Enantioselective Synthesis of C-O Axially Chiral Diaryl Ethers via NHC-Catalyzed Atroposelective Desymmetrization

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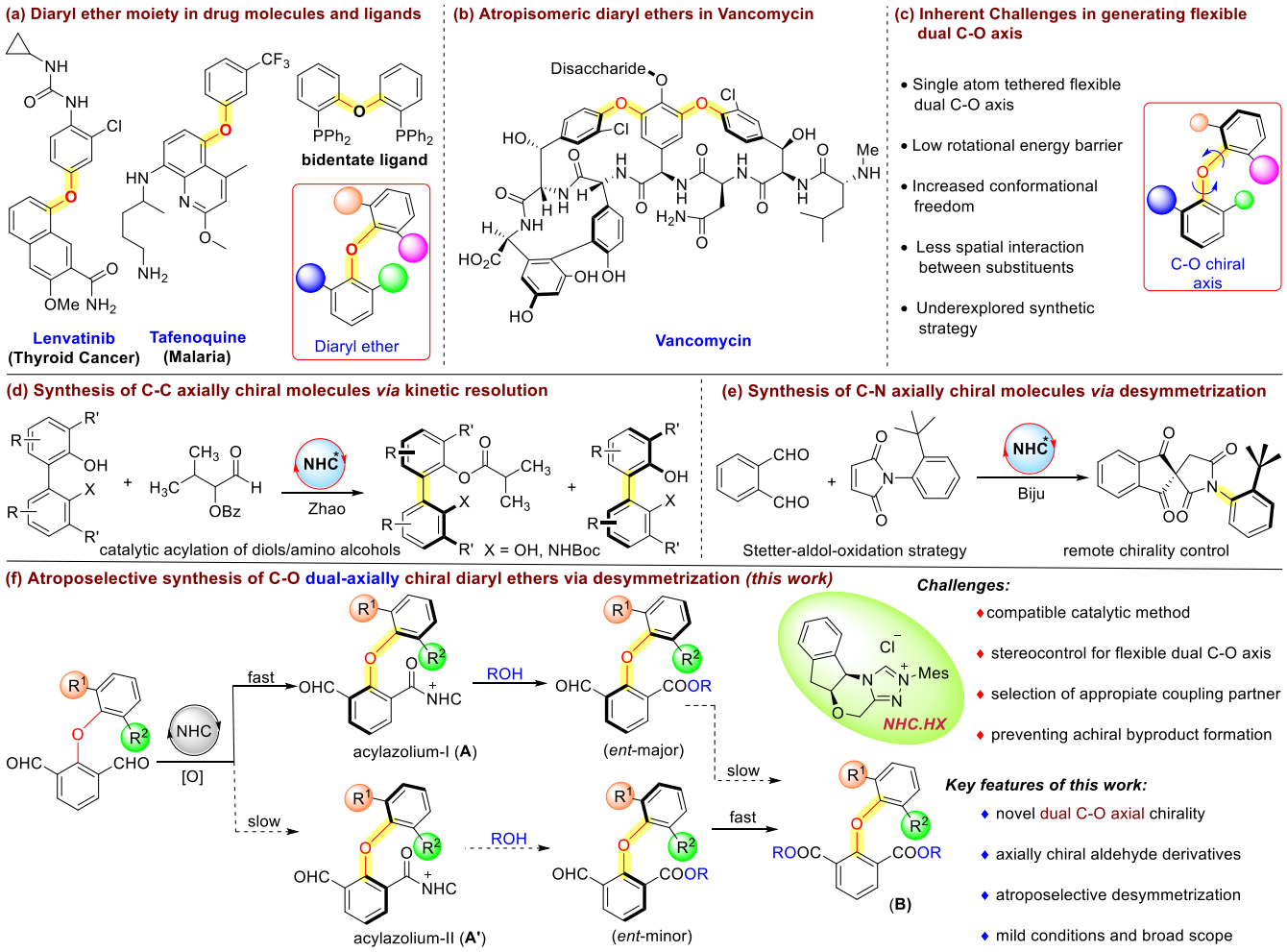
Abstract: *Axially chiral diaryl ethers, a distinguished class of atropisomers possessing unique dual C-O axis, hold immense potential for diverse research domains. In contrast to the catalytic enantioselective synthesis of conventional single axis bearing atropisomers, the atroposelective synthesis of axially chiral ethers containing flexible C-O axis remains a significant challenge. Herein, we demonstrate the first N-heterocyclic carbene (NHC)-catalyzed synthesis of axially chiral diaryl ethers via atroposelective esterification of dialdehyde-containing diaryl ethers. Mechanistically, the reaction proceeds via NHC-catalyzed desymmetrization strategy to afford the corresponding axially chiral diaryl ether atropisomers in good yields and high enantioselectivities under mild conditions. The derivatization of the synthesized product expands the utility of present strategy via access to a library of C-O axially chiral compounds. The temperature dependency and preliminary investigations on the racemization barrier of C-O bonds are also presented.*

The diaryl ether unit is present in various drug molecules and natural products.[1] For example, lenvatinib is used as an anticancer drug,[2] and tefenoquine is an antimalarial drug (Scheme 1a).[3] Additionally, they serve as the basic framework for bidentate phosphine ligands in catalysis.[4] More importantly, two diaryl ether chiral axes exist in the cyclic peptide aglycone of antibiotic vancomycin (Scheme 1b).[5] The pervasiveness, essential nature, and applicability of C-O axially chiral diaryl ether in medicinal chemistry drive the requirement for establishing novel catalytic methods for the atroposelective synthesis of diaryl ether atropoisomers. Consequently, inspite of the wide pharmaceutical application of diaryl ethers, the atroposelective generation of C-O axially chiral diaryl ether has received limited attention from the synthetic community.[6] The inherent difficulties in developing atroposelctive synthesis of C-O axially chiral diaryl ethers include: (*a*) the requirement of simultaneous rotational control around both C-O axes makes achieving atroposelectivity more difficult in this case compared to conventional single axis chirality, (*b*) comparatively low rotational barrier, (*c*) it is rather difficult to recognize and regulate the specific atropoisomers due to greater conformational space of flexible dual C-O axis, (*d*) the introduction of single atom between two axes reduces the special proximity and electronic interactions among the substituents attached to each axis, and (*e*) designing and systematically controlling axial chirality in this system is challenging due to the lack of established synthetic strategies (Scheme 1c).

The pioneering works on the enzymatic approach to C-O axially chiral compounds developed by the Clayden group[7] and organocatalyzed method established by the Gustafson group[8] have limitations in terms of substrate scope and enantioselectivity. Very recently, there are only two reports by Zheng[9] and Yang[10] for the atroposelective synthesis of diaryl ethers using chiral Brønsted acid catalysis. From this perspective, the development of a straightforward organocatalytic atroposelective approach will be highly desirable, and we envisioned the atroposelective synthesis of C-O axially chiral diaryl ethers using N-heterocyclic carbene (NHC)-catalyzed desymmetrization approach.[11]

Atroposelective NHC-catalyzed transformations are well known for the synthesis of axially chiral molecules.[12] In one of the pioneering reports, Zhao and co-workers demonstrated the NHC-catalyzed kinetic resolution of a variety of 1,1'-biaryl 2,2'-diols and related amino alcohols for the construction of axially chiral biaryls, where the reaction proceeds via an atroposelective acylation strategy (Scheme 1d).[13] Moreover, carbene-catalyzed strategies are utilized by various groups including Zhao,[14] Wang,[15] Zhu,[16] Du,[17] Ye,[18] and Chi[19] for the atroposelective synthesis of biaryls and related C-C axially chiral compounds. Additionally, NHCs are also employed for the atroposelective synthesis of C-N axially chiral compounds.[20] The NHC-catalyzed desymmetrization of compounds bearing a prochiral C-N axis is one of the effective techniques for the generation of C-N atropisomers.[21] Recently, we have disclosed the Stetter/aldol/ oxidation strategy to desymmetrize prochiral maleimides leading to the synthesis of C-N axially chiral N-aryl succinimides (Scheme 1e).[22,23] Very recently, we have demonstrated the synthesis of N-N axially chiral 3-amino quinazolinones via NHC-catalyzed atroposelective amidation strategy.[24]

While NHC catalysis has been widely utilized to synthesize compounds bearing C-C and C-N chiral axis, the preparation of more challenging C-O axially chiral diaryl ethers via NHC catalysis has not been realized so far. Considering the importance of diaryl ethers in drug discovery and asymmetric catalysis, and our interest in the NHC-catalyzed synthesis of axially chiral molecules, we envisioned that the symmetry breaking of a dialdehyde-containing diaryl ether having the prochiral C-O axis via NHC-catalyzed atroposelective esterification could lead to the synthesis of axially chiral diaryl ethers (Scheme 1e). Mechanistically, the reaction proceeds via the generation of the chiral NHC-bound acylazolium intermediate (**A**) produced from isophthalaldehyde derivative in the presence of carbene and an external oxidant, followed by the trapping with an alcohol. But the challenge associated with this process is the selection of suitable alcohol nucleophiles, which can balance between reactivity and selectivity via fine tuning of both electronic and steric interactions for the restricted rotation around a more flexible C-O dual axis. Another challenge for this desymmetrization approach is to prevent the formation of the achiral byproduct **B** via diesterification. Addressing these challenges, herein, we disclose the first NHC-catalyzed enantioselective synthesis of axially chiral diaryl ethers via atroposelective esterification of dialdehydes bearing prochiral C-O axis with β-naphthol derivatives via the desymmetrization strategy.



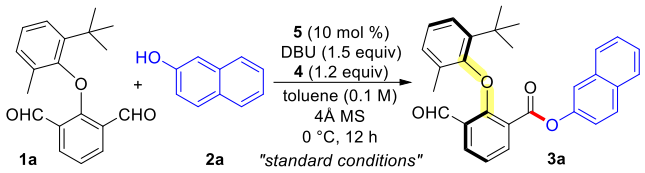
Scheme 1. Importance of diaryl ethers and NHC-catalyzed synthesis of axially chiral molecules

The preliminary studies were aimed at finding the appropriate nucleophile for the atroposelective esterification employing isophthalaldehyde **1a** to break its symmetry. After screening various nucleophiles, 2-naphthol **2a** was found to be viable coupling partner for this reaction. Treatment of the dialdehyde **1a** with 2-naphthol **2a** in the presence of NHC produced from the triazolium salt **5** using DBU in toluene under oxidative conditions using bisquinone **4** afforded the desired axially chiral diaryl ether **3a** in 60% yield, 99:1 enantiomeric ratio (er) with only traces of the diester product (Table 1, entry 1). The other widely used azolium salts **6** and **7** were found to be less effective in catalyzing this atroposelective esterification (entries 2, 3). The screening of various bases and solvents indicated that DBU is the optimal base and toluene is the best solvent for this desymmetrization (entries 4-9). Performing the reaction at 25 °C instead of 0 °C slightly improved the yield but the selectivity was slightly reduced (entry 10). The reduced yield of **3a** when the reaction was conducted without 4Å MS indicated its role of additive in this reaction (entry 11). Interestingly, when the stoichiometry of **1a** was increased to 1.4 equiv, the product **3a** was formed in 80% yield and 99:1 er (entry 12). When the reaction was carried out using 1.4 equiv each of **1a** and oxidant **4** for 3 h, the axially chiral diaryl ether **3a** was isolated in 86% yield and 99:1 er (entry 13).[25] Notably, the use of alcohols such as *i*-Pr-OH as nucleophile did not afford the desired esterified products under the present reaction conditions.

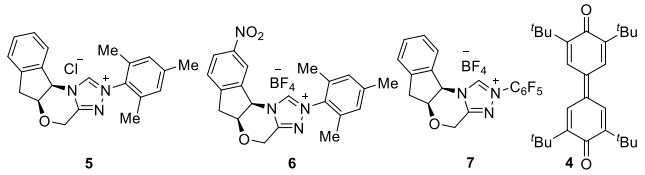
After identifying the optimized reaction conditions, the scope and limitations of the current strategy has been examined. First, the impact of substituents on 2-naphthol ring has been tested (Scheme 2). A series of 2-naphthols bearing electron-donating, neutral as well as heteroatom substituent at 7-position of the ring underwent efficient atroposelective esterification with **1a** leading to the synthesis of the corresponding axially chiral diaryl ethers in good to excellent yields with excellent er values (**3a**-**3f**). Moreover, electronically dissimilar substituents at 6-position of the 2-naphthol ring were also well tolerated (**3g**-**3l**). The 4-bromo substitution on 2-naphthol also did not affect the outcome of this desymmetrization, and the product **3m** was formed in 79% yield and 94:6 er. In addition, 2-naphthol substrates having substitution at 2-position also turned out to be effective resulting in the synthesis of the corresponding diaryl ether atropisomers in good to excellent yields with good er values (**3n**, **3o**).

Then, the scope of the reaction was evaluated with differently substituted diaryl ethers. The halogens as well as aryl substitution at the 4-position of aryl ring of diaryl ether was tolerated and the target axially chiral products were formed in high yields and selectivities (**3p**-**3s**). Instead of methyl group at the 2-position, other electronically different substituents at 2-positions could be employed as substrates for this desymmetrization reaction (**3t**-**3w**). For the 2-chloro derivative **3w**, the structure and stereochemistry of the C-O axis was confirmed using X-ray

Table 1. Optimization of the reaction conditions[a]



entry	variation of standard conditions	yield of **3a**[b]	er of **3a**[c]
1	none	70	99:1
2	**6** instead of **5**	62	99:1
3	**7** instead of **5**	66	97:3
4	Cs_2CO_3 instead of DBU	64	97:3
5	DABCO instead of DBU	66	99:1
6	DIPEA instead of DBU	60	97:3
7	$PhCF_3$ instead of toluene	62	97:3
8	CH_2Cl_2 instead of toluene	58	96:4
9	THF instead of toluene	68	97:3
10	25 °C instead of 0 °C	72	97:3
11	without 4Å MS	65	99:1
12	1.4 equiv of **1a**	80	99:1
13[d]	3 h instead of 12 h	88 (86)[e]	99:1



[a] Standard conditions: **1a** (0.15 mmol), **2a** (0.125 mmol), **4** (1.2 equiv), **5** (10 mol %), DBU (1.2 equiv), 4Å MS (30 mg), toluene (1.3 mL), 0 °C and 12 h. [b] The yields were determined by ^{1}H NMR analysis of crude product using CH_2Br_2 as the internal standard. [c]The er value was determined by HPLC analysis on a chiral stationary phase. [d]1.4 equiv of **1a** and **4** were used. [e] Isolated yield is given in parenthesis.

analysis.[26] Interestingly, this atroposelective esterification approach was not only limited to 2-naphthol as a nucleophilic coupling partner. The desired product **3x** was formed in 70% yield with >99.5:0.5 er using 1-naphthol as the nucleophile. The use of 9-phenanthrol and sesamol as the acylating agents afforded the desired products in high yields and er values (**3y**, **3z**). The indole and quinoline-derived alcohols also worked indicating the versatility of the current methodology (**3aa**, **3ab**). Furthermore, 2-naphthalenethiol was also a suitable nucleophile furnishing the expected axially chiral diaryl ether in 60% yield with 95:5 er (**3ac**).

To get insight into the mechanism of regulating the enantioselectivity in the present case, two control experiments were performed. When the reaction of **1a** and **2a** was performed using 0.55 equiv of oxidant **4** (instead of 1.4 equiv) under the optimized conditions, the desired product **3a** was formed in 52% yield and 97:3 er and the diester product **8a** was not observed (Scheme 3, eq 1). The formation of **3a** in high er sheds light on the crucial role of desymmetrization (k_R:k_S = 32:1) in controlling enantioselectivity. Moreover, treatment of racemic **3a** with **2a** under the optimized conditions using 0.55 equiv of **4** resulted in the smooth kinetic resolution with **3a** formed in 35% yield and 99:1 er (*s* factor = 14), and the diester **8a** was isolated in 52% yield (eq 2). It is reasonable to assume that **3a** survives esterification and ***ent*-3a** undergoes esterification to form the diester **8a**. These studies tend to indicate that the origin of enantioselectivity in the present reaction is via the desymmetrization alone and rule out the possibility of cooperative desymmetrization and a downstream kinetic resolution.[27]

Next, the thermal stability of C-O axis of diaryl ethers was examined to get insight into the racemization barrier of these compounds. The change in ee value of the aldehyde **3a** was determined while heating in toluene. Significantly, the ee value remained constant up to ~60 °C demonstrating the restricted rotation around the C-O bond in **3a**. The increase in temperature beyond 60 °C enabled the rotation around the C-O axis. The ee reached 0% at ~130 °C indicating complete racemization (Figure 1). On the other hand, compound **3r** exhibited configurational stability up to ~80 °C, while it was converted to racemic at ~150 °C. We have also measured the racemization barrier of diaryl ethers **3a** and **3r** experimentally by using Curran's method.[28] The experimental value of $\Delta G_{rot}^{\ddagger}$ for compound **3a** was found to 30.5 kcal/mol by measuring ee values at different time intervals while maintaining a temperature of 105 °C. Similarly, for compound **3r**, the racemization barrier was 31.2 kcal/mol. The half-life of racemization for both the compounds was also determined. At 25 °C, the $t_{1/2}$ of racemization for compound **3a** and **3r** was calculated to be 43.8 and 142.6 years respectively.

Further, various functionalizations of **3a** were carried out to demonstrate the synthetic utility of the present methodology. The reduction of **3a** using $NaBH_4$ in methanol afforded the benzyl alcohol derivative **9a** in 85% yield and 97:3 er (Scheme 4). The addition of PhMgBr to the aldehyde moiety of **3a** resulted in the diastereoselective synthesis of the secondary alcohol **10a** in 80% yield, >20:1 dr and 97:3 er. Moreover, treatment of **3a** with 1-naphthol and ***rac*-5** under the oxidative conditions furnished the C-O axially chiral unsymmetrical diester product **11a** in 62% yield with 98:2 er. In addition, the Baeyer-Villiger oxidation of **3a** resulted in the formation of the corresponding axially chiral phenol derivative **12a** in 55% yield and 95:5 er. The Wittig reaction of **3a** using the stable ester-bearing ylide resulted in the formation of the target olefin derivative **13a** in 78% yield, 8:1 *E:Z* ratio and 98:2 er. Finally, the reductive amination of **3a** was performed using $TsNH_2$ under acidic conditions to form the axially chiral benzyl amine derivative **14a** in 80% yield with 97:3 er.

In conclusion, we have demonstrated the first NHC-organocatalytic approach for the generation of C-O axially chiral diaryl ether derivatives. Mechanistically, the reaction involves NHC-catalyzed desymmetrization of isophthalaldehyde derivatives bearing prochiral dual C-O axis resulting in the synthesis of various axially chiral diaryl ether derivatives in excellent yields and selectivities. The rotation barrier experiment indicates good configurational stabilities of C-O bonds of diaryl ethers allowing diverse functionalization of products. The present work on NHC catalysis in creating challenging C-O axially chiral diaryl ethers offers an appealing alternative path towards developing novel atropisomerism with well demonstrated broad applications.

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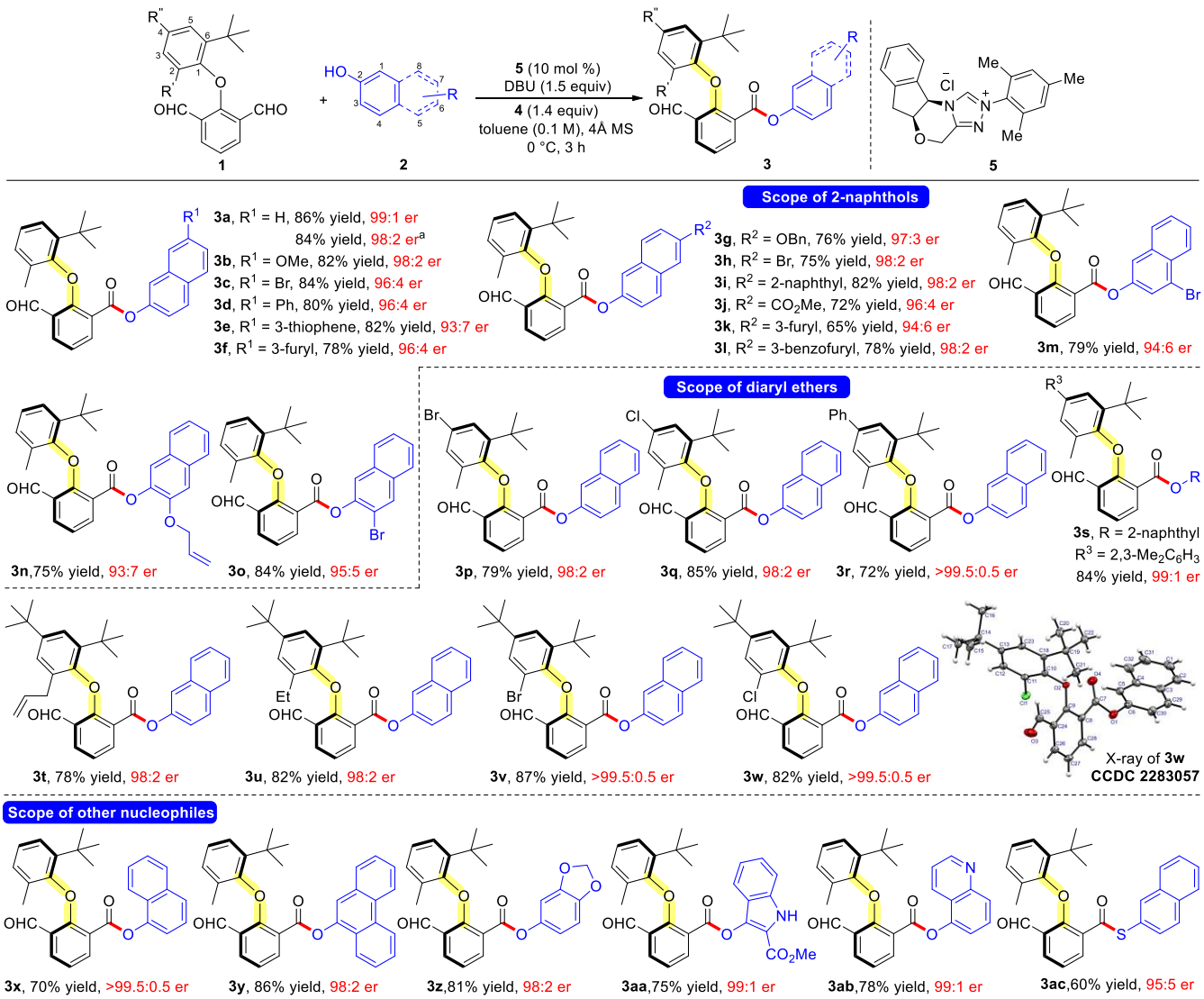
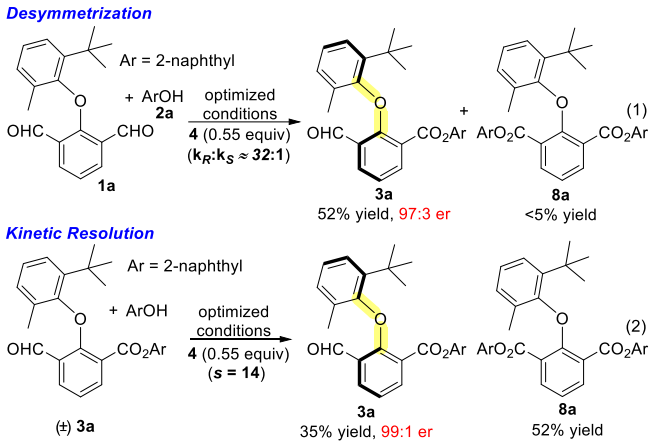
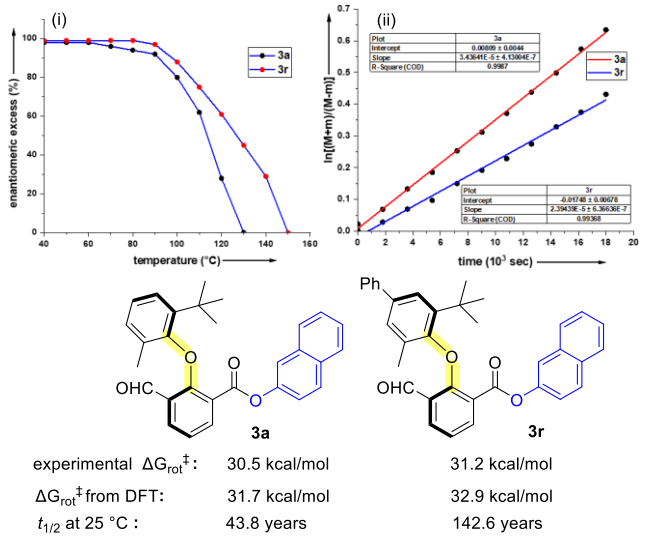


Scheme 2. Substrate scope of the reaction: General reaction conditions: **1** (0.28 mmol), **2** (0.2 mmol), **5** (10 mol %), DBU (1.5 equiv), **4** (1.4 equiv), 4Å MS (50 mg), toluene (2.0 mL), 0 °C and 3 h. Given are isolated yield of the column chromatography purified products. The er was established by HPLC analysis on a chiral stationary phase. [a] The yield and er for 1.0 mmol scale reaction.



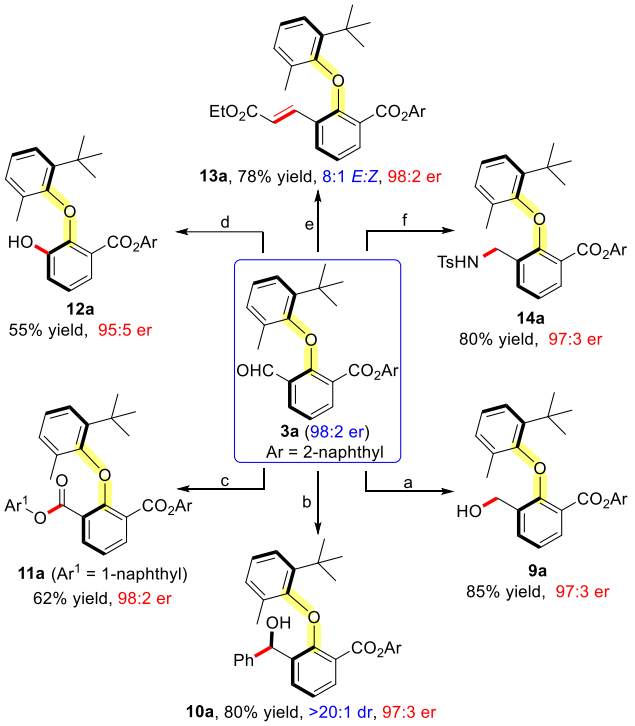
Scheme 3. Control experiments

the C-O racemization barrier using DFT studies. We thank Dr. Kuruva Balanna, Mr. Soumen Barik, and Ms. Shilpa Barik for helpful discussions.



	3a	3r
experimental $\Delta G_{rot}^{\ddagger}$:	30.5 kcal/mol	31.2 kcal/mol
$\Delta G_{rot}^{\ddagger}$ from DFT:	31.7 kcal/mol	32.9 kcal/mol
$t_{1/2}$ at 25 °C :	43.8 years	142.6 years

Figure 1. Determination of the racemization barrier: (i) effect of C-O bond rotation on temperature (ii) plot for determining the racemization barrier.



Scheme 4. Synthetic transformations of axially chiral diary ethers: Reaction conditions: a) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 3 h; b) PhMgBr (1.1 equiv), THF, 0 °C, 12 h; c) 1-naphthol (1.1 equiv), ***rac-5*** (10 mol %), DBU (1.5 equiv), **4** (1.4 equiv), 4Å MS , toluene, 0 °C and 3 h; d) *m*-CPBA (1.2 equiv), CH_2Cl_2, 0 °C, 12 h; e) ethyl 2-(triphenyl-λ^5-phosphaneylidene)acetate (1.5 equiv), CH_2Cl_2, 25 °C, 12 h; f) $TsNH_2$ (1.2 equiv), $Ti(OiPr)_4$ (4.0 equiv), DCM, 40 °C, 12 h then $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 3 h.

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[26] CCDC 2283057 (**3w**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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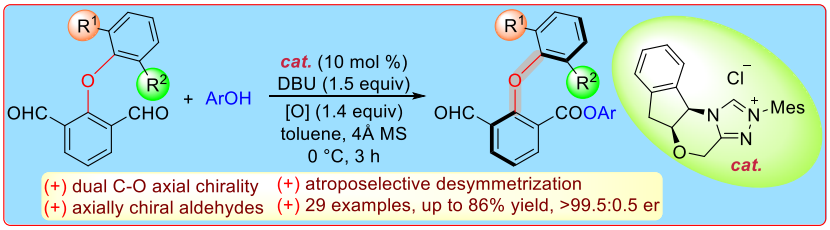

The atroposelective synthesis of C-O axially chiral diaryl ethers is demonstrated by the N-heterocyclic carbene (NHC)-catalyzed enantioselective esterification of dialdehyde containing diaryl ethers. The reaction proceeds via a desymmetrization of isophthalaldehyde derivatives bearing prochiral dual C-O axis affording atropoisomeric diaryl ethers with broad scope under mild conditions.