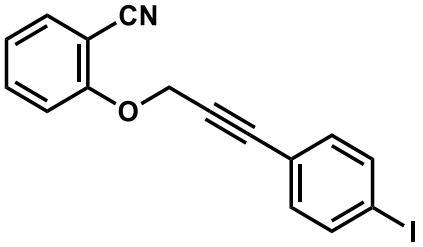
Prepared according to the general procedure 2-(prop-2-ynyloxy)benzonitrile (**176a**) and from 4-bromoiodobenzene (585 mg, 2.07 mmol) for 45 min at 45 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (598 mg, 1.92 mmol, 93%). M. p. 108-109 °C; R_f = 0.40 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (t, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.15 (dd, *J* = 18.8, 8.1 Hz, 3H), 6.98 (t, *J* = 7.4 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.6, 134.6, 134.3, 133.6, 132.0, 123.7, 122.0, 121.1, 116.7, 113.4, 102.9, 87.6, 84.1, 57.7; IR ν_{max}/cm^{-1} (solid): 2233, 1601, 1487, 1458, 1290, 1231, 1015, 826, 738; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{11}NOBr$: 312.0024; found 312.0027.

2-((3-(4-Fluorophenyl)prop-2-yn-1-yl)oxy)benzonitrile (177k)



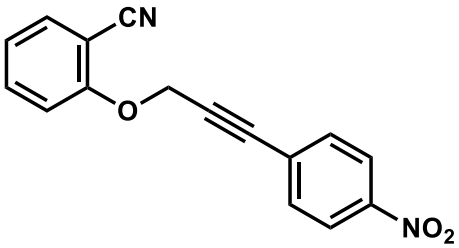
Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 4-fluoroiodobenzene (459 mg, 238 µl, 2.07 mmol) for 25 min at 30 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (378 mg, 1.51 mmol, 73%). M. p. 64-65 °C; R_f = 0.63 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 – 7.42 (m, 2H), 7.31 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.02 – 6.83 (m, 3H), 4.95 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.7, 134.6, 134.3, 134.1, 121.9, 118.30, 118.25, 116.7, 116.3, 115.9, 113.4, 102.9, 87.7, 82.7, 57.70; IR ν_{max}/cm^{-1} (solid): 2227, 1700, 1559, 1541, 1508, 1491, 1458, 1231, 1017, 838; HRMS m/z $[M+H]^+$ Calculated for $C_{16}H_{11}NOF$: 252.0825; found 252.0820.

2-((3-(4-Iodophenyl)prop-2-yn-1-yl)oxy)benzonitrile (177l)



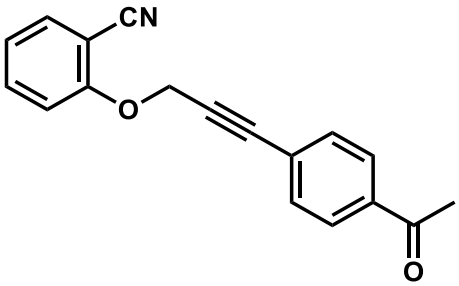
Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 1,4-diiodobenzene (340 mg, 1.03 mmol) for 30 min at 35 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (114 mg, 0.32 mmol, 31%). M. p. 123-125 °C; R_f = 0.64 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 – 7.44 (m, 4H), 7.16 – 6.93 (m, 4H), 4.95 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.63, 137.94, 134.57, 134.32, 133.63, 121.98, 121.67, 116.63, 113.38, 102.98, 95.49, 87.79, 84.31, 57.72.

2-((3-(4-nitrophenyl)prop-2-yn-1-yl)oxy)benzonitrile (177m)



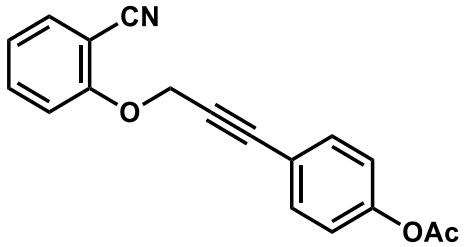
Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 1-iodo-4-nitrobenzene (515 mg; 2.07 mmol) for 30 min at 40 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a light brown solid (535 mg, 1.92 mmol, 93%). M. p. 120-121 °C; R_f = 0.24 (hexane-ethyl acetate, 4:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.09 (d, J = 8.8 Hz, 2H), 7.61 – 7.42 (m, 4H), 7.11 (d, J = 8.5 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 5.01 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.47, 147.91, 134.68, 134.42, 133.00, 128.94, 123.96, 122.26, 116.53, 113.31, 103.06, 88.04, 86.61, 57.54.

2-((3-(4-Acetylphenyl)prop-2-yn-1-yl)oxy)benzonitrile (177n)



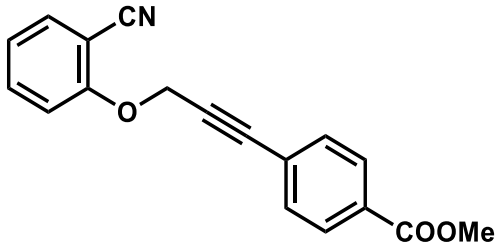
Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and 4-iodoacetophenone (509 mg, 2.07 mmol) for 30 min at 40 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (508 mg, 1.85 mmol, 89%). M. p. 88-89 °C; R_f = 0.26 (hexane-ethyl acetate, 3:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.4 Hz, 2H), 7.51 (d, *J* = 7.1 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.99 (t, *J* = 6.8 Hz, 1H), 4.99 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.6, 159.6, 137.2, 134.6, 134.3, 132.3, 128.6, 126.9, 122.1, 116.6, 113.4, 102.9, 87.8, 86.1, 57.6, 27.0; IR ν_{max}/cm^{-1} (solid): 2233, 1685, 1603, 1492, 1290, 1257, 1230, 1017, 844, 835, 734; HRMS m/z $[M+H]^+$ Calculated for $C_{18}H_{14}NO_2$: 276.1025; found 276.1018.

4-(3-(2-Cyanophenoxy)prop-1-yn-1-yl)phenyl acetate (177o)



Prepared according to the one-pot synthesis described for compound **177e** from 2-hydroxybenzonitrile (**175a**) and 4-iodophenyl acetate (611 mg, 2.33 mmol) for 5 h at 45 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a light brown solid (218 mg, 0.749 mmol, 32% for the two steps). M. p. 102-103 °C; R_f = 0.32 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54 – 7.41 (m, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.03 – 6.90 (m, 3H), 4.94 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.5, 159.7, 151.4, 134.6, 134.3, 133.4, 122.2, 121.9, 119.8, 116.7, 113.5, 102.8, 87.9, 83.0, 57.7, 21.5; IR ν_{max}/cm^{-1} (solid): 2234, 1769, 1599, 1506, 1492, 1229, 1198, 1016, 737; HRMS m/z $[M+Na]^+$ Calculated for $C_{18}H_{13}NO_3Na$: 314.0793; found 314.0791.

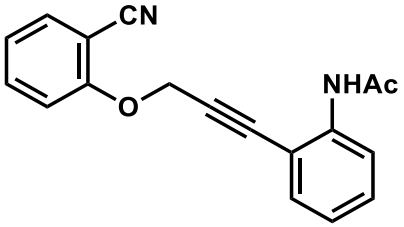
Methyl 4-(3-(2-cyanophenoxy)prop-1-yn-1-yl)benzoate (177p)



Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and methyl-4-iodobenzoate (542 mg, 2.07 mmol) for 30 min at 35 °C. Purification of the

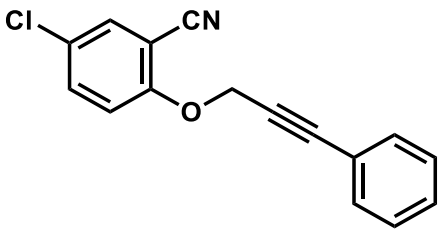
crude product by column chromatography on silica gel afforded the product as a drab solid (531 mg, 1.82 mmol, 88%). M. p. 94-95 °C; R_f = 0.50 (hexane-ethyl acetate, 7:3). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.98 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.7, 159.6, 134.6, 134.3, 132.1, 130.6, 129.8, 126.8, 122.0, 116.6, 113.4, 102.9, 87.8, 85.8, 57.6, 52.7; IR ν_{max}/cm^{-1} (solid): 2235, 1723, 1601, 1491, 1287, 1231, 1111, 1020, 860, 737.698; HRMS m/z $[M+H]^+$ Calculated for $C_{18}H_{14}NO_3$: 292.0974; found 292.0975.

N-(2-(3-(2-Cyanophenoxy)prop-1-yn-1-yl)phenyl)acetamide (177q)



Prepared according to the general procedure from 2-(prop-2-ynyloxy)benzonitrile (**176a**) and *N*-(2-iodophenyl)acetamide (362 mg, 2.30 mmol) for 2 h at 30-35 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (400 mg, 1.38 mmol, 60%). M. p. 119-120 °C; R_f = 0.35 (hexane-ethyl acetate, 3:2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.3 Hz, 1H), 7.64 (s, 1H), 7.57 – 7.46 (m, 2H), 7.33 – 7.20 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.97 (dt, *J* = 16.3, 7.5 Hz, 2H), 5.05 (s, 2H), 1.99 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.8, 159.4, 139.6, 134.7, 134.5, 132.3, 130.7, 123.8, 122.3, 120.1, 116.5, 113.2, 110.9, 103.0, 89.8, 84.2, 57.7, 25.1; IR ν_{max}/cm^{-1} (solid); 2233, 1699, 1600, 1581, 1517, 1492, 1446, 1301, 1231, 1016761, 740; HRMS m/z $[M+Na]^+$ Calculated for $C_{18}H_{14}N_2O_2Na$: 313.0953; found 313.0940.

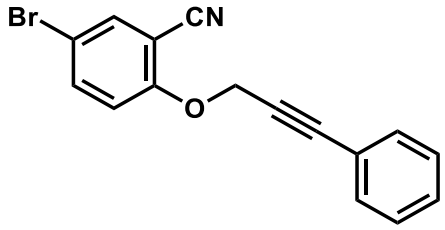
5-Chloro-2-(3-phenylprop-2-ynyloxy)benzonitrile (177r)



Prepared according to the general procedure from 5-chloro-2-(prop-2-ynyloxy)benzonitrile (**176b**) (382 mg, 2.00 mmol) and iodobenzene (340 mg, 1.67 mmol, 186 µl) for 30 min at 30-35 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (236 mg, 0.884 mmol, 44%). M. p. 79-80 °C; R_f = 0.38 (hexane-ethyl acetate, 7:1). ^{1}H NMR (250 MHz, $CDCl_3$)

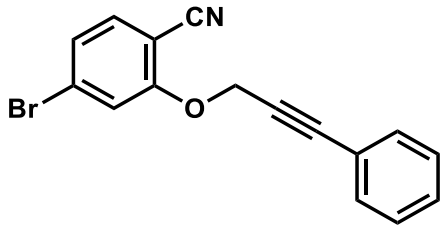
δ 7.49 – 7.37 (m, 2H), 7.37 – 7.29 (m, 2H), 7.28 – 7.20 (m, 3H), 7.09 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.4, 134.6, 133.5, 132.2, 129.5, 128.8, 126.8, 122.0, 115.4, 114.9, 104.3, 89.2, 82.4, 58.2; IR ν_{max}/cm^{-1} (solid): 2237, 1485, 1285, 1235, 1138, 1010, 1000, 817, 738, 694; HRMS m/z $[M+Na]^+$ Calculated for $C_{16}H_{10}NOClNa$: 290.0349; found 290.0359.

5-Bromo-2-(3-phenylprop-2-ynyloxy)benzonitrile (177s)



Prepared according to the general procedure from 5-bromo-2-(prop-2-ynyloxy)benzonitrile (**176c**) (354 mg, 1.50 mmol) and iodobenzene (255 mg, 1.25 mmol, 140 μl) for 30 min at 30-35 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a white crystalline solid (225 mg, 0.723 mmol, 58%). M. p. 86-87 °C; R_f = 0.33 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66 – 7.50 (m, 1H), 7.39 – 7.27 (m, 1H), 7.28 – 7.15 (m, 1H), 7.09 – 6.97 (m, 1H), 4.95 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.9, 137.4, 136.4, 132.2, 129.5, 128.8, 121.9, 115.3, 113.5, 104.7, 89.2, 82.3, 58.1; IR ν_{max}/cm^{-1} (solid): 2960, 2234, 1487, 1285, 1233, 1133, 1011, 813, 692; HRMS m/z $[M+Na]^+$ Calculated for $C_{16}H_{10}NOBrNa$: 333.9843; found 333.9856.

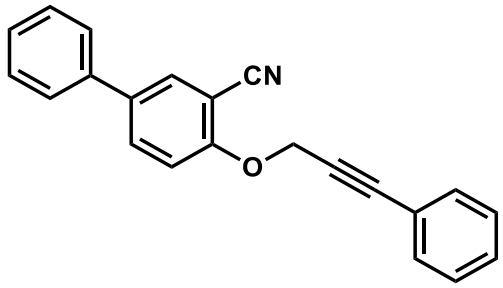
4-Bromo-2-(3-phenylprop-2-ynyloxy)benzonitrile (177t)



Prepared according to the one-pot synthesis described for compound **177e** from 4-bromo-2-hydroxybenzonitrile (500 mg, 2.53 mmol) and iodobenzene (396 mg, 1.94 mmol, 217 μl) for 3 h at 45-50 °C. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (112 mg, 0.360 mmol, 20%). M. p. 114-115 °C; R_f = 0.36 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 4H), 7.27 – 7.15 (m, 4H), 7.15 – 7.05 (m, 1H), 4.94 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 160.0, 134.9, 132.3, 129.6, 129.0, 128.8, 125.3, 121.9, 117.4, 116.0, 102.0, 89.5, 82.1,

58.2; IR ν_{max}/cm^{-1} (solid): 2234, 1587, 1484, 1230, 1012, 1000, 854, 815, 738, 693; HRMS m/z $[M+Na]^+$ Calculated for $C_{16}H_{10}NOBrNa$: 333.9843; found 333.9853.

4-((3-Phenylprop-2-yn-1-yl)oxy)-[1,1'-biphenyl]-3-carbonitrile (177u)



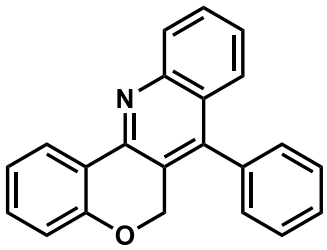
5-Bromo-2-(3-phenylprop-2-ynyloxy)benzonitrile (**177s**) (156 mg, 0.5 mmol), phenylboronic acid (183 mg, 0.75 mmol), palladium acetate (5.61 mg, 0.025 mmol, 5 mol%) and tri-*tert*-butylphosphonium tetrafluoroborate (7.25 mmol, 0.025 mmol, 5 mol%) and potassium carbonate (138 mg, 1.00 mmol) were added to a 20 ml round bottom flask and the system was charged with argon. Tetrahydrofurane (2.50 ml) and distilled water (2.50 ml) were added dropwise under argon atmosphere then the reaction mixture was stirred at 50 °C for 1.5 h. The reaction mixure was diluted with distilled water (10 ml) and extracted with ethyl acetate (4 x 10 ml). The combined organics were washed with brine (1 x 30 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification of the crude product by column chromatography on silica gel afforded the product as a drab oil (135 mg, 0.438 mmol, 86%). R_f = 0.35 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 2H), 7.43 – 7.37 (m, 2H), 7.40 – 7.25 (m, 4H), 7.29 – 7.15 (m, 5H), 4.97 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.0, 138.9, 135.3, 133.1, 132.6, 132.2, 129.5, 129.4, 128.8, 128.2, 127.1, 122.2, 116.7, 113.9, 103.3, 88.9, 82.9, 58.0; IR ν_{max}/cm^{-1} (solid): 2231, 1487, 1282, 1236, 1129, 1013, 999, 763, 738, 692; HRMS m/z $[M+Na]^+$ Calculated for $C_{22}H_{15}NONa$: 332.1051; found 332.1059.

7. 12. Synthesis and analitical data of 7-Aryl-6*H*-chromeno[4,3-*b*]quinolines

General procedure 4 for the synthesis of 7-aryl-6*H*-chromeno[4,3-*b*]quinolines

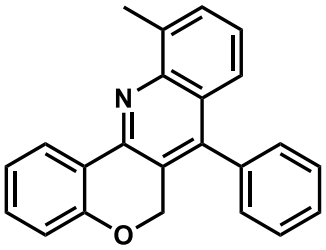
2-(3-Phenylprop-2-ynyloxy)benzonitrile **(177a)** (117 mg, 0.500 mmol), diaryl iodonium salt (0.600 mmol, 1.2 eq.) and copper(I)chloride (4.96 mg; 0.050 mmol, 10 mol%) were added to a 4 ml vial then the system was charged with argon. Ethyl acetate (1 ml) was added under argon atmosphere then the reaction mixture was stirred at 75°C for the appropriate time. Saturated sodium hydrogen carbonate solution (10 ml) was added to the mixture, the aqueous layer was extracted with dichloromethane (4 x 10 ml) the combined organics were washed with brine (1 x 25 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. The crude residue was purified by column chromatography.

7-Phenyl-*6H*-chromeno[4,3-*b*]quinoline (178aa)



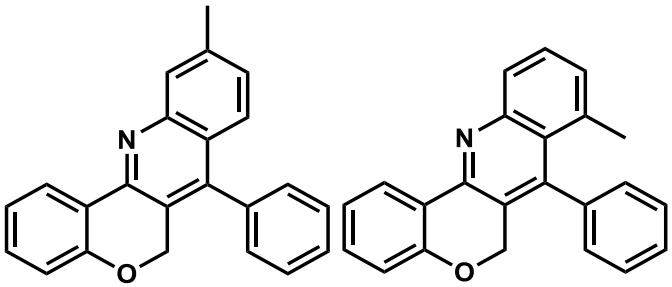
Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (120 mg, 0.388 mmol, 78%). M. p. 159-160 °C; R_f = 0.45 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.7 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.62 – 7.48 (m, 1H), 7.46 – 7.29 (m, 4H), 7.30 – 7.11 (m, 4H), 7.09 – 6.97 (m, 1H), 6.84 (d, *J* = 7.4 Hz, 1H), 4.96 (s, 2H).; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.7, 149.1, 148.4, 144.1, 135.3, 132.3, 130.0, 129.73, 129.65, 129.2, 128.9, 127.5, 126.6, 126.5, 126.21, 123.9, 123.2, 122.9, 117.6, 67.1; IR ν_{max}/cm^{-1} (solid): 2927, 2910, 1583, 1560, 1506, 1490, 1465, 1222, 1044, 769, 737, 700; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{16}NO$: 310.1232; found 310.1236.

11-Methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178ab)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and 2-methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**46b**) (292 mg, 0.600 mmol) for 5 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (52.0 mg, 0.161 mmol, 32%). M. p. 124-125 °C; R_f = 0.30 (hexane-ethyl acetate, 30:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ= 8.48 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.39 (d, *J* = 5.6 Hz, 4H), 7.30 – 6.98 (m, 7H), 6.84 (d, *J* = 8.1 Hz, 1H), 4.96 (s, 2H), 2.81 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 157.6, 147.6, 147.3, 144.2, 137.9, 135.8, 132.0, 129.9, 129.7, 129.1, 128.8, 127.4, 126.3, 126.2, 124.5, 124.3, 122.8, 122.7, 117.5, 67.2, 18.6; IR ν_{max}/cm^{-1} (solid): 2928, 2365, 1588, 1489, 1394, 1369, 1222, 1040, 769, 741; HRMS m/z $[M+H]^+$ Calculated for $C_{23}H_{18}NO$: 324.1388; found 324.1392.

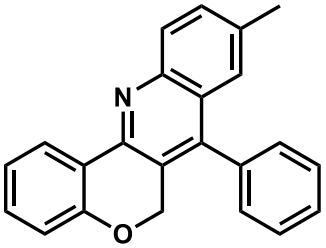
8-Methyl-7-phenyl-*6H*-chromeno[4,3-*b*]quinoline and 10-methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178ac)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and 3-methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**46c**) (292 mg, 0.600 mmol) for 20 min. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (105 mg, 0.325 mmol, 65%). M. p. 99-100 °C; R_f = 0.35 (hexane-ethyl acetate, 25:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.52 – 8.28 (m, 1H), 7.94 (d, *J* = 8.3 Hz, 0.5H), 7.84 (s, 0.5H), 7.50 – 6.94 (m, 9H), 6.82 (t, *J* = 7.6 Hz, 1H), 4.94 (s, 1H), 4.77 (s, 1H), 2.40 (s, 1.5H), 1.77 (s, 1.5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.7, 157.6, 149.6, 149.0, 148.6, 147.9, 144.3, 144.0, 140.0, 139.4, 136.1, 135.5, 132.1, 130.3, 129.7, 129.5, 129.3, 129.2,

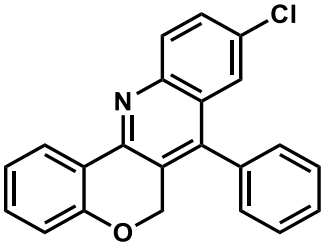
129.13, 129.06, 128.91, 128.87, 128.8, 128.6, 126.2, 126.1, 126.0, 125.5, 124.4, 124.0, 123.6, 122.83, 122.78, 122.4, 117.5, 117.4, 67.2, 67.1, 24.5, 22.1; IR ν_{max}/cm^{-1} (solid): 2928, 2366, 2340, 1701, 1577, 1558, 1539, 1506, 1487, 1219, 1042, 738; HRMS m/z $[M+H]^+$ Calculated for $C_{23}H_{18}NO$: 324.1388; found 324.1392.

9-Methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178ad)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and 4-methylphenyl(mesityl)iodonium trifluoromethanesulfonate (**46d**) (292 mg, 0.600 mmol) for 30 min. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (81.5 mg, 0.252 mmol, 50%). M. p. 193-194 °C; R_f = 0.35 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.3 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.29 (m, 4H), 7.28 – 6.96 (m, 5H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.94 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 148.2, 146.9, 143.5, 136.6, 135.5, 132.0, 129.7, 129.2, 128.9, 127.4, 126.1, 125.4, 124.0, 123.2, 122.9, 117.5, 67.2, 22.2; IR ν_{max}/cm^{-1} (solid): 2924, 2367, 2340, 1585, 1495, 1467, 1221, 1049, 1000, 831, 737; HRMS m/z $[M+H]^+$ Calculated for $C_{23}H_{18}NO$: 324.1388; found 324.1390.

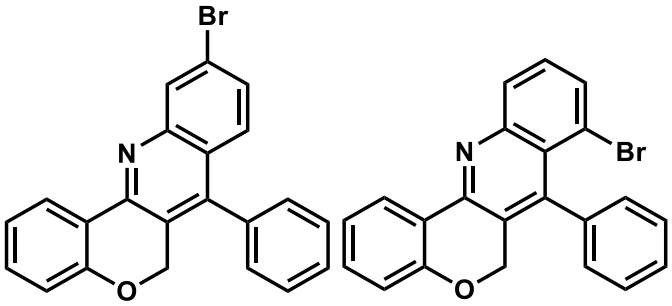
9-Chloro-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178af)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and (4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate (**46f**) (302 mg, 0.600 mmol) for 2 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (95.0 mg, 0.277 mmol, 55%). M. p. 174-175 °C; R_f = 0.38 (hexane-ethyl acetate, 20:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.47 – 8.25 (m, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.54 – 7.36 (m, 4H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.28 – 7.20 (m, 1H), 7.19 – 7.10 (m, 2H), 7.03 (t, *J* =

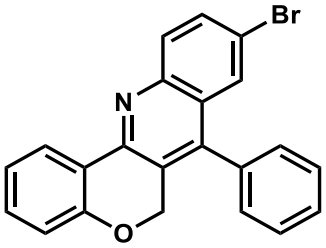
7.4 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 4.94 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 149.3, 146.8, 143.3, 134.6, 132.5, 132.4, 131.6, 130.6, 129.5, 129.4, 129.3, 128.1, 126.1, 125.3, 124.0, 123.5, 122.9, 117.6, 67.0; IR ν_{max}/cm^{-1} (solid): 2369, 1585, 1489, 1373, 1223, 1047, 833, 737; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOCl$: 344.0842; found 344.0844.

8-Bromo-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline and 10-bromo-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178ah)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and 3-bromophenyl(mesityl)iodonium trifluoromethanesulfonate (**46h**) (331 mg, 0.600 mmol) for 3 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (94.0 mg, 0.243 mmol, 49%). M. p. 120-121 °C; R_f = 0.40 (hexane-ethyl acetate, 20:1).^{1}H NMR (250 MHz, $CDCl_3$) δ 8.49 (d, *J* = 7.7 Hz, 1H), 8.36 (s, 0.4H), 8.17 (d, *J* = 8.0 Hz, 0.6H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.63 – 7.09 (m, 8H), 7.05 – 6.87 (m, 1H), 5.07 (s, 1H), 4.94 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.7, 157.6, 150.0, 149.9, 149.0, 148.8, 144.19, 144.19, 136.8, 134.7, 134.3, 134.2, 132.68, 132.65, 132.2, 131.0, 129.94, 129.90, 129.8, 129.6, 129.3, 129.2, 128.79, 128.75, 128.0, 126.3, 126.2, 125.8, 125.5, 125.1, 124.0, 123.5, 123.1, 123.0, 122.9, 119.5, 117.6, 117.5, 67.3, 67.0; IR ν_{max}/cm^{-1} (solid): 2366, 2342, 1584, 1570, 1487, 1245, 1221, 1043, 737; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOBr$: 388.0337; found 388.0339.

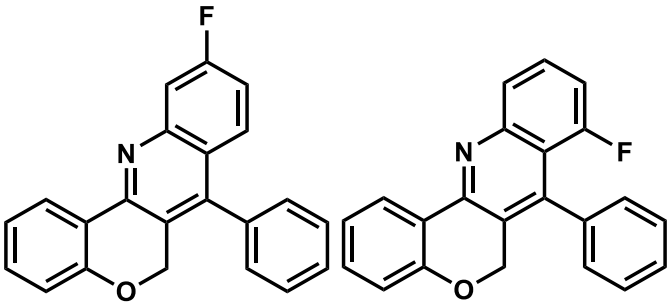
9-Bromo-7-phenyl-6H-chromeno[4,3-b]quinoline (178ai)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and (4-bromophenyl)(mesityl)iodonium

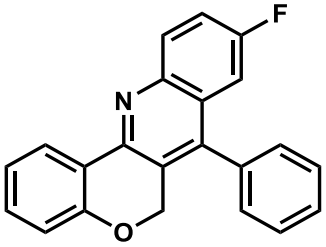
trifluoromethanesulfonate (**46i**) (331 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (90.0 mg, 0.232 mmol, 47%). M. p. 199-200 °C; R_f = 0.38 (hexane-ethyl acetate, 20:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 7.60 (dd, *J1* = 7.5 Hz, *J2* = 2.5 Hz, 1H), 7.52 – 7.34 (m, 4H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.20 – 7.10 (m, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.7, 149.4, 146.9, 143.3, 134.5, 133.2, 132.6, 131.6, 129.5, 129.4, 129.3, 128.63, 128.59, 126.2, 124.0, 123.5, 123.0, 120.7, 117.6, 67.0; IR ν_{max}/cm^{-1} (solid): 2365, 2343, 1580, 1560, 1489, 1223, 1044, 832, 737; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOBr$: 388.0337; found 388.0342.

8-Fluoro-7-phenyl-*6H*-chromeno[4,3-*b*]quinoline and 10-fluoro-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178ak)



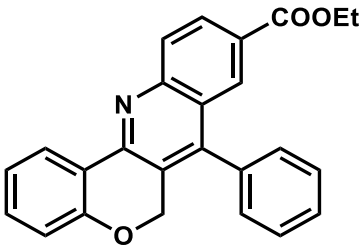
Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and 3-fluorophenyl(mesityl)iodonium trifluoromethanesulfonate (**46k**) (294 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (106 mg, 0.324 mmol, 65%). M. p. 141-142 °C; R_f = 0.36 (hexane-ethyl acetate, 15:1).^{1}H NMR (250 MHz, $CDCl_3$) δ 8.52 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 0.4H), 7.81 (dd, *J* = 10.2, 2.7 Hz, 0.6H), 7.64 – 6.83 (m, 10H), 5.09 (s, 1H), 5.01 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.4, 157.8, 157.7, 150.2, 149.7, 144.3, 141.4, 137.7, 137.6, 135.0, 132.7, 132.6, 129.54, 129.47, 129.32, 129.26, 129.1, 128.8, 128.7, 128.5, 128.21, 128.15, 126.4, 126.33, 126.28, 124.8, 124.5, 123.6, 123.3, 122.9, 122.53, 122.50, 117.6, 116.9, 116.5, 113.6, 113.3, 112.1, 111.7, 67.0, 66.7; IR ν_{max}/cm^{-1} (solid): 2366, 2342, 1583, 1487, 1468, 1222, 1137, 1043, 738; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOF$: 328.1138; found 328.1139.

9-Fluoro-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178al)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and (4-fluorophenyl)(mesityl)iodonium trifluoromethanesulfonate (**46l**) (294 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a light yellow solid (90.0 mg, 0.274 mmol, 55%). M. p. 140-141 °C; R_f = 0.35 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.6 Hz, 1H), 8.00 (dd, *J* = 9.1, 5.6 Hz, 1H), 7.50 – 7.34 (m, 3H), 7.32 – 7.07 (m, 4H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.94 (dd, *J* = 10.0, 2.5 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 4.93 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.8, 158.8, 157.5, 148.6, 148.5, 145.4, 143.6, 143.5, 134.8, 132.4, 132.3, 129.5, 129.4, 129.2, 128.3, 128.2, 126.0, 123.9, 123.6, 122.9, 120.0, 119.6, 117.6, 110.2, 109.8, 67.1; IR ν_{max}/cm^{-1} (solid): 2367, 2339, 1558, 1489, 1222, 1044, 833, 769; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOF$: 328.1138; found 328.1144.

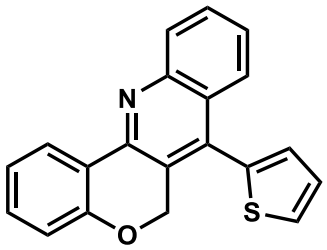
7-Phenyl-6*H*-chromeno[4,3-*b*]quinoline-9-carboxylate (178an)



Prepared according to the general procedure from 2-(3-phenylprop-2-ynyloxy)benzonitrile (**177a**) and 4-ethoxycarbonyl(mesityl)iodonium trifluoromethanesulfonate (**46n**) (327 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (133 mg, 0.341 mmol, 70%). M. p. 146-147 °C; R_f = 0.30 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.8 Hz, 1H), 8.22 – 7.95 (m, 3H), 7.44 (s, 3H), 7.31 – 7.10 (m, 3H), 7.04 (t, *J* = 7.1 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 4.98 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.6, 157.9, 151.0, 150.2, 145.5, 134.4, 132.9, 130.1, 129.6, 129.33, 129.27, 128.2, 126.7, 126.4, 123.9, 123.5, 123.0, 117.7, 67.0, 61.6, 14.7; IR ν_{max}/cm^{-1} (solid): 2928, 2370, 1715, 1586,

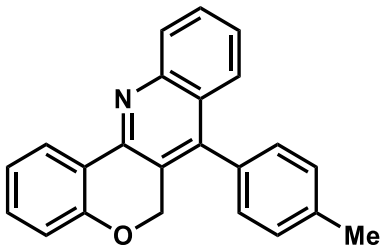
1467, 1293, 1251, 1226, 1103, 1048, 848, 737; HRMS m/z $[M+H]^+$ Calculated for $C_{25}H_{20}NO_3$: 382.1443; found 382.1444.

7-(Thiophen-2-yl)-6*H*-chromeno[4,3-*b*]quinoline (178ba)



Prepared according to the general procedure from 2-((3-(thiophen-2-yl)prop-2-yn-1-yl)oxy)benzonitrile (**177b**) (120 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 40 min. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (75.0 mg, 0.238 mmol, 48%). M. p. 147-148 °C; R_f = 0.35 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.49 (m, 2H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.37 – 7.17 (m, 2H), 7.18 – 7.09 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 2.8 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 5.09 (s, 2H), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 149.0, 148.3, 137.0, 134.6, 132.3, 130.0, 129.9, 129.3, 128.2, 128.0, 127.9, 126.9, 126.3, 126.2, 125.2, 123.7, 122.9, 117.6, 67.2; IR ν_{max}/cm^{-1} (solid): 2927, 2367, 2341, 1586, 1558, 1496, 1465, 1215, 1042, 768, 704; HRMS m/z $[M+H]^+$ Calculated for $C_{20}H_{14}NOS$: 316.0796; found 316.0800.

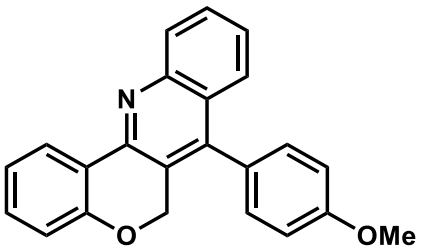
7-(p-Tolyl)-6*H*-chromeno[4,3-*b*]quinoline (178ea)



Prepared according to the general procedure from 2-((3-(p-tolyl)prop-2-yn-1-yl)oxy)benzonitrile (**178e**) (124 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 35 min. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (115 mg, 0.356 mmol, 71%). M. p. 137-138 °C; R_f = 0.30 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.60 (dd, *J1* = 7.68 Hz, *J2* = 1.25 Hz 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 7.1 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.46 – 7.31 (m, 4H), 7.27 – 7.13 (m, 3H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.14 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (62.5

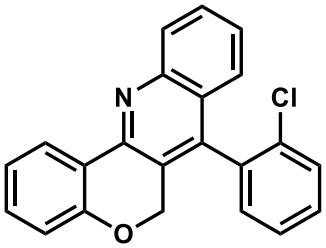
MHz, $CDCl_3$) δ 157.7, 149.1, 148.4, 144.3, 138.8, 132.21, 132.20, 130.0, 129.9, 129.7, 129.6, 127.7, 126.6, 126.5, 126.2, 124.0, 123.3, 122.9, 117.6, 67.2, 21.8; IR ν_{max}/cm^{-1} (solid): 2927, 2363, 2342, 1587, 1495, 1465, 1223, 1043, 769, 745; HRMS m/z $[M+H]^+$ Calculated for $C_{23}H_{18}NO$: 324.1388; found 324.1395.

7-(4-Methoxyphenyl)-6*H*-chromeno[4,3-*b*]quinoline (178fa)



Prepared according to the general procedure from 2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177f**) (132 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 40 min. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (59 mg, 0.172 mmol, 34%). M. p. 164-165 °C; R_f = 0.29 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 8.9 Hz, 2H), 7.16 – 6.98 (m, 3H), 6.95 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 5.01 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 160.1, 157.7, 149.1, 148.4, 144.0, 132.2, 130.9, 130.0, 129.7, 127.8, 127.2, 126.6, 126.5, 126.2, 124.0, 123.5, 122.9, 117.5, 114.6, 67.2, 55.8; IR ν_{max}/cm^{-1} (solid): 2908, 2368, 2341, 1519, 1499, 1248, 1042, 737; HRMS m/z $[M+H]^+$ Calculated for $C_{23}H_{18}NO_2$: 340.1338; found 340.1336.

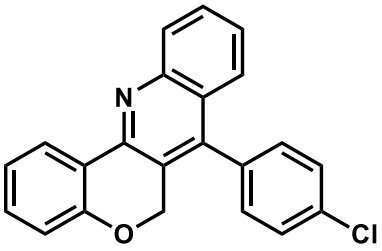
7-(2-Chlorophenyl)-6*H*-chromeno[4,3-*b*]quinoline (178ga)



Prepared according to the general procedure from 2-((3-(2-chlorophenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177g**) (134 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (125 mg, 0.364 mmol, 73%). M. p. 112-113 °C; R_f = 0.29 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.61 (d, *J* = 7.7 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.71 (t,

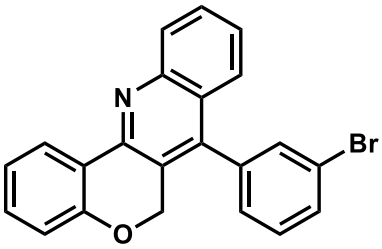
J = 7.6 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.54 – 7.26 (m, 6H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 5.09 (q, *J* = 14.1 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.7, 149.1, 148.5, 141.0, 134.2, 134.1, 132.3, 131.3, 130.6, 130.4, 130.2, 129.9, 127.6, 127.0, 126.9, 126.2, 126.0, 123.8, 122.9, 117.7, 67.0; IR ν_{max}/cm^{-1} (solid): 2927, 2366, 2339, 1585, 1473, 1221, 1042, 769, 741; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOCl$: 344.0842; found 344.0845.

7-(4-Chlorophenyl)-6*H*-chromeno[4,3-*b*]quinoline (178ha)



Prepared according to the general procedure from 2-((3-(4-chlorophenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177h**) (130 mg, 0.489 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (277 mg, 0.587 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (121 mg, 0.353 mmol, 75%). M. p. 202-203 °C; R_f = 0.38 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.9 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.81 – 7.63 (m, 1H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.49 – 7.32 (m, 3H), 7.31 – 7.12 (m, 3H), 6.99 (d, *J* = 7.5 Hz, 1H), 5.09 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 149.1, 148.3, 142.8, 135.2, 133.6, 132.4, 131.1, 130.1, 129.9, 129.5, 127.2, 126.8, 126.2, 123.7, 123.2, 123.0, 117.6, 67.0. IR ν_{max}/cm^{-1} (solid):2973, 2370, 2341, 1588, 1488, 1221, 1090, 1044, 837, 770; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOCl$: 344.0842; found 344.0844.

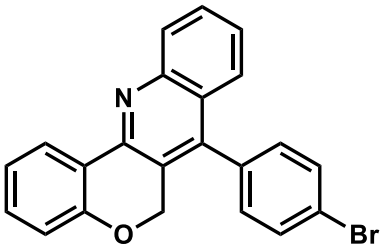
7-(3-Bromophenyl)-6*H*-chromeno[4,3-*b*]quinoline (178ia)



Prepared according to the general procedure from 2-((3-(3-bromophenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177i**) (156 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 30 min. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (129 mg, 0.333 mmol, 67%). M. p. 162-163 °C; R_f = 0.33 (hexane-ethyl acetate,

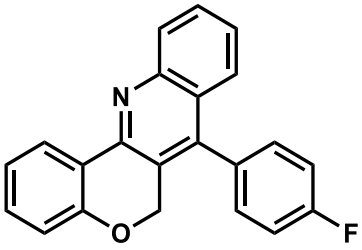
15:1).^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.5 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.58 – 7.33 (m, 5H), 7.31 – 7.13 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 149.1, 148.3, 142.3, 137.4, 132.5, 132.4, 132.1, 130.8, 130.1, 129.9, 128.3, 127.0, 126.9, 126.18, 126.15, 123.7, 123.4, 123.2, 123.0, 117.6, 66.9; IR ν_{max}/cm^{-1} (solid): 2928, 2368, 2341, 1584, 1560, 1472, 1223, 1044, 770, 701; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOBr$: 388.0337; found 388.0342.

7-(4-Bromophenyl)-6*H*-chromeno[4,3-*b*]quinoline (178ja)



Prepared according to the general procedure from 2-((3-(4-bromophenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177j**) (156 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (140 mg, 0.362 mmol, 72%). M. p. 183-184 °C; R_f = 0.33 (hexane-ethyl acetate, 15:1).^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.4 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 3H), 7.52 – 7.30 (m, 3H), 7.20 (d, *J* = 7.5 Hz, 3H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 149.1, 148.3, 142.8, 134.1, 132.5, 132.4, 131.3, 130.1, 129.9, 127.1, 126.8, 126.18, 126.16, 123.7, 123.3, 123.2, 123.0, 117.6, 67.0; IR ν_{max}/cm^{-1} (solid): 2928, 2366, 2341, 1487, 1222, 1043, 1014, 835, 771, 701; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOBr$: 388.0337; found 388.0338.

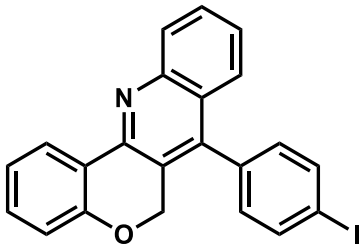
7-(4-Fluorophenyl)-6*H*-chromeno[4,3-*b*]quinoline (178ka)



Prepared according to the general procedure from 2-((3-(4-fluorophenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177k**) (81.0 mg, 0.323 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (183 mg, 0.387 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid

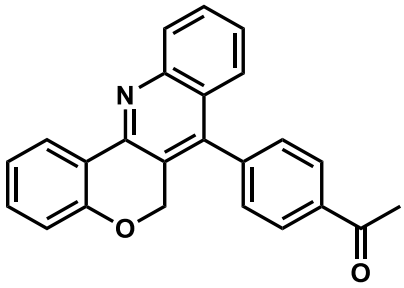
(63.0 mg, 0.193 mmol, 60%). M. p. 181-182 °C; R_f = 0.28 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.8 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.79 – 7.60 (m, 1H), 7.53 – 7.15 (m, 8H), 6.99 (d, *J* = 7.6 Hz, 1H), 5.09 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 149.1, 148.3, 143.0, 132.4, 131.5, 131.4, 131.1, 131.0, 130.0, 129.8, 127.4, 126.7, 126.2, 123.8, 123.4, 123.0, 117.6, 116.5, 116.2, 67.0; IR ν_{max}/cm^{-1} (solid): 2932, 2365, 2342, 1496, 1221, 1044, 847, 769, 735; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOF$: 328.1138; found 328.1139.

7-(4-Fluorophenyl)-6*H*-chromeno[4,3-*b*]quinoline (178la)



Prepared according to the general procedure from 2-((3-(4-iodophenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177l**) (85.0 mg, 0.237 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (134 mg, 0.284 mmol) for 50 min. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (55.2 mg, 0.127 mmol, 54%). R_f = 0.40 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 7.7, 1.8 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 9.0, 2.6 Hz, 2H), 7.64 – 7.52 (m, 1H), 7.39 – 7.21 (m, 3H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.91 (dd, *J* = 18.6, 8.2 Hz, 3H), 4.98 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.60, 149.10, 148.40, 142.77, 138.39, 134.77, 132.34, 131.50, 130.12, 129.86, 127.03, 126.77, 126.16, 123.77, 123.08, 122.96, 117.58, 94.99, 66.97.

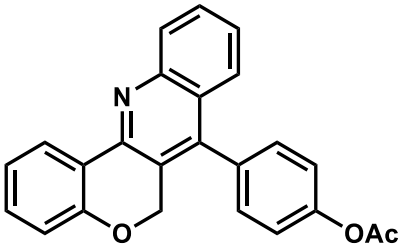
1-(4-(6*H*-chromeno[4,3-b]quinolin-7-yl)phenyl)ethan-1-one (178na)



Prepared according to the general procedure from 2-((3-(4-acetylphenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177n**) (176 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 75 min. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow

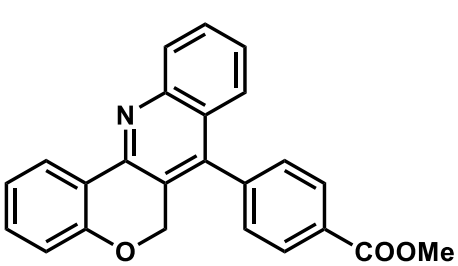
solid (126 mg, 0.359 mmol, 72%). M. p. 185-186 °C; R_f = 0.31 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.53 (d, *J* = 7.7 Hz, 1H), 8.27 – 8.04 (m, 3H), 7.67 (dt, *J* = 8.5, 4.2 Hz, 1H), 7.51 – 7.30 (m, 5H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 5.05 (s, 2H), 2.70 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.9, 157.6, 149.0, 148.3, 142.8, 140.2, 137.5, 132.4, 130.1, 130.0, 129.1, 126.9, 126.8, 126.2, 126.1, 123.7, 122.99, 122.96, 117.6, 66.9, 27.2; IR ν_{max}/cm^{-1} (solid): 2928, 2364, 2341, 1685, 1586, 1468, 1359, 1222, 1045, 769; HRMS m/z $[M+H]^+$ Calculated for $C_{24}H_{18}NO_2$: 352.1338; found 352.1342.

4-(6*H*-chromeno[4,3-b]quinolin-7-yl)phenyl acetate (178oa)



Prepared according to the general procedure from 4-(3-(2-cyanophenoxy)prop-1-yn-1-yl)phenyl acetate (**177o**) (146 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 2 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (88.0 mg, 0.240 mmol, 48%). M. p. 124-125 °C; R_f = 0.32 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.48 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.32 – 7.15 (m, 6H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.98 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.7, 157.7, 151.2, 149.1, 148.4, 143.1, 132.7, 132.3, 130.8, 130.0, 129.8, 127.4, 126.7, 126.4, 126.2, 123.9, 123.4, 122.9, 122.5, 117.6, 67.1, 21.6; IR ν_{max}/cm^{-1} (solid): 2365, 1771, 1751, 1495, 1200, 1045, 771, 730; HRMS m/z $[M+H]^+$ Calculated for $C_{24}H_{18}NO_3$: 368.1287; found 368.1271.

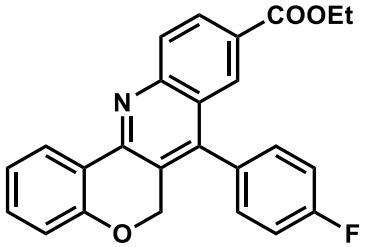
Methyl 4-(6*H*-chromeno[4,3-*b*]quinolin-7-yl)benzoate (178pa)



Prepared according to the general procedure from methyl 4-(3-(2-cyanophenoxy)prop-1-yn-1-yl)benzoate (**177p**) (146 mg, 0.500 mmol) and phenyl(mesityl)iodonium

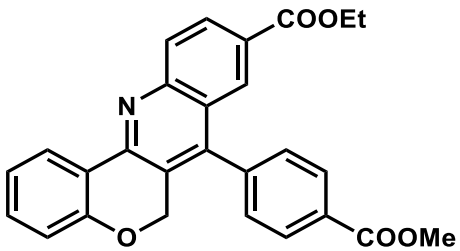
trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 1.5 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (146 mg, 0.398 mmol, 80%). M. p. 188-189 °C; R_f = 0.44 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.6 Hz, 1H), 8.32 – 8.12 (m, 3H), 7.77 – 7.61 (m, 1H), 7.47 – 7.31 (m, 5H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 5.06 (s, 2H), 3.99 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.0, 157.6, 149.0, 148.3, 142.9, 140.1, 132.4, 130.8, 130.4, 130.1, 129.9, 129.8, 126.9, 126.8, 126.2, 126.1, 123.7, 123.0, 117.6, 66.9, 52.8; IR ν_{max}/cm^{-1} (solid): 2926, 2368, 1725, 1588, 1286, 1104, 1043, 769; HRMS m/z $[M+H]^+$ Calculated for $C_{24}H_{18}NO_3$: 368.1287; found 368.1291.

Ethyl 7-(4-fluorophenyl)-6*H*-chromeno[4,3-*b*]quinoline-9-carboxylate (178kn)



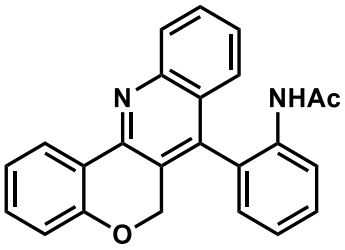
Prepared according to the general procedure from 2-((3-(4-fluorophenyl)prop-2-yn-1-yl)oxy)benzonitrile (**177k**) (126 mg, 0.500 mmol) and 4-ethoxycarbonyl-phenyl(mesityl)iodonium trifluoromethanesulfonate (**46n**) (327 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (101 mg, 0.253 mmol, 51%). M. p. 202-203 °C; R_f = 0.20 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.1 Hz, 1H), 8.24 – 7.98 (m, 3H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 4H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.00 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.5, 157.9, 151.0, 150.3, 144.3, 132.9, 131.6, 131.4, 130.2, 129.3, 129.2, 128.4, 126.7, 126.4, 124.1, 123.4, 123.0, 117.6, 116.7, 116.4, 66.9, 61.7, 14.7; IR ν_{max}/cm^{-1} (solid): 2926, 2362, 2341; 1716, 1293, 1275, 1252, 1224, 1102, 1048, 851, 734; HRMS m/z $[M+H]^+$ Calculated for $C_{25}H_{19}NO_3F$: 400.1349; found 400.1350.

7-(4-(Methoxycarbonyl)phenyl)-6*H*-chromeno[4,3-*b*]quinoline-9-carboxylate (178pn)



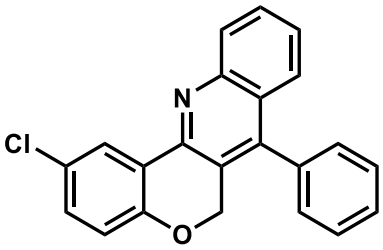
Prepared according to the general procedure from methyl 4-(3-(2-cyanophenoxy)prop-1-yn-1-yl)benzoate (**177p**) (146 mg, 0.500 mmol) and 4-ethoxycarbonyl-phenyl(mesityl)iodonium trifluoromethanesulfonate (**46n**) (327 mg, 0.600 mmol) for 2.5 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (148 mg, 0.337 mmol, 67%). M. p. 204-205 °C; R_f = 0.25 (hexane-ethyl acetate, 7:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.51 (d, *J* = 7.5 Hz, 1H), 8.34 – 8.09 (m, 5H), 7.48 – 7.33 (m, 3H), 7.17 (t, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.07 (s, 2H), 4.34 (q, *J* = 6.6 Hz, 2H), 4.01 (s, 3H), 1.35 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.9, 166.4, 157.9, 151.0, 150.2, 144.2, 139.3, 133.0, 131.1, 130.6, 130.2, 129.8, 129.5, 129.0, 128.5, 126.4, 126.1, 123.7, 123.3, 123.1, 117.7, 66.8, 61.7, 52.8, 14.7; IR ν_{max}/cm^{-1} (solid): 2930, 2365, 2342, 1720, 1290, 1252, 1104, 1047, 734 ; HRMS m/z $[M+H]^+$ Calculated for $C_{27}H_{22}NO_5$: 440.1498; found 440.1496.

***N*-(2-(6*H*-chromeno[4,3-*b*]quinolin-7-yl)phenyl)acetamide (178qa)**



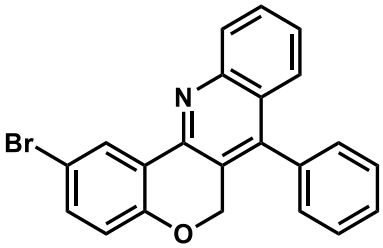
Prepared according to the general procedure from 4-(3-(2-cyanophenoxy)prop-1-yn-1-yl)phenyl acetate (**177q**) (145 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 1.5 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow solid (84.0 mg, 0.230 mmol, 46%). M. p. 83-84 °C; R_f = 0.32 (hexane-ethyl acetate, 2:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.51 (d, *J* = 7.8 Hz, 1H), 8.20 (dd, *J* = 15.8, 8.3 Hz, 2H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.57 – 7.22 (m, 5H), 7.14 (d, *J* = 7.3 Hz, 2H), 7.02 – 6.82 (m, 2H), 5.15 – 4.82 (m, 2H), 1.69 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.0, 157.8, 149.5, 148.6, 139.6, 135.8, 132.6, 130.3, 127.3, 126.9, 126.1, 125.9, 125.33, 125.26, 124.5, 123.6, 123.3, 123.0, 117.7, 66.9, 24.6; IR ν_{max}/cm^{-1} (solid): 1700, 1582, 1519, 1449, 1300, 1230, 1044, 1004, 768, 731; HRMS m/z $[M+H]^+$ Calculated for $C_{24}H_{19}N_2O_2$: 367.1447; found 367.1431.

2-Chloro-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178ra)



Prepared according to the general procedure from 5-chloro-2-(3-phenylprop-2-ynyloxy)benzonitrile (**177r**) (134 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 30 min. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (133 mg, 0.388 mmol, 78%). M. p. 164-165 °C; R_f = 0.43 (hexane-ethyl acetate, 10:1).). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.63 – 7.45 (m, 4H), 7.45 – 7.36 (m, 1H), 7.29 (d, *J* = 5.8 Hz, 3H), 6.91 (d, *J* = 8.6 Hz, 1H), 5.10 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.1, 148.3, 147.8, 144.4, 135.1, 131.9, 130.0, 129.9, 129.6, 129.2, 129.1, 128.1, 127.6, 127.0, 126.5, 125.8, 125.1, 122.7, 119.0, 67.2; IR ν_{max}/cm^{-1} (solid): 2956, 2365, 2341, 1584, 1492, 1437, 1250, 1002, 824, 768, ; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOCl$: 344.0842; found 344.0849.

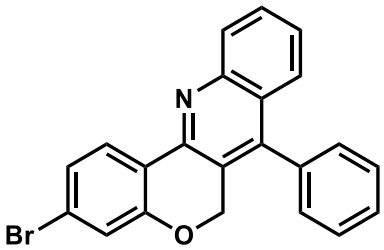
2-Bromo-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178sa)



Prepared according to the general procedure from 5-bromo-2-(3-phenylprop-2-ynyloxy)benzonitrile (**177s**) (156 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (154 mg, 0.398 mmol, 80%). M. p. 179-180 °C; R_f = 0.34 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.5 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.53 (m, 1H), 7.51 – 7.36 (m, 4H), 7.36 – 7.25 (m, 2H), 7.23 – 7.14 (m, 2H), 6.75 (d, *J* = 8.7 Hz, 1H), 4.99 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.6, 148.3, 147.7, 144.4, 135.0, 134.8, 130.02, 129.96, 129.6, 129.2, 129.1, 128.7, 127.6, 127.0, 126.5, 125.6, 122.7, 119.5, 115.5, 67.2; IR ν_{max}/cm^{-1} (solid): 2957, 2857, 2364, 2342, 1581, 1491, 1480, 1435,

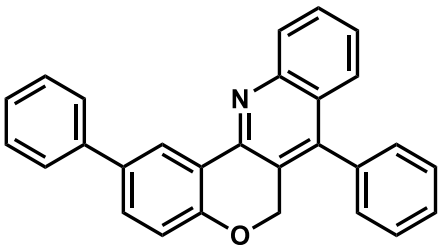
1248, 1002, 824, 767, 702; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOBr$: 388.0337; found 388.0345.

3-Bromo-7-phenyl-6*H*-chromeno[4,3-*b*]quinoline (178ta)



Prepared according to the general procedure from 4-bromo-2-(3-phenylprop-2-ynyloxy)benzonitrile (**177t**) (78 mg, 0.250 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (142 mg, 0.300 mmol) for 1 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (65.0 mg, 0.168 mmol, 67%). M. p. 184-185 °C; R_f = 0.33 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.48 – 7.31 (m, 4H), 7.30 – 7.21 (m, 1H), 7.16 (d, *J* = 6.8 Hz, 3H), 7.03 (s, 1H), 4.97 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.1, 148.4, 148.2, 144.3, 135.1, 130.0, 129.9, 129.6, 129.2, 129.0, 127.5, 127.4, 126.8, 126.5, 126.1, 125.6, 122.9, 122.6, 120.8, 67.4; IR ν_{max}/cm^{-1} (solid): 2963, 2935, 2909, 2364, 2342, 2328, 1582, 1488, 1423, 1217, 1041, 873, 769, 704; HRMS m/z $[M+H]^+$ Calculated for $C_{22}H_{15}NOBr$: 388.0337; found 388.0351.

2,7-Diphenyl-6*H*-chromeno[4,3-*b*]quinoline (178ua)

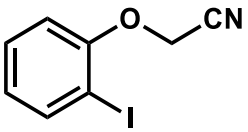


Prepared according to the general procedure from 4-((3-phenylprop-2-yn-1-yl)oxy)-[1,1'-biphenyl]-3-carbonitrile (**177u**) (77.3 mg, 0.250 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (142 mg, 0.300 mmol) for 30 min. Purification of the crude product by column chromatography on silica gel afforded the product as a green solid (67.5 mg, 0.175 mmol, 70%). M. p. 194-195 °C; R_f = 0.30 (hexane-ethyl acetate, 15:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.50 (m, 4H), 7.50 – 7.32 (m, 6H), 7.32 – 7.14 (m, 4H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.06 (s, 2H); . ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.2, 149.0, 148.4, 144.2, 141.1, 136.0, 135.3, 131.0,

130.0, 129.8, 129.6, 129.2, 129.1, 129.0, 127.5, 127.4, 126.6, 126.5, 124.6, 124.0, 123.1, 118.0, 67.3; IR ν_{max}/cm^{-1} (solid): 2962, 2363, 2342, 1560, 1506, 1488, 1460, 1251, 1227, 1047, 1003, 767, 737, 700; HRMS m/z $[M+H]^+$ Calculated for $C_{28}H_{20}NO$: 386.1545; found 386.1552.

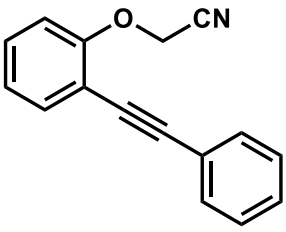
7. 13. Synthesis and analytical data of 12-phenyl-6*H*-chromeno[3,4-*b*]quinoline (182) and 2-bromo-6*H*-chromeno[4,3-*b*]quinoline (188)

2-(2-iodophenoxy)acetonitrile (180)



Prepared according to the modified procedure of Malinakova.[145] Potassium carbonate (3.14 g, 22.7 mmol) and 2-iodophenol (**179**) (1.00 g, 4.55 mmol) were added to a 100 ml round bottom flask fitted with a rubber septum then the system was charged with argon. Acetone (45 ml) was added under argon atmosphere then 2-bromoacetonitrile (1.58 g, 13.2 mmol, 918 μl) was added dropwise. The resulted mixture was stirred at 50 °C for 2-3 h then at room temperature for 16 h. Potassium carbonate was filtered off and the reaction mixure was evaporated. Purification of the crude product by column chromatography on silica gel afforded the product as a brown oil (1.13 g, 4.36 mmol, 95%); R_f = 0.40 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.75 (dd, *J*= 7.8, 1.5, 1.5 Hz, 1H), 7.34 – 7.23 (m, 1H), 6.91 (dd, *J* = 8.2, 1.0, 1.0 Hz, 1H), 6.79 (td, *J* = 7.6, 1.1 Hz, 1H), 4.74 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.9, 140.6, 130.2, 125.6, 115.1, 114.2, 87.1, 55.2.

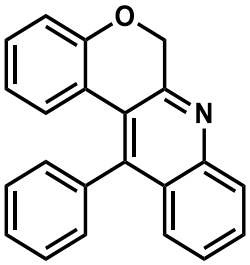
2-(2-(phenylethynyl)phenoxy)acetonitrile (181)



Prepared by Sonogashira reaction according to procedure of 2-(2-(phenylethynyl)phenyl)acetonitrile (**171**) from 2-(2-iodophenoxy)acetonitrile (**180**) (600 mg, 2.32 mmol) and phenylacetylene (355 mg, 3.48 mmol, 382 μl) at 50 °C for 1 h.

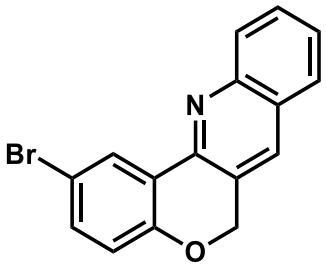
Purification of the crude product by column chromatography on silica gel afforded the product as a brown oil (470 mg, 2.02 mmol, 87%); R_f = 0.30 (hexane-ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 3H), 7.41 – 7.32 (m, 4H), 7.17 – 7.01 (m, 2H), 4.89 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.3, 134.4, 132.1, 130.2, 198.0, 128.8, 124.0, 123.4, 115.4, 114.9, 114.8, 95.1, 84.8, 55.2.

12-phenyl-6*H*-chromeno[3,4-*b*]quinoline (182)



Prepared according to the synthesis of 7-aryl-6*H*-chromeno[4,3-*b*]quinolines from 2-(2-(phenylethynyl)phenoxy)acetonitrile (**181**) (117 mg, 0.500 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (283 mg, 0.600 mmol) for 16 h. Purification of the crude product by column chromatography on silica gel afforded the product as a drab solid (23.0 mg, 0.074 mmol, 15%); R_f = 0.30 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 5.5 Hz, 4H), 7.39 – 7.29 (m, 1H), 7.28 – 7.20 (m, 2H), 7.10 – 6.92 (m, 2H), 6.57 (dt, *J* = 14.6, 6.9 Hz, 2H), 5.24 (s, 2H), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.0, 155.6, 146.8, 143.5, 137.7, 130.1, 129.9, 129.8, 129.6, 129.3, 129.2, 128.8, 128.8, 127.0, 126.9, 122.4, 122.0, 121.8, 118.2, 72.1.

2-bromo-6H-chromeno[4,3-b]quinoline (191)



Prepared according to the synthesis of 7-aryl-6*H*-chromeno[4,3-*b*]quinolines from 5-bromo-2-(prop-2-yn-1-yloxy)benzonitrile (**176c**) (47.0 mg, 0.200 mmol) and phenyl(mesityl)iodonium trifluoromethanesulfonate (**46a**) (113 mg, 0.240 mmol) for 5 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (17.0 mg, 0.055 mmol, 28%); R_f = 0.35 (hexane-ethyl acetate, 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.5 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.1 Hz,

1H), 7.78 (d, *J* = 1.2 Hz, 1H), 7.74 – 7.56 (m, 2H), 7.51 – 7.31 (m, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.27 (d, *J* = 1.1 Hz, 2H); MS (EI, 70 eV): *m/z* (%): 311(100), 232(9), 203(50), 176(22),116(55), 88(55), 63(24).

7. 14. Single crystal X-ray mesurements

	178aa	**178ea**	**178ka**
Empirical formula	C_{22} H_{15} N O	C_{23} H_{17} N O	C_{22} H_{14} F N O
Formula weight	309.35	323.38	327.34
Temperature	292(2)	293(2)	293(2)
Radiation and	Mo-Kα, λ =0.71075Å	Mo-Kα, λ =0.71073Å	Mo-Kα, λ =0.71073Å
Crystal system	triclinic	triclinic	monoclinic
Space group	*P* -1	*P* -1	*P* $2_1/c$
Unit cell dimensions	*a* =5.7757(5)Å	*a* =5.9402(4)Å	*a* =8.9262(6)Å
	b =11.9628(12)Å	*b* =11.5058(10)Å	*b* =7.7725(5)Å
	c =11.9927(12)Å	*c* =13.0682(10)Å	*c* =23.1696(13)Å
	α =70.251(3)°	α =106.220(2)°	α =90°
	β =89.805(2)°	β =97.779(2)°	β =99.618(2)°
	γ =87.300(2)°	γ =93.070(2)°	γ =90°
Volume	778.95(13)Å^3	845.80(11)Å^3	1584.89(17)Å^3
Z	2	2	4
Density (calculated)	1.319 Mg/m^3	1.270 Mg/m^3	1.372 Mg/m^3
Absorption coefficient,	0.081 mm^{-1}	0.077 mm^{-1}	0.092 mm^{-1}
F(000)	324	340	680
Crystal colour	colourless	colourless	colourless
Crystal description	chunk	prism	prism
Crystal size	0.50 x 0.30 x 0.10 mm	0.50 x 0.30 x 0.20 mm	0.50 x 0.30 x 0.30 mm
Absorption correction	Numerical	Numerical	Empirical
Max. and min.	0.9684 0.9891	0.9911 0.9720	1.0000 0.7770
θ–range for data	3.449 ≤ θ ≤ 27.430°	3.273 ≤ θ ≤ 25.348°	3.149 ≤ θ ≤ 27.484°
Index ranges	-7 ≤ *h* ≤7;-15≤ *k* ≤15;-15	-7 ≤ *h* ≤7;-13≤ *k* ≤13;-15	-11 ≤ *h* ≤11;-10≤ *k* ≤10;-
Reflections collected	24463	37115	58690
Completeness to 2θ	0.999	0.999	0.999
Independent reflections	3552 [*R*(int) =0.0349]	3090 [*R*(int) =0.0297]	3633 [*R*(int) =0.0410]
Reflections *I*>2σ(*I*)	2231	2161	2560
Refinement method	full-matrix least-squares	full-matrix least-squares	full-matrix least-squares
Data / restraints /	3552 /0 /217	3090 /0 /227	3633 /0 /226
Goodness-of-fit on F^2	1.157	1.131	1.151
Final *R* indices	*R*1 =0.0549, *wR*2 =0.1539	*R*1 =0.0603, *wR*2 =0.1815	*R*1 =0.0502, *wR*2 =0.1434
R indices (all data)	*R*1 =0.0837, *wR*2 =0.1962	*R*1 =0.0753, *wR*2 =0.2058	*R*1 =0.0663, *wR*2 =0.1590
Max. and mean	0.000;0.000	0.000;0.000	0.001;0.000
Largest diff. peak and	0.281;-0.187 e.Å^{-3}	0.302;-0.143 e.Å^{-3}	0.237;-0.243 e.Å^{-3}

Table S5a. *Crystal data and structure refinement*

	178ha	**178ja**	**178la**
Empirical formula	C_{22} H_{14} Cl N O	C_{22} H_{14} Br N O	C_{22} H_{14} I N O
Formula weight	343.79	388.25	435.24
Temperature	103(2)	293(2)	293(2)
Radiation and wavelength	Mo-Kα, λ =0.71075Å	Mo-Kα, λ =0.71073Å	Mo-Kα, λ =0.71073Å
Crystal system	triclinic	triclinic	triclinic
Space group	*P* -1	*P* -1	*P* -1
Unit cell dimensions	*a* =7.4903(4)Å	*a* =7.6071(3)Å	*a* =9.3211(16)Å
	b =9.0845(4)Å	*b* =9.2638(4)Å	*b* =10.0363(16)Å
	c =11.8757(5)Å	*c* =12.1145(5)Å	*c* =10.8596(18)Å
	α =82.5440(10)°	α =82.5090(10)°	α =104.778(4)°
	β =89.737(2)°	β =89.7080(10)°	β =105.031(4)°
	γ =87.3080(10)°	γ =88.5560(10)°	γ =108.640(4)°
Volume	800.37(6)Å^3	846.16(6)Å^3	864.0(2)Å^3
Z	2	2	2
Density (calculated)	1.427 Mg/m^3	1.524 Mg/m^3	1.673 Mg/m^3
Absorption coefficient, μ	0.248 mm^{-1}	2.438 mm^{-1}	1.862 mm^{-1}
F(000)	356	392	428
Crystal colour	colourless	colourless	colourless
Crystal description	prism	prism	prism
Crystal size	0.20 x 0.20 x 0.20 mm	0.40 x 0.32 x 0.30 mm	0.50 x 0.30 x 0.20 mm
Absorption correction	Numerical	Empirical	Numerical
Max. and min.	0.9611 0.9163	1.0000 0.6629	0.6160 0.3095
θ–range for data	3.022 ≤ θ ≤ 28.263°	3.168 ≤ θ ≤ 27.452°	3.289 ≤ θ ≤ 27.484°
Index ranges	-9 ≤ *h* ≤9;-12≤ *k* ≤12;-15 ≤ *l*	-9 ≤ *h* ≤9;-12≤ *k* ≤12;-15 ≤ *l*	-12 ≤ *h* ≤12;-13≤ *k* ≤13;-14
Reflections collected	33703	33703	20650
Completeness to 2θ	0.998	0.998	0.988
Independent reflections	3921 [*R*(int) =0.0434]	3853 [*R*(int) =0.0338]	3848 [*R*(int) =0.0399]
Reflections *I*>2σ(*I*)	3446	3125	3670
Refinement method	full-matrix least-squares on	full-matrix least-squares on	full-matrix least-squares on
Data / restraints /	3921 /0 /226	3853 /0 /226	3848 /0 /226
Goodness-of-fit on F^2	1.105	1.102	1.170
Final *R* indices [*I*>2σ(*I*)]	*R*1 =0.0382, *wR*2 =0.0993	*R*1 =0.0398, *wR*2 =0.0976	*R*1 =0.0366, *wR*2 =0.0900
R indices (all data)	*R*1 =0.0451, *wR*2 =0.1109	*R*1 =0.0501, *wR*2 =0.1085	*R*1 =0.0378, *wR*2 =0.0914
Max. and mean shift/esd	0.001;0.000	0.001;0.000	0.001;0.000
Largest diff. peak and hole	0.505;-0.324 e.Å^{-3}	0.520;-0.376 e.Å^{-3}	1.740;-0.358 e.Å^{-3}

Table S5b. *Crystal data and structure refinement*

Experimental

Crystal data of **178aa***:* $C_{22}H_{15}NO$, *Fwt.*: 309.35, colourless, chunk, size: 0.5 x 0.3 x 0.1 mm, triclinic crystal system, space group *P*-1, *a* = 5.7757(5)Å, *b* = 11.9628(12)Å, *c* = 11.9927(12)Å, α = 70.251(3)°, β = 89.805(2)°, γ = 87.300(2)°, *V* = 778.95(13)Å^3, *T* = 292(2)K, *Z*= 2, *F*(000) = 324, D_x = 1.319 Mg/m^3, μ 0.081mm^{-1}. A crystal of **178aa** was mounted on a loop. Cell parameters were determined by least-squares using 13451 (3.45° ≤ θ ≤ 27.43°) reflections. Intensity data were collected on a diffractometer (graphite monochromator; Mo-*K*α radiation, λ = 0.71075Å) at 292(2) K in the range 3.449° ≤ θ ≤ 27.430°.[146] A total of 24463 reflections were collected of which 3552 were unique [*R*(int) = 0.0349, *R(*σ) = 0.0238]; intensities of 2231 reflections were greater than 2σ(*I*). Completeness to θ is 0.996. Numerical absorption correction (NUMABS)[147] was applied to the data (the minimum and maximum transmission factors were 0.9684 and 0.9891). The structure was solved by direct methods.[148][149] Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms yielded *R*1 = 0.0549 and *wR*2 = 0.1539 for 1332 [*I*>2σ(*I*)] and *R*1 = 0.0837 and *wR*2 = 0.1962 for all (3552) intensity data, (number of parameters = 217, goodness-of-fit = 1.157, the maximum and mean shift/esd is 0.000 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.281 and -0.187e.Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2)+(0.10990.0000P)^2+0.0000P]$, where $P = (F_o^2+2F_c^2)/3$. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the atom they were bonded to.

Crystal data of **178ea**: $C_{23}H_{17}NO$, *Fwt.*: 323.38, colourless, prism, size: 0.5 x 0.3 x 0.2 mm, triclinic, space group *P* -1, *a* = 5.9402(4)Å, *b* = 11.5058(10)Å, *c* = 13.0682(10)Å, α = 106.220(2)°, β = 97.779(2)°, γ = 93.070(2)°, *V* = 845.80(11)Å^3, *T* = 293(2)K, *Z*= 2, *F*(000) = 340, D_x = 1.270 Mg/m^3, μ 0.077mm^{-1}. A crystal of **178ea** was mounted on a loop. Cell parameters were determined by least-squares using 23452 (3.28° ≤ θ ≤ 27.49°) reflections. Intensity data were collected on a(n) RAXIS-RAPID diffractometer (monochromator; Mo-*K*α radiation, λ = 0.71073Å) at 293(2) K in the range 3.273 ≤ θ ≤ 25.348.[146] A total of 37115 reflections were collected of which 3090 were unique [*R*(int)

= 0.0297, $R(\sigma)$ = 0.0141]; intensities of 2161 reflections were greater than 2σ (*I*). Completeness to θ = 0.998. Numerical absorption correction[147] was applied to the data (the minimum and maximum transmission factors were 0.9720 and 0.9911).

The structure was solved by direct methods.[148] Anisotropic full-matrix least-squares refinement[149] on F^2 for all non-hydrogen atoms yielded $R1$ = 0.0603 and $wR2$ = 0.1815 for 1332 [$I>2\sigma$ (I)] and $R1$ = 0.0753 and $wR2$ = 0.2058 for all (3090) intensity data, (number of parameters = 227, goodness-of-fit = 1.131, the maximum and mean shift/esd is 0.000 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.302 and -0.143e.Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2)+(0.13480.0000P)^2+0.0000P]$ where $P = (F_o^2+2F_c^2)/3$. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded to.

Crystal data of **178ka***:* $C_{22}H_{14}FNO$, *Fwt.*: 327.34, colourless, prism, size: 0.5 x 0.3 x 0.3 mm, monoclinic, space group *P* 21/c, a = 8.9262(6)Å, b = 7.7725(5)Å, c = 23.1696(13)Å, α = 90°, β = 99.618(2)°, γ = 90°, V = 1584.89(17)Å^3, T = 293(2)K, Z= 4, F(000) = 680, D_x = 1.372 Mg/m^3, μ 0.092mm^{-1}. A crystal of **178ka** was mounted on loop. Cell parameters were determined by least-squares using 31127 (3.15≤ θ ≤ 27.54°) reflections. Intensity data were collected on a(n) RAXIS-RAPID diffractometer (graphite monochromator; Mo-*K*α radiation, λ = 0.71073Å) at 293(2) K in the range 3.149 ≤ θ ≤ 27.484 [CrystalClear]. A total of 58690 reflections were collected of which 3633were unique [R(int) = 0.0410, $R(\sigma)$ = 0.0173]; intensities of 2560 reflections were greater than 2σ (*I*). Completeness to θ = 0.999. Numerical absorption correction[147] was applied to the data (the minimum and maximum transmission factors were 0.7770 and 1.0000).

The structure was solved by direct methods.[148] Anisotropic full-matrix least-squares refinement[149] on F^2 for all non-hydrogen atoms yielded $R1$ = 0.0502 and $wR2$ = 0.1434 for 1332 [$I>2\sigma$ (I)] and $R1$ = 0.0663 and $wR2$ = 0.1590 for all (3633) intensity data, (number of parameters = 226, goodness-of-fit = 1.151, the maximum and mean shift/esd is 0.001 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.237 and -0.243e.Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2)+(0.08850.0568P)^2+0.0568P]$ where$P = (F_o^2+2F_c^2)/3$. Hydrogen atomic

positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the atom they were bonded to.

Crystal data of **178ha***:* $C_{22}H_{14}ClNO$, *Fwt.*: 343.79, colourless, prism, size: 0.2 x 0.2 x 0.2 mm, triclinic, space group *P* -1, *a* = 7.4903(4)Å, *b* = 9.0845(4)Å, *c* = 11.8757(5)Å, α = 82.5440(10)°, β = 89.737(2)°, γ = 87.3080(10)°, *V* = 800.37(6)Å^3, *T* = 103(2)K, *Z*= 2, *F*(000) = 356, D_x = 1.427 Mg/m^3, μ 0.248mm^{-1}. A crystal of **178ha** was mounted on a loop. Cell parameters were determined by least-squares using 23766 (3.02 ≤ θ ≤ 28.27°) reflections. Intensity data were collected on a RAXIS-RAPID diffractometer (graphite monochromator; Mo-*K*α radiation, λ = 0.71075Å) at 293(2) K in the range 3.022 ≤ θ ≤ 28.263.[146] A total of 33703 reflections were collected of which 3921were unique [*R*(int) = 0.0434, *R*(σ) = 0.0225]; intensities of 3446 reflections were greater than 2σ (*I*). Completeness to θ = 0.991. Numerical absorption correction[147] was applied to the data (the minimum and maximum transmission factors were 0.9163 and 0.9611).
The structure was solved by direct methods.[148] Anisotropic full-matrix least-squares refinement[149] on F^2 for all non-hydrogen atoms yielded *R*1 = 0.0382 and *wR*2 = 0.0994 for 1332 [*I*>2σ (*I*)] and *R*1 = 0.0451 and *wR*2 = 0.1109 for all (3921) intensity data, (number of parameters = 226, goodness-of-fit = 1.106, the maximum and mean shift/esd is 0.001 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.505 and -0.324e.Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2)+(0.05670.3622P)^2+0.3622P]$ where$P = (F_o^2+2F_c^2)/3$. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the atom they were bonded to.

Crystal data of **178ja***:* $C_{22}H_{14}BrNO$, *Fwt.*: 388.25, colourless, prism, size: 0.40 x 0.32 x 0.30 mm, triclinic, space group *P* -1, *a* = 7.6071(3)Å, *b* = 9.2638(4)Å, *c* = 12.1145(5)Å, α = 82.5090(10)°, β = 89.7080(10)°, γ = 88.5560(10)°, *V* = 846.16(6)Å^3, *T* = 293(2)K, *Z*= 2, *F*(000) = 392, D_x = 1.524 Mg/m^3, μ 2.438mm^{-1}. A crystal of **178ja** was mounted on a loop. Cell parameters were determined by least-squares using 23031 (3.17 ≤ θ ≤

27.45°) reflections. Intensity data were collected on a(n) RAXIS-RAPID diffractometer (graphite monochromator; Mo-*K*α radiation, λ = 0.71073Å) at 293(2) K in the range 3.168 ≤ θ ≤ 27.452.[146] A total of 33703 reflections were collected of which 3853 were unique [*R*(int) = 0.0338, *R*(σ) = 0.0173]; intensities of 3125 reflections were greater than 2σ (*I*). Completeness to θ = 0.998. Numerical absorption correction[147] was applied to the data (the minimum and maximum transmission factors were 0.6629 and 1.0000).

The structure was solved by direct methods.[148] Anisotropic full-matrix least-squares refinement[149] on F^2 for all non-hydrogen atoms yielded *R*1 = 0.0398 and *wR*2 = 0.0976for 1332 [*I*>2σ (*I*)] and *R*1 = 0.0501 and *wR*2 = 0.1084 for all (3853) intensity data, (number of parameters = 226, goodness-of-fit = 1.102, the maximum and mean shift/esd is 0.001 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.520 and -0.376e.Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2)+(0.05680.2908P)^2+0.2908P]$ where$P = (F_o^2+2F_c^2)/3$. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the atom they were bonded to.

Crystal data of **178la***:* $C_{22}H_{14}INO$, *Fwt.*: 435.24, colourless, prism, size: 0.5 x 0.3 x 0.2 mm, triclinic, space group *P* -1, *a* = 9.3211(16)Å, *b* = 10.0363(16)Å, *c* = 10.8596(18)Å, α = 104.778(4)°, β = 105.031(4)°, γ = 108.640(4)°, *V* = 864.0(2)Å^3, *T* = 293(2)K, *Z*= 2, *F*(000) = 428, D_x = 1.673 Mg/m^3, μ 1.862mm^{-1}. A crystal of **178la** was mounted on a loop. Cell parameters were determined by least-squares using 15499 (3.29 ≤ θ ≤ 27.49°) reflections. Intensity data were collected on a RAXIS-RAPID diffractometer (graphite monochromator; Mo-*K*α radiation, λ = 0.71073Å) at 293(2) K in the range 3.289 ≤ θ ≤ 27.484.[146] A total of 20650 reflections were collected of which 3848were unique [*R*(int) = 0.0399, *R*(σ) = 0.0202]; intensities of 3670 reflections were greater than 2σ (*I*). Completeness to θ = 0.973. Numerical absorption correction[147] was applied to the data (the minimum and maximum transmission factors were 0.616 and 0.3095).

The structure was solved by direct methods.[148] Anisotropic full-matrix least-squares refinement[149] on F^2 for all non-hydrogen atoms yielded *R*1 = 0.0366 and *wR*2 = 0.0900for 1332 [*I*>2σ (*I*)] and *R*1 = 0.0378 and *wR*2 = 0.0914 for all (3848) intensity data, (number of parameters = 226, goodness-of-fit = 1.170, the maximum and mean shift/esd is 0.001

and 0.000). The maximum and minimum residual electron density in the final difference map was 1.740 and -0.358e.Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2)+(0.05570.2347P)^2+0.2347P]$ where$P = (F_o^2+2F_c^2)/3$. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the atom they were bonded to.

Acknowledgement

Crystallographic data for the crystal structure of **178aa** (CCDC 1430075) has been deposited with the Cambridge Crystallographic Data Centre.

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[38]ADATLAP
a doktori értekezés nyilvánosságra hozatalához

I. A doktori értekezés adatai

A szerző neve: Aradi Klára
MTMT-azonosító: 10054462
A doktori értekezés címe és alcíme:
Copper-catalyzed synthesis of heterocycles *via* oxidative ring closure reactions of aromatic nitriles with diaryliodonium salts

DOI-azonosító[39]: 10.15476/ELTE.2016.080
A doktori iskola neve: ELTE Kémia Doktori Iskola
A doktori iskolán belüli doktori program neve: Szintetikus kémia, anyagtudomány, biomolekuláris kémia
A témavezető neve és tudományos fokozata: Dr. Novák Zoltán, PhD., habil.
A témavezető munkahelye: ELTE TTK Kémiai Intézet Szerves Kémia Tanszék

II. Nyilatkozatok

A doktori értekezés szerzőjeként[40]

a) hozzájárulok, hogy a doktori fokozat megszerzését követően a doktori értekezésem és a tézisek nyilvánosságra kerüljenek az ELTE Digitális Intézményi Tudástárban. Felhatalmazom a Természettudományi Kar Tudományszervezési és Egyetemközi Kapcsolatok Osztályának ügyintézőjét, Bíró Évát, hogy az értekezést és a téziseket feltöltse az ELTE Digitális Intézményi Tudástárba, és ennek során kitöltse a feltöltéshez szükséges nyilatkozatokat.

b) kérem, hogy a mellékelt kérelemben részletezett szabadalmi, illetőleg oltalmi bejelentés közzétételéig a doktori értekezést ne bocsássák nyilvánosságra az Egyetemi Könyvtárban és az ELTE Digitális Intézményi Tudástárban;[41]

c) kérem, hogy a nemzetbiztonsági okból minősített adatot tartalmazó doktori értekezést a minősítés *(dátum)*-ig tartó időtartama alatt ne bocsássák nyilvánosságra az Egyetemi Könyvtárban és az ELTE Digitális Intézményi Tudástárban;[42]

d) kérem, hogy a mű kiadására vonatkozó mellékelt kiadó szerződésre tekintettel a doktori értekezést a könyv megjelenéséig ne bocsássák nyilvánosságra az Egyetemi Könyvtárban, és az ELTE Digitális Intézményi Tudástárban csak a könyv bibliográfiai adatait tegyék közzé. Ha a könyv a fokozatszerzést követőn egy évig nem jelenik meg, hozzájárulok, hogy a doktori értekezésem és a tézisek nyilvánosságra kerüljenek az Egyetemi Könyvtárban és az ELTE Digitális Intézményi Tudástárban.[43]

2. A doktori értekezés szerzőjeként kijelentem, hogy

a) az ELTE Digitális Intézményi Tudástárba feltöltendő doktori értekezés és a tézisek saját eredeti , önálló szellemi munkám és legjobb tudomásom szerint nem sértem vele senki szerzői jogait;

b) a doktori értekezés és a tézisek nyomtatott változatai és az elektronikus adathordozón benyújtott tartalmak (szöveg és ábrák) mindenben megegyeznek.

3. A doktori értekezés szerzőjeként hozzájárulok a doktori értekezés és a tézisek szövegének plágiumkereső adatbázisba helyezéséhez és plágiumellenőrző vizsgálatok lefuttatásához.

Kelt: Budapest, 2016. május 11.

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a doktori értekezés szerzőjének aláírása

[38] Beiktatta az Egyetemi Doktori Szabályzat módosításáról szóló CXXXIX/2014. (VI. 30.) Szen. sz. határozat. Hatályos: 2014. VII.1. napjától.
[39] A kari hivatal ügyintézője tölti ki.
[40] A megfelelő szöveg aláhúzandó.
[41] A doktori értekezés benyújtásával egyidejűleg be kell adni a tudományági doktori tanácshoz a szabadalmi, illetőleg oltalmi bejelentést tanúsító okiratot és a nyilvánosságra hozatal elhalasztása iránti kérelmet.
[42] A doktori értekezés benyújtásával egyidejűleg be kell nyújtani a minősített adatra vonatkozó közokiratot.
[43] A doktori értekezés benyújtásával egyidejűleg be kell nyújtani a mű kiadásáról szóló kiadói szerződést.