



NHCs-catalyzed enantioselective synthesis of biaryl axially chiral imides

Yingtao Wu^{1,†}, Xin Guan^{1,†}, Xueyun Lu^{1,†}, Kehan Jiao², Jiaqiong Sun^{1,2,*}, Lihan Zhu^{1,*}, Xinhu Hu^{3,*}, Jiao Qu², Guangfan Zheng^{1,*}, Qian Zhang¹

¹Key Laboratory of Functional Organic Molecule Design & Synthesis of Jilin Province, Department of Chemistry, Northeast Normal University, Changchun 130024, Jilin, China.

²School of Environment, Northeast Normal University, Changchun 130117, Jilin, China.

³School of Chemistry and Chemical Engineering, Shenyang University of Chemical Technology, Shenyang 110142, Liaoning, China.

[†]These authors contributed equally to this work.

***Correspondence to:** Jiaqiong Sun, Key Laboratory of Functional Organic Molecule Design & Synthesis of Jilin Province, Department of Chemistry, Northeast Normal University, Changchun 130024, Jilin, China. E-mail: [sunjq295@nenu.edu.cn](mailto:sunj295@nenu.edu.cn)

Lihan Zhu, Key Laboratory of Functional Organic Molecule Design & Synthesis of Jilin Province, Department of Chemistry, Northeast Normal University, Changchun 130024, Jilin, China. E-mail: zhulh168@nenu.edu.cn

Xinhu Hu, School of Chemistry and Chemical Engineering, Shenyang University of Chemical Technology, Shenyang 110142, Liaoning, China. E-mail: jlhuxinhu@163.com

Guangfan Zheng, Key Laboratory of Functional Organic Molecule Design & Synthesis of Jilin Province, Department of Chemistry, Northeast Normal University, Changchun 130024, Jilin, China. E-mail: zhenggf265@nenu.edu.cn

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Abstract

The synthesis of biaryl axially chiral amides and their derivatives—compounds that have shown promise as additives or catalysts in asymmetric catalysis—has traditionally relied on transition-metal catalysts. Herein, we report an NHC-catalyzed organocatalytic atropenantioselective amidation between axially prochiral biaryl dialdehydes and amides that efficiently affords axially chiral imides. This method operates under metal-free and mild conditions, exhibits broad functional group tolerance and substrate scope, and delivers products with excellent enantioselectivities. Furthermore, a wide variety of axially chiral imides, amides, and related derivatives can be accessed through enantio-retentive transformations, offering a versatile and attractive strategy for their synthesis.

Keywords: NHC catalysis, atropenantioselective amidation, desymmetrization, biaryl axially chiral imides

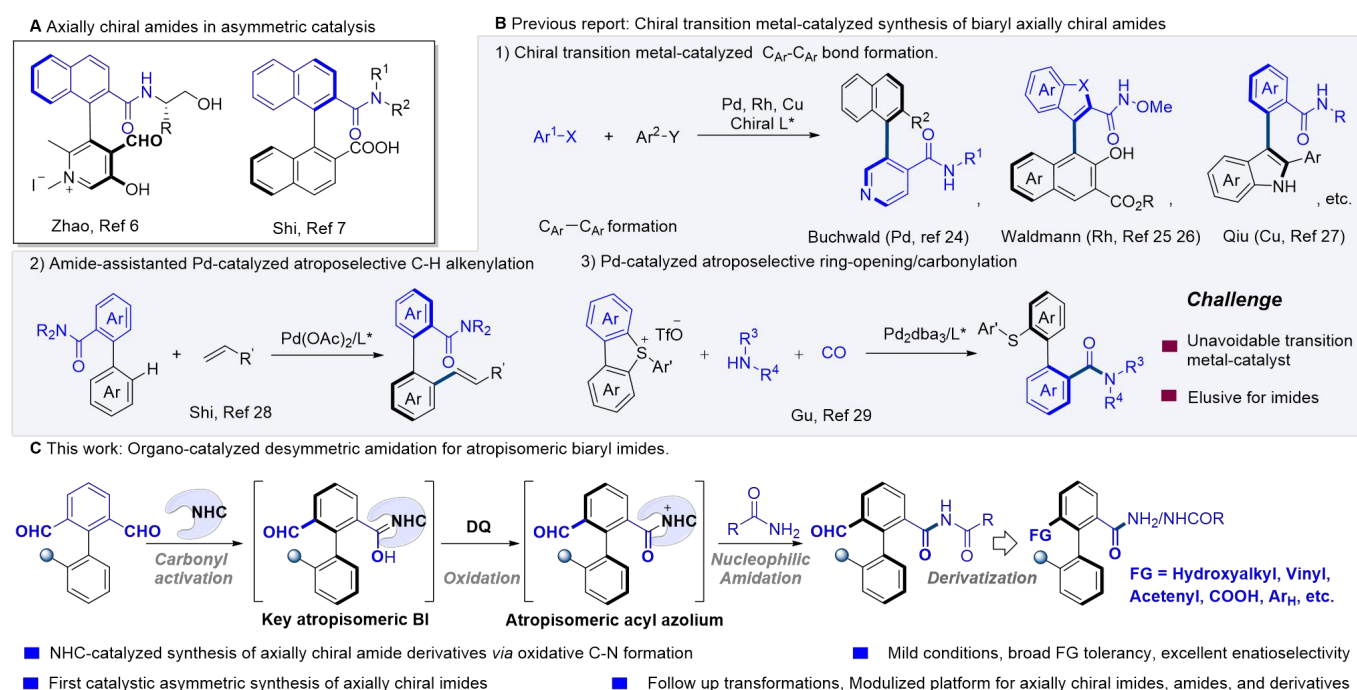
1. Introduction

The asymmetric synthesis of biaryl axially chiral frameworks has attracted considerable interest owing to their widespread presence in biologically active molecules^[1,2], pharmaceuticals^[3,4], and functional materials^[5,6], as well as their privileged role as chiral ligands and catalysts^[7–11]. Significant advances have been achieved in the construction of such axially chiral architectures^[12–17]. In particular, biaryl axially chiral amides and their derivatives have emerged as highly promising additives or catalysts in asymmetric reactions, exemplified by the carbonyl catalysis developed by Zhao *et al.*^[18,19] and their efficient application as chiral additives/ligands in asymmetric C–H functionalization by the Shi group^[20–23] (Scheme 1A). Despite the importance of axially chiral amides, catalytic methods for their synthesis remain underdeveloped. To date, only three primary strategies have been reported (Scheme 1B): (1) transition-metal-catalyzed enantioselective arylation of amide-substituted aromatics for constructing a C_{Ar}–C_{Ar} axis^[24–27]; (2) Pd-catalyzed atropenantioselective C–H functionalization using amides as directing groups^[28]; and (3) Pd-catalyzed atroposelective ring-opening/carbonylation of cyclic diarylsulfonium salts^[29]. Despite impressive progress, these successful transformations still rely on transition-metal catalysts. Achieving modular and flexible access to highly enantioenriched biaryl axially chiral amides and their derivatives under metal-free conditions remains a challenging issue. Furthermore, existing data indicate a lack of research on the catalytic synthesis of axially chiral biaryl imides.

The unique capability of N-Heterocyclic carbenes (NHCs) to activate carbonyl group has made them extensively utilized in organic synthesis and asymmetric catalysis^[30–41]. Desymmetrization^[42–46], that disrupts symmetry to convert *meso* or prochiral compounds



into enantiomerically enriched products, offers an attractive and efficient strategy for constructing complex chiral molecules. Systematic work by Chi^[47-50], Vesely^[51], Biju^[52], Ye^[53], and our group^[54,55] has demonstrated the utility of NHC-catalyzed enantioselective desymmetrization of prochiral dialdehydes, enabling access to carbonyl compounds bearing central^[47-49], planar^[50,51], and axial^[52-68] chirality. Mechanistically, NHC catalysis generates chiral Breslow intermediates from dialdehydes, which then undergo functionalization to afford enantioenriched products. We envisioned that NHC-catalyzed desymmetrization of axially prochiral biaryl dialdehydes could provide a viable route to challenging asymmetric amidations^[69-77] with high reactivity and selectivity. However, several obstacles must be overcome: (1) precise modulation of nucleophilicity is essential to avoid condensation between the amidating reagent and the aldehydes; and (2) over-functionalization of the dialdehyde substrates must be controlled. As part of our continuous research in NHC catalysis^[78-83] and axial chirality^[54,55,64,67,84], we herein report the first enantioselective synthesis of axially chiral biaryl imides via NHC-catalyzed desymmetrization of biaryl dialdehydes with amines (Scheme 1C).



Scheme 1. Catalytic enantioselective synthesis of biaryl axially chiral amides/imides. DQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; NHC: N-heterocyclic carbene.

2. Experimental

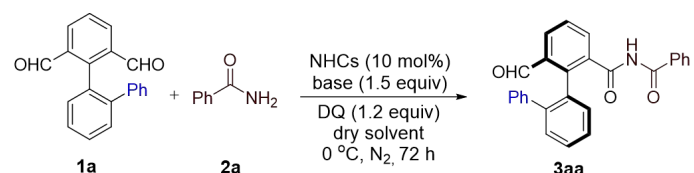
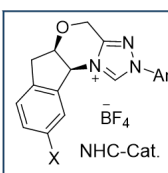
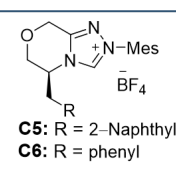
Representative Synthesis of Product R-3aa (standard conditions A): The reaction was conducted in a flame-dried screw-cap tube equipped with a Teflon-coated magnetic stir bar. Under a nitrogen atmosphere in a glovebox, the tube was charged with C1 (8.36 mg, 20 mol%), Cs₂CO₃ (49.0 mg, 1.5 equiv), and 1a (29 mg, 0.1 mmol). Anhydrous dichloromethane (1.0 mL) was added, and the mixture was stirred for 5 minutes. Benzamide 2a (36.3 mg, 3.0 equiv) and DQ (48 mg, 1.2 equiv) were then added. The tube was sealed with a septum-equipped PTFE screw cap (Thermo Scientific), removed from the glovebox, and the reaction mixture was stirred at 30 °C for 72 h. After the reaction was complete, as indicated by TLC analysis, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using petroleum ether/ethyl acetate 4:1 (v/v) to give product R-3aa. Further details are provided in the Supporting Information.

3. Results and Discussion

To validate our hypothesis, we initiated the investigation using biaryl dialdehyde 1a as a model axially prochiral substrate and benzamide 2a as the amidation reagent to identify optimal reaction conditions. Key optimization results are summarized in Table 1. In the initial trial, treatment of 1a (0.1 mmol) with 2a (3.0 equiv) and DQ (1.2 equiv) in DCM (1.0 mL), catalyzed by the aminoindanol-derived precatalyst C1 (10 mol%) bearing an *N*-mesityl group at 0 °C under a N₂ atmosphere for 72 h, afforded the desired amidation product 3aa with excellent enantioselectivity, albeit in low yield (Table 1, entry 1). Several solvents, including CHCl₃, THF, and MTBE, supported the transformation but were less effective than DCM (entries 2-4). The use of MeCN improved the yield at the cost of reduced enantioselectivity (entry 5). After evaluation, DCM was selected as the optimal solvent for further parameter screening. Alternative organic (DBU) and inorganic bases (K₂CO₃, K₃PO₄) proved inferior (entries 6-8). Notably, raising the temperature to 30 °C improved both the yield (50%) and enantioselectivity (99% ee, entry 9). We next examined structural variations of the NHC catalyst. Replacing the *N*-mesityl group in C1 with the sterically more hindered *tri*-ethyl-phenyl group (C2) led to a lower

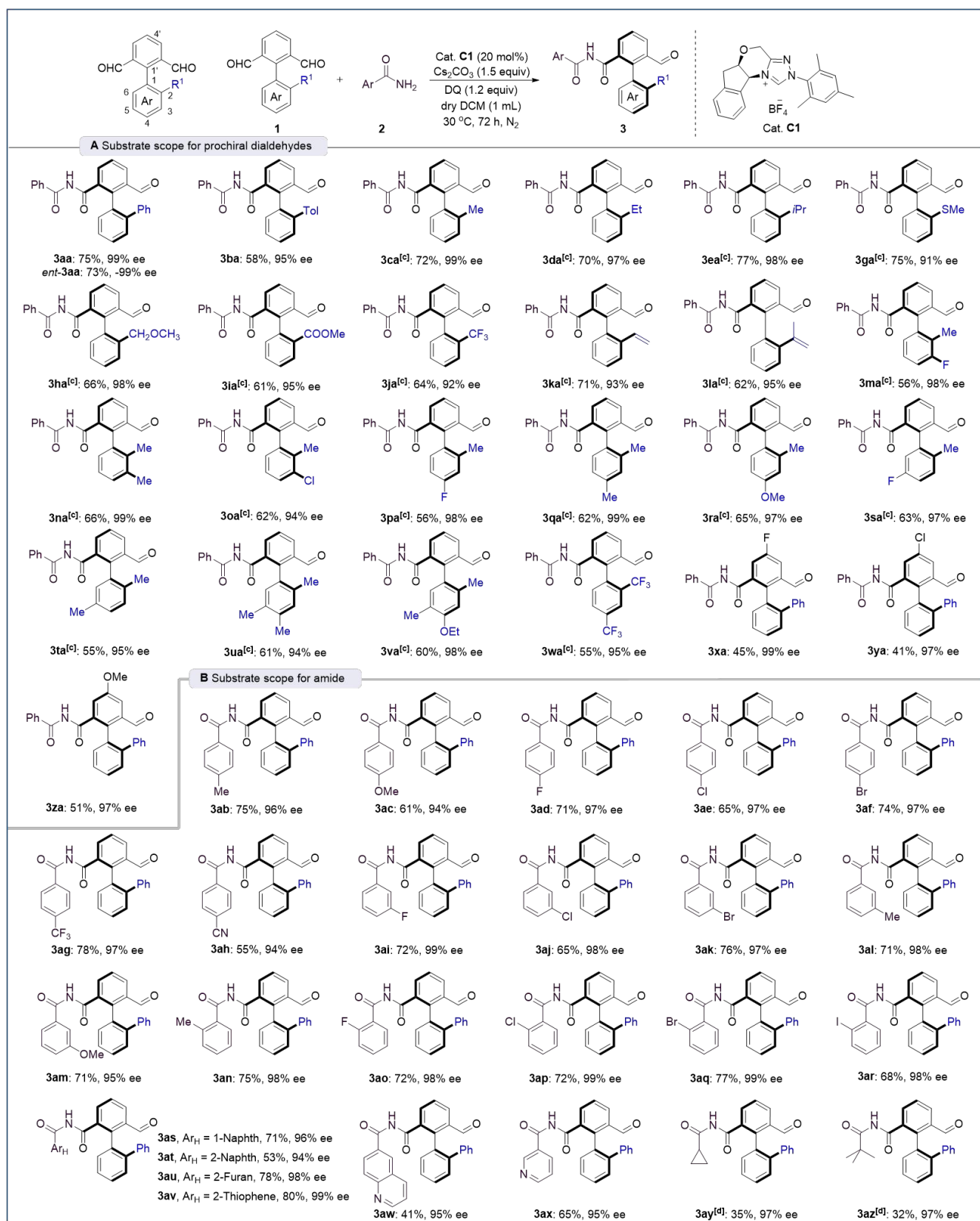
yield (34%) with no significant change in enantioselectivity (entry 10). The more electron-deficient pentafluorophenyl-substituted catalyst **C3** was ineffective (entry 11). Catalyst **C4**, featuring a bromo-substituted indanol ring, provided **3aa** in 40% yield and 99% ee (entry 12). Aryl-alanine-derived catalysts **C5** and **C6** did not improve the outcome (entry 13 and 14). Finally, increasing the catalyst loading to 20 mol% markedly enhanced the conversion, delivering **3aa** in 75% yield with retained enantioselectivity (99% ee, entry 15). Accordingly, the conditions in entry 15 were established as the standard for subsequent studies.

Table 1. Screening reaction conditions^a.

  C1: Ar = Mes, X = H C2: Ar = 2,6-diethylphenyl, X = H C3: Ar = C₆F₅, X = H C4: Ar = Mes, X = Br  C5: R = 2-Naphthyl C6: R = phenyl						
Entry	NHC Cat	Solvent	Base	Conv. (%)	3aa (%)	
					Yield	ee
1	C1	DCM	Cs ₂ CO ₃	40	35	98
2	C1	CHCl ₃	Cs ₂ CO ₃	50	30	95
3	C1	THF	Cs ₂ CO ₃	50	23	99
4	C1	MTBE	Cs ₂ CO ₃	30	17	60
5	C1	MeCN	Cs ₂ CO ₃	69	60	94
6	C1	DCM	DBU	65	31	94
7	C1	DCM	K ₂ CO ₃	30	10	70
8	C1	DCM	K ₃ PO ₄	29	Trace	--
9 ^b	C1	DCM	Cs ₂ CO ₃	65	50	99
10 ^b	C2	DCM	Cs ₂ CO ₃	60	34	98
11 ^b	C3	DCM	Cs ₂ CO ₃	--	Trace	--
12 ^b	C4	DCM	Cs ₂ CO ₃	79	40	99
13 ^b	C5	DCM	Cs ₂ CO ₃	98	60	87
14 ^b	C6	DCM	Cs ₂ CO ₃	50	18	32
15 ^{b,c}	C1	DCM	Cs ₂ CO ₃	98	77(75)	99

^a: Unless otherwise noted, all the reactions were carried out with **1a** (0.1 mmol), **2a** (3.0 equiv), NHCs (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 CH₂Br₂ as the internal standard; isolated yield was provided in parentheses. ee was determined by chiral-phase HPLC analysis; ^b: 30 °C; ^c: **C1** (20 mol%). DQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; HPLC: high-performance liquid chromatography; NHCs: N-Heterocyclic carbenes; DCM: dichloromethane; THF: tetrahydrofuran; MTBE: methyl tert-butyl ether; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

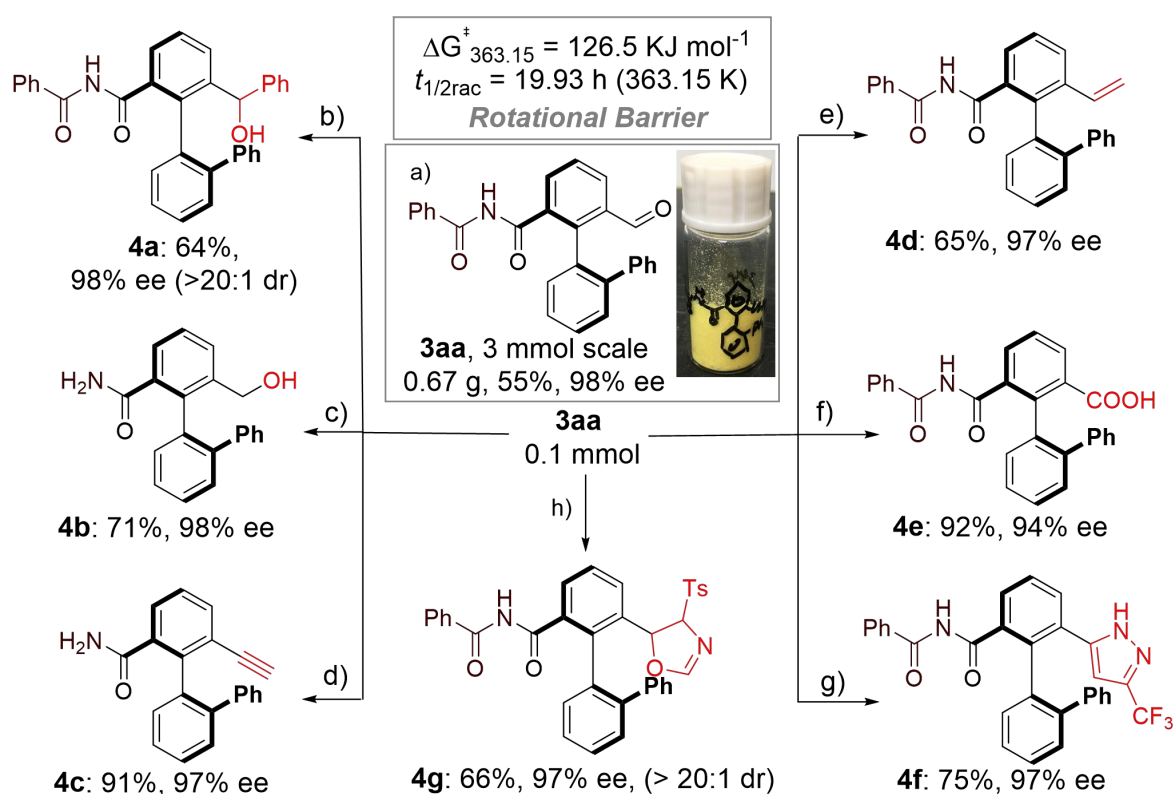
We next evaluated the scope and limitations of the atroposelective oxidative amidation under the standard reaction conditions. The investigation began with axially prochiral biaryl dialdehydes (Scheme 2A). A range of blocking groups at the 2-position including aryl (**3aa**, **3ab**), alkyl (**3ca**–**3ea**), thiomethyl (**3ga**), methoxymethyl (**3ha**), ester carbonyl (**3ia**), trifluoromethyl (**3ja**), and alkenyl (**3ka**, **3la**) substituents were well tolerated in the atroposelective aldehyde C–H amidation, affording the corresponding axially chiral imides in yields ranging from 58% to 77% with excellent enantioselectivities (up to 99% ee). Employing *ent*-**C1** as the catalyst afforded *ent*-**3aa** in 73% yield with >99% ee. Dialdehydes bearing disubstituted or trisubstituted arenes with a fixed methyl group at the 2-position also proved to be viable substrates, delivering products **3ma**–**3va** in moderate yields (56–66%) and high enantiomeric ratios (94–99% ee). Notably, the presence of a 2,4-bis(trifluoromethyl) substituent on the aryl ring did not significantly impair reactivity or selectivity, as product **3wa** was obtained in 51% yield and 97% ee. Further evaluation of 4'-substituted dialdehydes containing a fixed phenyl group at the 2-position afforded the desired axially chiral imides **3xa**–**3za** with excellent enantioselectivities and moderate yields. However, the naphthalene-based dialdehyde **1a'** afforded product **1a'a** in only 32% yield with 70% ee.



Scheme 2. Substrate scope for catalytic synthesis of axially chiral imide. ^{a,b} Condition A: Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.3 mmol), **C1** (20 mol%), DQ (1.2 equiv), Cs_2CO_3 (1.5 equiv), and dry DCM (1.0 mL) at 30 °C under N_2 atmosphere for 72 h; ^b: Isolated yield, ee was determined by chiral-phase HPLC analysis; ^c: Reactions were carried out with **C1** (10 mol%); ^d: Reactions were carried out with **2** (5.0 equiv). DQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; DCM: dichloromethane; HPLC: high-performance liquid chromatography.

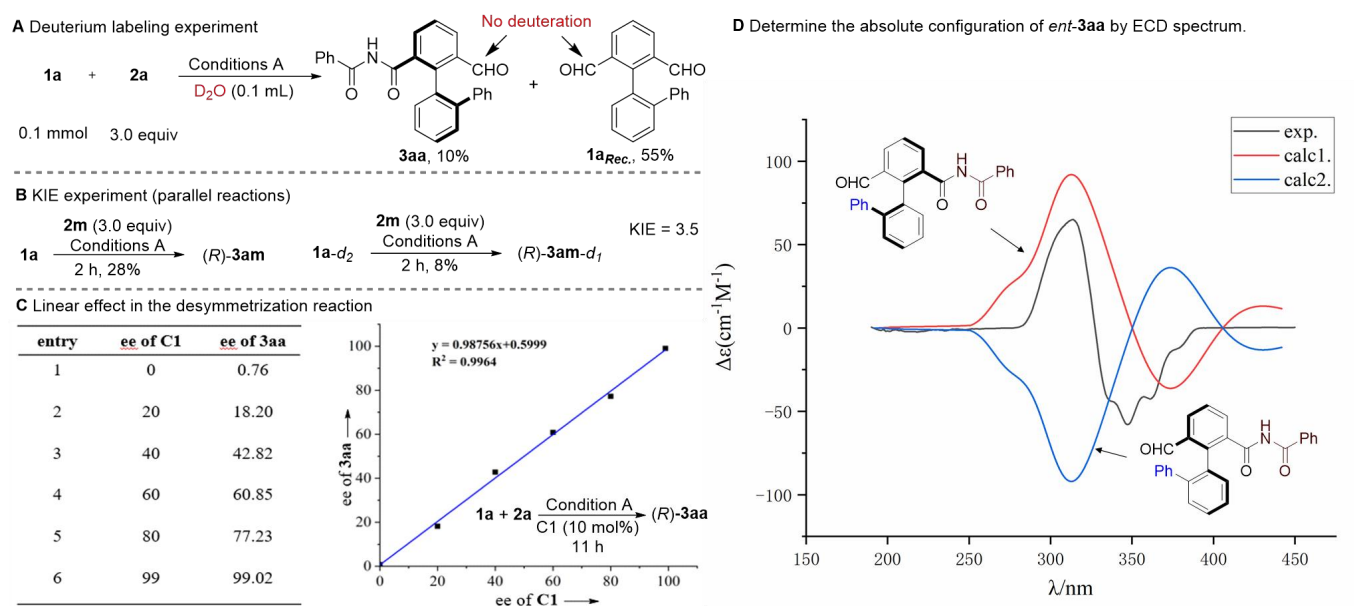
The scope of amide coupling partners was also examined (Scheme 2B). Aryl amides featuring electron-donating, halogen, or electron-withdrawing groups at the *para*-position reacted smoothly to furnish products **3ab–3ah** in 55–78% yield and 94–99% ee, demonstrating broad electronic tolerance. Substituents at the *meta*- or *ortho*-positions had minimal impact on reaction efficiency and enantiocontrol, as evidenced by the formation of enantioenriched products **3ai–3ar**. Notably, the incorporation of halogen atoms, particularly iodine (**3ar**) and bromine (**3af**, **3ak**, **3aq**), offers valuable handles for further functionalization via cross-coupling reactions. The method was also compatible with fused-ring arenes (**3as**, **3at**), electron-rich (**3au**, **3av**), and electron-deficient heteroaromatic amides (**3aw**, **3ax**). Finally, alkyl amides (**3ay**, **3az**) proved applicable, affording products with excellent enantioselectivity, albeit with somewhat reduced reactivity.

To further demonstrate the synthetic utility of the enantioselective oxidative amidation system, gram-scale synthesis and derivatization were carried out. The reaction was conducted on a 3.0 mmol scale, affording (*R*)-**3aa** in 55% yield (0.67 g) with 98% ee (Scheme 3a). This reduction in yield is presumably due to the poor solubility of the amide, creating a heterogeneous mixture. In the larger-scale setup, this inhomogeneity likely caused the amide to precipitate and settle at the bottom of the flask, thereby compromising the reaction efficiency. The formyl and imine groups serve as highly versatile functional handles for further transformations. For instance, diastereoselective nucleophilic addition of PhMgBr to **3aa** yielded axially chiral secondary alcohol **4a** with 65% yield, 98% ee, and > 20:1 dr (Scheme 3b). Reduction of the formyl group in **3aa** with NaBH₄, followed by cascade hydrolysis of the imide, provided axially chiral alcohol **4b** in 71% yield and 98% ee (Scheme 3c). Seyferth–Gilbert homologation of **3aa** produced alkynyl-containing axially chiral amide **4c** in 91% yield and 97% ee (Scheme 3d), while a Wittig reaction delivered alkenyl-substituted axially chiral imide **4d** in 65% yield and 97% ee (Scheme 3e). Oxidation of the formyl group afforded valuable axially chiral carboxylic acid **4e** in 92% yield, albeit with slightly reduced enantioselectivity (Scheme 3f). Cascade annulation of **3aa** with TsNHNH₂ and 2-bromo-3,3,3-trifluoropropene yielded pyrazole **4f** (Scheme 3g), and cycloaddition with tosylmethyl isocyanide furnished product **4g** in 66% yield and 97% ee with excellent diastereoselectivity (Scheme 3h). The rotational barrier of the C(aryl)–C(aryl) bond in **3aa** was determined to be $\Delta G^\ddagger_{\text{rac}} = 126.5 \text{ kJ/mol}$, corresponding to a half-life of 19.9 hours at 90 °C in *i*-PrOH. This high configurational stability ensures significant chiral retention during subsequent transformations, establishing a robust strategy for the synthesis of axially chiral imides, amides, and related derivatives.



Scheme 3. Large-scale synthesis and follow-up transformations. Reaction conditions: (a) C1 (20 mol%), Cs₂CO₃ (1.5 equiv), DQ (1.2 equiv), dry DCM (0.1 M), 25 °C, N₂, 72 h; (b) PhMgBr (1.1 equiv), dry THF (0.1 M), 0 °C, 48 h, 2, H₃O⁺; (c) NaBH₄ (1.0 equiv), THF/CH₃OH = 3:1 (0.1 M), 0 °C, 12 h; (d) P-(1-diazo-2-oxopropyl)-diMethylester (1.5 equiv), K₂CO₃ (2.0 equiv), MeOH (1 mL), rt, 3 h; (e) (PPh)₃P-CH₃Br⁺ (1.2 equiv), nBuLi (1.2 equiv), dry THF (0.1 M), 0 °C, 30 min, then drop 3aa, rt, 12 h; (f) NaClO₂ (3.7 equiv), NaH₂PO₄ (5.0 equiv), 2-methylbut-2-ene (13.0 equiv), ^tBuOH (0.15 M), rt, overnight; (g) TsNHNH₂ (1.2 equiv), 2-Bromo-3,3,3-trifluoropropene (2.0 equiv), DBU (3.0 equiv), PhMe (1 mL), 60 °C, 6 h; (h) Tosylmethyl isocyanide (1.0 equiv), Cs₂CO₃ (2.0 equiv), DMF (0.05 M), 25 °C, N₂, 8 h. DCM: dichloromethane; THF: tetrahydrofuran; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

We carried out a series of mechanistic studies to elucidate the reaction pathway. Deuterium labeling experiments showed that no deuterium was incorporated into either the product or the recovered starting materials (Scheme 4A), suggesting that cleavage of the aldehyde C–H bond is irreversible under the reaction conditions. The kinetic isotope effect (KIE) was measured through parallel reactions of **1a** and **1a-d₂** with **2m** over 2 hours, yielding a KIE value of 3.5 (Scheme 4B). This result indicates that C–H bond cleavage is likely involved in the rate-determining step. Furthermore, the absence of nonlinear effects, as shown in Scheme 4C, supports the participation of a single chiral catalyst molecule in the enantioselectivity-determining step. The absolute configuration of the products was determined by electronic circular dichroism analysis of *ent*-**3aa**, which was assigned as *S* (Scheme 4D). Accordingly, the absolute configurations of all other products were assigned by analogy as *R*. Considering that no bisubstituted byproducts were detected in the reaction system, we conclude that the enantioselectivity is primarily governed by a desymmetrization process, although a minor contribution from kinetic resolution to the slight enhancement of the ee value cannot be entirely ruled out (Figure S1). Finally, we propose a plausible reaction mechanism, as depicted in Figure S2. It commences with the desymmetrizing nucleophilic addition of the NHC to the dialdehyde, followed by a 1,2-HAT to generate the key Breslow intermediate. This intermediate subsequently undergoes oxidation and, finally, a nucleophilic amination to construct the axially chiral imide scaffold.



Scheme 4. Mechanistic investigation.

4. Conclusion

In conclusion, we have developed a robust and efficient method for the catalytic synthesis of axially chiral imides through NHC-catalyzed desymmetrization and amidation of axially prochiral biaryl dialdehydes. Comprehensive mechanistic studies indicate that the reaction proceeds via an irreversible, rate- and enantio-determining activation of the aldehyde, followed by oxidation and tandem C–N bond formation. This strategy proceeds under mild conditions, delivers excellent enantioselectivities (up to 99% ee), and exhibits a broad substrate scope (50 examples). The practicality of the organocatalytic amidation system is demonstrated through scalable synthesis and a variety of enantioretentive transformations. Overall, the NHC-catalyzed desymmetrization and functionalization of prochiral biaryl dialdehydes establish a versatile platform for accessing challenging axially chiral imides and their derivatives.

Supplementary materials

The supplementary material for this article is available at: [Supplementary materials](#).

Declarations

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AI-assisted tools were used for limited language polishing. All scientific content and conclusions were reviewed and approved by the authors.

Authors contribution

Zheng G, Sun J: Conceptualization, writing-original draft, writing-review & editing.

Wu Y, Jiao K: Investigation.

Guan X, Lu X: Methodology, investigation.

Zhu L: Investigation, formal analysis.

Hu X: Investigation, resources.

Zhang Q: Writing-original draft, writing-review & editing.

Qu J: Writing-review & editing.

All authors were involved in data interpretation and discussions.

Conflicts of interest

Guangfan Zheng is an Editorial Board Member of *Chiral Chemistry*. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available within the article and its supplementary materials. Other questions regarding this study can be directed to the corresponding authors.

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