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Synthesis of axially chiral diaryl ethers *via* NHC-catalyzed atroposelective esterification†‡

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Axially chiral diaryl ethers bearing two potential axes find unique applications in bioactive molecules and catalysis. However, only very few catalytic methods have been developed to construct structurally diverse diaryl ethers. We herein describe an NHC-catalyzed atroposelective esterification of prochiral dialdehydes, leading to the construction of enantioenriched axially chiral diaryl ethers. Mechanistic studies indicate that the matched kinetic resolutions play an essential role in the challenging chiral induction of flexible dual-axial chirality by removing minor enantiomers *via* over-functionalization. This protocol features mild conditions, excellent enantioselectivity, broad substrate scope, and applicability to late-stage functionalization, and provides a modular platform for the synthesis of axially chiral diaryl ethers and their derivatives.

Introduction

Atropisomerically enriched chiral frameworks find widespread applications in materials science,[1] bioactive molecules,[2] and asymmetric catalysis.[3] Accordingly, significant progress has been achieved in the catalytic construction of axially chiral scaffolds, including biaryl atropisomers,[4] axially chiral styrenes,[5] amines,[6] amides,[7] boranes,[8] *etc.* As distinctive atropisomers, axially chiral diaryl ethers bearing two potential axes find unique applications in bioactive molecules.[9] However, construction of C–O axially chiral diaryl ethers has received limited attention from organic chemists, probably owing to the challenges in more flexible dual-axial chirality control. In 1998, Fuji and coworkers[10a] discovered the first atropisomerism in diaryl ethers.[10] In 2008, the Clayden group[11] pioneered the first enantioselective synthesis of an axially chiral diaryl ether, that with sole dual-axial chirality. Developing a catalytic methodology for the asymmetric construction of diaryl ether-type atropisomers is highly desirable but more challenging. In this regard, Turner, Clayden, and co-workers[12] developed an unprecedented biocatalyzed enantioselective construction of diaryl ether atropisomers *via* desymmetrizative oxidation/reduction of diols/dialdehydes (Scheme 1a). Even with the

conceptual breakthrough, only one example of axially chiral diaryl ether was obtained. The Gustafson group[13] developed the first organocatalyzed chiral induction through enantioselective C–H alkylation, although yields and enantioselectivities were not high (Scheme 1b). Very recently, the Zeng and Zhong[14] group developed elegant chiral phosphoric acid (CPA) catalyzed asymmetric reductive amination of axially prochiral diaryl ethers (Scheme 1c) *via* dynamic kinetic resolution (DKR). Later, Yang's[15] group developed CPA-catalyzed electrophilic remote amination of axially prochiral diaryl ethers, leading to highly enantioselective construction of diaryl ether-type atropisomers (Scheme 1d). Despite such significant progress, the development of a novel catalytic methodology for direct access to diaryl ether-type atropisomers is still an emerging area and in great demand.

On the other hand, N-heterocyclic carbene catalysts (NHCs) exhibit unique reactivity in activating the carbonyl group.[16] NHC-catalyzed transformations provide attractive alternatives for constructing axially chiral compounds[17] *via* desymmetrization,[18] or (dynamic) kinetic resolution.[19] NHC-catalyzed desymmetrization of axially prochiral dialdehydes[18g] provides chiral-NHC-bounded atropisomeric Breslow Intermediates (BIs) as critical intermediates, leading to the direct access to highly atropisomerically enriched aldehydes *via* two-step single electron oxidation and nucleophilic coupling. At the same time, the second enantiodifferentiation step for aldehydes could amplify the stereoinduction ability of the chiral catalyst, which might provide opportunities for challenging chiral induction of flexible dual-axial chirality, in analogy to the Horeau principle.[20] As part of our continued interests in NHC-catalyzed transformations[21] and asymmetric catalysis,[18g,22] we now report an asymmetric esterification approach to axially chiral diaryl

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a) Biocatalyzed construction of diaryl ether atropisomers. (Turner & Clayden, **2010**)

b) Chiral PTC-catalyzed C–H alkylation (Gustafson, **2018**)

c) CPA-catalyzed DKR reductive amination. (Zhong & Zeng, **2023**)
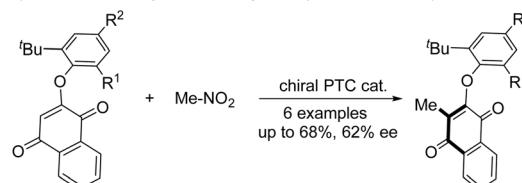
d) CPA-catalyzed desymmetrizative electrophilic amination. (Yang, **2023**)
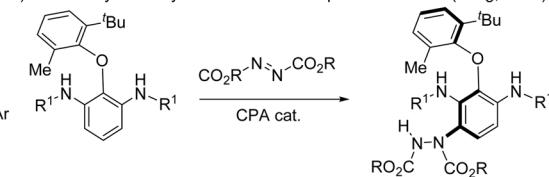
e) This work: NHCs-catalyzed atroposelective synthesis of C–O dual-axially chiral diaryl ethers employing stereoinduction amplification strategy.
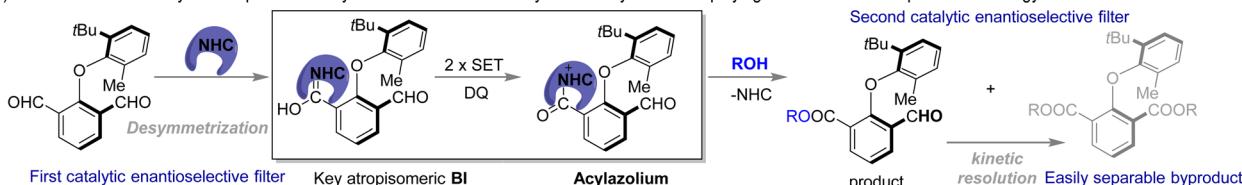
Scheme 1 Catalytic asymmetric construction of diaryl ether-type atropisomers.

ethers by chiral NHC-catalyzed desymmetrization of dicarbaldehydes[23] with alcohols/phenols[23a–c,24] (Scheme 1e). The over-esterification could act as an additional stereocontrolling filter to improve the enantioselectivity, leading to excellent chiral induction for C–O axially chiral diaryl ethers.

Results and discussion

To probe the feasibility of our designed reaction, we commenced our investigation employing dicarbaldehydes (**1a**) and MeOH (**2a**) as the reactants in the model esterification reaction. Encouragingly, in the initial study, treatment of **1a** and **2a** in DCM employing C1 as the catalyst, DQ (1.2 equiv.) as the oxidant, and Cs_2CO_3 (1.5 equiv.) as the base at 0 °C under a N_2 atmosphere for 72 h yielded the desired esterification product **3aa** in 91% yield and 90% ee, along with a 5% diester byproduct **4aa** (Table 1, entry 1). Next, a series of NHCs were screened (entries 2–9), and C1 was proven to be the best choice for this atroposelective esterification. Switching the Mes group of C1 to 2,4,6-triBrC_6H_2 (entry 2) or C_6F_5 (entry 5) had nearly no reactivity. The screening of various solvents indicated that DCM was the best solvent for this esterification (entries 10–16). Most of the solvents, such as DCE, MTBE, EtOAc, and toluene, gave acceptable yields and enantioselectivities. THF exhibited excellent chiral induction, delivering **3aa** in 68% yield and 98% ee; however, diester **4aa** was identified with a 19% yield because of high activity.

Switching the catalyst loading to 15 mol% caused an increased yield of diester **4aa** (11%), and **3aa** was isolated in 88% yield and 94% ee (entry 17). This result indicates that the formation of byproduct **4aa** could impact the enantioselectivity of **3aa**. Unfortunately, the screening of various bases failed to

afford improved results (entries 18–21); thus, entry 17 was identified as the standard conditions for the variation of the substrate.

With the optimized conditions in hand, the scope and limitation of the atroposelective esterification system were examined (Scheme 2). First, the substrate scope of the alcohols was evaluated by the coupling with 2-(2-(*tert*-butyl)-6-methylphenoxy)isophthalaldehyde (**1a**) (Scheme 2A). A series of alcohols bearing primary alkyl (**3aa, 3ab**), secondary alkyl (**3ac, 3ad**), strained rings (**3ac, 3ad**), trifluoromethyl (**3ae**), TMS (**3af**), terminal (**3ag**) and internal (**3ah**) alkenyl, alkynyl (**3ai**), and benzyl groups (**3aj**) were well tolerated, delivering diaryl ether-type atropisomers in 55–88% yield and 83–96% ee. The absolute stereochemistry of **3aa** was determined as the *S* configuration by HPLC compared with the known compounds[14] (for details see the ESI†). Phenol was also a suitable substrate, generating **3ak–3am** with up to 96% ee. Fused ring (**3an**), pyridine (**3ao**), isoquinoline (**3ap**), benzo-thiophene (**3aq**) benzofuran (**3ar**), and indole (**3as**) substituted phenols were all well tolerated, offering desired products with high enantioselectivity (in most cases >90% ee) and moderate yield (48–79%). Mild conditions and broad functional group tolerance encouraged us to carry out late-stage functionalization of natural products and bioactive compounds. Natural products including carvacrol (**3au**) and sesamol (**3av**), bioactive molecules such as methyl salicylate (**3aw**), paroxypropione (**3ax**), tyrosine (**3ay**), estrone (**3az**), estradiol (**3aa′**), and ethynyl estradiol (**3ab′**), and drugs such as acetaminophen (**3at**) and vitamin E (**3ac′**) were well tolerated in this system and delivered the axially chiral diaryl ethers in acceptable yields with good to excellent stereoselectivities (84–99% ee, or 20 : 1 dr). Non-cyclic secondary alcohols such as *i*PrOH (41%, 60% ee)

Table 1 Optimization of the reaction conditions[a]

Entry	NHC cat.	Solvent	Base	3aa (%) Yield ee	4aa (%)
1	C1	DCM	Cs₂CO₃	91 90	5
2	C2	DCM	Cs₂CO₃	7 35	Trace
3	C3	DCM	Cs₂CO₃	73 86	2
4	C4	DCM	Cs₂CO₃	84–67	11
5	C5	DCM	Cs₂CO₃	9–40	Trace
6	C6	DCM	Cs₂CO₃	74 91	2
7	C7	DCM	Cs₂CO₃	40 87	Trace
8	C8	DCM	Cs₂CO₃	59–16	31
9	C9	DCM	Cs₂CO₃	60 41	35
10	C1	CHCl₃	Cs₂CO₃	83 75	6
11	C1	DCE	Cs₂CO₃	86 91	10
12	C1	THF	Cs₂CO₃	68 98	19
13	C1	MTBE	Cs₂CO₃	87 91	8
14	C1	EtOAc	Cs₂CO₃	81 90	12
15	C1	MeCN	Cs₂CO₃	82 80	16
16	C1	Toluene	Cs₂CO₃	79 93	11
17[b]	**C1**	**DCM**	**Cs₂CO₃**	**89 (88) 94**	**11**
18[b]	C1	DCM	K₂CO₃	80 89	11
19[b]	C1	DCM	K₃PO₄	90 90	10
20[b]	C1	DCM	DBU	80 91	9
21[b]	C1	DCM	DMAP	82 89	8

[a] Conditions: **1a** (0.1 mmol), **2a** (5.0 equiv.), NHC (10 mol%), base (1.5 equiv.) and DQ (1.2 equiv.), solvent (1.0 mL), 0 °C, N₂ atmosphere, 72 h. Yields were determined by ¹H NMR spectroscopic analysis of the crude reaction mixture employing CH_2Br_2 as the internal standard; ee was determined by chiral-phase HPLC analysis. [b] **C1** (15 mol%).

and Ph₂CHOH (70%, 74% ee) were tested; however, they gave decreased enantioselectivity. For tertiary alcohols (*t*BuOH), the esterification did not work at all. Other S-centered and N-centered nucleophiles were employed but failed to give satisfactory results (Scheme S1†).

Then, the scope of axially prochiral dialdehydes was explored (Scheme 2B). Dicarbaldehydes bearing halogens (**3ba**, **3ca**), pyridinyl (**3do**), indolyl (**3eo**), substituted aryl (**3fr–3ir**, **3kr**), naphthyl (**3jr**), thienyl (**3lr**), and furyl (**3mr**) on the aromatic ring could deliver the desired products with excellent enantioselectivity (in all cases >90% ee). Dicarbaldehydes with electron-donating methyl groups were well tolerated, giving the desired products **3nr** and **3or** with excellent ee. When the blocking group (methyl) of dicarbaldehyde was switched to bromine, nearly no reduction of ee was detected (**3nr** *vs* **3or**); however, when changing to the phenyl group, a drop in ee value to 77% was observed.

We conducted large-scale synthesis and follow-up transformations to further evaluate the synthetic value of the atroposelective esterification system. We successfully achieved gram-scale synthesis, obtaining compound **3ar** with 70% yield and 96% ee (Scheme 3a). The racemization barrier of **3ar** was up to $\Delta G^{\neq}_{rac} = 134.05$ kJ mol⁻¹, corresponding to a half-life of 143.7 hours at 100 °C (*i*-PrOH). This relatively high racemization barrier of axially chiral diaryl ethers allows for excellent chiral retention in further transformations and thus might serve as a modular platform for diaryl ether-type atropisomers. Treatment of **3ar** with P-(1-diazo-2-oxopropyl)-dimethyl ester produces transesterified alkyne **7a** in 71% yield and 96% ee (Scheme 3b). Wittig reaction of **3ar** could generate olefin-substituted diaryl ether-type atropisomers (Scheme 3c, 61%, 96% ee). **3ar** could be reduced to **7c** with 75% yield and 96% ee employing NaBH₄ in THF/MeOH (Scheme 3d). Further treatment of **7c** with 4-methoxy aniline in PhMe employing LiHMDS as the base results in an axially chiral amide (Scheme 3e). Condensation of the aldehyde group with NH₂OH generated an oxime in 65% yield and 96% ee (Scheme 3f). Oxidation of the aldehyde group or hydrolysis of ester groups could yield chiral carboxylic acid **7f** and **7g** in good yields (Scheme 3g and h). Further condensation of **7g** with diethylamine delivered amide **7h** in 55% yield and 95% ee (Scheme 3i). Furthermore, cyclization of **3ar** with TsNHNH₂ and 2-bromo-3,3,3-trifluoropropene delivered pyrazole substituted diaryl ether **7i** (Scheme 3j). No detectable enantioselectivity erosion was observed in all cases.

A series of mechanistic investigations were then conducted to probe the catalytic cycle and enantio-determining step of this esterification reaction (Scheme 4). Isotope exchange experiments resulted in no deuterium incorporation at the aldehyde group of **3aa**-*d₃*; reversible formation of the Breslow intermediate could be excluded (Scheme 4a). A parallel KIE experiment employing **1a** and **1a**-*d₂* in the coupling with MeOH gives KIE = 3.1 (Scheme 4b), indicating that BI formation might be involved in the rate-determining step. While optimizing the conditions, we found that the formation of diester byproducts could increase the ee value of the main product. We carried out a control experiment, and the results are shown in Scheme 4c. When the esterification was carried out with 60 mol% DQ, *S*-**3ar** (51%, 90% ee) was obtained with <5% **4ar**; compared with **3ar** (98% ee) under standard conditions, an additional stereo-controlling filter might exist beyond the desymmetrization. Furthermore, racemic **3ar** could undergo efficient kinetic resolution, delivering *S*-**3ar** (38%, 98% ee) along with **4ar** (56%). The minor enantiomer obtained after desymmetrization reacted fast in an over-functionalization ($V_R : V_s \approx 4 : 1$). Removing minor enantiomers by the formation of diester byproducts is critical in improving the enantioselectivity (90% ee to 98% ee). On investigating the linear effect of desymmetrization of aldehydes, a linear correlation between the ee value of **C1** and product **3ar** was observed (Scheme 4d). The absence of a nonlinear effect indicated that a single NHC is presumably involved in the stereo-determining step.
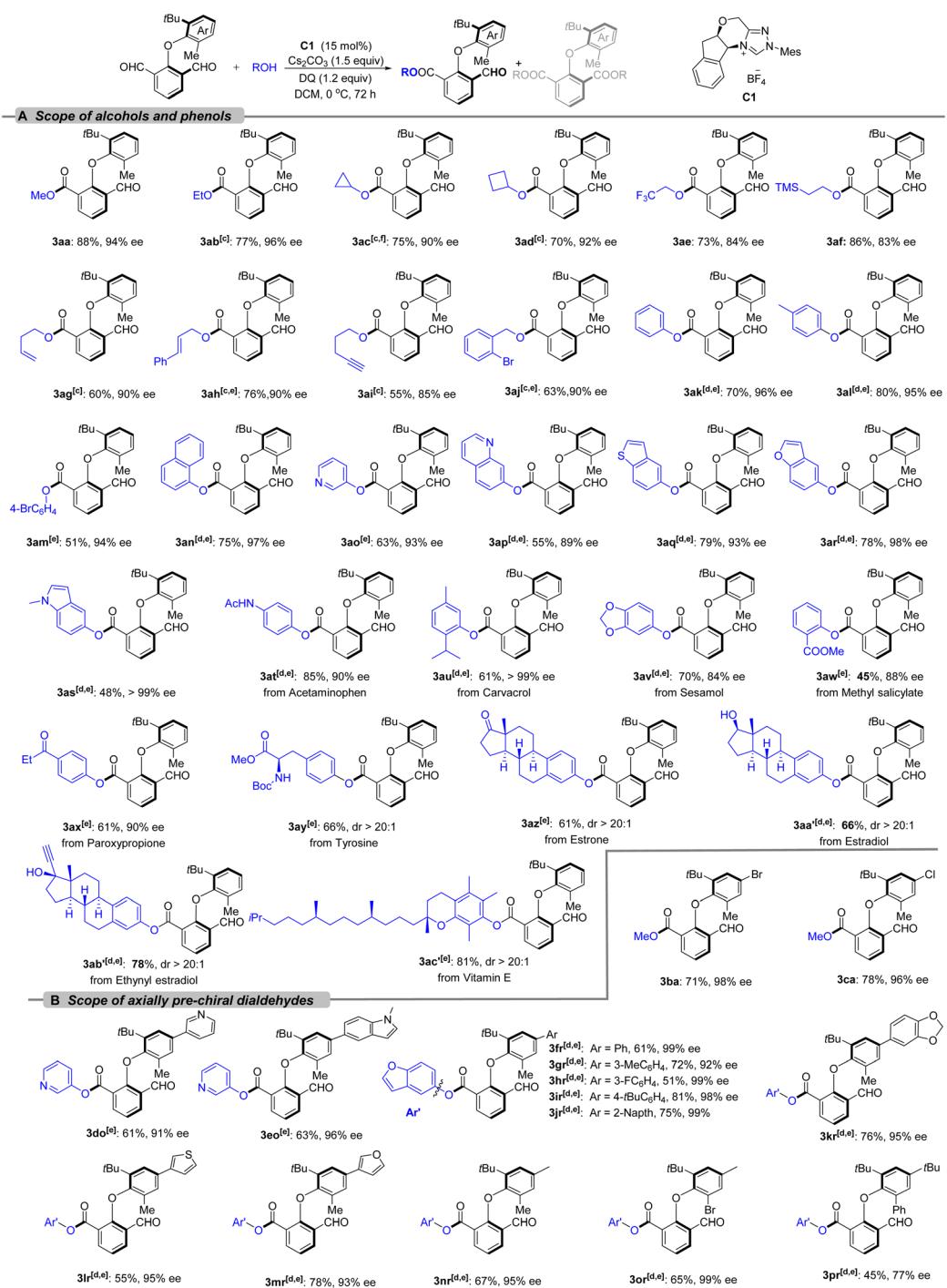
Scheme 2 Scope for the desymmetrizing esterification of axially pre-chiral dialdehydes.[a,b] [a] Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.5 mmol), **C1** (15 mol%), DQ (1.2 equiv.), Cs$_2$CO$_3$ (1.5 equiv.), and dry DCM (1.0 mL) at 0 °C under a N$_2$ atmosphere for 72 h. [b] The isolated yield and ee were determined by chiral-phase HPLC analysis. [c] THF was used instead of DCM. [d] Reactions were performed at −20 °C. [e] Reactions were carried out with **2** (3.0 equiv.). [f] Reactions were carried out with **C1** (10 mol%).
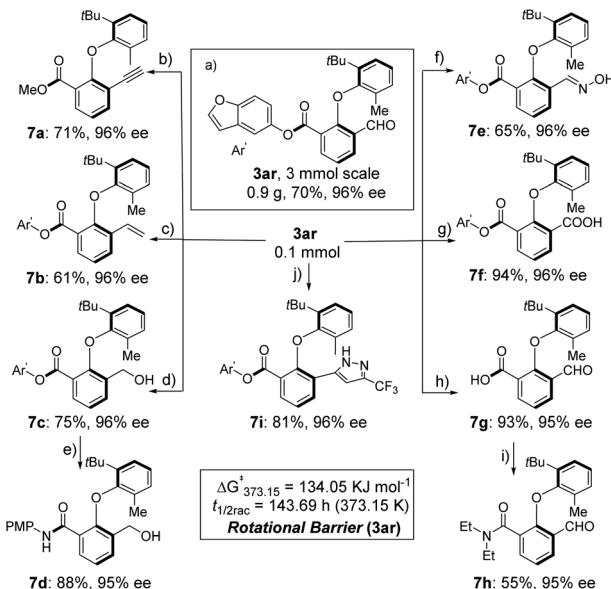
Scheme 3 Large-scale synthesis and follow-up transformations. Reaction conditions: (a) **C1** (15 mol%), Cs₂CO₃ (1.5 equiv.), DQ (1.2 equiv.), dry DCM (0.1 M), −20 °C, N₂, 72 h; (b) P-(1-diazo-2-oxo-propyl)-dimethylester (1.5 equiv.), K₂CO₃ (2.0 equiv.), MeOH (1 mL), rt, 12 h; (c) [MePPh₃]⁺Br⁻ (1.2 equiv.), ⁿBuLi (1.2 equiv.), dry THF (0.1 M), 0 °C, 30 min, then **3ar**, rt, 12 h; (d) NaBH₄ (1.0 equiv.), THF/CH₃OH = 3 : 1 (0.1 M), 0 °C, 12 h; (e) 4-methoxyaniline (2.0 equiv.), LiHMDS (3.0 equiv.), PhMe (1 mL), rt, 12 h; (f) NaOAc (2.0 equiv.), NH₂OH·HCl (2.0 equiv.), MeOH (0.9 mL), H₂O (0.1 mL), rt, 3 h; (g) NaClO₂ (3.7 equiv.), NaH₂PO₄ (5.0 equiv.), 2-methylbut-2-ene (13.0 equiv.), ᵗBuOH (0.15 M), rt, overnight; (h) LiOH·H₂O (4.0 equiv.), THF and H₂O (v/v = 1 : 1), rt, 24 h; (i) diethylamine (1.2 equiv.), EDCl (1.5 equiv.), DMAP (1.5 equiv.), DCM (1.5 mL), rt, 24 h; (j) TsNHNH₂ (1.2 equiv.), 2-bromo-3,3,3-trifluoropropene (2.0 equiv.), DBU (3.0 equiv.), PhMe (1 mL), 60 °C, 6 h.
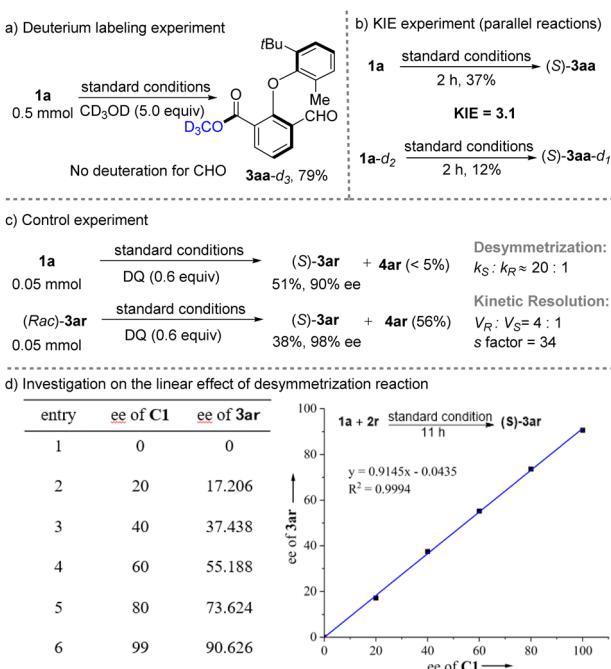
Scheme 4 Mechanistic studies and proposed mechanism. $s = \ln[(1 - \text{Conv.})(1 - ee_s)]/\ln[(1 - \text{Conv.})(1 + ee_s)]$.

Conclusions

In summary, we have developed NHC-catalyzed facile and robust desymmetrization of readily accessible dialdehydes, leading to direct access to axially chiral diaryl ether derivatives. Mechanistic studies indicate that esterification proceeds via irreversible rate- and enantio-determination activation of the aldehyde followed by oxidative esterification. The matched kinetic resolutions play a critical role in enhancing the enantioselectivity by sacrificing minor enantiomers. The synthetic value of the esterification was further highlighted by the late-stage functionalization of natural products, bioactive molecules, and medicines (10 examples, up to 99% ee or >20 : 1 dr), and scale-up synthesis. This protocol features excellent chiral induction, mild conditions, good functional group tolerance, and broad substrate scope. The NHC-catalyzed desymmetrizative functionalization of axially prochiral diaryl ethers may provide modularized platforms for synthesizing challenging diaryl ether-type atropisomers and their derivatives.

Data availability

Detailed synthetic procedures and complete characterization data for all new compounds can be found in the ESI.‡

Author contributions

G. Z. and Q. Z. conceived the concept and directed the investigations. Y. W. conducted the majority of the experimental work. X. G., H. Z., M. L., and T. L. contributed to the preparation of substrates. J. S., G. Z., and Q. Z. wrote the manuscript with input from all the authors.

Conflicts of interest

There are no conflicts to declare.

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