ATROPISOMERIC BIS-HETEROCYCLES AS CHIRAL POOLS FOR ASYMMETRIC TRANSFORMATIONS

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Abstract. *Atropisomeric compounds that is those compounds that are chiral due to the hindered rotation around a bond have attract the attention of numerous scientist in both industrial and academic environments. The success of such molecules in organic chemistry has been demonstrated by the BINOL and by the Buchwald ligands. Many of these molecules are C-C atropisomers were the C-C stands for the bond around which the rotation is restricted. Less attention has been payed to other bonds having the same property. In this account, we will describe the development, from the first example of atropisomeric N-N compounds, tetra-substituted-hydrazines, of atropisomeric 3,3'-biquinazoline-4,4'-diones as new class of N-N atropisomers. We have established effective synthetic methodology for the synthesis of a variety of these molecules as well as their functionalization. Finally, we will show that these compounds are effective in controlling the stereochemistry of the new chiral centers when engaged in substrate controlled asymmetric reactions involving prochiral groups attached to their 2-position.*

Contents

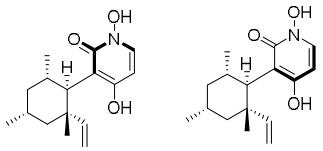
1. Introduction

1.1. Atropisomerism

Axially chiral compounds, unlike molecules that feature central chirality (point chirality), lack stereogenic center(s) and yet can exist as enantiomers. Atropisomers, belong to the class of axially chiral compounds. In this case, the enantiomers exist due to the restricted rotation around a single bond.[1]

Since the first discovery of axially chiral molecules, atropisomerism has been observed in many chemical entities and so a suitable classification should be made. Atropisomers are often broken down into several classes, based on the type of hybridisation of the atom involved in the hindered rotation or by the type of bonds around which the rotation is blocked (*e.g.* C-C, C-N, N-N). The first common class is the sp^2-sp^2 family. This group is exemplified by biaryls that are either tri- or tetra- *ortho*-substituted.

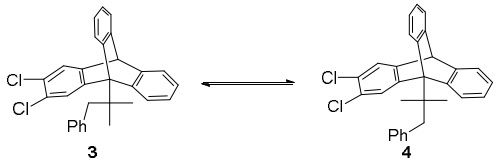
The sp^2-sp^3 class is found in some natural products, for example, cordypyridone A (**1**) and its atropisomer, cordypyridone B (**2**), which are diastereoisomers and only interconvert upon extended heating (Figure 1).[2]



cordypyridone A (**1**) cordypyridone B (**2**)

Figure 1. Example of sp^2-sp^3 atropisomer.

Atropisomerism about sp^3-sp^3 bonds usually only occurs in non-natural systems especially designed to hinder rotation. The framework within which atropisomerism of this type has been found is in the system derived from triptycenes **3** and **4**, extensively studied by Oki and co-workers (Figure 2).[3]



3 **4**

Figure 2. Example of sp^3-sp^3 atropisomers.

Atropisomers have found important technological applications such as chiral dopant in liquid crystals,[4] and as key element of some molecular devices in which the single bond is a shaft connecting two parts of a molecule that rotate with respect to each other.[5,6,7] This principle has been used in chiroptic molecular switches, ratchets and motors.[8,9] Research in this field has been awarded with the Nobel Prize in chemistry.[10] In addition to these applications, atropisomers, formed the core of many important ligands for metals in asymmetric catalysis. The best known examples of this phenomenon are the biaryls, which have found great application in asymmetric synthesis, most importantly as ligands for metals in asymmetric catalysis.[11]

Asymmetric catalysis has been advanced by the discovery and application of the atropisomeric ligand BINAP.[12] The chiral environment imposed by the orthogonal naphthalene rings as well as the chelating nature of this ligand has proven effective for inducing high stereoselectivity in a variety of asymmetric reactions.[11] Over the past several years, the Buchwald/Hartwig groups have developed a series of bulky electron-rich atropisomeric aryl-phosphines that have garnered much attention for their ability to effect various C–C, C–N, and C–O bond formations.[13-17]

After years of domination of the field by binaphthyls, a range of other atropisomeric systems have come into favour.[18,19,20-22] While the more traditional systems display hindered rotation around C–C bonds, there is increasing interest in ligand systems which rely upon hindered rotation around other bonds, particularly C–N[20] and N–N.[21] Although the majority of these systems display hindered rotation due to steric factors, certain N–N bonds may also have an electronic barrier to rotation. This account wishes to give an overview on our work in the field of atropisomeric N-N bi-heterocycles and shows that they can be potentially exploited as ligands and chiral auxiliaries for asymmetric organic synthesis. This chapter will begin with the description of the earlier studies on the restricted rotation around the N-N bond of tetra-substituted-hydrazines and how this lead to the development of atropisomeric N-N heterocycles. This material constitute the prologue for the description of our work on *N,N*-biquinazolinones as scaffolds with potential application in asymmetric organic syntheses.

1.2. N-N Atropisomers

Compounds like di-, tri- and tetra-substituted-hydrazine have shown to have higher barriers to rotation around their N-N bond compared to other single bonds.[23-25] This is probably caused by the repulsion

between the lone pairs on the nitrogen when the molecule is close to a planar conformation.[24,26-28] One of the early example of such phenomenon have been demonstrated in compound **5**. The barrier of rotation around the N-N bond was found to be greater than 97 kJ mol^{-1} as determined from VT ^{1}H-NMR experiments.[29] However, the fact that part of the molecule is locked into a heterocyclic moiety was cause of concern about the real nature of the rotational barrier. Indeed, it was later proved that the locked conformation of the imide carbonyls in **5** increases the barrier of rotation of the molecule (Figure 3).[30] Further calculation of tetraformyl hydrazine indicate that generally, rotation around the N-N bond is a relatively high-energy process, >140 kJ mol^{-1}. However, it was also found that there is the possibility of multi-step pathway that can yield the same result with substantially lower activation barriers of ≈80 kJ mol^{-1}. This discrepancy was attributed to some changes in the geometry and the electronic density properties of the molecule. Overall, in this system the contribution of both factors was found to be approximatively equal.[30]

The barrier of rotation of more complex tetraacyl hydrazines, like l,2-dibenzoyl-l,2-dipropanoylhydrazine **6**, and its analogue **7** were also studied (Figure 3). ^{1}H-NMR spectrum of compound **6**, displayed an ABX_3 system for the methylene groups. This demonstrate slow rotation around the N-N bond at least on the NMR time scale. Variable temperature ^{1}H-NMR (VT NMR) experiments on **6** were performed to establish whether the barrier of rotation was due to steric repulsion between the oxygen atoms in the carbonyl groups or simply by the repulsion of the lone pairs on the nitrogen. The results obtained (free energy barrier of 82-84 kJ-mol^{-1}) were in good agreement with theoretical results.[30] The conclusion is that the rotation barrier is due to the steric reasons rather than electronic factors (in the absence of steric repulsion the barrier is around 80 kJ-mol^{-1}. The presence of a chiral axis was also proved by the introduction, into the hydrazine scaffold, of a chiral, acyl substituent which would cause the formation of a diastereomeric mixture. Indeed, proton and carbon spectra of compound **7** indicated the presence of two diastereoisomers in the ratio of 2:1. Compound **7** was also used as probe to assess the real barrier of rotation in this substituted hydrazine. Coalescence of the methylene doublets of **7** at a temperature of 135 °C and 140 °C in DMSO solution resulted in a calculated barrier of 82-84 kJ mol^{-1} for the interconversion of the diastereoisomers. This was found in good agreement with theoretical calculations.[30]

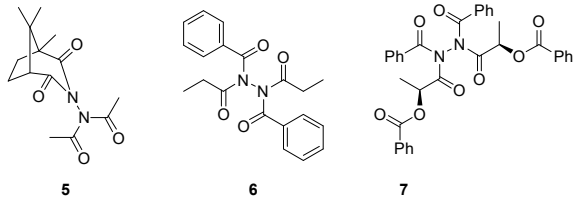


Figure 3. Example of tetra-substituted-hydrazines as N-N atropisomers.

The presence of a chiral axis in similar systems, was also proved earlier by the Atkinson group.[31] The group was able to demonstrate that the barrier to N-N bond rotation in *N*-acyl-quinazolinones *e.g.* **8** is sufficient to allow separation of the diastereoisomers when another chiral center was present in the molecule (Figure 4). Amide **8** has been separated into two diastereoisomers which did not interconvert on heating at 200 °C for a short period of time. Both molecules comprise two orthogonal planes, containing the quinazolinone and imide respectively, with the N-N bond as a chiral axis.

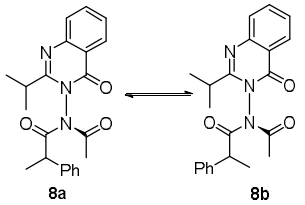
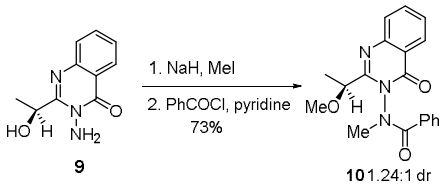


Figure 4. Atropisomeric 3-[*N*-acetyl-*N*-(2-phenylpropanoyl)amino]-2-isopropyl-3,4-dihydroquinazoline-4-one **8**.

Diastereoisomers **8a** and **8b** were interconverted by rotation around their N-N bonds by heating **8b** in toluene at three different temperatures. From these data, a $AG^{\ddagger}$=121.3 kJ mol^{-1} for its interconversion into **8a** was estimated.

Further studies by Atkinson's group demonstrated that the N-N bond in 3-amino-quinazolinones *N*-substituted with two different groups, have a chiral axis at room temperature.[28] Compound **10**, synthesized in two steps from amino quinazolinone **9** was obtained as mixture of two diastereoisomers in the ratio of 1.24 to 1. Again, also in this case, the orthogonality of the two planes containing the quinazolinone ring and the exocyclic amide unit, gave rise to the axial chirality around the N-N bond. The ^{1}H-NMR spectra of both diastereoisomers of 3-(*N*-methyl-*N*-benzoy1amino)-quinazolinone **10** at room temperature showed the presence of both amide rotamers generated by the rotation around the N-CO bond of the acyl substituent (Scheme 1).[28]



Scheme 1. Synthesis of atropisomeric (S)-3-(*N*-benzoyl-*N*-methylamino)-2-(1-methoxyethyl)-3,4-dihydroquinazoline-4-one **10**.

All the above results pointed to the fact that an opportunely substituted N-N bond can be exploited in the construction of ligands suitable for metal catalyzed asymmetric reactions. This is especially true in light of the fact that if the N-N bond is part of an heteroaromatic scaffold the barrier of rotation is even higher. This property can be exploited for the design of atropisomeric N-N bisheterocycles ligands (analogue to the Buchwald ligands) for asymmetric reaction. In the following paragraph, a brief description of early examples of such compounds will be given. This will pave the way to the description of our own work on the synthesis and application in asymmetric transformations of symmetrical and unsymmetrical biquinazolinones.

1.3. Atropisomeric *N,N*-bisazaheterocycles

Generally, *N,N*-bisazaheterocycles gained significant importance in view of their pharmacological activity as potential anti-inflammatory,[32] and antimicrobial[33,34] agents just to cite a few. 1-(3-quinazolinyl)-2-thio-5-(2-aminophenyl)-1,3,4-triazole (**11**) showed a broad spectrum antibacterial activity, meanwhile, *N,N*-bisimidazole **12** (Figure 5) has potent anti-filarial activity.[35]

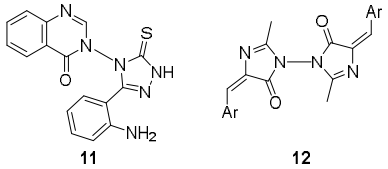
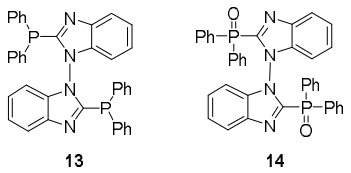


Figure 5. Examples of N-N heterocycles with biological properties.

There are numerous examples of these structures and an excellent review has been published.[36] In this review only the synthesis and references to their biological properties were described. No mention of atropisomerism of these compounds was reported, although this phenomenon would have been extremely likely in at least some of the reported structures.

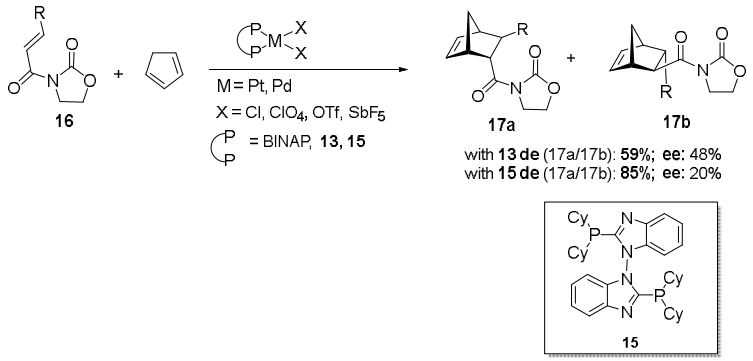
This class of compounds are not only important for their biological activities but they have also been used for the synthesis of chiral phosphines ligands. One of the early example of *N,N*-bisazaheterocycles is represented by 2,2'-bis(diphenylphosphino)-1,l'-dibenzimidazole (bimip, **13**) the first atropisomeric diphosphine, along with its oxide, with hindered rotation around a nitrogen-nitrogen bond (Figure 6).[21]



13 **14**

Figure 6. *N,N*-benzoimidazole diphosphines and phosphine oxide as chiral ligands.

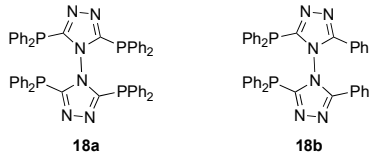
Structural characterization of these bisheterocycles proved their configurational stability at room temperature. The results showed that these compounds can perform well as chiral ligands in metal assisted reactions.[21,37] Compound **13** along with other C-C heteroaromatic bisphosphines was evaluated in the Pd (II) and Pt (II) catalysed [4+2] cycloaddition of cyclopentadiene and *N*-2-alkenoyl-1,3-oxazolidine-2-ones **16** (Scheme 2). The aim of the study was the elucidation of the effects of the electronic properties of the ligands in the stereochemical course of the reaction. The best stereo-selection results were obtained with the complexes produced from electron-rich ligands, which were found to give also the kinetically most active catalysts.[38] The authors used the oxidative potential value E as parameter to determine the electronic availability of the phosphorus atom in the chelation process.[39] In this study, the authors postulated that electron-poor diphosphines could be, at least in principle, more active than their electron-rich counterpart due to their scarce donation ability toward the metal center. This would result in a higher Lewis acid character on the metal, thus favouring the coordination of the catalyst to the dienophile. Compound **13** performed less well in term of conversion (50%) and enantiomeric excess (ee) of the product (20%), with respect to its analogous **15** (60% conversion, 48% ee). Both ligands were underperforming with respect to other C-C heteroaromatic ligands studied,[38] which all achieved 100% conversion with both de and ee in the order of 87-99%. These results were attributed to the electronic properties of the ligands with electron rich ligands performing better than the electron poor **13** and **15**.



Scheme 2. Evaluation of *N,N*-bis-benzoimidazole derived phosphine ligands in asymmetric Diels-Alder reaction.

On a similar ground, Rozhenko and colleague,[40] reported the synthesis of the atropisomeric bistriazoles diphosphane ligands **18** (Figure 7), the elucidation of their structure in the solid state, as well as their most favourable conformations as determined by quantum-chemical calculations. Calculations at RI-BP86/TZVP approximation level showed that the local minimum in energy for compound **18a** corresponds to a structure with a C_2 symmetrical conformation. Further optimization of this geometry using Grimme's B97-D functional leads to a conformation where two pairs of phenyl groups are almost parallel to each other, which implies a π,π-stacking interaction between them. In the case of both structures, the atropisomerism arises from hindered rotation about the bond connecting the two aromatic fragments. The presence of sterically bulky groups accounts for a high barrier for rotation. The evaluation of the energy barrier to racemization was also reported.[40] The calculated activation energy values ($\Delta G^{\neq}$ 40.5 and 42.5 kcal/mol)

preclude racemization under ordinary conditions and allow to predict that phosphanylated bistriazoles could be used as atropisomeric ligands. Despite this result, no application in asymmetric catalysis were reported by the authors.



18a **18b**

Figure 7. Atropisomeric N-N 3,3',5,5'-tetrakis(diphenylphosphaneyl)-4,4'-bis(1,2,4-triazole) **18a** and 3,3'-bis(diphenylphosphaneyl)-5,5'-diphenyl-4,4'-bis(1,2,4-triazole) **18b**.

From the above discussion, it clearly emerges that N-N compounds shows potential for being used as chiral ligand and chiral auxiliaries in asymmetric reactions. In particular, quinazolinone ring, when opportunely substituted, has demonstrated that can generate atropisomeric compounds and even to be able to participate in asymmetric reactions.[41,42]

2. 3,3′-Biquinazoline-4,4′-diones (BiQs)

As we have seen above, *N,N*-tetra-substituted-hydrazine have a significant barrier of rotation around the N-N bond when opportunely substituted and that when one of the two nitrogen is locked into an heterocycle, this barrier is even higher.[30] In light of this, if the other nitrogen is also locked into an heterocyclic moiety the rotational barrier should, in principle, be even higher. For this reason, 3,3′-biquinazoline-4,4′-diones (from now on I'd like to use BiQ acronym for these compounds) are very attractive compounds. In addition, these molecules have a very stable nature and most importantly, their molecular geometry dictates that the carbonyl oxygen is usually in a conformation which is known to increase the barrier to rotation.[30] While a variety of 3,3′-biquinazoline-4,4′-diones have been described,[36,43,44] no mention of any atropisomeric behavior of these molecules have been reported even if some of them contained substituents which could be expected to show diastereotopicity (^{1}H-NMR spectra), an indication of atropisomeric behavior.

2.1. Atropisomerism in 2,2'-disubstituted-3,3′-biquinazoline-4,4′-diones

With the aim to investigate the presence of any evidence of atropisomerism in this overlooked class of heterocycles, Coogan and colleagues began to examine the synthesis of different 2,2'-disubstituted-3,3′-biquinazoline-4,4′-diones and demonstrate, for the first time, the existence of the axial chirality in these systems.[45] In addition, with the presence of suitable coordinating heteroatoms (P, N, S) in 2,2' positions and the presence of a stereo stable chiral axis, such compounds could potentially lead to the design of novel ligands for transition metal catalyzed asymmetric reactions.

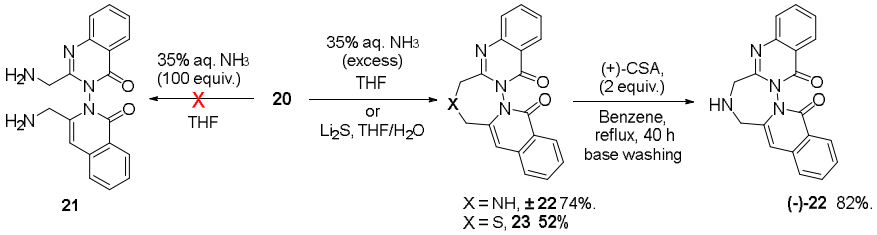
2,2'-Bis-(bromomethyl)-BiQ **20** was prepared in two steps (58% yield) from bis-anthraniloyl hydrazine **19** and bromoacetyl bromide (Scheme 3).[46] The bromomethylene protons of **20** were observed as an AB system [doublets at 4.43, 4.32] indicating that chirality due to the slow rotation around the N–N bond was present at least on the NMR time scale). VT NMR experiment showed line broadening above 60 °C.

19 **20**

Scheme 3. Synthesis of 2,2'-bisbromomethyl-biquinazoline-4,4'-dione **20**.

However, free rotation around the N–N bond was not observed even at 135 °C, as demonstrated by the non-coalescence of the methylene signals. This result was consistent with a minimum rotational barrier of about 85 kJ mol^{-1}.

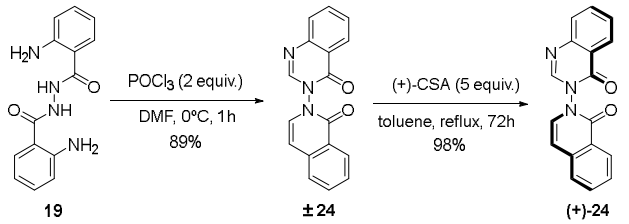
Transformation of **20** into the corresponding diamine **21** by treatment with ammonia in THF was not successful. Quite surprisingly, no sign of the desired compound was observed but the tricyclic derivative **22** was isolated instead. Again, ^{1}H-NMR analysis revealed the presence of the signal corresponding to the two-methylene unit as an AB system [doublet at 4.00 and 3.93 ppm, *J*=13.2 Hz). In this case, it was possible to separate the atropisomeric enantiomers. This was accomplished with the formation of two diasteromeric salts, treating **±22** with 2 equivalents of camphor sulfonic acid (+)-CSA. This was evidenced by the appearance of two sets of signals in the methylene region. Taking advantage of the high crystallinity of these compounds, it was possible to obtain a single diastereoisomer of **22** (diastereoisomer ratio of >10:1) by means of an asymmetric transformation of second kind.[47] This was accomplished refluxing the bridged amine **±21** in benzene containing (+)-CSA (2 equiv.) for 40 h. This data indicated that the product isolated was the result of selective transformation rather than a preferential decomposition of one enantiomer with respect to the other. Moreover, the isolated (-)-**22** had a specific rotation of -643 (c 0.1, CH_2Cl_2) (Scheme 4), which was increased to $[\alpha]_D$ -688 (c 0.011, CH_2Cl_2) by crystallization. Importantly, the nature of the solvent used for this transformation of the second kind was extremely important. When **±21** was refluxed in 1,2-dichloroethane only a racemic material was recovered.[45]



Scheme 4. Synthesis of tricyclic amine ±**22** and its deracemization *via* asymmetric transformation of second kind.

It was postulated that this acid catalyzed deracemization occurred by protonation of the quinazolinone nitrogen rather that the bridged secondary amine as the likely event. In this case, the formation of the amidinium ion (in resonance with N-3) is capable to disrupt the barrier around the N-N bond and facilitate the rotation around this bond.[46]

To further confirm these results, the corresponding bridges sulfide **23** was synthesized from **20** by treatment with Li_2S in a THF-water mixture. This compound, also displayed diastereotopicity in the methylene groups (4.45, 3.74, *J*=13.6 Hz). In this case, because the greater separation between the signals of the diastereotopic protons, it was possible to measure the rate of mutual exchange between the diastereotopic protons using spin saturation transfer techniques.[21] Unfortunately, no discernible reduction in signal intensity was observed even at 120 °C. This was consistent with an estimated rate of exchange ($k_{rotation}$) of 0.5 s^{-1} at 120 °C. In case of a first order process with no entropy change (ΔS=0), such a rate correlates with a free energy barrier in the order of 99 kJ mol^{-1}. This translate into a racemization half-life of about 13 h at 20 °C. To better understand the real value of the barrier of rotation around the N-N bond, 3,3'-biquinazoline-4,4'-dione ±**24**, the simplest of the 2,2'-biquinazoline-4,4'-dione, was synthesized according to the procedure depicted in Scheme 5. Deracemization studies on (±)-**24** [to (+)-**24**, $[\alpha]_D$=94; c=1, CH_2Cl_2)], with (+)-CSA showed a racemization half-life (measured by the change in its optical activity) of 58 minutes at 25 °C in a diluted dichloromethane solution. This translate into a rate of racemization of 2×10^{-4} s^{-1} corresponding to a rate of interconversion of atropisomers, of $k_{rot}=1\times10^{-4}$ s^{-1}.[46] This is then consistent with a free energy barrier to rotation of around 96 kJ mol^{-1}. This value confirmed that even the simplest 3,3′-biquinazoline-4,4′-diones such as **24** exist as a pair of atropisomers on the real timescale. Likewise, no loss of optical activity over one month was observed.[45]

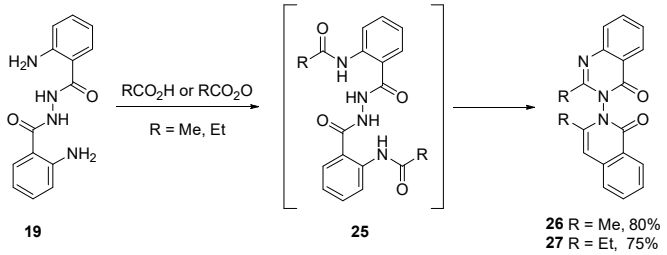


Scheme 5. Synthesis of racemic 3,3'-biquinazoline-4,4'-dione **24** and its deracemization.

To extend this study, in 2006 we began a research program aimed to further develop the chemistry of the BiQs, expand the range of substituents that can be incorporated into the 2,2' position and ultimately, to study the reactivity of the newly synthesized compounds.[48] In particular, the ultimate goal was to study the substrate controlled reaction of BiQ having prochiral groups in their lateral chains. In the next paragraphs this work will be described.

2.2. Synthesis of symmetrical 2,2'-disubstituted-3,3'-biquinazoline-4,4'-diones

One of the early synthesis of 2,2'-disubstituted-BiQ was published by Reddy and co-workers, who reported the preparation of symmetrical 2,2'-alkyl-biquinazoline-4,4'-diones from bis-anthraniloyl hydrazine **19** and the corresponding carboxylic acid/acid chloride or anhydride.[44,49] Quite strangely, in this publication, no mention of possible axial chirality was reported. Following this synthetic route, we were able to prepare compounds **26** and **27** in good yields (80% and 75% respectively) (Scheme 6). From the ^{1}H-NMR analysis it appeared that compound **27** was present in racemic form, as indicated by the presence of a complex multiplet at 2.8 ppm, assigned to the diastereotopic methylene group. This meant that indeed the N-N bond is a chiral axis, but the rotation around it is too fast at room temperature to allow the separation of the two enantiomers. Because our aim in this study was the exploration of both symmetrical and unsymmetrical biquinazolinediones with a broad range of substituents, we found this synthetic strategy not adequate. We turn then our attention to the possibility to synthesize the BiQ by coupling two different (or identically functionalized for the symmetric derivatives) heterocyclic moieties.



Scheme 6. Synthesis of symmetrical 2,2'-dialkyl-3,3'-biquinazoline-4,4'-diones.

2.3. Synthesis of unsymmetrical 2,2'-disubstituted-3,3'-biquinazoline-4,4'-diones

One promising strategy seemed to be the condensation of opportunely 2-substituted-3-aminoquinazolinones with functionalized benz[1,3]oxazin-4-ones, which would allow the synthesis of both symmetrical and unsymmetrical 3,3′-biquinazoline-4,4′-diones, and seemed a feasible route by analogy with the reliable route to 3-aminoquinazolinones via the treatment of benz[1,3]oxazin-4-ones with hydrazines (Figure 8).[3]

The synthesis of these two halves and their coupling to access unsymmetrical BiQ will be described in the following sections.

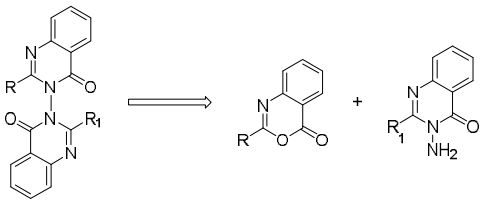
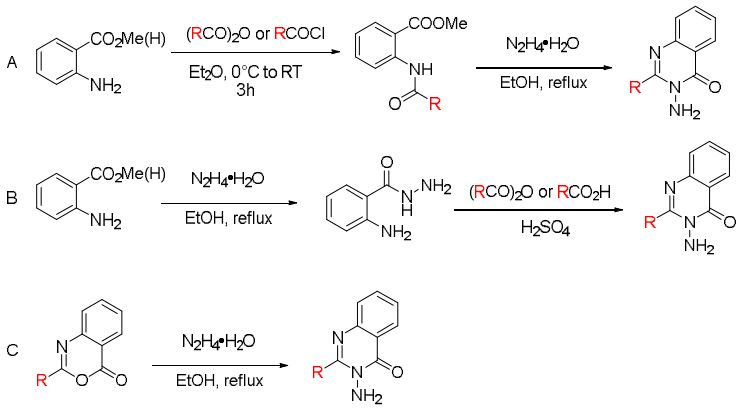


Figure 8. Retrosynthetic apporoach for the synthesis of unsymmetrical 3,3'-biquinazoline-4,4'-dione.

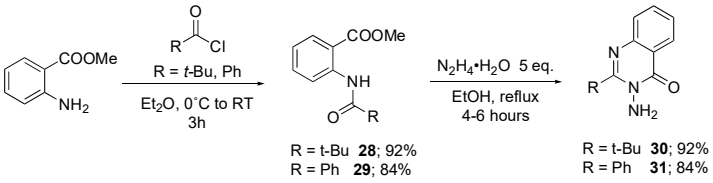
2.3.1. Synthesis of 2-alkyl-3-aminoquinazoline-4(3*H*)-ones

The preparation of 2-alkyl-3-aminoquinazoline-4(3*H*)-ones,[50,51] can be accomplished via several synthetic methods: a) and b) from methyl anthranilate, an opportune acylating agent[51,52] or orthoesters[53] and hydrazine hydrate; c) from the 2-substituted-benzoxazinone and hydrazine hydrate in refluxing alcoholic solvents (Scheme 7).[54]



Scheme 7. General synthetic methodologies for the preparation of 2-substituted-3-aminoquinazoline-4(3*H*)-ones.

For our purposes, we adopted the methods a and b which allow great flexibility in term of substituents that can be introduced into the quinazolinone scaffold. As a specific example, an ethereal solution of methyl anthranilate was treated with either pivaloyl chloride or benzoyl chloride at 0 °C then warmed to room temperature and stirred for 3-4 h. Amide **28** and **29** were easily isolated by crystallization from ethanol in 92% and 84% yields, (Scheme 8). These compounds were then treated with an excess of hydrazine monohydrate in refluxing ethanol. Usually, under these conditions the 3-aminoquinazolinone is directly obtained after 4-6 h. Isolation of the final compound was easily achieved by crystallization from alcoholic solvents.



Scheme 8. Preparation of 2-tert-butyl- **30** and 2-phenyl-3-aminoquinazoline-4(3*H*)-ones **31**.

Other more complex derivatives were prepared by modification of the above methodologies. Some examples of these compounds are represented in Figure 9.[48,55]

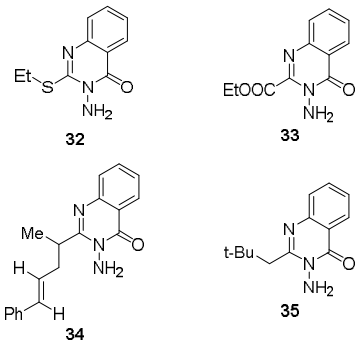
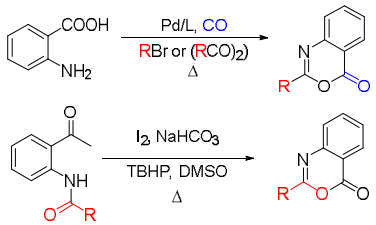


Figure 9. 2-Substituted-3-aminoquinazoline-4(3*H*)-ones used in the condensation reactions.

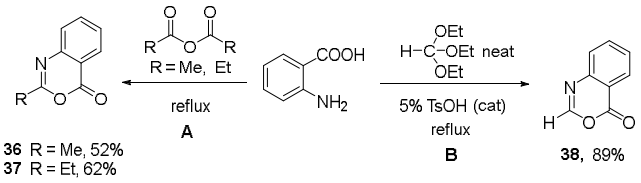
2.3.2. Synthesis of 4*H*-3,1-benzoxazine-4-ones

Benzoxazinones, are one of the most studied heterocycle due to its presence in a multitude of biological molecules with a great variety of therapeutic application. It is not surprising that many articles are found in the literature for their synthesis. Excellent reviews have been published on this topic.[56,57] Recent methodologies include transition metal-catalyzed carbonylation of α-halogenated anilines with carbon monoxide gas, alkyl halides and acid anhydrides.[58-61] Benzoxazinone synthesis has also been recently accomplished by selective oxidative decarbonylative cleavage of an unstrained $C(sp^3)–C(sp^2)$ bond employing iodine, sodium bicarbonate, and *t*-butyl hydroperoxide in DMSO at 95 °C (Scheme 9).[62]



Scheme 9. Modern methodologies for the synthesis of 2-substituted-4*H*-3,1-benzoxazine-4-ones.

In our study, the preparation of 2-substituted-benzoxazinone was accomplished by treating anthranilic acid with the desired anhydride (acting both as reagent, solvent and dehydrating agent), under refluxing conditions. Formation of an acyl intermediate that immediately loses water lead to the formation of the desired benzoxazinone.[63] Pure samples of the desired compound was obtained by simple crystallization from alcoholic solvents (Scheme 10A). 2-Methyl-[64] and 2-ethyl-4*H*-3,1-benzoxazine-4-ones[65] were prepared with this procedure. Higher substituted 4*H*-3,1-benzoxazine-4-ones, can be easily synthesized with the same methodology by just substituting the acetic anhydride with the desired substituted ones. For the synthesis of the parent 2-protio-benzoxazinone **38**, another route was followed. (Scheme 10B).[63,66]



Scheme 10. Synthetic procedure for the preparation of 2-methyl-, 2-ethyl- and 2-*H*-4*H*-3,1-benzoxazine-4-ones.

2.3.3. Synthesis of unsymmetrical 2,2'-disubstituted-3,3'-biquinazoline-4,4'-diones *via* condensation of 3-aminoquinazoline-4(3*H*)-ones and 4*H*-3,1-benzoxazine-4-ones

With both heterocyclic moieties in hand the synthesis of symmetrical and unsymmetrical biquinazolinone could begin. Initial investigations were attempted adapting the reaction conditions used in the synthesis of 3-aminoquinazoline-4-ones from the reaction 4*H*-3,1-benzoxazine-4-ones with hydrazines.[41,67] Unfortunately, refluxing a 1:1 mixture of 4*H*-3,1-benzoxazine-4-ones and 3-aminoquinazoline-4(3*H*)-ones in alcoholic solvents, failed to return the desired product, but instead the alcoholysis of the oxazine ring dominates the reaction in particular when unsubstituted 4*H*-3,1-benzoxazine-4-ones was used.[48] This data pointed toward a diminished nucleophilicity of 3-aminoquinazoline-4-ones when compared with hydrazine itself, again reflecting the electron-withdrawing nature of the quinazolinone ring. This aspect force us to seek other reaction conditions that would allow the coupling to occur. We envisaged that the use of "inert" higher boiling hydrocarbon solvents could be a suitable strategy. Indeed, in toluene condensation occurred, although with poor yields and unacceptably slow rates (reaction times of many days or weeks). Pleasingly, we discovered that addition of catalytic amount of an acid catalyst, such *p*-toluene sulfonic acid accelerated the reaction to such an extent that moderate to good yields could be achieved in a few hours. In addition, water removal by a Dean-Stark apparatus was found a necessary condition for the achievement of good yields. Remarkable, 3,3'-biquinazoline-4,4'-diones **39-43** were the only major products in the crude mixture. As a crystalline solid, these compounds were easily isolable at analytical purity by simple crystallization of the crude mixtures without the need for extractions, or chromatography.

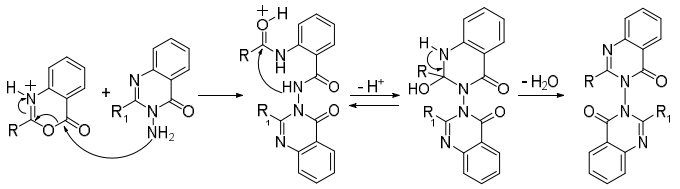
With this methodology, we could synthesize a range of unsymmetrical BiQ, the structure of which, along with yields and conditions are highlighted in Table 1.

Table 1. Selection of unsymmetrical 2,2'-disubstituted-3,3'-biquinazoline-4,4'-diones.

Entry	Benzoxazine	Amino-Q R^1	% cat	T (h)	BiQ	Yield (%)
1	Et (**37**)	Ph (**31**)	5	10	**39**	79
2	Et (**37**)	SEt (**32**)	5	10	**40**	44
3	Et (**37**)	COOEt (**33**)	8	24	**41**	51
4	Me (**36**)	Ph (**31**)	5	6	**42**	62
5	H (**38**)	*t*-Bu (**30**)	5	8	**43**	8
6	H (**38**)	$CH(Me)CH_2CH=CHPh$ (**34**)	5	24	**44**	47
7	Me (**36**)	*t*-Bu (**30**)	5	48	-	-
8	Me (**36**)	*t*-Bu (**30**)	5	3 days	-	-
9	Et (**37**)	*t*-Bu (**30**)	5	3 days	-	-

Despite the great simplicity of this methodology, this procedure was found not particular suitable for the coupling of the two halves having bulky substituents in 2'-position. For example, when a t-Bu group was present on the amino-quinazolinone partner (**30**), the desired BiQ **43** was obtained in sluggish yield (8%) and only when reacted with compound **38** (Table 1, entry 5). Any attempt to couple **30** with methyl- or ethyl-4*H*-3,1-benzoxazine-4-ones failed (Table 1, entry 7-9).[48] In these reactions, only the open amide, was observed in the reaction mixture. The use of harsher reaction conditions (strong dehydrating agents such as acetic anhydride or thionyl chloride at reflux), only resulted in the decomposition of the intermediate without providing any ring-closed product. These open amide products proved to be unstable and, in cases where the cyclisation to the desired product failed, were never isolated as homogeneous substances. A plausible reaction mechanism that explained the above results is highlighted in Scheme 11. All compounds in Table 1, synthesized by this route were obtained in racemic form. Although deracemization of some 3,3'-biquinazoline-4,4'-diones have been achieved (see above), attempts to apply this protocol to the newly synthesized BiQ **39-44** were all unsuccessful.

For this reason, we became interested in the synthesis of a BiQ bearing a non-racemic, chiral center in 2-position (2-chirally-substituted) or both 2,2'-position (2,2'-chirally-substituted) which would assist with the resolution of the chiral axis.

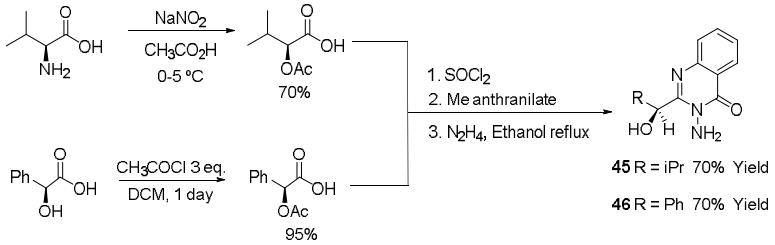


Scheme 11. Synthesis (and proposed mechanism) of unsymmetrical biquinazolindione.

2.4. Synthesis of 2-chirally-substituted-3,3'-biquinazoline-4,4'-diones

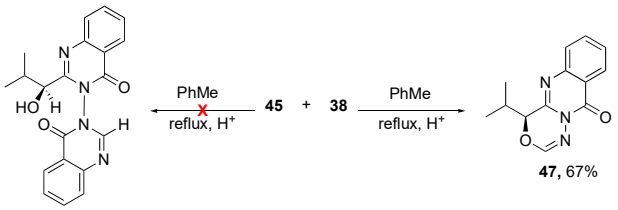
2-Chirally-substituted-3-aminoquinazolinones have been used as chiral ligands and catalysts in asymmetric reactions.[28,42,67-71] Incorporation of a chiral center into the 2-position of a 3-aminoquinazolinone seemed the simplest approach. It was hoped that this modification may be sufficient to give good control of the formation of the chiral axis. The choice fell on a chiral group containing a hydroxyl substituent which could also establish a hydrogen bond interaction to the amide intermediate in the condensation reaction and therefore control the formation of the chiral axis.

Moreover, depending upon its nature, further chemical modifications of the BiQ scaffold could be achieved. The approach adopted was an extension of the previously published procedure. Chiral building blocks derived from natural amino acids or from enantiomerically pure mandelic acid were used in the synthesis of 2-chirally-substituted-3-aminoquinazoline-4(3*H*)-ones. Preparation of compounds **45** and **46** was accomplished according to Scheme 12.



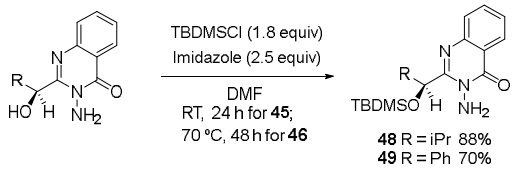
Scheme 12. Synthesis of 2-chirally-substituted-3-aminoquinazoline-4(3*H*)-ones.

As key example of this strategy, L-valine was converted into its acetoxy derivative by diazotization in neat acetic acid.[72] This compound or the acetoxymandelic acid were converted in the corresponding acid chloride with thionyl chloride. This was then reacted with methyl anthranilate to afford the corresponding chiral-anthranil amide that were cyclized to the chiral 3-aminoquinazoline-4(3*H*)-one with hydrazine monohydrate in refluxing ethanol. Simple crystallization of the crude mixture from ethanol allowed the isolation of the pure material in **70** % yield. Aminoquinazolinone **46** was prepared in a similar manner from mandelic acid. (Scheme 12)[72] With this chiral material, the synthesis of the asymmetric BiQs was then attempted. No reaction occurred when **45** or **46** and methyl and ether 4*H*-3,1-benzoxazine-4-ones were refluxed in toluene with the assistance of catalytic amounts of acid catalyst. We attributed this lack of reactivity to a well know problem of the steric hindrance of the two coupling partners. We then attempt the coupling between **45** and **38**. Interestingly, under the standard coupling conditions (toluene at reflux with a 5 mol% catalytic quantity of toluene-4-sulfonic acid under Dean-Stark conditions), we were unable to obtain the desired BiQ **52**. Instead, an unidentified side product was isolated (49% yield) crystallizing the crude mixture from methanol. ^{1}H-NMR and X-ray crystallography studies allowed us to establish the structure of this new compound as the heterocycle **47** (Scheme 13). We postulated that compound **38** under the above conditions acted as formate synthon (loss of anthranilate) that was cyclized to the compound **47**. Indeed when **45** or other more complex derivatives were treated with "acyl derivatives" such as acetic anhydride, or orthoesters under refluxing condition several new heterocyclic structures were synthesized.[48]



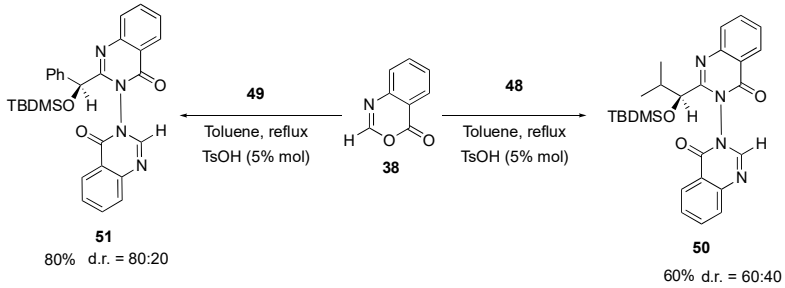
Scheme 13. Side reaction during the synthesis of BiQs.

It was then clear from the above results that protection of the alcoholic function in **45** and **46** proved to be necessary to allow the coupling to occur. Indeed, TBDMS protection of the hydroxyl group (TBDMSCl/imidazole, in DMF)[73] was the key synthetic step to achieve the synthesis (Scheme 14).



Scheme 14. Protection of 3-aminoquinazoline-4(3*H*)-ones **48** and **49** *via* TBDMSCl and imidazole.

Coupling between the benzoxazinone **38** and **48**/**49** was achieved by refluxing the two heterocycles in toluene in presence of acid catalyst under Dean-Stark conditions. Biquinazolinone **50** was obtained in 60% crude yield (as 60:40 mixture of diastereoisomer). Separation of the two diastereoisomers proved impossible (either via crystallization or chromatography with same R_f in different solvent systems). With phenyl derivative, BiQ **51** was obtained in 80% yield and in a better diastereomeric ratio of 80:20 (crude mixture). Crystallizations from petroleum ether afforded the pure product with the same d.r. Interestingly, a single diastereoisomer was isolated after three successive crystallizations from methanol. Unfortunately, this result was due to the fact that one isomer decomposes faster than the other in the crystallization solvent rather than a second kind transformation (Scheme 15).[72]

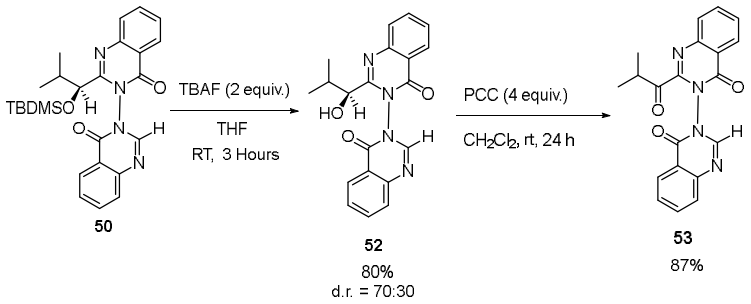


Scheme 15. Synthesis of 2-chirally-substituted unsymmetrical-BiQs **50** and **51**.

Having proved that the 2-chirally-substituted-3,3'-biquinazoline-4,4'-diones are easily accessed with a very practical methodology, we then wanted to prove that: a) these scaffolds were amenable of several transformations of their lateral chain, preferably creating prochiral groups without disrupting the axial chirality of the molecule; b) to investigate the substrate controlled reaction of this substituents without compromising the integrity of the BiQ structures or its homochirality. In our mind, the N-N chiral axis should be able to induce a high degree of stereo-control, thereby accessing new chiral centers in high d.r. and

ee's; c) develop a simple methodology that would allow the release of the newly formed chiral center with concomitant regeneration of bis-anthraniloyl hydrazine **19** that can be recycled in the formation of BiQ.

Modification of the lateral chain would allow access to more complex structure with a relative facility. One of the first target was the removal of the silicon protective group from **50**/**51**. This transformation was easily accomplished by treating **50** with 2 equivalents of TBAF in a THF solution. Alcohol **52** was obtained in 80% yield in a 70:30 d.r. after crystallization from methanol. We were also able to oxidize **52** to a keto derivative **53** using an excess of pyridinium chlorochromate supported on silica gel in dichloromethane. **53** was isolated in 87% yield after filtration of the catalyst and crystallizing the solid obtained from evaporation of dichloromethane from methanol.[72] The optical rotation of the pure product indicated that the N-N was indeed a chiral axis (Scheme 16).[72]

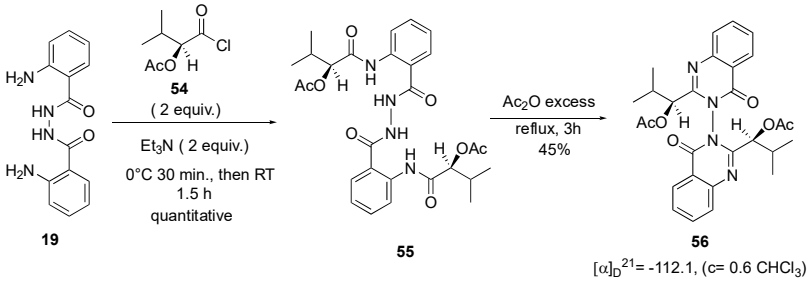


Scheme 16. Modification of the BiQ scaffold.

Although the procedure for the synthesis of this molecules is practical (no chromatography is necessary at any stage of the synthesis) it suffer from the limitation of the nature of the substituents that can be incorporated in the BiQ scaffold. From what we had described above is evident that only 2-*H*-benzoxazinone can be efficiently condensed with 2-substituted-3-aminoquinazoline-4(3*H*)-one having bulky substituents.

2.5. Synthesis of 2,2'-chirally-substituted-3,3'-biquinazoline-4,4'-diones

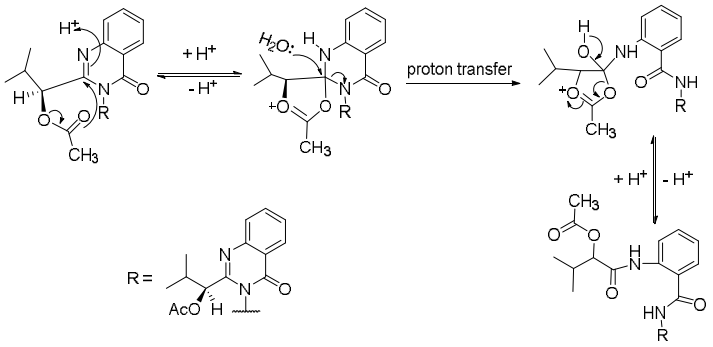
Symmetrically substituted BiQ with groups having a chiral center were synthesized by treating the chiral acid chloride **54** with bis-anthraniloyl hydrazine in cooled DMA to obtain the open bis-amide **55** in quantitative yields (Scheme 17).[74] Dehydration of **55** in acetic anhydride, afforded, after 3 h, the desired product **56** in almost quantitative yield as judged by the ^{1}H- and ^{13}C-NMR of the crude product. To be noted that the standard cyclization procedure (catalytic TsOH in refluxing toluene failed to afford the desired product).



Scheme 17. Synthesis of symmetrical 2-chirally-substituted-BiQ.

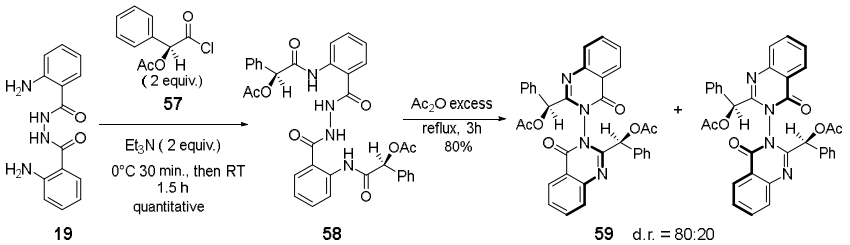
According to the ^{1}H-NMR spectroscopy, compound **56** was formed as single diastereoisomer, with the crude proton and carbon spectra showing no signals assignable to minor isomers. This seemed to indicate

that the newly formed chiral axis was generated with excellent atroposelectivity. Attempt to purify **56** by silica gel chromatography was partially successful, because its decomposition during the column chromatography. Because the acidic nature of the silica gel (and/or the presence of acetic acid from the condensation reaction) we postulated that the decomposition could be an acid catalyzed process, with anchimeric assistance of the acetoxy group of the chiral alcohol in 2'. In a close parallel with sugar chemistry[75] the α-acetoxy group may be able to generate an unstable spirocyclic system (Scheme 18) which is then decomposed, upon reaction with water, into the ring opened amide.[72] In addition, the dependence of this process upon bulkiness of the alkyl substituent (e.g. *i*-Pr) may indicate a Thorpe-Ingold effect (TI) at play in the initial step of the cyclization. This indicates that this step is accelerated by bulk substituents in the cyclizing chain.[76-78] Unfortunately, pure **56** also proved to be intrinsically unstable. A solid sample, kept at room temperature slowly decompose back to the open amide.[72]



Scheme 18. Proposed mechanism for the decomposition of compound **56**.

The synthesis of symmetrical non-racemic biquinazolinones was also attempted with a different group, to investigate whether the steric bulkiness was responsible for the susceptibility of this compound to hydrolysis. Biquinazolinones **59** was in this case obtained as a pair of diastereoisomers in 80:20 ratio in about 80% crude yield (^{1}H-NMR). Once again, every attempt to purify **59** by column chromatography or by crystallization led to decomposition (Scheme 19).



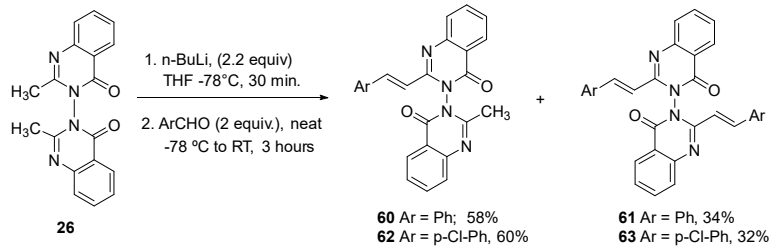
Scheme 19. Synthesis of symmetrical chiral BiQ **59**.

This result confirms again that steric hindrance is an important parameter for the synthesis and stability of these scaffolds. Due to their instability, no further studies were conducted on these substrates. Because the limitation in assembly the BiQ scaffold via condensation of bulky benzoxazinones and 3-amino-quinazolinones, we had to devise another synthetic strategy to further modify the lateral chain of the BiQ scaffolds.

3. Functionalization of symmetrical BiQ and their substrate controlled asymmetric reactions

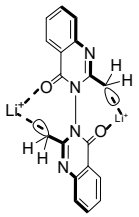
It was known from the literature, that simple 2-alkyl-substituted-quinazolinones can be easily functionalized via lithium chemistry.[79] Indeed, the methyl group in a quinazolinone ring is quite acidic and it

can be easily deprotonated with alkyl lithium reagents and further reacted with electrophiles.[80-83] We then envisage that the same protocol could be applied to the 2,2'-dialkyl-BiQ. As such, treatment of a solution of **26** in cooled (-78 °C), dry THF, with 2.2 equivalents of butyl lithium followed by the addition of neat benzaldehyde (or *p*-Cl-benzaldehyde) afforded, after acidic workup, a mixture of two different products in a roughly 2:1 ratio, easily separable by column chromatography. ^{1}H-NMR and mass spectrometric analysis revealed that one of the two compounds were the bis-styryl derivatives **61** and **63** while the major isomers were the biquinazolinone in which only one of the two halves have been functionalized with the aldehyde. (Scheme 20). Interestingly, in both cases, no trace of the intermediate alcohols was found in the crude mixture. Evidently, the extensive conjugation of the final product was the driving force for the spontaneous water elimination. In one case, when *o*-nitro benzaldehyde was used as electrophile, a small amount of the intermediate alcohol was present in the crude mixture. This was probably possible because the internal hydrogen bond between the nitro group and the hydroxyl group. However, this compound immediately decompose to the styryl derivative upon purification by column chromatography.[84] Wolfe and co-workers[79] reported that 2-methyl-3-*o*-tolyl-aminoquinazoline-4(3*H*)-one, when treated with LDA and benzaldehyde, led to the corresponding alcohol derivative in good yields with only small amounts of styryl derivatives seen. This alcohol was successfully transformed into the corresponding styryl derivative by treatment with LiOH in a THF-water mixture. Wolfe attributes the tendency of the alcohol to undergo dehydration from the severe steric repulsion between the 3-substituent (*o*-tolyl) and the bulky 2-(2-hydroxy-2-phenylethyl) substituent. We then postulated that the same steric effect was operating in this case. The steric hindrance of the BiQ could be responsible for the immediate dehydration of the hydroxyl derivative generated in the reaction of lithiated BiQ and benzaldehyde. In support to this theory, it is interesting to mention that Wolfe and Rathman observed that 2-methyl-quinazolinone bearing a less bulky group in the 3-position (with respect to the *o*-tolyl moiety) gave the corresponding carbinol derivative in good yields and without any sign of spontaneous dehydration, which occurred only under acidic hydrolytic conditions.



Scheme 20. Synthesis of 2-styryl- and 2,2'-distyryl-3,3'-biquinazoline-4,4'-diones **60-63** with *n*BuLi-aldehyde protocol.

Despite the screening of many reaction conditions (different deprotonating agents such as NaH, LDA, *t*BuLi, reaction temperatures and longer reaction times no improvement in the yield of the bis-styryl derivatives **61** and **63** was obtained.[85] From these data it seemed that the dianion obtained after deprotonation of **26** is intrinsically unreactive and not prone to react with electrophiles. We also hypothesized that the its stability could be due to the steric reasons. If the deprotonation of both methyl groups is not synchronous, the steric encumbrance of the methyl group, could limits the availability of the electronic doublet to the approaching electrophile. This steric interaction can be even greater after one of the two halves becomes bulkier due to the reaction with the electrophile. In this case, the approach of a second molecule of the electrophile is impeded and the anion is then reprotonated during the work up leading to the mono-styryl derivative. If instead, both groups are deprotonated at the same time, the dianion **64** could be engaged in a tight coordination with the lithium atom between the carbonyl oxygen and the lone pair of the dianion can locks the molecule in such a conformation that make any approach of the electrophile difficult (Figure 10).



64

Figure 10. Possible coordination of dianion **64**.

The high crystalline nature of these substrates however, allowed us to obtain the crystal structure of the bis-styryl derivative **61**. Figure 11 clearly shows the chirality around the N-N bond. One of the two quinazolinone rings is planar with the side chain parallel to the ring plane, meanwhile the other ring is in an almost perpendicular position relative to the other half of the molecule. To further confirm the atropoisomeric nature of the BiQ scaffold, compound **61** was treated with 2 equivalents of (+)-CSA in refluxing toluene for 16 h. After this period, ^{1}H-NMR spectroscopic analysis of this mixture revealed two sets of signals for the double bond, thus confirming the presence of two diastereomeric salts. To investigate a possible asymmetric transformation, deracemization experiments on **61** were attempted. Unfortunately, heating the two diastereomeric salts either at 80 °C (in toluene) or at 110 °C (in *p*-xylene) for 48 h, returned the two diastereoisomer salts unmodified. Higher temperatures were also unsuccessful, and alongside the two diastereoisomeric salts (in a 1:1 ratio), decomposition was observed.[85]

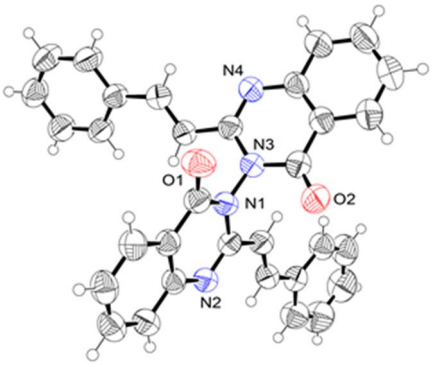


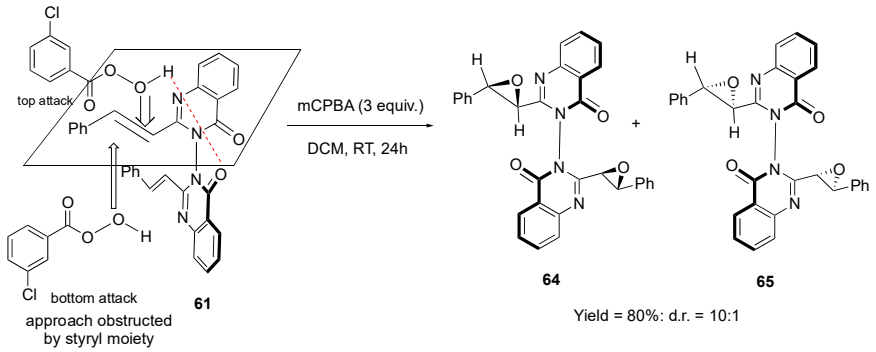
Figure 11. Crystal structure of compound **61**.

3.1. Substrate controlled reactions of 2,2'-disubstituted-3,3'-biquinazoline-4,4'-diones

The synthesis of mono and bis-styryl derivatives opened the way to investigate how the geometry of these scaffold can influence the stereochemistry of reactions involving their side chain. Indeed, a double bond is amenable of many interesting, substrate controlled transformations. Among them, Diels-Alder (DA), 1,3-dipolar cycloaddition, epoxidation, and cyclopropanation could all be used as suitable model reaction for this purpose.

One of the easiest way to test for the efficiency of asymmetric induction by the chiral axes of 3,3'-biquinazoline-4,4'-dione was to attempt the epoxidation of the styryl double bond on both **60** and **61**. From a vast choice of oxidizing agents, commonly employed in epoxidation reactions, the 3-chloroperbenzoic acid (*m*-CPBA) was initially used for this study. Compound **61** was easily epoxidized in 24 h with MCPBA in dichloromethane. In the absence of any stereo-control, three diastereoisomers in a 1:2:1 ratio are expected (formation of four new chiral centers). Remarkably, from the analysis of the ^{1}H-NMR spectrum of the crude reaction mixture, only two major isomers were detected in a 9:1 ratio, confirming that this reaction proceeds with high diastereoselectivity. Traces of a third diastereoisomer were barely detectable. The major

diastereoisomer **64** was obtained in 88% yield after a simple crystallization of the crude mixture from ethanol. The origin of this high stereoselectivity can be attributed to the geometry of the BiQ during the reaction. If the spatial disposition of the two halves of the molecule are like that in the crystal structure (Figure 11), a situation like the one depicted in Scheme 21 is likely to occur.



Scheme 21. Epoxidation of **61** with mCPBA with proposed transition state. The configuration of the two diastereoisomers is arbitrary.

As can be observed, the attack of the electrophilic peroxide on one side of the double bond in blocked by the presence of the styryl moiety of the other halve of the molecule. In addition, a possible hydrogen bonding between the acid and the carbonyl group could also favor the proposed geometry which can explain the diastereoselectivity observed. This was also observed by the fact that epoxidation of mono styryl derivative **60**, under identical conditions, gave a mixture of diastereoisomers with a poorer diastereoselectivity (4:1). In this case it is highly probable that the methyl group is not bulky enough to allow a great differentiation between the two faces of the double bond (Figure 12). Influence of several reaction parameters (solvent, temperatures and time) were also attempted, with no improvement in the diastereoselectivity of the reaction.[85]

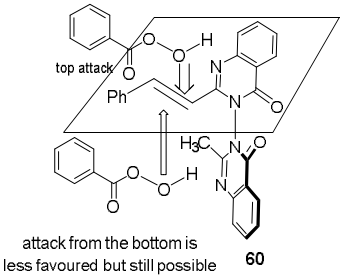
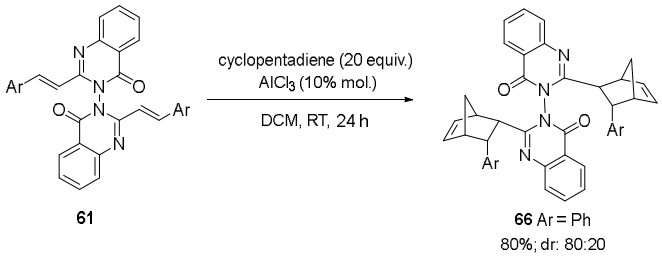


Figure 12. Transition state for the epoxidation of the mono-styryl BiQ **60**.

Following from the positive asymmetric induction by the chiral axis on the diastereoselective epoxidation of styryl quinazolinones, the study of the stereochemical outcome of the DA reaction between the prochiral double bond of **61** and cyclopentadiene was performed. Without catalyst. the reaction only returned unreacted **61** and cyclopentadiene dimer (^{1}H-NMR of the crude material). Attempt to force the cycloaddition by increasing the temperature (reflux) led only to an intractable formation of tars, probably due to the polymerization of the styryl BiQ. The use of Lewis acid catalysis as well as the replacement of toluene with dichloromethane proved to be necessary for the success of the reaction (Scheme 22).[86] When aluminum chloride was used as Lewis acid, the DA adduct **66** was obtained in 80% yield and with a diasteromeric ratio of 80:20.



Scheme 22. DA reaction between **61** and cyclopentadiene.

A plausible explanation for this outcome was proposed with the coordination of $AlCl_3$ with both ring of the BiQ as illustrated in Figure 13. The rate of the reaction is increased presumably because the coordination to the carbonyl group of the quinazolinone rings lower the energy of both the HOMO and LUMO making the BiQ scaffold a better dienophile. This coordination also locks the molecule in a conformation in which one face of the double bond is less crowded, so the diene prefers to react from the less hindered *Re* face of the double bond.

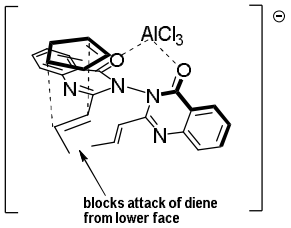


Figure 13. Proposed coordination of Lewis acid and BiQ **61**.

Other Lewis acids were also screened and copper trifluoromethanesulfonate was found to be the preferred catalyst. Indeed, with 10% $Cu(OTf)_2$ in DCM, reaction between **61** and cyclopentadiene at room temperature furnished two main adducts (**66a** and **66b**), in 85% overall yield with a diastereoisomeric ratio of 10:3 for the two major diastereoisomers. Traces of two other DA adducts (**66c** and **66d**) were also observed in ^{1}H-NMR analysis of crude mixture (Figure 14). The major diastereoisomer **66a** was isolated in 58% yield by crystallization from acetonitrile/methanol mixture. Attempts to reduce the amount of Lewis acid failed to give the products in good yield and with any significant change in the diastereoisomeric ratio. When the DA reaction was carried out at 0 °C in CH_2Cl_2 in the presence of either 10% $AlCl_3$ or 10% $Cu(OTf)_2$, no formation of the cycloadducts was observed. DA reaction of bis-*p*-Cl-styryl derivative **62** identical stereochemical results were obtained. In this case, the major diastereoisomer **66a** was isolated by silica gel column chromatography in 45% yield. This data suggested that the electronic contribution of the styryl derivative is not important for the course of the reaction.

The results obtained above were quite remarkable especially considering the high number of stereoisomer that can be formed in this transformation. Formation of the DA adducts on both the two lateral chains of the biquinazolinones, introduce eight new chiral centers. In addition, the possibility of *endo* and *exo* attacks on both Re-Si and Si-Re faces of the two olefins (for each of the M and P chiral axis configuration) further increase the number of possible stereoisomers. The *exo-endo* stereochemistry of the major diastereoisomer was determined by X-ray crystallography (Figure 15) since the analysis of the coupling constant pattern of the bridgehead protons in the ^{1}H-NMR spectra of isolated **14a** was impossible because the signals belonging to the bridgehead protons appeared as two broad singlets making impossible to use them as a stereochemical probe. From the crystal structure of the major adduct it could be seen that both the two-phenyl groups have an *exo* orientation, whereas the two BiQ rings have *endo* orientations with assigned stereochemistry M, 1S, 2S, 3R, 4S, 1′S, 2′S, 3′R, 4′S.[85]

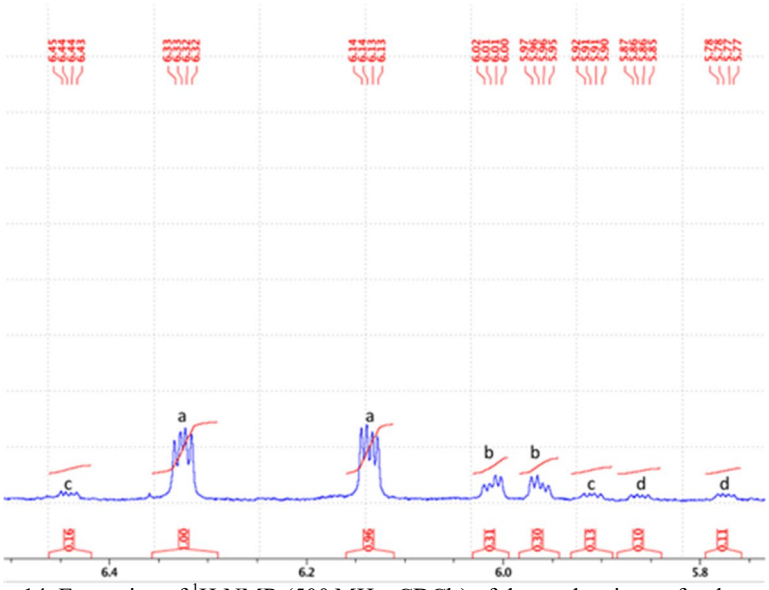


Figure 14. Expansion of ^{1}H-NMR (500 MHz, $CDCl_3$) of the crude mixture for the reaction between **61** and cyclopentadiene in presence of 10% mol. copper triflate.

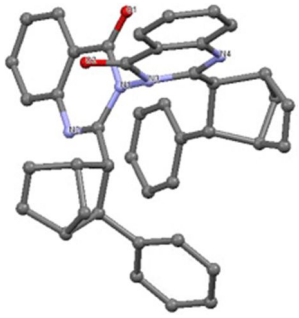
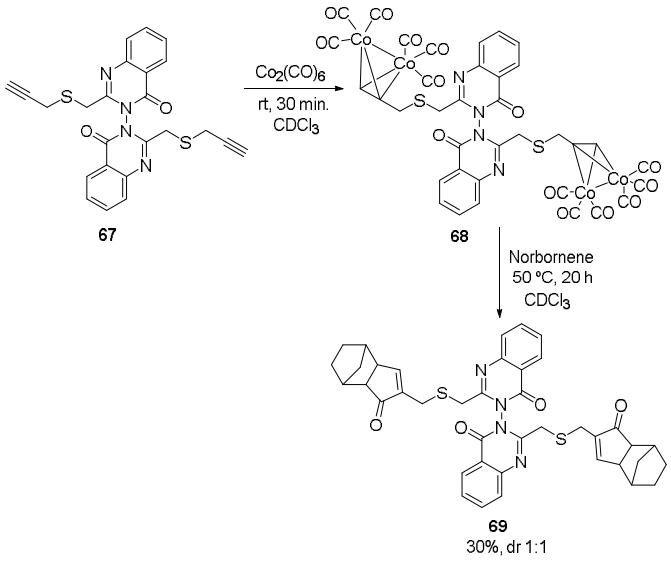


Figure 15. X-Ray structure of adduct **66** (major diastereoisomers).

Pleased by these results we then investigate the auxiliary-driven, asymmetric Pauson-Khand (PK) cycloadditions.[87] The PK is a [2+2+1] cyclo-addition reaction between an alkyne, alkene, and CO generated from $Co_2(CO)_8$, that allow the synthesis of structurally diverse cyclopentenones. Moyano and co-workers[88,89] showed that chiral alkynyl sulfides are capable to control the diastereoselectivity of these reactions, because of the chelation of the sulfides on one of the diastereotopic cobalt atoms in the dicobalt acetylene complex. We envisaged that BiQ **67** could be an excellent substrate for a PK reaction. Indeed, symmetrical biquinazolinone **67** almost immediately (30 minutes, in $CDCl_3$) was turned into the cobalt complex **68**. Despite its fast formation, its reactivity with norbornene was very slow at room temperature. PK product was not detected by ^{1}H-NMR spectroscopy even after 24 h at room temperature. Heating the mixture at 50 °C for 20 h afforded the desired compound **69** as a mixture of two diastereoisomers (1:1 ratio, by ^{1}H-NMR spectroscopy). Compound **69** was isolated in 30% yield by silica gel column chromatography.[85]

PK reaction has been shown to have a high degree of both regio- and stereoselectivity and that when norbornene is used, the products are almost invariably obtained with an *exo*-configuration and that the reaction yields almost exclusively the 2-substituted-ketone when the alkyne is terminal.[87,90,91] With these observations in mind, several of the theoretical stereoisomers that can be generated by the formation of four

new chiral centers could be ruled out. In case of compound **67**, among three theoretical diastereoisomers (1:2:1 ratio) only a mixture of two diastereoisomers in a 1:1 ratio, was observed in the ^{1}H-NMR spectrum of the crude product. In the case of a total absence of stereo control, we should have observed the presence of three diastereoisomers with a 1:2:1 ratio. It was evident from the above result that a certain grade of stereo control from the BiQ substrate was obtained (Scheme 23).[85]



Scheme 23. PK reaction of symmetric BiQ **67**.

Despite the success of the BiQ scaffold to control the stereochemistry of the epoxidation, DA and PK reactions, other similar reactions such as 1,3-dipolar cycloaddition under diverse conditions failed to give the expected adducts. In almost all cases, the starting materials were invariably recovered. All these results were in agreement with the results reported by Hameter[92] who found that the attempted 1,3-dipolar cycloaddition of *C*-phenyl-*N*-methyl nitrone with electron poor alkene failed to give the desired adduct even under very harsh conditions (15 days in refluxing in toluene). In addition, the very bulky nature of the final cyclo-adduct can also be the cause of this lack of reactivity. One exception was observed in the attempt to cyclopropanate the double bond of **61**. In this case, cyclopropanation under Simmons-Smith conditions, led to the formation of intractable material presumably derived by the polymerization of the styryl BiQ.

3.2. Attempt to remove the newly formed chiral center

Once demonstrated that BiQ scaffolds can induce the formation of stereoisomerically enriched molecules, the next and final step in our research program was to find a way to release these newly formed chiral substituents from the BiQ scaffold.

To study this process, we decided to use the DA adduct **66** as model substrate. Initially, we envisaged that acidic and basic hydrolysis would be a reasonable approach. Unfortunately, compound **66a** was recovered totally unchanged after reflux with 6 N HCl in ethanol for 48 h. More concentrated acid (12 N), only caused a slight decomposition of **66a**. Lewis acids were also investigated. One attempt (copper triflate in THF/water at 40 °C for 24 h) was unsuccessful. Interestingly, when **66a** was treated with the Schwartz reagent (zirconocene chloride hydride, $(C_5H_5)_2ZrHCl$), we could detect by ^{1}H-NMR spectroscopy of the crude mixture, some degree of cleavage, however we were not able to identify the nature of the product, which may be derived by the cleavage of the amide-like bond (N-3 single bond CO) in the biquinazolinone ring.[93-95] With the unsuccessful results obtained with acidic conditions we turned our attention to other cleavage procedures. The use of basic conditions was the obvious choice. Treatment of **65a** with a 1 M

LiOH in THF/H_2O, both at room temperature and at 50 °C, were unproductive and unreacted starting material was invariably recovered. Further studies are now in progress to understand in full the outcome of this reaction.

4. Conclusions and further work

In conclusion of this chapter, we hope to have been able to show that bis-azaheterocycles have the potential to be used as ligand and/or chiral auxiliaries in asymmetric organic reactions. All began with the earlier studies on the rotation around the N-N bond in simple tetra-substituted-hydrazines which have been found to be indeed atropisomeric. This research has then been extended to more complex systems where one of the nitrogen involved in the N-N bond was incorporated into a heterocyclic moiety. This resulted in an even greater barrier of rotation, paving the way to the development of atropisomeric N-N bis-heterocycles. Some of them have been successfully used in metal catalyzed cycloadditions although with inferior results compared to their C-C analogues that are still the dominant catalyst and chiral auxiliaries in asymmetric organic synthesis. Our own work in the field, described in the above pages, have been somewhat rewarding. We have been able to demonstrate that unsubstituted 3,3'-biquinazoline-4,4'-dione **24** are atropisomeric compounds and that other 2,2'-disubstituted analogues are atropisomeric as well. We have successfully developed the chemistry necessary to synthesize a great variety of symmetrical and unsymmetrical BiQs. The beauty of this chemistry is that no need of tedious chromatography is necessary for their isolation. The high crystallinity of such structures allows their isolation by simple crystallization, a suitable property for a potential large-scale synthesis. We also proved that 2,2'-substituents can be further functionalized by the most commons organic reactions without destroying the BiQ structure. Alkyl substituents can be easily deprotonated by organolithium reagents and further reacted with electrophile to access new structures. We have been able to show that 2,2-dimethyl-3,3'-biquinazoline-4,4'-diones can be easily converted, by this route, to the corresponding styryl derivative that undergoes substrate controlled asymmetric reactions. Despite all these interesting results, we were not able to release the newly formed chiral structures (DA adduct and epoxide) from the BiQ scaffold with regeneration bis-anthraniloyl hydrazine that can be re-used for the formation of other BiQs. Further work in this direction is necessary and if successful would open a very interesting use of biquinazolinones in asymmetric synthesis.

Acknowledgment

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