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Atroposelective Access to 1,3-Oxazepine-Containing Bridged Biaryls via Carbene-Catalyzed Desymmetrization of Imines

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Abstract: We disclose herein an atroposelective synthesis of novel bridged biaryls containing medium-sized rings via N-heterocyclic carbene organocatalysis. The reaction starts with addition of the carbene catalyst to the aminophenol-derived aldimine substrate. Subsequent oxidation and intramolecular desymmetrization lead to the formation of 1,3-oxazepine-containing bridged biaryls in good yields and excellent enantioselectivities. These novel bridged biaryl products can be readily transformed into chiral phosphite ligands. Preliminary density function theory calculations suggest that the origin of enantioselectivity arises from the more favorable frontier molecular orbital interactions in the transition state leading to the major product.

Introduction

Axially chiral bridged biaryl compounds are an important class of biaryl atropisomers, due to their widespread occurrence in natural products and chiral catalysts/ligands in asymmetric catalysis (Figure 1a).[1] Compared with normal biaryl atropisomers,[2] axially chiral bridged biaryl compounds (in which two of the *ortho* substituents are tethered by bridging atoms) are structurally more unique and the synthesis of these molecules remains much less developed and more challenging. One of the main challenges deals with the discovery and construction of configurationally stable bridged biaryl systems with suitable tether length,[3a] otherwise the atropisomers would be non-resolvable due to rapid racemization under/below ambient temperature.[3b–f] Besides, most of the reported works focus on introducing additional stereogenic centers in the bridge, thereby allowing access to the more thermodynamically favorable diastereomeric atropisomer,[4] a strategy known as the central-to-axial chirality relay.[5] In sharp contrast, the synthesis of bridged biaryls bearing no stereogenic centers in the bridge is still in its infancy (Figure 1b). Progress in this field mainly comes from the chiral phosphoric acid-catalyzed[6a] and transition metal-catalyzed[6b–c] enantioselective synthesis of helicenes,[6] which are structurally related to the axially bridged biaryls; only recently Yan and co-workers reported a chiral squaramide catalyzed atroposelective construction of nine-membered carbonate bridged biaryls via *ortho*-quinone methide intermediates.[7]

The application of N-heterocyclic carbenes (NHCs) as organocatalysts has led to the development of numerous synthetically useful reactions.[8] Recently, NHC organocatalysis has been recognized as a powerful tool for the preparation of axially chiral compounds.[9] Most works among that focus on the construction of common biaryl atropisomers;[10] only one work from Zhao group reported a NHC-catalyzed cascade reaction to access axially chiral bridged biaryls bearing a chiral eight-membered lactone unit.[11] Here we disclose a carbene-catalyzed imine activation for the synthesis of axially chiral 1,3-oxazepine-bridged biaryls with single stereogenic element (Figure 1d). Our reaction is initiated via the addition of a NHC catalyst to an imine derived from an amino alcohol and an aldehyde to eventually form an *aza*-Breslow intermediate (**I**).[12] Oxidation of this *aza*-Breslow intermediate leads to an electron-deficient imidoyl azolium intermediate **II**,[13] which finally undergoes an intramolecular desymmetrization to afford the axially chiral 1,3-oxazepine-bridged biaryl products in good yields with excellent enantioselectivities. It should be noted that NHC-catalyzed activation of imines remains much less explored compared to the activation of carbonyl

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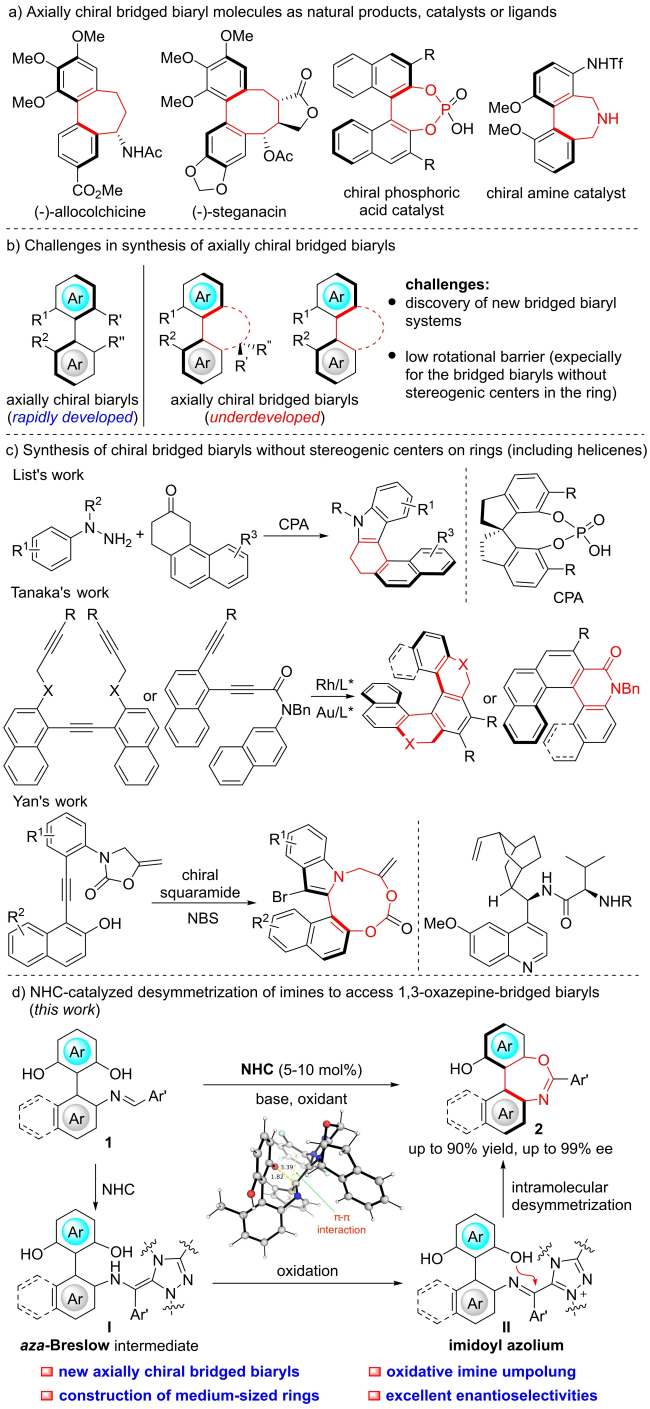


Figure 1. Application of the axially chiral bridged biaryls and their synthesis.

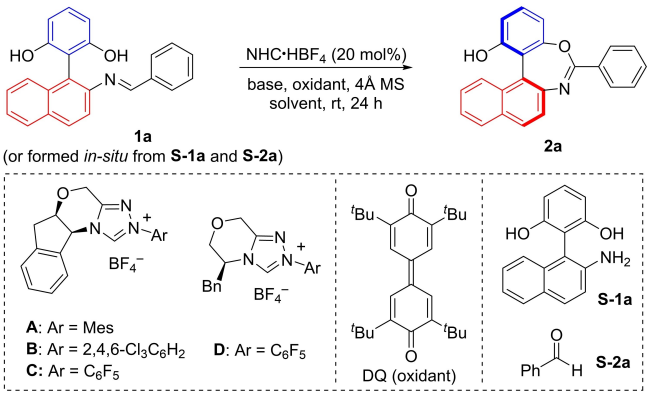
compounds.[14] Related carbene-catalyzed formation of *aza*-Breslow intermediates for imine umpolung and asymmetric reactions have been reported by Lupton,[15a] Biju[15b] and our group.[15c–d] Besides, the carbene-catalyzed oxidative imine umpolung for enantioselective [4+2] cycloaddition has been achieved by Fu[16a] and us[16b] in the mean time. This work represents the first success in developing oxidative imine umpolung to access the axially chiral compounds. We foresee that leading examples capitalizing on our methodology can be developed to open up new avenues for the construction of novel axially chiral bridged biaryls for a variety of applications.

Results and Discussion

We initiated our studies using aldimine **1a** as the model substrates with tetra-*tert*-butyldiphenyl-quinone (DQ) as an oxidant[17] to search for suitable conditions, with key results summarized in Table 1. The aminoindanol-derived precatalyst bearing a *N*-mesityl substituent (**A**)[18a] led to the formation of the axially chiral 1,3-oxazepine-bridged biaryl (**2a**) in excellent enantioselectivity, albeit with low yield (Table 1, entry 1). Gratifyingly, replacing the *N*-mesityl unit of **A** with an electron- deficient trichlorophenyl group (to get catalyst **B**)[18b] gave the product in a dramatically improved yield (72 % yield) and equally excellent ee value (entry 2). When precatalyst (**C**)[18c] with a more electron-deficient *N*-pentafluorophenyl substitute was examined (entry 3), the desired product was isolated in comparable results (entry 4). The use of phenylalanine-derived catalyst **D**[18d] also gave similar yield and enantioselectivity (entry 4). Control experiments showed that the reaction could not happen when carbene catalyst was not used (entry 5). Only trace amount of product **3a** was observed in the absence of DQ oxidant under nitrogen atmosphere (entry 6). Screening of bases (entries 7–8) revealed that the use of *N*,*N*-diisopropylethylamin (DIEA) gave an improved yield (entry 8). Further investigation on solvents showed that $CHCl_3$ could slightly improve the enantioselectivity (entries 9–10). Notably, when we performed the reaction in open air without DQ oxidant, the product was also obtained and only with a slightly drop in yield (entry 11). Replacing DQ oxidant by the cheap inorganic oxidant (MnO_2) afforded the same results (entry 12). Besides, the reaction could be performed in one-pot (entry 13), which avoid the isolation of unstable imine substrates and enhance the practicality of this method. Finally, the NHC catalyst loading could be reduced to 10 mol % with the product obtained in 80 % isolated yield and 98 % ee (entry 14).

With the optimal reaction conditions in hand, we next evaluated the scope of this one-pot carbene catalyzed atroposelective desymmetrization reaction and the results are shown in Scheme 1. A wide range of aldehydes were compatible in this reaction, giving the axially chiral 1,3-oxazepine-bridged biaryl products in good yields (53–85 % over 2 steps) and excellent enantioselectivities (97–98 % ee). In the case of phenyl-substituted aldehydes, electron-donating and electron-withdrawing groups at *para* or *meta* position were all tolerated, and the desired products formed in consistently excellent enantioselectivities (**2a**–**2k**). The absolute configuration of **2k** was confirmed by X-ray analysis.[19] Introducing a fluorine atom at the *ortho* position of phenyl group, the desired product (**2l**) was obtained in 53 % yield and 97 % ee. The disubstituted benzaldehydes were converted into the products in satisfactory results (**2m** and **2n**). Moreover, fused aromatic-ring-containing aldehyde

Table 1: Optimization of the reaction conditions.[a]



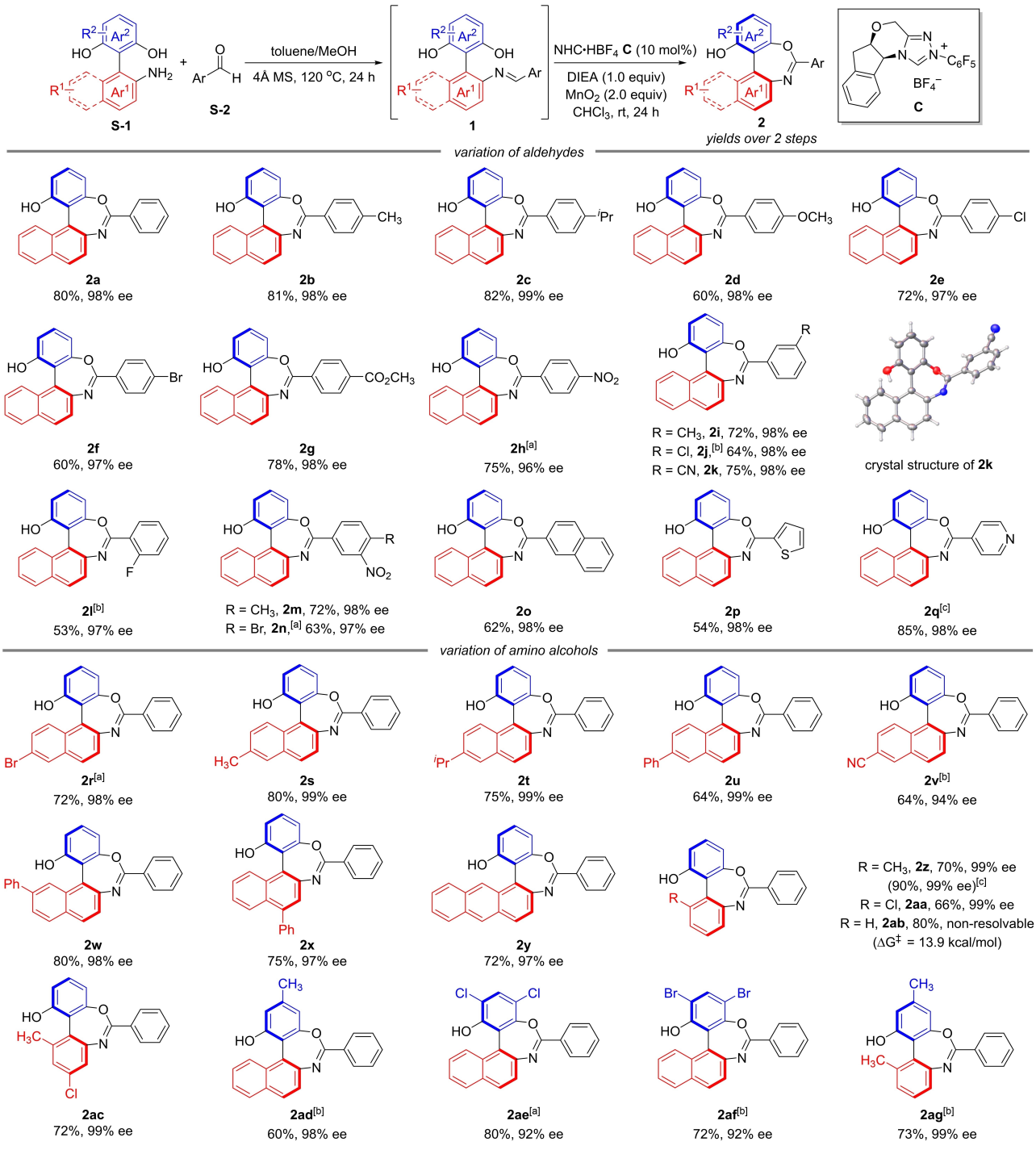
entry	conditions	yield [%][b]	Ee [%][c]
1	NHC·HBF$_4$ **A**, DQ, Cs_2CO_3, CH_2Cl_2	8	97
2	NHC·HBF$_4$ **B**, DQ, Cs_2CO_3, CH_2Cl_2	72	97
3	NHC·HBF$_4$ **C**, DQ, Cs_2CO_3, CH_2Cl_2	73	97
4	NHC·HBF$_4$ **D**, DQ, Cs_2CO_3, CH_2Cl_2	71	97
5	DQ, Cs_2CO_3, CH_2Cl_2 (no NHC·HBF$_4$)	0	–
6	NHC·HBF$_4$ **C**, Cs_2CO_3, CH_2Cl_2 (no DQ)[d]	trace	–
7	NHC·HBF$_4$ **C**, DQ, K_2CO_3, CH_2Cl_2	72	97
8	NHC·HBF$_4$ **C**, DQ, DIEA, CH_2Cl_2	81	97
9	NHC·HBF$_4$ **C**, DQ, DIEA, THF	trace	–
10	NHC·HBF$_4$ **C**, DQ, DIEA, $CHCl_3$	81	98
11	NHC·HBF$_4$ **C**, air (oxidant), DIEA, $CHCl_3$	76	98
12[e]	NHC·HBF$_4$ **C**, MnO_2, DIEA, $CHCl_3$	81	98
13[e,f]	NHC·HBF$_4$ **C**, MnO_2, DIEA, $CHCl_3$ (imine formed in situ)	80	98
14[e,f,g]	NHC·HBF$_4$ **C** (10 mol%), MnO_2, DIEA, $CHCl_3$ (imine formed in situ)	80	98

[a] Reaction conditions: **1a** (0.1 mmol), base (1.0 equiv), NHC·HBF$_4$ (20 mol%), 4 Å MS (100 mg) and DQ (1.2 equiv) in solvent (1.0 mL) at rt (20 °C); [b] Isolated yield; [c] Enantiomeric ratio of **2a** was determined via HPLC on a chiral stationary phase; [d] Under nitrogen atmosphere; [e] Activated MnO_2 (2.0 equiv) was used; [f] Imine **1a** formed in situ from **S-1a** and **S-2a** (see Supporting Information for details); [g] 10 mol% of catalyst loading.

and heterocyclic aldehydes were also compatible in this reaction (**2o**–**2q**). However, aliphatic aldehydes such as phenylpropyl aldehyde and cyclohexanecarboxaldehyde proved unsuitable in our reaction.

We next examined the scope of amino alcohols. The electronic and steric effects of the substituents at different positions of the naphthalene ring have no dramatic impact on the reaction, affording the corresponding products in 64–80% yields and 94–99% ee (**2r**–**2x**). Switching the naphthalene ring to anthracene ring gave the desired product **2y** in 72% yield and 97% ee. Moreover, naphthalene ring could be replaced by benzene ring (**2z**–**2ac**). Introducing methyl group or chlorine atom at the 6-position of the benzene ring (Ar^1), products **2z** and **2aa** could be isolated in good yields and extremely high enantioselectivities (99% ee). Notably, the desired product **2z** was isolated in excellent yield (90%) when pure imine substrate was used directly. This result indicates that the imine desymmetrization step proceeded almost completely. When the substituent on the 6-position of benzene ring (Ar^1) was replaced by hydrogen atom, non-resolvable bridged biaryl **2ab** was obtained. The computed rotational barrier for structure **2ab** is 13.9 kcal mol^{-1}, which is much lower than the rotational barrier required to isolate the individual atropisomers (24 kcal mol^{-1}).[2b] We therefore note the critical importance of the substituents on the 6-position of benzene ring (Ar^1) in providing steric hinderance for maintaining atropisomeric integrity (see Supporting Information, Scheme S1). Incorporating an additional chlorine atom at the 4-position of the benzene ring, similar results were obtained for product **2ac** (comparing to **2z**). Additionally, both electron-donating and electron-withdrawing substituents can be installed on the phenol ring (Ar^2), with the target axially chiral bridged biaryls afforded in good yields with high optical purities (**2ad** to **2ag**). Nonetheless, the excellent enantioselectivity could be slightly compromised when halogen atoms were embedded at the *ortho* position of hydroxyl groups (**2ae** and **2af**).

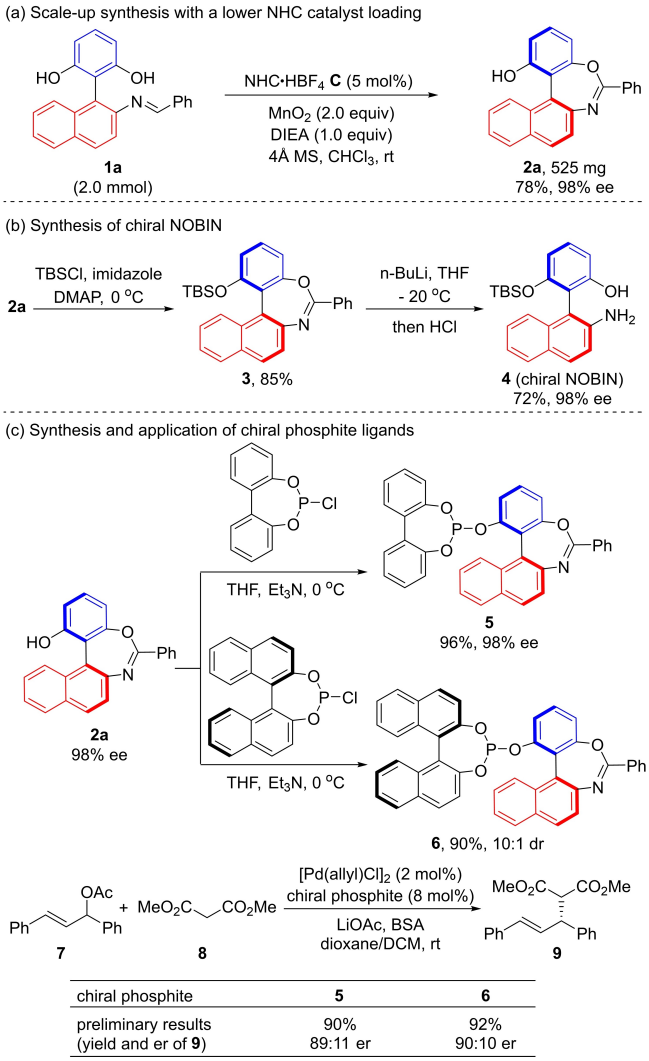
We then focus our attention on the synthetic application of the axially chiral 1,3-oxazepine-bridged biaryl products. First, a large scale reaction of imine (**1a**) catalyzed by 5 mol% NHC catalyst gave the product **2a** in a similar results (78% yield, 98% ee) compared to the above small scale reaction (Scheme 2a). Protecting the hydroxyl group of compound **2a** with TBSCl reagent gave the product **3** in 85% yield. Treatment of the compound **3** with *n*-BuLi at low temperature followed by hydrolysis with aqueous HCl, the chiral NOBIN[10e–f] product **4** was accessed in 72% yield



Scheme 1. Scope of NHC-catalyzed desymmetrization of imines. Reaction conditions: For step 1, **S-1** (0.11 mmol), **S-2** (0.1 mmol) and 4 Å MS (100 mg) was stirred in toluene/MeOH at 120 °C for 24 h and then remove the solvent to form imine in situ for next step; For step 2, DIEA (1.0 equiv), NHC·HBF_4 **C** (10 mol%), MnO_2 (2.0 equiv) and anhydrous $CHCl_3$ (1.0 mL) was added and stirred at rt (20 °C) for 24 h; [a] 12 h for step 2; [b] 18 h for step 2; [c] Imine was used directly for step 2.

and 98% ee (Scheme 2b). Moreover, the product **2a** could also be transformed to chiral phosphite ligands **5** and **6** by treatment with an achiral diphenol- and a chiral BINOL-derived phosphite chloride, respectively. Then these two chiral phosphite ligands were applied in the palladium-catalyzed asymmetric allylic alkylation between compound **7** and dimethyl malonate **8**. Preliminary results showed that ligands **5** and **6** gave the desired product **9** in comparable excellent yields and good enantioselectivities (Scheme 2c).

The stereochemical stabilities of the axially bridged birayls were evaluated using both experimental and computational methods (Figure 2). We first monitored the ee value



chiral phosphite	5	6
preliminary results (yield and er of **9**)	90% 89:11 er	92% 90:10 er

Scheme 2. Practical utilities of our reaction.

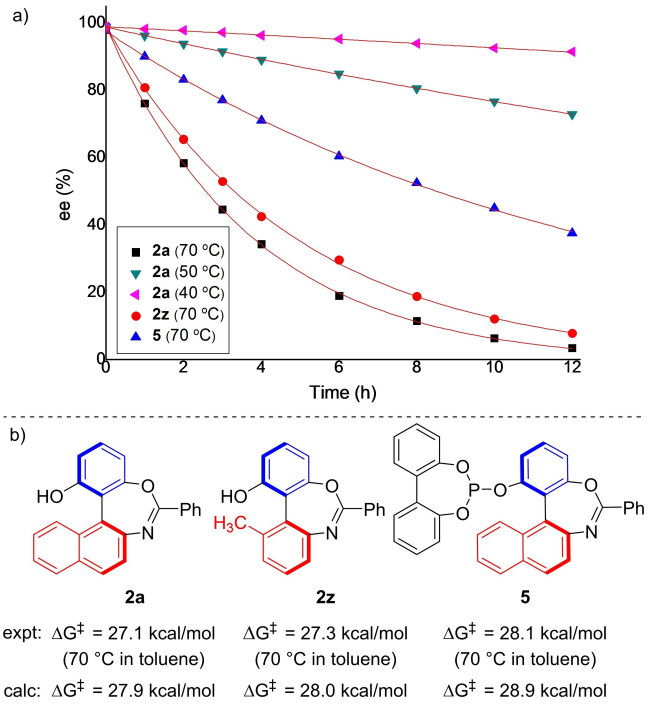


Figure 2. Determination of the rotational barrier of 1,3-oxazepine-bridged biaryls. a) The enantiomerization results over the time for **2a**, **2z** and **5**. b) The experimental and computed results of rotational barrier for **2a**, **2z** and **5**.

of **2a** over 12 h at different temperatures in toluene, and found **2a** enantiomerized quickly at 70 °C, but much slower at 50 °C and 40 °C (Figure 2a). Notably, No diminished ee value of **2a** were observed after storing in a freezer for a couple of months. Next, we determined the rotational barriers of several representative compounds in toluene at 70 °C. Bridged biarys **2a** and **2z** showed almost the same rotational barriers (27.1 kcal mol^{-1} vs 27.3 kcal mol^{-1}) due to their similar steric hindrance at *ortho* position around the axis. Theoretically, bridged biary **5** is more configurationally stable than **2a**, as compound **5** has a larger *ortho* substituent than compound **2a**. The rotational barrier of compound **5** was experimentally determined as 28.1 kcal mol^{-1}, which is indeed higher than compound **2a**. Additional density functional theory (DFT) calculations on the rotational barriers for structures **2a**, **2z**, and **5** gave excellent agreement with the experimental values (Figures S1 and 2b).

To understand the origin of the observed atroposelectivity, we further performed DFT studies on the enantio-determining desymmetrization step where one of the hydroxyl groups on the aryl ring selectively attacks the imine carbon. As we are only interested in the relative activation barrier difference, for simplicity, we considered the TSs for which the deprotonated phenoxide (which can be formed reversibly in the presence of the basic reaction conditions) attacks the imine carbon. Taking into account of the most favorable conformation stabilized by non-covalent interactions such as π-π interactions between aryl ring of the NHC catalyst moiety and the phenyl ring of the substrate, the DFT optimized transition state structures for the enantio-determining step are shown in Figure 3. Frontier molecular orbitals (FMO) analysis suggest that **TS-major** is lower in activation barrier as it benefits from productive orbital overlap as the σ_{C-O} bond is formed (there are some σ_{C-O} bonding characteristics in its HOMO and some σ^*_{C-O} anti-bonding characteristics in its LUMO), whereas there is some σ^*_{C-O} anti-bonding characteristics in the HOMO of **TS-minor**, which may suggest that it is less favorable due to poor orbital overlap (see Supporting Information, Figure S3). In addition, distortion-interaction[20a–b]/activation strain (DI-AS) model[20b–f] analysis confirms that **TS-major** has more favorable interaction than **TS-minor** while the distortion in both TSs is similar (see Supporting Information, Figure S4). Therefore, the chiral carbene catalyst moiety has non-covalent interactions that position the TSs in a way that the favors the formation of major product that benefit from more favorable orbital and non-covalent interactions over the formation of the minor product, thereby achieving stereoinduction.

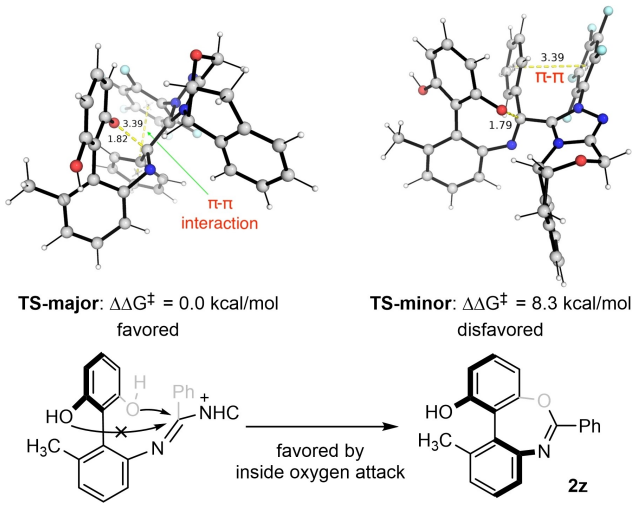


Figure 3. DFT optimized transition state structures of the enantioselectivity-determining step and relative Gibbs energy for the activation barriers.

Conclusion

In summary, we have developed a carbene-catalyzed activation of aldimines for the atroposelective synthesis of 1,3-oxazepine-containing bridged biaryls. Aminophenol-derived aldimines underwent the atroposelective desymmetrization reaction in a highly enantioselective manner under the influence of NHC catalysts and oxidants. The new bridged biaryl products afforded in this reaction contain a phenolic hydroxyl group and can be readily transformed into chiral phosphite ligands. DFT calculations pinpoint the importance of orbital and non-covalent interactions in effecting enantioselectivity in the transition state for the desymmetrization step, and underscore the role of substituents at the 6-position of the benzene ring (Ar^1) in providing sterics for preventing facile axial rotation and thereby maintaining high levels of enantioselectivity. Further explorations of the use of this novel bridged biaryl scaffold in the design of new chiral ligands and catalytic asymmetric reactions are under way in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Atropisomerism · Bridged Biaryls · N-Heterocyclic Carbenes · Organocatalysis · Umpolung

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[19] Deposition number 2182790 (**2k**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Research Articles

Organocatalysis

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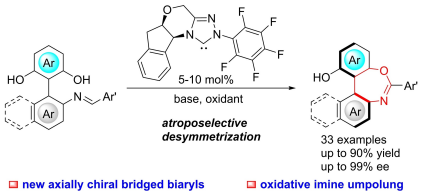
Atroposelective Access to 1,3-Oxazepine-Containing Bridged Biaryls via Carbene-Catalyzed Desymmetrization of Imines



An atroposelective synthesis of novel bridged biaryls containing 1,3-oxazepine medium-sized rings is enabled by N-heterocyclic carbene organocatalysis. Addition of the carbene catalyst to the aminophenol-derived aldimine substrate followed by oxidation and intramolecular desymmetrization gave the desired bridged biaryls in good yields (up to 90% yield) and excellent enantioselectivities (up to 99% ee).