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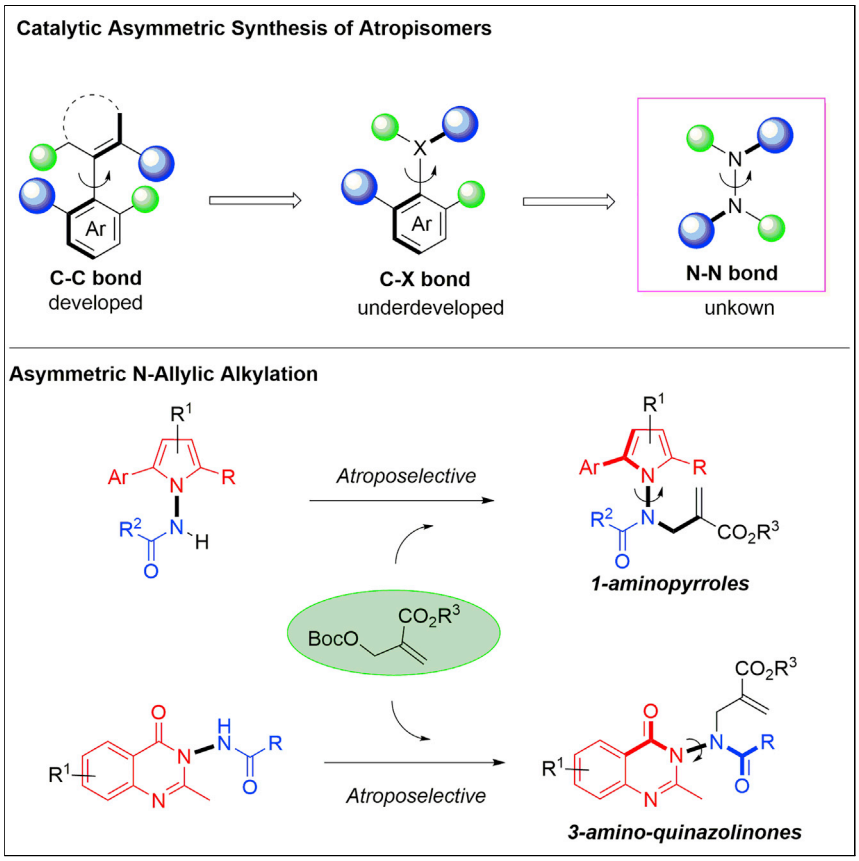
Rational design and atroposelective synthesis of N–N axially chiral compounds



The N–N bond is widely present in natural products, pharmaceutical agents, and organic materials. However, atroposelective creation of N–N axial chirality has never been reported. Herein, the first catalytic asymmetric synthesis of N–N axially chiral compounds has been accomplished. These N–N axially chiral frameworks are a new addition to the families of axially chiral molecules. DFT calculations have been applied to understand the origin of enantioselectivity and provide guidance for the design of additional molecules of this type.

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Highlights

N–N axial chirality construction

Catalytic asymmetric N-allylic alkylation reaction

Facile access to enantioenriched 1-aminopyrroles and 3-aminoquinazolinones

Broad scope, good yields, and excellent enantioselectivities

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Rational design and atroposelective synthesis of N–N axially chiral compounds

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SUMMARY

The first catalytic asymmetric synthesis of N–N axially chiral compounds has been accomplished via a quinidine catalyzed N-allylic alkylation reaction. These N–N axially chiral frameworks are a new addition to the families of axially chiral molecules and to the atropisomerism involving heteroatom(s), e.g., N, O, and S. The reaction takes place smoothly under mild conditions and displays excellent functional group tolerance, allowing facile access to a variety of N–N axially chiral 1-aminopyrroles and 3-aminoquinazolinones in high yields and excellent enantioselectivities. DFT calculations have been applied to understand the origin of enantioselectivity and provide guidance for the design of additional molecules of this type. The investigation of N–N axis atropisomerism holds promise for new discoveries in medicinal chemistry and asymmetric catalysis.

INTRODUCTION

Atropisomerism, also known as axial chirality, is ubiquitous in nature and arises from the restricted rotation about a single bond. Although the first report can be traced back to 1922,[1] only the past 2 decades have seen tremendous development of this intensively pursued research area. The extreme popularity of axial chirality can be linked to the discovery of privileged axially chiral ligands and their wide applications to asymmetric catalysis and synthesis. Moreover, atropisomerism is fundamentally important in natural products and in the pharmaceutical industry, and atropisomers are being increasingly employed in the synthesis of new materials, such as molecular devices and functional materials.[2–8] Different atropisomers are illustrated in Figure 1, among which axially chiral biaryl backbones connected by C–C bonds are most common and well recognized.[9–13] With intensive investigations of synthetic approaches to efficiently access axially chiral biaryl compounds, this class of molecules is a very well-established key structural motif in numerous pharmaceutical agents and natural products (Knipholone in Figure 1A).[14–17] Moreover, biaryl atropisomersm is present in extremely valuable chiral ligands used in asymmetric catalysis such as BINOL, NOBIN, and BINAM.[18,19] Other C–C bond-linked atropisomers include styrenes and aryl amides, which have been recently developed and examined as potential ligands in metal catalysis or as organic catalysts.[20–30] When a carbon atom is connected to a heteroatom, e.g., N, O, or S, atropisomerism may arise due to restricted rotation about the C–X bond.[8,31,32] The importance of C–X axial chirality was largely neglected, likely due to the perception of reduced rotation barriers induced by the deplanarization of the heteroatom-containing plane. With their presence in bioactive molecules and roles as chiral ligands,[33,34] C–X axial chirality has attracted the attention of the synthetics community in recent

The bigger picture

Stereoisomers could vary significantly in their biological activities and functions. As a type of stereoisomerism, atropisomerism involves stable isomers interconvertible by rotation about a single bond. Any forces imposing a high enough energy barrier to rotation may create atropisomers. The N–N bonds are widely present in natural products, pharmaceutical agents, and organic materials. Few examples of atropisomers involving rotation about N–N bonds exist. We present the catalytic asymmetric synthesis of N–N axially chiral 1-aminopyrroles and 3-aminoquinazolinones. Density functional theory calculations elucidate the origins of enantioselectivity and demonstrate remote enantiomeric control. N–N atropisomers are attractive compounds for further investigation as pharmaceuticals.

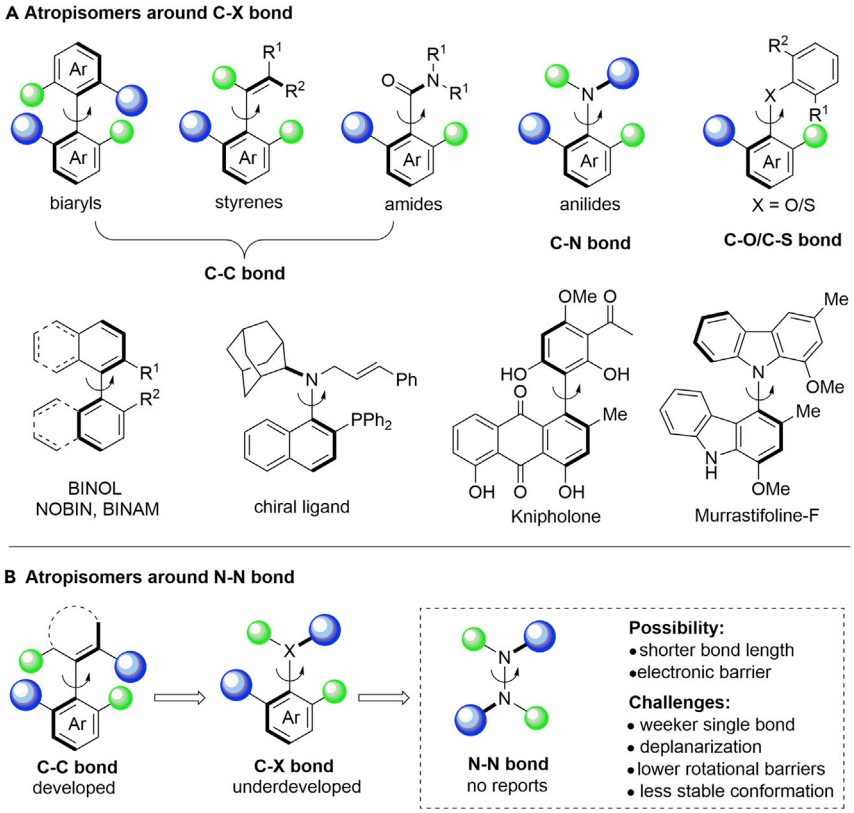

Figure 1. The profile of catalytic asymmetric synthesis of atropisomers

years.[29,35–46] In view of the ubiquitous presence and extreme importance of atropisomers, as well as their applications to medicinal chemistry and asymmetric catalysis, it is important to develop new types of axially chiral compounds.

We report the feasibility of establishing axial chirality, based on restricted X–X single bond rotation. Given our long-time interest in nitrogen-containing organic molecules, we focused our attention on molecular architectures bearing an N–N bond. Forces (including H-bonding, ionic interactions, and π-stacking) imposing an energy barrier of > 23 kcal mol^{-1} to rotation may create atropisomers.[47] Thus, a N–N single bond with carefully designed steric elements may exhibit atropisomerism[48–52] (Figure 1B). The shorter length of the N–N bond combined with a more crowded axis, due to the electronic barrier stemming from the repulsive interaction between the lone pairs on the two nitrogen atoms, are among the factors favoring the formation of such atropisomers. However, the low rotational barrier resulting from deplanarization of the two N-containing planes upon rotation makes access to such axial chirality challenging.

The N–N bond is widely present in natural products, pharmaceutical agents, and organic materials.[53] As illustrated in Figure 2A, besipiridine (I) contains a 1-aminoindole core and compound II has an 1-aminopyrrole core, and they are evaluated for the potential utility for the treatment of Alzheimer's disease and for the modulation of ecdysone receptors, respectively.[54,55] The substituted 4-quinazolinones (III and IV) have been regarded as hypnotics and anticonvulsants.[56,57] Notably, the potential existence of N–N axial chirality in the earlier mentioned compounds (I–IV) was not

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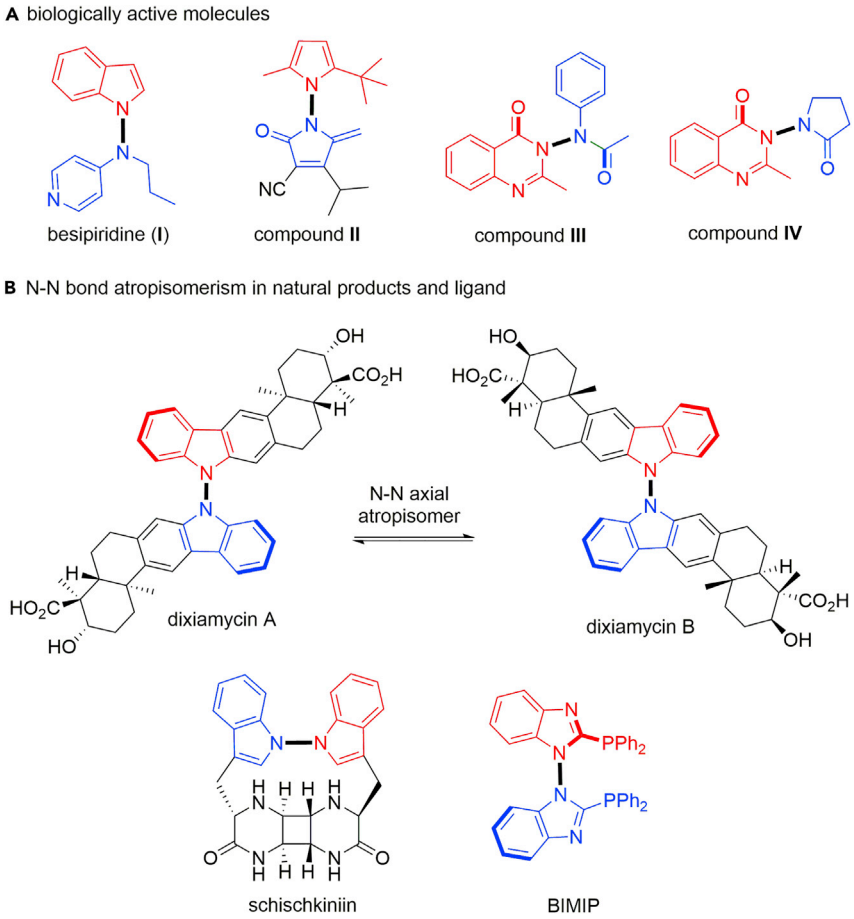


Figure 2. The existence of N–N bonds in bioactive compounds, natural products, and ligands

reported. Although various molecular structures containing N–N bond motifs have been constructed, no attention was paid to the N–N atropisomerism phenomenon.[58–60] However, from the perspective of drug discovery and development, the N–N bond atropisomerism is important, since different atropisomers may vary significantly in their biological activities and functions.[14,61–63] In this context, dixiamycins serve as an excellent example. In 2012, dixiamycin A and dixiamycin B were isolated as a pair of atropisomers arising from the restricted rotation about the N–N bond (Figure 2B).[64,65] It was reported that dixiamycin A exhibits a higher activity against *Staph. aureus* and *B. thuringiensis* than its atropisomer dixiamycin B. In addition, 2,2′-bis(diphenylphosphino)-1,1′- bibenzimidazole (BIMIP) was reported as an atropisomeric diphosphine ligand with hindered rotation around the N-N Bond.[66,67] Therefore, the development of catalytic asymmetric approaches to access N–N axially chiral atropisomers is a promising research direction, with likely applications in many areas.

The nitrogen atoms in the N–N atropisomers may be derived from different substructures, giving rise to the possibility of forming diverse N–N axially chiral compounds. We decided to select a carbamate or amide nitrogen as one of the two nitrogen atoms, due to the ubiquitous presence of such functionalities in organic molecules. The other nitrogen atom can be part of an aryl ring, ideally, an aryl moiety forming structure with potential biological significance. Therefore, 1-aminopyrroles

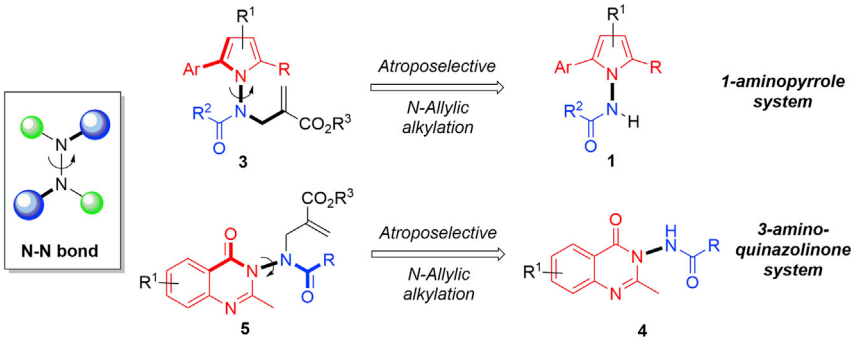


Figure 3. Constructing N–N bond chirality: Our proposal

and 3-aminoquinazolinones were chosen to be the core structures, since N–N axial bond, pyrrole, and quinazolinone rings were present in biologically active molecules (compounds **II**–**IV** in Figure 2). Since both classes of compounds contain configurationally labile N–N bond axes, we reasoned that they would be ideal substrates for evaluating potential N–N atropisomer formation via synthetic manipulations. Simple *N*-allylic alkylations were anticipated to introduce a significant rotational barrier to the existing N–N axis, thus allowing for derivatization of configurationally stable N–N atropisomers (Figure 3). We report the first example of an enantioselective preparation of N–N axial atropisomers and describe the asymmetric synthesis of two distinct classes of axially chiral 1-aminopyrroles **3** and 3-aminoquinazolinones **5**. Our investigations prove the feasibility of forming N–N atropisomers in an enantioselective manner.

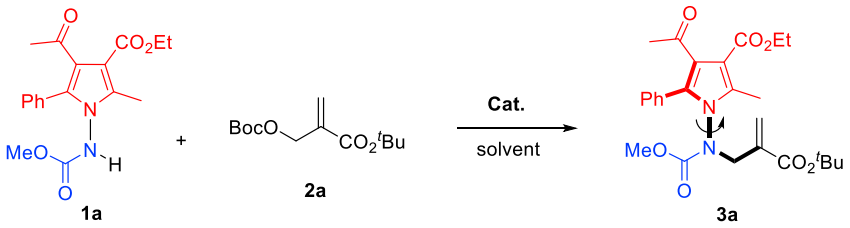
RESULTS AND DISCUSSION

Atropisomeric synthesis of 1-aminopyrroles

To initiate our investigation, 1-aminopyrrole[68,69] **1a** was chosen as the starting substrate, which was subjected to atropselective *N*-allylic alkylation reaction (Table 1). The Morita–Baylis–Hillman (MBH) adduct **2a** was selected as the alkylating agent, and various commercially available chiral amine catalysts were tested,[70] and the results are summarized in Table 1. The rotation about the N–N bond in **1a** is facile and no atropisomers were observed. 4-(Dimethylamino)pyridine (DMAP) efficiently catalyzed the reaction between **1a** and **2a**, and the desired *N*-alkylation product 1-aminopyrrole **3a** was formed in excellent yield (entry 1). We were pleased to discover that such *N*-alkylation introduced sufficient N–N bond rotation constraint, leading to the formation of a pair of atropisomers (see the supplemental information for HPLC analysis on a chiral stationary phase). Importantly, the two atropisomers were sufficiently stable and not interconvertible at room temperature. Consequently, we turned our attention to the catalytic asymmetric formation of such atropisomers. When cinchonine (**A**) was employed as the catalyst, alkylation product **3a** was obtained with 70% ee (entry 2). The subsequent solvent screening identified chloroform as the solvent of choice (entries 3–6). The reaction was further examined with different bases, and among a few readily available cinchona alkaloids, quinidine (**D**) was found to be best (entries 7–11). Under the catalysis of quinidine, the atropselective *N*-allylic alkylation reaction occurred smoothly at room temperature in chloroform, affording the N–N axially chiral 1-aminopyrrole **3a** in 96% yield and 94% ee.

Next, with the optimal reaction conditions in hand, substrate scope was examined (Figure 4). The projected reaction was applicable to a wide range of 1-aminopyrroles **1** and MBH adducts **2**. The ester group of MBH adducts **2** can be varied, from

Table 1. Optimization of the reaction conditions



A: cinchonine **C: cinchonidine** **E: β-ICD**

B: quinine **D: quinidine** **F: hydroquinine**

Entry	Cat.	Solvent	Yield (%)[a]	*ee* (%)[b]
1	DMAP	CH_3CN	98	0
2	A	CH_3CN	95	70
3	A	CH_2Cl_2	88	90
4	A	toluene	90	85
5	A	dichloroethane	88	86
6	A	$CHCl_3$	93	91
7	B	$CHCl_3$	95	92
8	C	$CHCl_3$	90	90
9	D	$CHCl_3$	96	94
10	E	$CHCl_3$	96	46
11	F	$CHCl_3$	94	90

Reaction conditions: unless indicated otherwise, the reaction was carried out at 0.1 mmol scale with 10 mol % of catalyst in a solvent (1 mL) at room temperature for 12 h, and the molar ratio of **1a**:**2a** was 1:1.8.
[a]Isolated yield.
[b]The *ee* value was determined by HPLC.

^{t}Bu (**3a**), Me (**3b**), Et (**3c**), Bn (**3d**), and benzhydryl (**3e**), to anthracene-9-ylmethyl (**3f**), with consistently excellent ee values and high yields. Moreover, the ester moiety of the carbamate was also well tolerated (**3g**, **3h**). The neighboring substituent of 1-aminopyrroles appeared to be inconsequential to the reaction results, and excellent enantioselectivity was retained (**3i**, **3j**). The electron-withdrawing substituents on the pyrrole ring were also evaluated, and the reaction worked equally well for different types of substituents, regardless of their positions (**3k–3o**).

In particular, we examined the tolerance of the reaction to different aromatic substituents adjacent to the pyrrole nitrogen (Figure 5). In all the examined cases, the axially chiral 1-aminopyrroles were obtained in high chemical yields and with very good enantioselectivities. Electronic properties of the substituents had influence on the reaction; higher enantioselectivities were observed for pyrroles containing electron-rich aryl groups, in comparison with substrates containing electron-poor aromatic substituents. The reaction was applicable to pyrroles bearing a di-substituted phenyl group (**3y–3c′**). Although pyrrole substrates with 2-naphathyl (**3d′**), 2-furanyl (**3e′**), and 2-thiophenyl (**3f′–3g′**) groups were found to be excellent substrates, the employment of 4-pyridinyl-bearing pyrrole led to the formation of product (**3h′**) with only moderate ee value. It should also be noted that alkylation products **3w** and **3x** with a bulky *ortho*- substituent do not possess axially stereogenic C–C bond.

Atropisomeric synthesis of 3-aminoquinazolinones

Having established the existence of N–N axially chirality in pyrrole-amides and achieved their enantioselective synthesis, we were then curious to find out if such

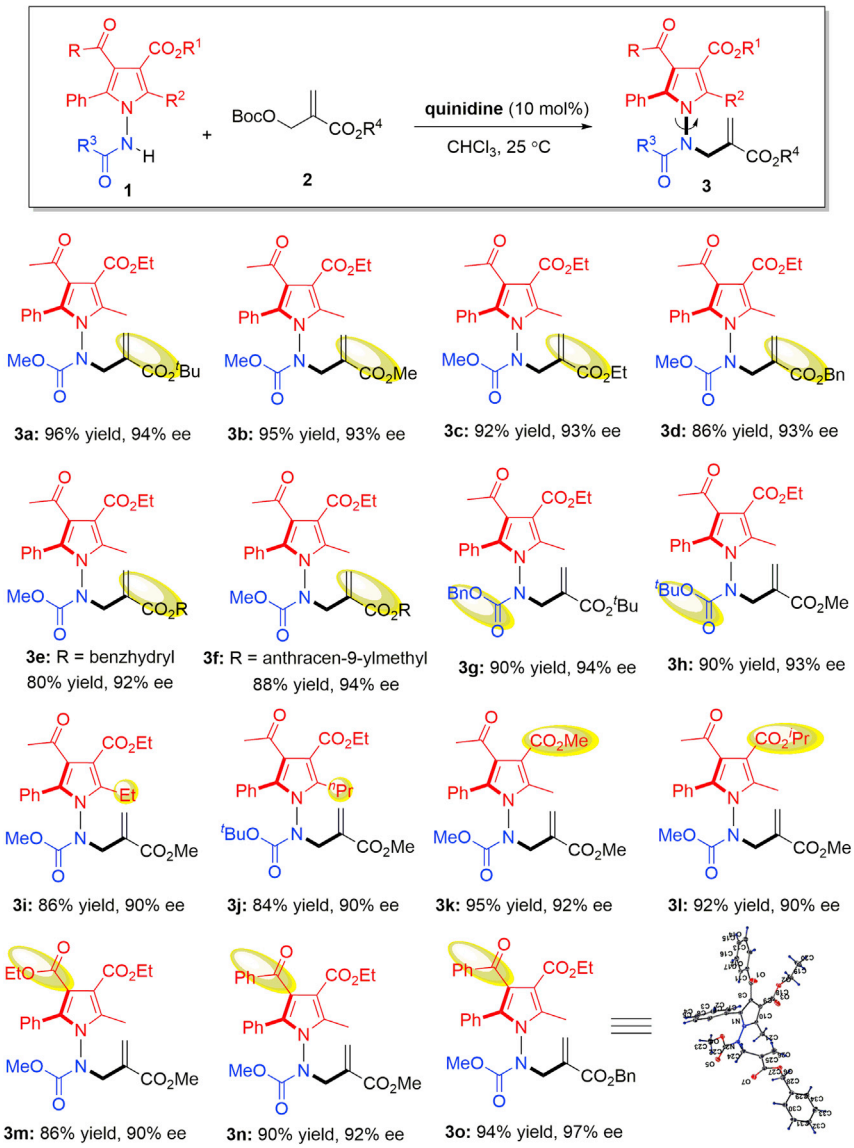


Figure 4. Substrate scope

Reaction conditions: **1** (0.1 mmol), **2** (0.18 mmol), quinidine (10 mol %), in 1.0 mL of $CHCl_3$, at 25°C, for 12 h. The absolute configuration of **3o** was determined to be *R* via X-ray analysis (CCDC: 2009439).

N–N chirality could be extended to quinazolinones, a class of privileged structural units commonly found in natural products, bioactive molecules, and chiral ligands.[71–73] The catalytic asymmetric synthesis of axially chiral quinazolinones has been an interesting research topic. The atroposelective bromination of 3-arylquinazolinones to construct enantiomerically enriched C–N atropisomers and the direct chiral phosphoric-acid-catalyzed direct creation of axially chiral arylquinazolinones were reported by Miller[74,75] and Tan,[76] respectively. Very recently, Luo, Zhu, and coworkers disclosed a palladium-catalyzed atroposelective coupling-cyclization strategy for the construction of axially chiral 2-aryl- and 2,3-diarylquinazolinones.[77] As illustrated earlier (Figure 2, compounds III and IV), 4-quinazolinones containing an N–N bond have been studied for their potential therapeutic uses. However, atroposelective synthesis of N–N axially chiral quinazolinones remain unknown.

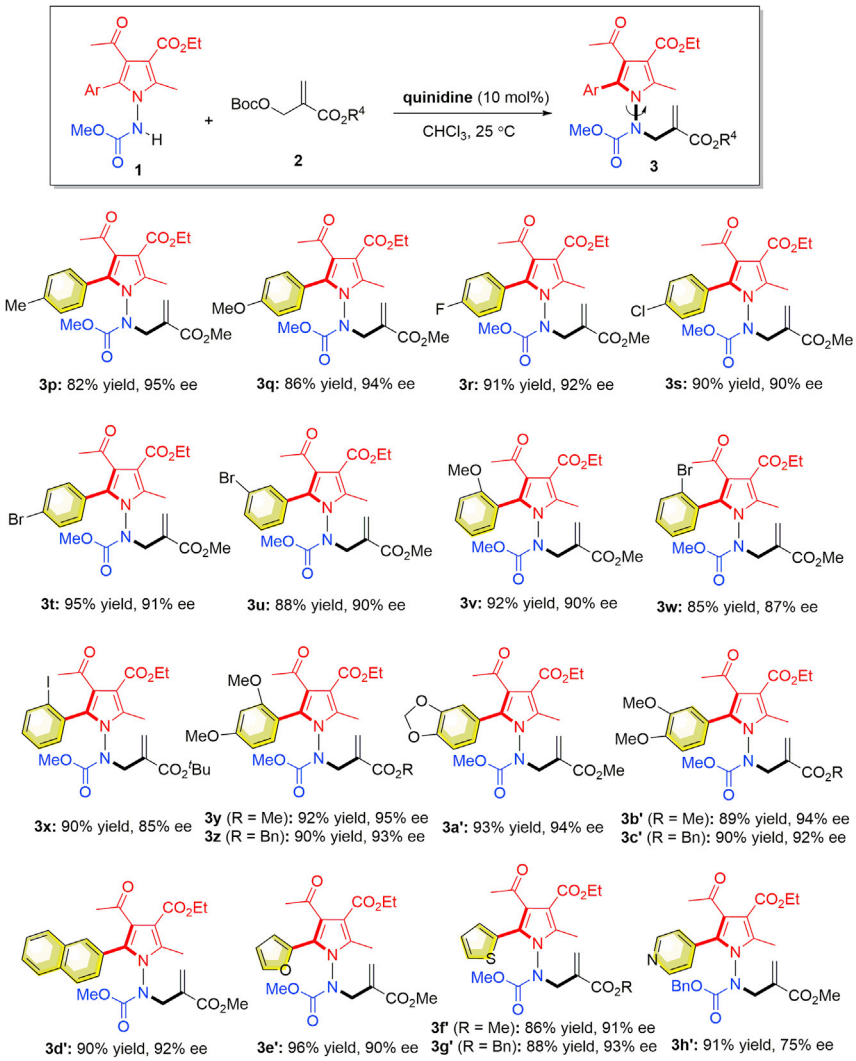


Figure 5. Substrate scope of the aromatic ring

Reaction conditions: **1** (0.1 mmol), **2** (0.18 mmol), quinidine (10 mol %), in 1.0 mL of $CHCl_3$, at 25°C, for 12 h.

The catalytic enantioselective *N*-allylic alkylation of 3-aminoquinazolinones for the atroposelective synthesis of chiral quinazolinones bearing an N–N bond was then explored, and the results are summarized in Figure 6. In the presence of a catalytic amount of quinidine, quinazolinone **4a** reacted smoothly with MBH adduct **2b** to afford chiral **5a** bearing an axial N–N bond in 80% yield and 74% ee. We then carried out further optimization experiments (see supplemental information for details) to enhance the reaction outcome. Under the optimized reaction conditions, i.e., running reaction at −20°C in chlorobenzene, 3-aminoquinazolinone **5a** was obtained in 86% yield and with an ee value of 95%. Subsequently, a variety of N–N axially chiral 3-aminoquinazolinones bearing different substituents were synthesized, and all the products were obtained in high yields and with excellent enantioselectivities (**5a–5o**) (Figure 6). Notably, the protective groups on the exo-nitrogen atom could be varied, from ester groups (**5a–5c**), to an acetyl group (**5d**), and to benzoyl groups (**5e–5l**). Furthermore, different substituents could be installed on the benzene ring of quinazolinones (**5m-5o**). When 2-phenyl substituted

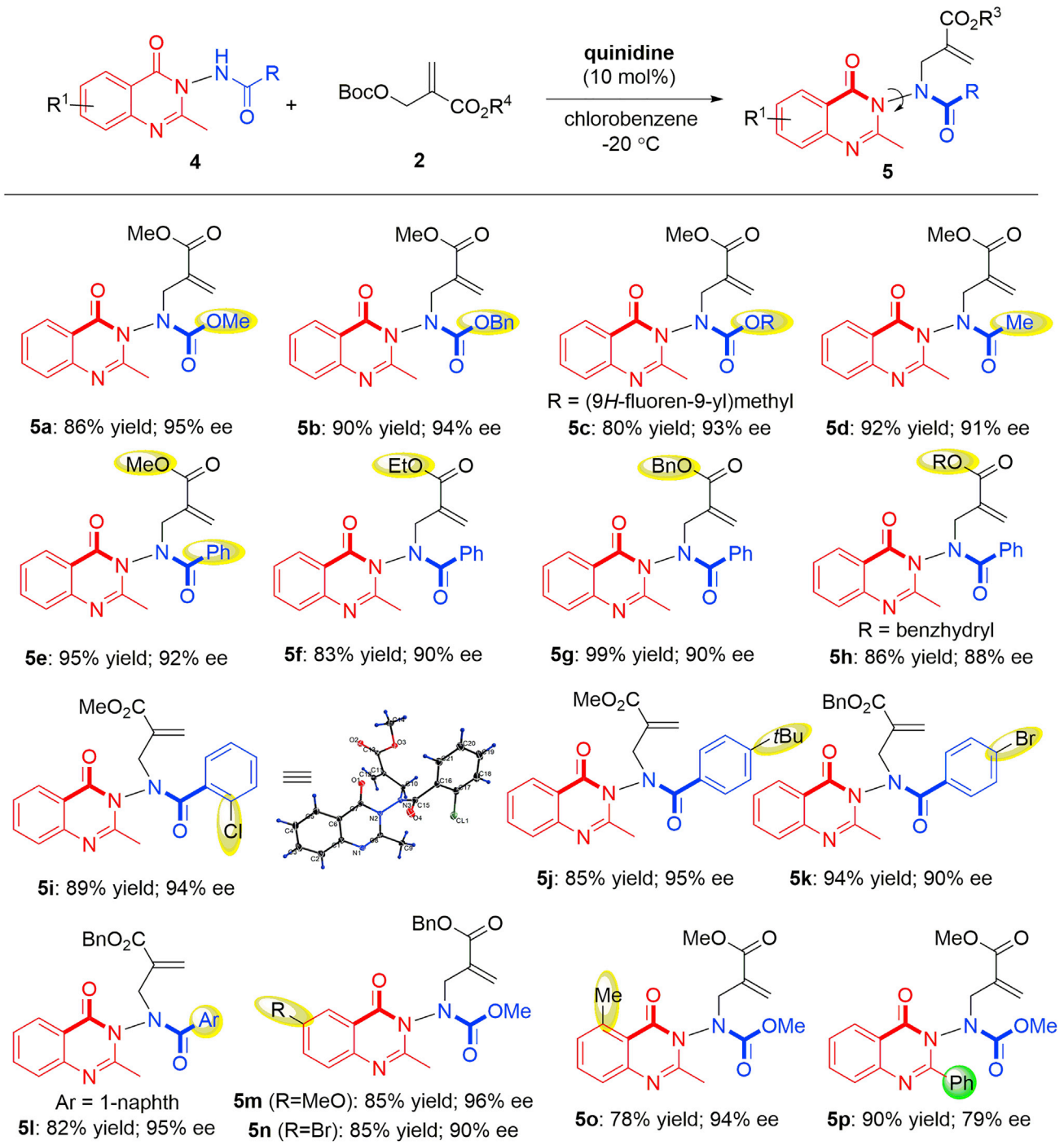


Figure 6. Atroposelective synthesis of N–N axial 3-aminoquinazolinones

Reaction conditions: **4** (0.1 mmol), **2** (0.18 mmol), quinidine (10 mol %), in 1.0 mL of chlorobenzene, at −20°C, for 48 h. The absolute configuration of **5i** was determined to be *R* via X-ray analysis (CCDC: 2012732).

3-aminoquinazolinone was employed, the corresponding product was obtained in excellent yield, but with decreased enantioselectivity (**5p**).

To provide a theoretical understanding of the configurational stability of these N–N axially chiral products 3 and 5, racemization experiments and density functional

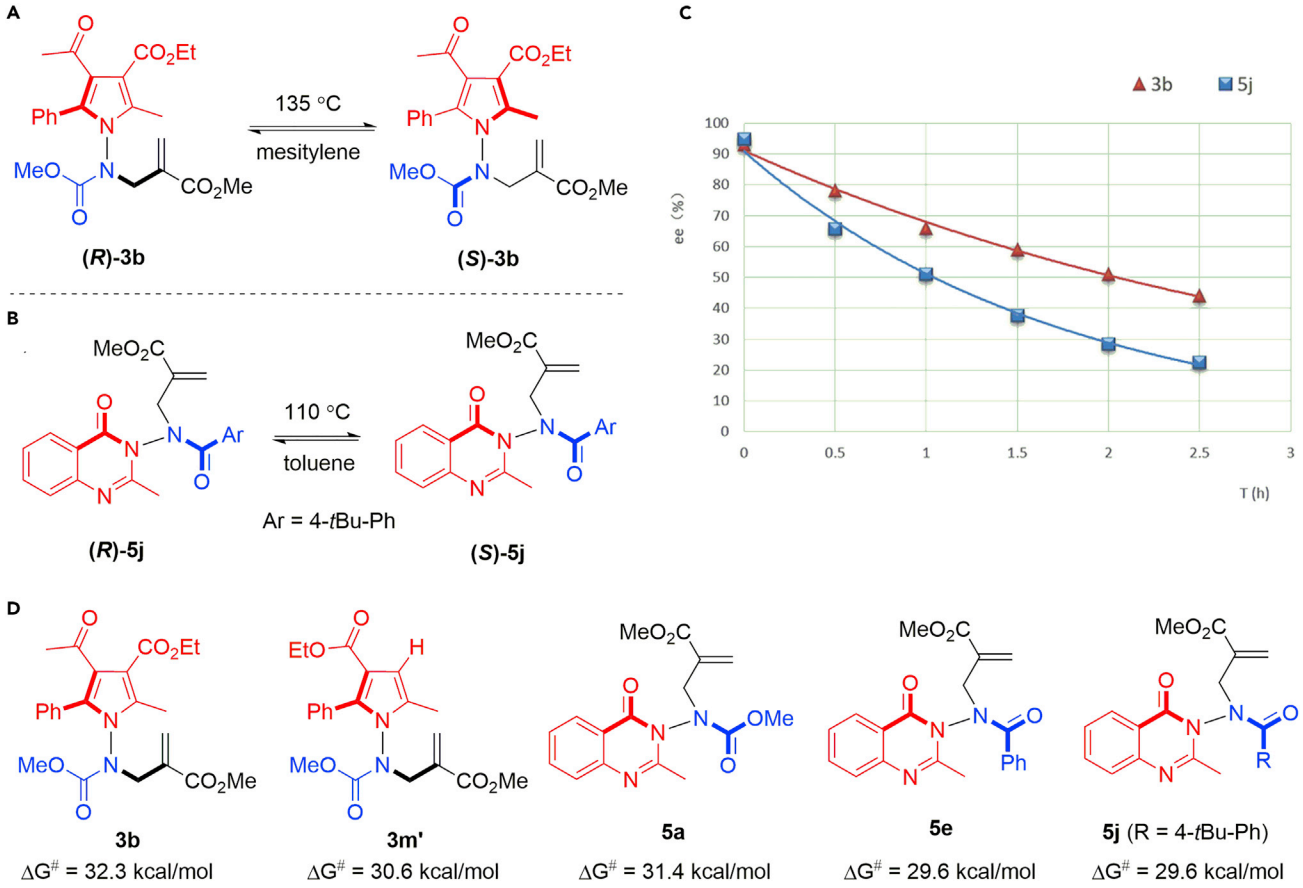


Figure 7. Examination of the stability of N–N axial chirality
(A–C) Racemization experiments.
(D) Rotational barriers.

theory (DFT) calculations were performed to obtain rotational barriers. As illustrated in Figure 7, the racemization experiments of 1-aminopyrrole **3b** and 3-aminoquinazolinone **5j** were carried out in mesitylene at 135°C and toluene at 110°C, respectively. The ee values of both **3b** and **5j** decreased over the time (Figure 7C). Through these experiments, the rotational barriers of **3b** and **5j** were determined to be 32.3 and 29.6 kcal/mol, respectively. Computationally, the rotational barrier of **3b** was calculated to be 31.7 kcal/mol, which was determined through a rotational scan of the N–N bond and it represents an upper bound of this barrier. Furthermore, the rotational barriers of 1-aminopyrrole **3m'**, and 3-aminoquinazolinones **5a** and **5e** were also experimentally determined (Figure 7D). In general, 1-aminopyrroles appear to be more configurationally stable than 3-aminoquinazolinones, which could be rationalized by "buttressing effect".[78–80] In a fully substituted pyrrole ring, the two substituents at the 2- and 5-positions are pushed toward the N–N axis, leading to a more crowded coplanar transition state; thus, higher rotational barrier. Within the 3-aminoquinazolinone system, N-carbamoyl **5a** has higher rotational barrier than the N-aroyl **5e** and **5j**. We speculate that the electron-pair repulsion between oxygen atom of quinazolinone and the N-carbamoyl oxygen increases the rotational energy barrier for N-carbamoyl **5a**, which could be attenuated by a flexible orientation of the N-aroyl carbonyl group in **5e** and **5j**.

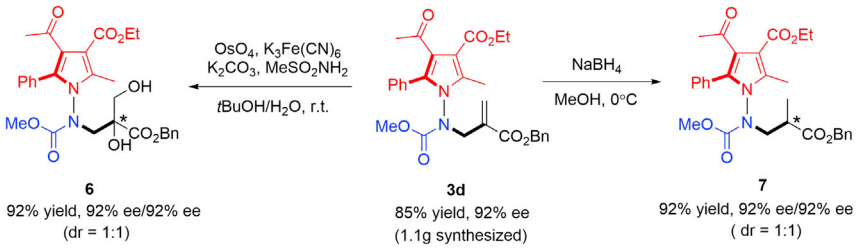


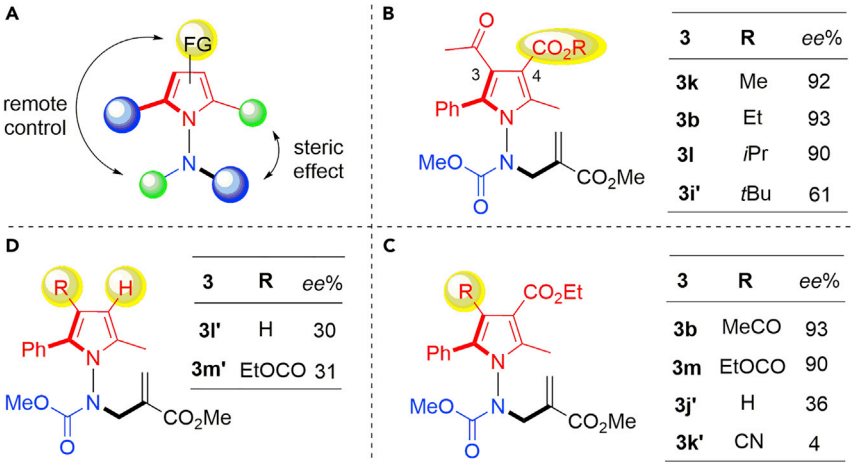
Figure 8. Further transformations

Furthermore, to demonstrate the stereointegrity of N–N axial chirality under different catalytic conditions, follow-up reactions have been carried out. As shown in Figure 8, a convenient gram-scale synthesis of 1-aminopyrrole **3d** was performed under standard reaction conditions. Subsequent reduction of **3d** with $NaBH_4$ furnished saturated **7** in excellent yield. Alternatively, dihydroxylation oxidation of **3d** led to the diol product **6**. Notably, both the reductive and oxidative transformations occurred readily, without erosion of enantiomeric purity.

Interestingly, a stereochemical observation with respect to the formation of N–N axially chiral 1-aminopyrroles revealed a remote control of axial chirality far from the reaction site (Figure 9A).[37,38,81,82] Although the steric effect of the four *ortho*-substituents was well recognized as an essential factor, the more distant functional groups (FGs) at the C3- or C4-position of pyrrole ring could significantly affect the chirality transfer from quinidine catalyst to the prochiral N–N axis. For instance, the ester group at the C4-position had some influence on enantioselectivity. The ee value decreased with the increase in steric hindrance of ester group. When the $CO_2{}^tBu$ (**3i′**) was employed, only a moderate enantioselectivity of 61% ee was obtained (Figure 9B). In addition, it seems that the electron-withdrawing groups (EWGs) at the C3-position played a crucial role in the enantiomeric control. The EWG could be ketone (**3b**) or ester (**3m**) group. However, changing this EWG to an H atom (**3j′**) or cyano group (**3k′**) would result in a significant drop in enantioselectivities (Figure 9C). Furthermore, the substrate **3l′** without any substituents at the C3- and C4-position led to a poor ee value of 30%. The low ee value of **3m′** suggested that the presence of alkoxycarbonyl group at the 4-position of pyrrole is important for stereochemical control in current reaction system (Figure 9D). This remote control of the axial chirality of N–N bond implied the existence of other forces beyond steric effects that influence the enantioselectivity-determining transition state.

To reveal the origins of enantioselectivity, DFT calculations at the ωB97X-D/6-311++G(d,p), CPCM//B3LYP-D3/6-31G(d), CPCM level of theory were performed. The proposed catalytic cycle proceeds through a widely accepted mechanism of MBH chemistry: the addition of quinidine to the MBH adduct via S_N2' pathway initializes the reaction. This is followed by another S_N2' process of adding N–N substrate to the quinidinium species, which is stereochemical determining step. The transition state was studied for both 1-aminopyrrole and 3-aminoquinazolinone systems (see supplemental information for details).

Calculations performed on the 1-aminopyrrole system show that the favored transition state has a lower barrier by 3.0 kcal/mol (Figure 10). Both transition-state structures exhibit hydrogen bonding interactions between the apical ketone substituent of the pyrrole ring and the hydroxy group of the catalyst. In order to maintain this interaction in the transition state corresponding to the disfavored enantiomer, the



3	R	ee%
3k	Me	92
3b	Et	93
3l	*i*Pr	90
3i'	*t*Bu	61

3	R	ee%
3l'	H	30
3m'	EtOCO	31

3	R	ee%
3b	MeCO	93
3m	EtOCO	90
3j'	H	36
3k'	CN	4

Figure 9. Remote control of the N–N axial chirality of 1-aminopyrroles

quinidine catalyst must rotate about its quinuclidine N-acrylate C bond, bringing its quinoline ring in close proximity to the phenyl substituent of the pyrrole. The energy difference occurs due to C–H repulsions between the phenyl group and the C4-carbon of the quinoline ring (2.73 Å). There are also H–H steric repulsions between the H atom at the C5-position of the quinoline ring and a hydrogen atom on the acrylate-quinidine adduct (1.86 Å).

Based on calculations on the 3-aminoquinazolinone system, the minor enantiomer is disfavored by 1.8 kcal/mol (Figure 11). Again, in order to maintain optimal hydrogen bonding interactions with the 3-aminoquinazolinone substrate, the quinidine

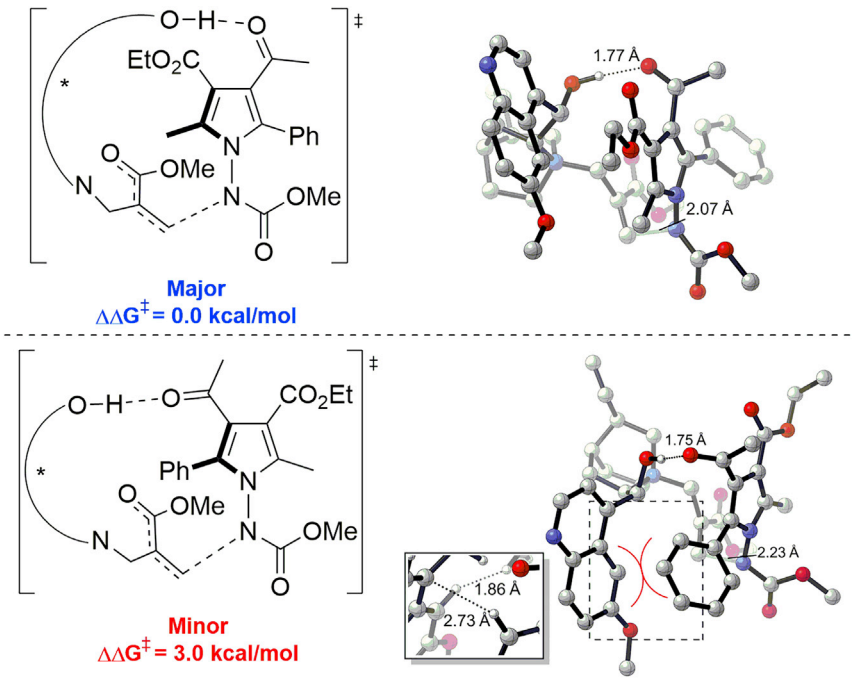


Figure 10. Stereoselectivity-determining transition states for substrate 3b

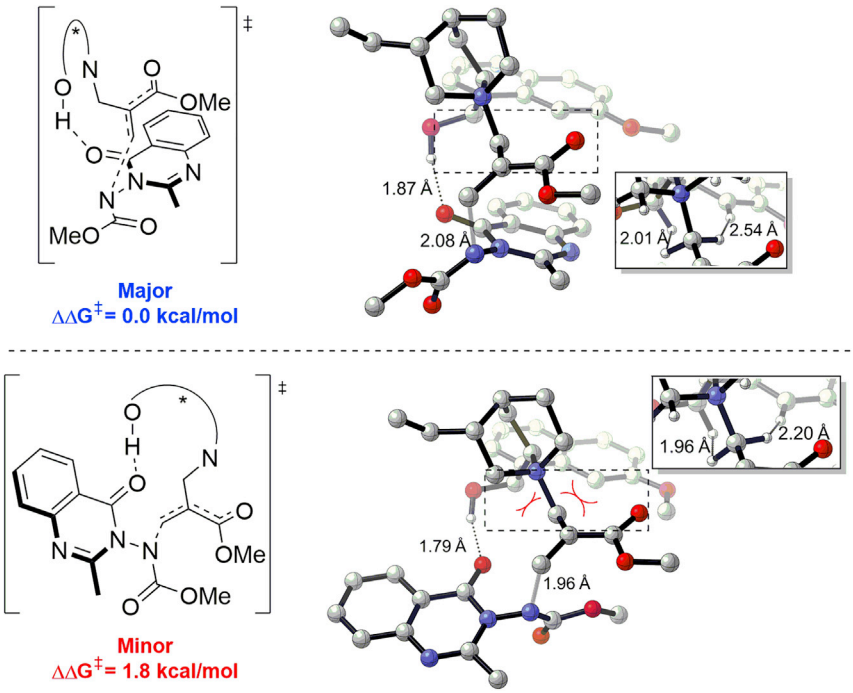


Figure 11. Stereoselectivity-determining transition states for substrate 5a

catalyst must rotate about its exocyclic chiral C-quinuclidine C bond in such a way that the quinoline ring approaches more sterically congested areas, creating an H–H steric repulsion between the hydrogen atom at the C5 position of quinoline and another on the acrylate (2.20 Å). Also, by way of this rotation, a hydrogen atom of the exocyclic chiral carbon rotates into close proximity of another hydrogen atom on the acrylate to create an additional disfavorable repulsion (1.96 Å).

Conclusion

In conclusion, we designed and successfully synthesized N–N atropisomers for the first time. The highly catalytic enantioselective synthesis of N–N axially chiral compounds has been accomplished via a quinidine-catalyzed *N*-allylic alkylation reaction. The reaction took place smoothly under mild conditions and displayed excellent functional group tolerance, allowing for the synthesis of a variety of N–N axially chiral 1-aminopyrroles and 3-aminoquinazolinones in good yields and excellent enantioselectivities. DFT calculations revealed that the origins of enantioselectivity stem from hydrogen bonding interactions between the quinidine catalyst and the substrate. The success of the asymmetric synthesis of N–N axially chiral compounds opens a new avenue to atropisomerism, and future applications in drug discovery and ligand development are anticipated. We are currently investigating other types of N–N axially chiral compounds, and related applications to asymmetric catalysis and medicinal chemistry are being evaluated in our laboratory and will be reported in due course.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Yixin Lu (chmlyx@nus.edu.sg).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

The crystal structures of the product **3o** & **5i** in this article have been deposited in the Cambridge Crystallographic Data Center under the accession number CCDC: 2009439 and CCDC: 2012732. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

METHODS

Full experimental procedures are provided in the supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2021.07.013.

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AUTHOR CONTRIBUTIONS

Methodology, G.-J.M.; investigation, G.-J.M. and W.Z.; DFT calculation, J.W. and A.N.; writing – original draft & review & editing, G.-J.M., J.W., K.N.H., and Y.L.; conceptualization & project administration, G.-J.M., K.N.H., and Y.L.; supervision, Y.L.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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