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Synthesis and substrate-controlled reactions of 2,2′-unsaturated biquinazolinones

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ABSTRACT

A series of BiQuinazolinones bearing either double or triple bonds in their lateral chains have been synthesized. These compounds were then subjected to substrate-controlled reactions such as Diels-Alder, epoxidation and Pauson-Khand reactions. The stereoselective outcome observed in these transformations is very promising for the future application of BiQuinazolinones as chiral auxiliaries.

1. Introduction

Chiral auxiliaries and templates are effective tools for the asymmetric synthesis of homochiral molecules.[1] Most chiral auxiliaries are small heterocyclic compounds, which rely on sterically demanding functional groups to control the conformation of their ring systems. Under ideal circumstances, the conformation of an auxiliary should be constrained to ensure that its prochiral centre reacts with a reagent via diastereoisomeric transition states, which are sufficiently different in energy to ensure that only a single diastereoisomer is formed as product. As remarkable auxiliaries and scaffolds, chiral biaryls are widely used in a large number of efficient stereo-differentiating reactions.[2] Atropisomers, which arise from restricted rotation in bonds to aromatic rings, can be seen as chiral modifications of the aromatic rings themselves. The famous and powerful atropisomeric phosphine ligands such as BINAP are in essence modifications to triphenylphosphine.

Enantiomerically pure non-biaryl atropisomers have found uses in different asymmetric syntheses, and the most well studied class to date are anilides (Fig. 1).

These atropisomeric amides were obtained in pure enantiomeric form by the Simpkins[3,4] group and employed by others as chiral auxiliaries to different asymmetric transformations such as iodolactonization,[5] and cycloadditions.[6] Clayden and co-workers have demonstrated that the aldehydic group on atropisomeric naphthimides stereoselectively undergo nucleophilic addition from a variety of lithiated substrates (Fig. 2).[7]

In continuation of previously conducted studies with symmetrical 3,3′-biquinazoline-4,4′-diones[8–10] and unsymmetrical 2,2′-disubstituted-3,3′-biquinazoline-4,4′-diones,[11] we have recently reported a facile route for the synthesis of 2-substituted bisquinazolinones incorporating a chiral center into one or both of their lateral chains.[12] In all these studies we have unambiguously proved that the BiQs can have high barriers to rotation around the N–N bond and thus are able to form stable atropisomers. In particular 2,2′-H,H′-3,3′-biquinazoline-4,4′–dione was found to have a minimum rotational barrier of 96 kJ mol^{-1}, whereas the 2-chirally substituted BiQs were generated as mixtures of diastereoisomers. Both results confirm the atropoisomeric nature of the BiQ scaffold.

The synthesis of these axially chiral bis-heterocycles, was accomplished either via condensation of 2-substituted-3-aminoquinazolinones and 4H-3,1-benzoxazin-4-one or by an acylation-dehydration sequence of bisanthraniloyl hydrazine.[8–10]

Given our interest in the preparation and application of this class of molecule to substrate controlled asymmetric reactions, in this paper we report the synthesis of symmetrical and

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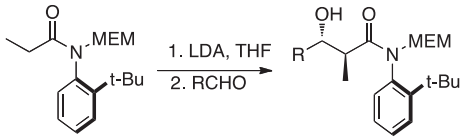


Fig. 1. Stereoselective aldol reaction of atropisomeric benzamide.

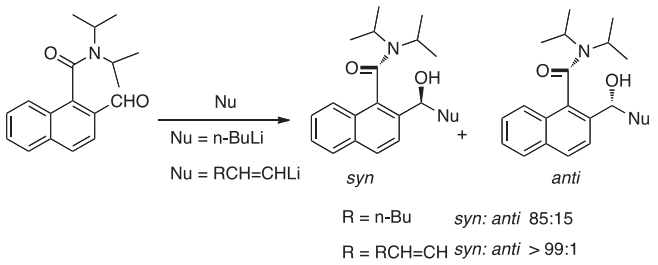


Fig. 2. Nucleophilic addition of lithiated compounds to aldehydic groups on atropoisomeric naphthimides.

unsymmetrical biquinazolinones bearing prochiral unsaturation, and the preliminary results on their application in selected asymmetric reactions.

In this scenario, double and triple bond containing moieties appeared immediately to us to be very appealing functionalities, due to the fact that they can be asymmetrically transformed into a variety of other functional groups like e.g. epoxides, Diels-Alder and Pauson-Khand adducts (Fig. 3).

2. Results and discussion

2.1. Synthesis of 2,2'-unsaturated BiQs

In our experience, condensation of 2-substituted-3-aminoquinazolinones with 4H-3,1-benzoxazin-4-one is a synthetic methodology quite sensitive to the steric hindrance of the functional group present in the lateral chains of the aminoquinazolinone. Therefore, we envisaged that modification of an alkyl group of the bisquinazolinone could be a suitable approach to access a variety of new structures.

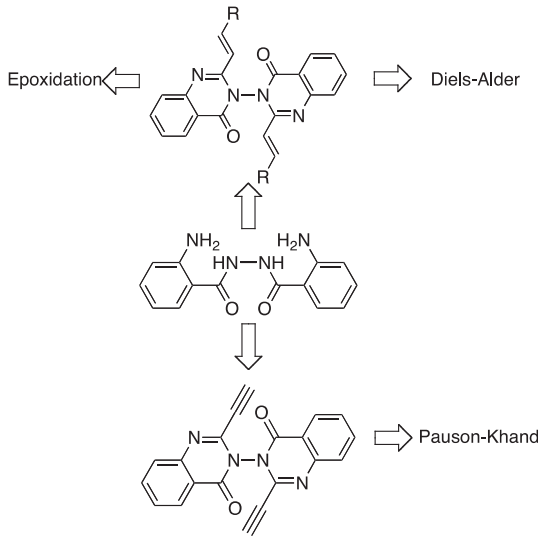


Fig. 3. Strategies for the synthesis and substrate-controlled reactions of 2,2′-unsaturated biquinazolinones.

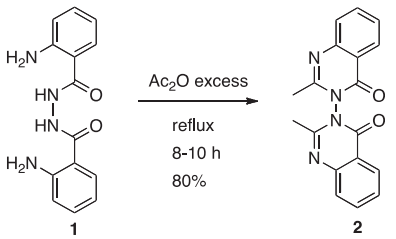
Symmetrical 2,2-dimethylbiquinazolinone **2** was easily synthesized on a multigram scale, from bisanthraniloyl hydrazine **1** and acetic anhydride (Scheme 1).[13,14] The desired product **2**, was collected in 80% yield by simple filtration and purified by recrystallization from toluene.

With **2** in hand, we started to investigate the preparation of the 2,2'-bis-styrylbiquinazolinone. Initially, we envisioned that acid catalysed condensation of carbonyl compounds with 2,2'-dimethyl-3,3'-biquinazoline-4,4'-dione (**2**) would be a feasible way to introduce an alcohol group, which could be dehydrated to the corresponding styryl derivative. All attempts to prepare styryl BiQs via acid catalysed condensation of benzadehyde with **2** gave the desired product in only very low yield.

Formation of an intractable and insoluble material during this reaction could be interpreted as a catalysed formation of benzaldehyde polymers (or copolymer with styryl derivative) or oligomers.[15]

The poor results obtained forced us to abandon this route and to turn our attention toward alternative strategies. From an extensive literature screening, it arose that "monomeric" methyl or ethyl substituted quinazolinone and 3-aminoquinazolinones are easily functionalized by metalation with organometallic bases and further reaction with electrophiles.[16–18] We therefore envisioned the possibility to apply this strategy to our advantage. Addition of a 2.5 M butyl lithium solution to a −78 °C solution of 2,2′-dimethyl-3,3′-biquinazolin-4,4′-one (**2**) in THF provided the lithiated species as indicated from the resulting bright red solution, followed by formation of a bright red precipitate. When benzaldehyde was added an almost immediate reaction occurred. Workup of the resulting solution afforded a bright yellow crystalline solid. ^{1}H NMR spectroscopic analysis (two sets of doublets at 6.42 and 8.05 ppm and an extra singlet at 2.3 ppm), and APCI mass analysis (two peaks, at *m*/*z* 495 [M+1] and at *m*/*z* 407 [M+1]) of the crude reaction mixture suggested the presence of structures **3** and **4**, which were indeed isolated by column chromatography on silica gel (ethyl acetate/hexane 1:3) in 34% and 58% yield respectively. By the same procedure we were also able to synthesize the *p*-chlorostyryl derivatives **5** (32% yield) and **6** (60% yield) (Scheme 2). When the reaction was carried out under the same conditions but in the presence of different bases such as LDA, LiHMDS and KHMDS, the corresponding styryl derivatives were obtained but in lower yield when compared with those carried out with nBuLi.

In contrast with literature results, which for LDA metalation of monomeric 2-methyl-3-substituted quinazolinones[19] and further reaction with benzaldehyde, always report the formation of the corresponding alcohol derivative as major product (and only small amount of styryl derivative detected), reaction between the lithiated biquinazolinone **2** and benzaldehyde lacks of the isolation of the hydroxyl derivative. In our case, spontaneous dehydration occurred because the increase in the conjugation of the double bond with the quinazolinone rings. The formation of the monostyryl derivatives **4** can instead be tentatively explained invoking



Scheme 1. Synthesis of 2,2'-dimethyl BiQs 2.