N-Heterocyclic Carbene-Catalyzed Atroposelective Synthesis of N-N Axially Chiral 3-Amino Quinazolinones

Kuruva Balanna,† Soumen Barik,† Shilpa Barik,† Sayan Shee,† Niket Manoj,† Rajesh G. Gonnade,‡ and Akkattu T. Biju*,†

† Department of Organic Chemistry, Indian Institute of Science, Bangalore-560012, India

‡ Centre for Materials Characterization, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, India

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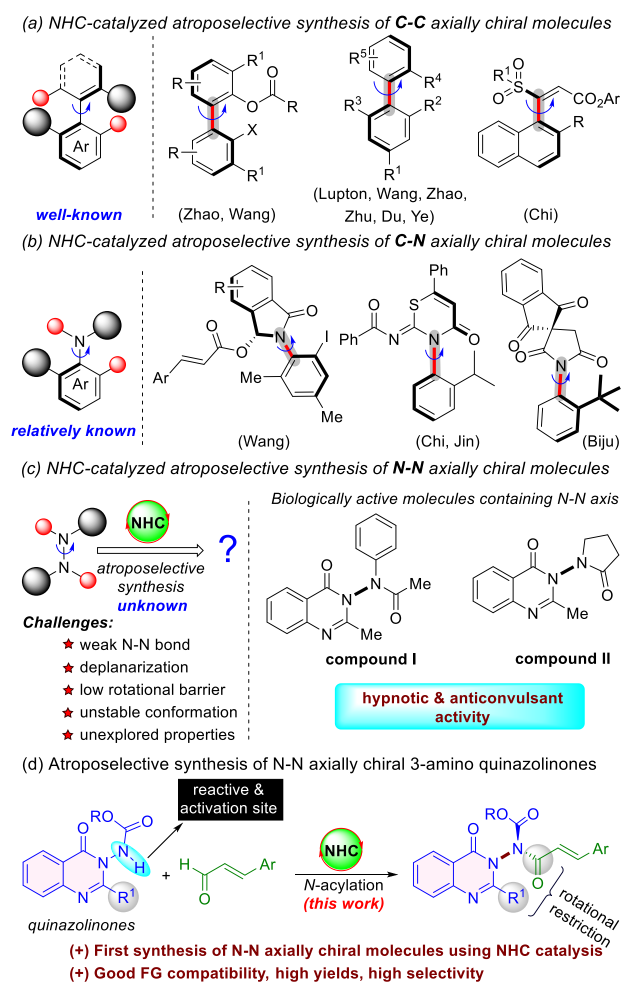
ABSTRACT: Although the atroposelective synthesis of biaryls and related compounds bearing axially chiral C-C bonds are well-known, the synthesis of axially chiral C-N bond-containing compounds are relatively less explored, and the construction of axially chiral N-N bonds has received only scant attention. Demonstrated herein is the N-heterocyclic carbene (NHC)-catalyzed selective amidation reaction leading to the atroposelective synthesis of N-N axially chiral 3-amino quinazolinones. The NHC-catalyzed reaction of quinazolinones containing a free N-H moiety with α,β-unsaturated aldehydes under oxidative conditions furnished the atropisomeric quinazolinone derivatives under mild conditions and broad scope. Preliminary studies on experimental and DFT-based N-N rotational barrier determination is also presented.

Introduction

Organic compounds having an axially chiral element-element bond have attracted enormous attention recently as these compounds have potential applications in drug discovery and they are useful as chiral ligands/catalysts.[1,2] Among these compounds, axially chiral biaryls bearing a C-C axis are valuable as these core structures are frequently found in natural products and bioactive molecules.[3] Consequently, catalytic atroposelective synthesis of axially chiral biaryls and related compounds have received considerable attention.[3] Moreover, several innovative catalytic strategies are uncovered for the atroposelective construction of axially chiral C-N bonds.[4] Intriguingly, however, catalytic strategies for the atroposelective synthesis of N-N axially chiral compounds have received only limited attention although these compounds are important motifs in biologically important molecules and chiral catalysts.[5] This may be due to the relatively low rotational barrier for N-N bonds although the shorter N-N bond length and the crowded N-N axis favor stable atropisomers. Only recently, the catalytic atroposelective synthesis of N-N axially chiral molecules were demonstrated by Lu,[6] Liu,[7] Li,[8] Zhao[9] and Shi groups.[10] Although N-heterocyclic carbenes (NHCs) are widely used for the synthesis of axially chiral molecules,[11] NHCs are not employed for the atroposelective synthesis of N-N axially chiral compounds.[12] Herein, we demonstrate the first NHC-catalyzed atroposelective synthesis of N-N axially chiral 3-amino quinazolinones.

Using the unique activation modes employing NHCs, atroposelective construction of differently substituted axially chiral C-C bonds leading to the synthesis of biaryls and related compounds are possible. In the last decade, a variety of structurally diverse C-C axially chiral biaryls and styrenes were demonstrated using carbene-catalyzed strategies involving kinetic resolutions, desymmetrizations, (benz)annulations, central to axial chirality transfers, etc. by the groups of Zhao,[13] Wang,[14] Lupton,[15] Zhu,[16] Du,[17] Ye,[18] and Chi (Scheme 1a).[19]

Scheme 1. NHC-Catalysis for the Synthesis of Axially Chiral Molecules

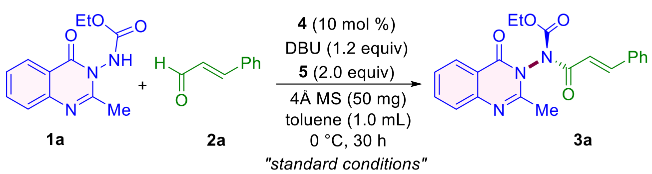


Moreover, NHCs are also useful for the atroposelective synthesis of C-N axially chiral compounds. The synthesis of C-N axially chiral anilides was disclosed by Wang and co-workers using the kinetic resolution strategy,[20] and the synthesis of axially chiral thiazines was accomplished by Chi, Jin and co-workers, where the reaction proceeds via the alkynyl acylazoliums (Scheme 1b).[21] We have recently reported the synthesis of C-N axially chiral *N*-aryl succinimides by the NHC-catalyzed desymmetrization of *N*-aryl maleimides.[22,23] Given the difficulties associated with the construction of axially chiral N-N bonds and considering the importance of N-N axially chiral compounds in medicine and catalysis (Scheme 1c), herein, we report the NHC-catalyzed oxidative amidation of enals with quinazolinones under mild conditions proceeding without the aid of a coupling agent or an acyl transfer agent (Scheme 1d).

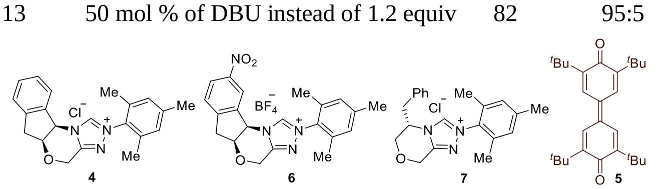
Results and Discussion

In one of the preliminary experiments, treatment of the quinazolinone derivative **1a** with *trans*-cinnamaldehyde **2a** in the presence of the chiral carbene generated from the precatalyst **4** with the aid of DBU as the base under oxidative conditions

Table 1. Optimization of the reaction conditions[a]



entry	variation of the standard conditions[a]	yield of 3a (%)[b]	er of 3a[c]
1	none	95	97:3
2	reaction without **4**	<5	-nd-
3	25 °C instead of 0 °C	97	95:5
4	**6** instead of **4**	85	93:7
5	**7** instead of **4**	82	10:90
6	DABCO instead of DBU	91	88:12
7	Cs_2CO_3 instead of DBU	96	93:7
8	KO*t*-Bu instead of DBU	91	96:4
9	THF instead of toluene	89	93:7
10	CH_2Cl_2 instead of toluene	94	93:7
11	trifluorotoluene instead of toluene	89	93:7
12	5 mol % of **4** instead of 10 mol %	55	98:2
13	50 mol % of DBU instead of 1.2 equiv	82	95:5



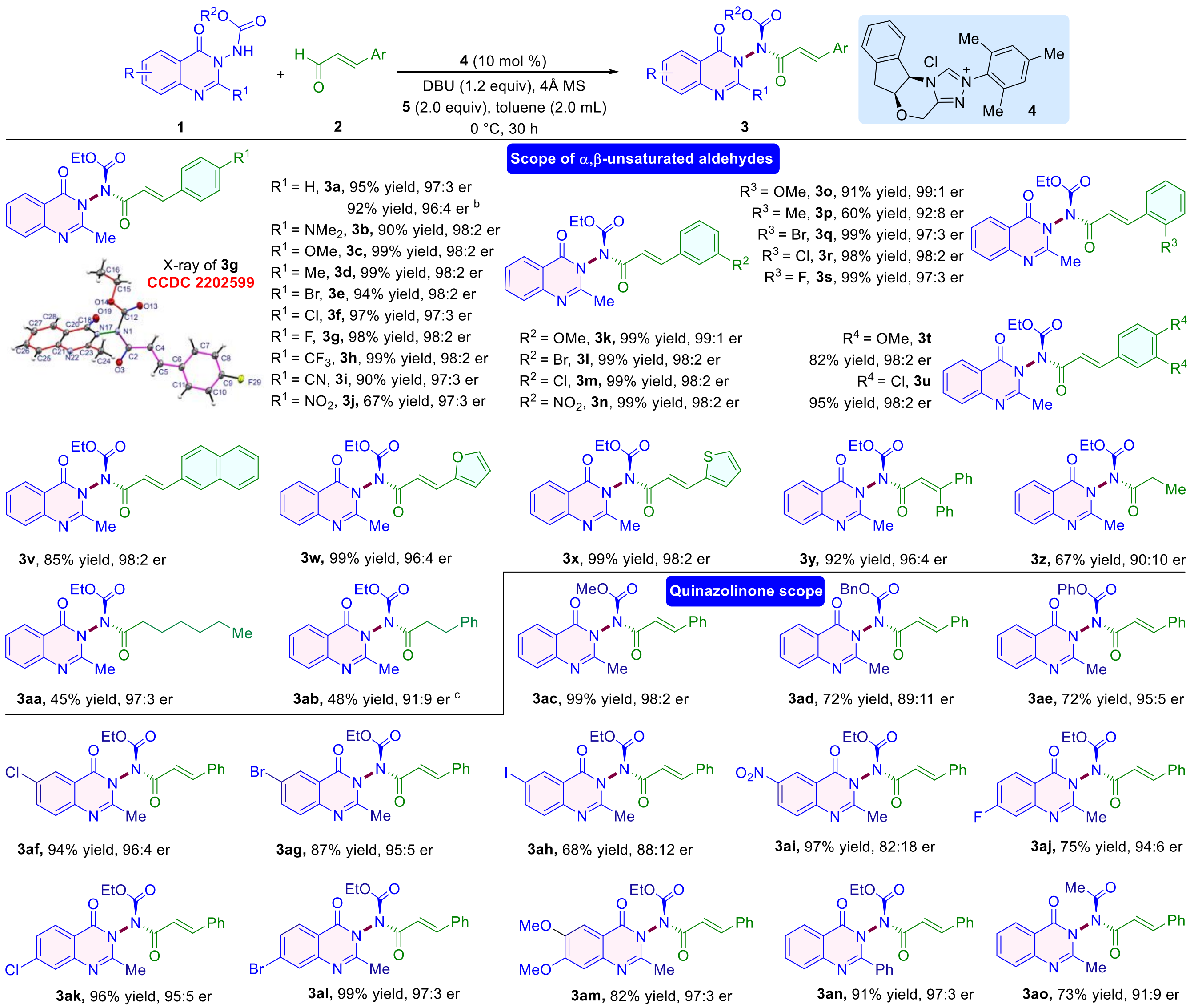
[a] Standard conditions: **1a** (0.125 mmol), **2a** (0.25 mmol), **4** (10 mol %), **5** (2.0 equiv), DBU (1.2 equiv), 4Å MS (50 mg), toluene (1.0 mL), 0 °C and 30 h. [b] Yield of the column chromatography purified products are provided. [c] The er value was determined by HPLC analysis on a chiral stationary phase.

using bisquinone **5** furnished the desired amidation product **3a** with the axially chiral N-N bond in 95% yield and 97:3 enantiomer ratio (er) (Table 1, entry 1).[24] This amidation reaction did not work in the absence of the NHC precatalyst **4** and performing the reaction at 25 °C instead of 0 °C provided reduced er of **3a** (entries 2, 3). The NHC precatalyst **4** was optimal and the other chiral triazolium salts **6** and **7** afforded **3a** in reduced er values although maintaining good reactivity (entries 4, 5). The screening of different bases and solvents revealed that DBU is the optimal base and toluene is the best solvent for this amidation reaction (entries 6-11). Moreover, decreasing the loading of the carbene precursor **4** resulted in a reduced yield of the product, although the enantioselectivity was maintained (entry 12). In addition, performing the reaction with 50 mol % of DBU resulted in a reduced yield and selectivity of **3a** (entries 12, 13). The variation of the reaction parameters indicated that entry 1 is the best condition for this atroposelective amidation reaction.

Having identified the reaction conditions, we then examined the substrate scope of this NHC-catalyzed atroposelective amidation reaction. Initially, the variation on enals was tested (Scheme 2). Various electronically dissimilar α,β-unsaturated aldehydes bearing electron-releasing, -neutral and -withdrawing substituents at the 4-position of the β-aryl ring underwent smooth amidation reaction under the optimized conditions resulting in the atroposelective synthesis of N-N axially chiral quinazolinone derivatives **3a-3j** in good to excellent yields and er values (>97:3 er in all cases). The desired product **3a** was formed in 92% yield and 96:4 er when performed on a 1.0 mmol scale indicating that the present method is scalable and practical. In the case of product **3g**, the structure and stereochemistry of the N-N axis was confirmed using X-ray analysis.[25] Moreover, electronically different substituents were well-tolerated at the 3-position and 2-position of the β-aryl ring, and disubstitution was also feasible under the present mild conditions. In all the cases, the quinazolinone product was formed in good to excellent yields and excellent er values (**3k-3v**; >97:3 er in all cases). In addition, the reaction performed using β-heteroaryl enals afforded the target products in excellent yields and er values (**3w, 3x**). Interestingly, the reaction using β,β-diphenyl cinnamaldehyde afforded the product **3y** in 92% yield with 96:4 er. Furthermore, the reaction performed using aliphatic linear aldehydes furnished the desired products in moderate to good yields and er values (**3z-3ab**).

Next, the tolerance of the quinazolinone moiety was examined. The carboethoxy moiety attached to the *exo*-nitrogen could be varied with Me, Bn and even phenyl and in all cases, the reactivity as well as selectivity was preserved (**3ac, 3ae**). Moreover, substitution at the carbocyclic ring of quinazolinone with halides and $-NO_2$ groups at the 6-position and halides at the 7-position did not affect the reactivity and the axially chiral functionalized quinazolinones were formed in good yields and er values (**3af-3al**). Notably, the reaction conducted using 6,7-dimethoxy quinazolinone derivative afforded the product **3am** in 82% yield and 97:3 er. The 2-methyl substituent on quinazolinone, which was key for restricting the rotation around the N-N axis could be changed to phenyl group for the synthesis of **3an** without affecting the reactivity and selectivity thus demonstrating the usefulness of the present atroposelective amidation reaction. Finally, the N-carbamate functionality can

Scheme 2. Substrate Scope of the NHC-Catalyzed for the Synthesis of N-N Axially Chiral Quinazolinone Derivatives[a]



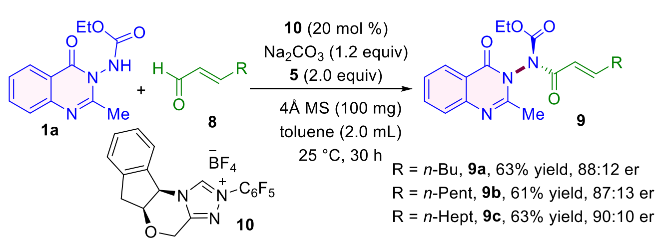
[a] Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), **4** (10 mol %), DBU (1.2 equiv), **5** (2.0 equiv), 4Å MS (100 mg), toluene (2.0 mL), 0 °C and 30 h. Given are isolated yield of the column chromatography purified products. The er was established by HPLC analysis on a chiral stationary phase. [b] The yield and er for a 1.0 mmol scale reaction. [c] The reaction was carried out using 20 mol % of **4**.

be replaced with the N-Ac moiety, and the target product **3ao** was isolated in 73% yield and 91:9 er.

The aliphatic enals did not afford the axially chiral quinazolinone products under the present conditions. However, under a modified condition using NHC generated from the triazolium salt **10**, delightfully, linear aliphatic enals afforded the N-N axially chiral quinazolinone derivatives (Scheme 3). Aliphatic enals bearing *n*-Bu, *n*-Pent and *n*-Hept groups at the β-position of enals afforded the desired axially chiral products **9a-9c** in good yields and reasonable er values.

To get insight into the atropisomerism arising from the restricted rotation around the N-N bond, using experimental and computational methods, the N-N rotational barrier for **3a** and **3an** has been determined. Using the Curran method for establishing the rotational barrier,[26] the $\Delta G_{rot}^{\ddagger}$ for the N-N bond in **3a** was determined as 32.4 kcal/mol by checking the variation

Scheme 3. Reaction using β-alkyl enals



of er values with time maintaining the temperature at 120 °C (Figure 1). With the aid of density functional theory (DFT) studies, the calculated N-N rotational barrier for **3a** was 30.9 kcal/mol, which is in good agreement with the experimental value. Similarly, the N-N rotational barrier for **3an** was determined as 29.4 kcal/mol and 29.0 kcal/mol using experimental (performed at 85 °C) and DFT studies respectively. The relatively higher rotational barrier for the methyl substituted **3a** over phenyl substituted **3an** may be due to the better sterics offered by the methyl group restricting the rotation around the N-N axis.

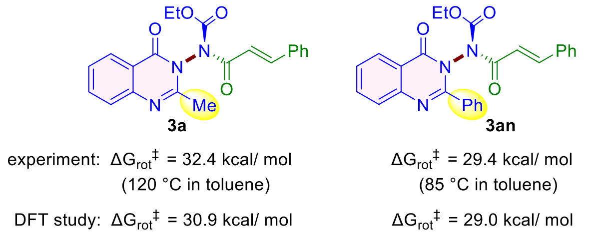
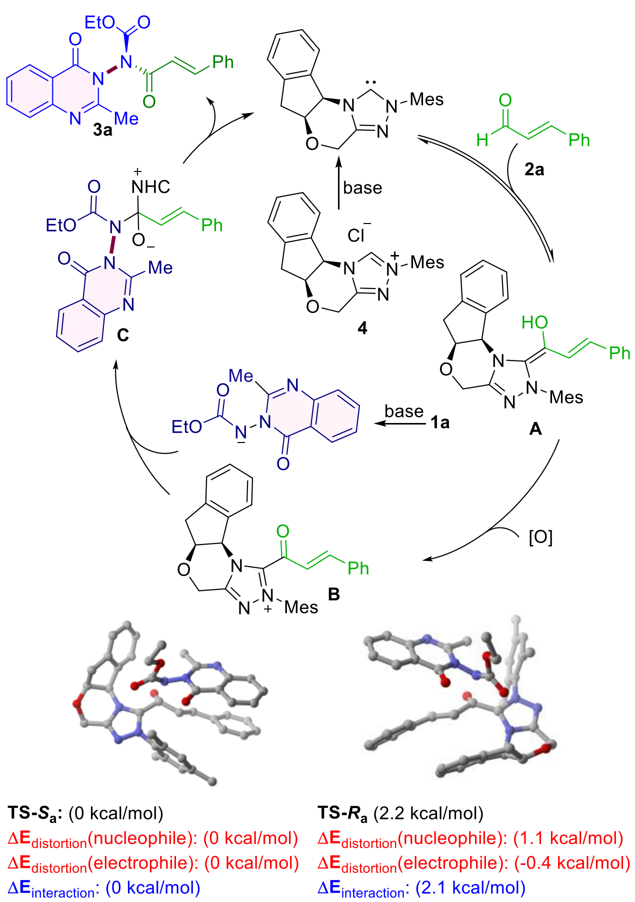


Figure 1. N-N Rotational barrier determination using experiments and DFT studies

The proposed mechanism of the atroposelective synthesis of N-N axially chiral 3-amino quinazolinone reaction is shown in Scheme 4. The NHC generated from **4** undergoes nucleophilic attack on **2a** to form the extended Breslow intermediate **A**.[27] In the presence of oxidant **5**, **A** undergoes oxidation to generate the α,β-unsaturated acylazolium intermediate **B**. Nucleophilic 1,2 addition of the anion generated from quinazolinone **1a** onto the intermediate **B** from the top face generates the tetrahedral intermediate **C**, which afforded the product **3a** with the regeneration of the free carbene. To understand the origin of axial enantioinduction, we calculated the structures and free energies of the diastereomeric N-N bond formation transition states at the M06-2X functional.[28] This system has a quite interesting stereochemical model as the axial chirality in the product is dictated by the 'N-N axial chirality' of the incoming nucleophile and is completely independent of the prochiral face of the acylazolium electrophile attacked. This is unlike most other NHC-catalyzed asymmetric transformations as here the generated tetrahedral chiral centre **C** is destroyed in the subsequent step, leaving only the N-N axial chirality. Once the C-N bond is formed, the interconversion via N-N bond rotation is arrested, resulting in a stable atropisomer.

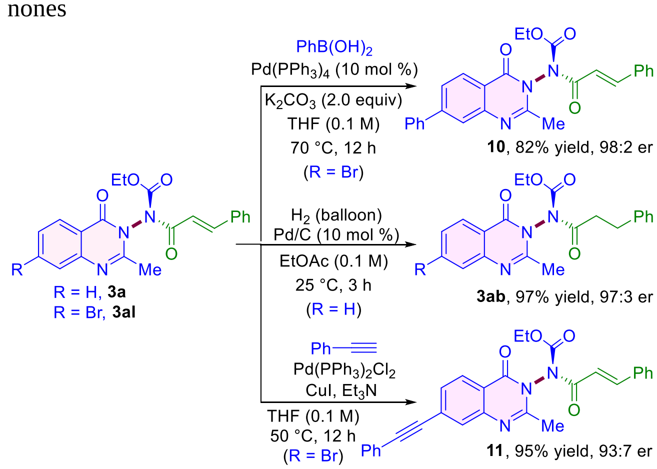
Scheme 4. Tentative Mechanism of the Reaction and the Envisioned Mode of Enantioinduction



We first considered the neutral quinazolinone as the nucleophilic species attacking the acylazolium cation. However, the tetrahedral intermediate, **C** (Scheme 4) could not be optimised. The poor nucleophilicity of the amide could be a probable reason for the instability of **C**. As the reaction was carried out in basic conditions (excess DBU) we considered the deprotonated amide as the nucleophile and studied the diastereomeric TSs for its attack on the electrophile. After carefully looking at the various possible conformers, we found the lowest energy TSs which would result in enantiomers *R* and *S*. The **TS-*Sa*** leading to the S enantiomer is of the lowest energy, which agrees with the absolute configuration determined by X-ray studies. The calculated er of 97.5:2.5 is in excellent agreement with the experimentally obtained er of 97:3. A distortion-interaction analysis indicates that the higher interaction between the nucleophile and electrophile is primarily responsible for high enantioinduction.

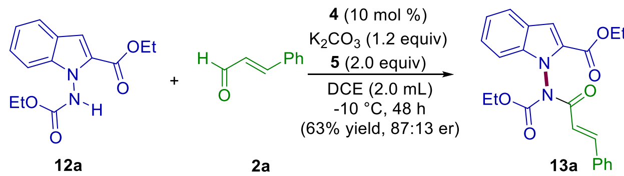
We also performed the functionalization of the synthesized N-N axially chiral quinazolinones. The hydrogenation of the α,β-unsaturated amide moiety of **3a** was carried out using H_2 gas and Pd/C resulting in the formation of the saturated amide product **3ab** in 97% yield and 97:3 er (Scheme 5). Moreover, the Pd-catalyzed cross-coupling of the bromo-derivative **3al** was also conducted. The Suzuki-Miyaura coupling of **3al** with the boronic acid afforded the biphenyl derivative **10** in 82% yield and 98:2 er. In addition, the Pd-catalyzed Sonogashira coupling of **3al** with phenyl acetylene furnished the alkyne **11** in 95% yield and 93:7 er.

Scheme 5. Functionalization of N-N axially chiral quinazolinones



This NHC-catalyzed atroposelective synthesis of axially chiral N-N bonds is not limited to axially chiral quinazolinones construction but instead a suitably substituted N-amino indole **12a** can couple with the enal **2a** under a slightly modified reaction condition to afford the N-N axially chiral functionalized indole **13a** in 63% yield and 87:13 er (Scheme 6).

Scheme 6. NHC-catalyzed atroposelective synthesis of N-N axially chiral indoles.



In conclusion, we have synthesized N-N atropisomers for the first time in NHC catalysis. The enantioselective synthesis of N-N axially chiral quinazolinones has been accomplished via the NHC-catalyzed *N*-acylation reaction. The reaction took place smoothly under mild conditions and displayed excellent functional group tolerance, allowing the synthesis of a variety of N-N axially chiral 3-amino quinazolinones in excellent yields and excellent enantioselectivities. The successful NHC-catalyzed asymmetric synthesis of N-N axially chiral molecules likely presents an alternate pathway to atropisomerism, with potential applications in drug development and ligand preparation.

ASSOCIATED CONTENT

Supporting Information

Details on experimental procedures, characterization, and NMR spectra and HPLC data of all spectra of Functionalized N-N axially chiral quinazolinone derivatives (PDF), and X-ray data of **3g** (cif).
The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* atbiju@iisc.ac.in

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS

NHC: N-Heterocyclic Carbenes

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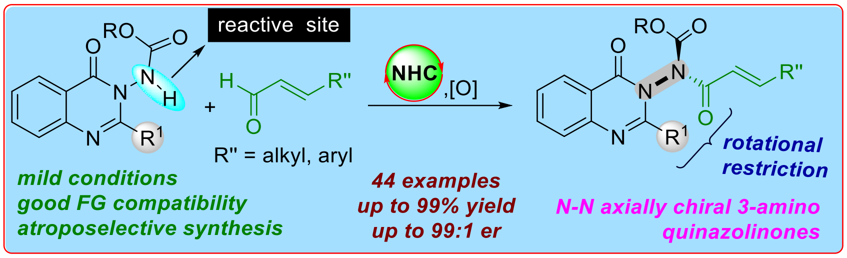

The atroposelective synthesis of N-N axially chiral 3-amino quinazolinones is reported by the N-heterocyclic carbene (NHC)-catalyzed selective amidation reaction. The carbene-catalyzed reaction of quinazolinones bearing a free N-H moiety with enals under oxidative conditions afforded atropisomeric quinazolinone derivatives under mild conditions and broad scope. A preliminary experimental and theoretical examination of the N-N rotational barrier is presented.