Carbene-Catalyzed Atroposelective Synthesis of Axially Chiral Styrenes Bearing Acyclic Alkenes

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Article

Keywords: asymmetric catalysis, axially chiral styrenes, acyclic alkenes

Posted Date: July 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-739850/v1

Version of Record: A version of this preprint was published at Nature Communications on January 10th, 2022. See the published version at https://doi.org/10.1038/s41467-021-27771-x.

Abstract

Axially chiral styrenes bearing a chiral axis between a sterically non-congested acyclic alkene and an aryl ring are difficult to prepare due to low rotational barrier of the axis. Disclosed here is an *N*-heterocyclic carbene (NHC) catalytic asymmetric solution to this problem. Our reaction involves ynals, sulfinic acids, and phenols as the substrates with an NHC as the catalyst. Key steps involve selective 1,4-addition of sulfinic anion to acetylenic acylazolium intermediate and sequential *E*-selective protonation to set up the chiral axis. Our reaction affords axially chiral styrenes bearing a chiral axis as the product with up to >99:1 *e.r.,* >20:1 *E*/*Z* selectivity, and excellent yields. The sulfone and carboxylic ester moieties in our styrene products are common moieties in bioactive molecules and asymmetric catalysis.

Introduction

Axially chiral molecules are widely used as catalysts and ligands in asymmetric catalysis.[1-3] This class of natural or synthetic molecules has also shown an increasing presence in bioactive molecules for medical[4-7] and agricultural[8, 9] uses. Among the well-known axially chiral scaffolds, most of the chiral axis is between two aromatic moieties. Many synthetic and preparation methods are now available for relatively efficient and scalable access to this class of molecules such as axially chiral biaryls.[10-14] Additionally, axially chiral molecules such as benzamides[15-17] and anilides[18-22] have also received considerable attention. In contrast, axially chiral styrenes, which bear a chiral axis between a simple alkene and an aryl ring, are much less developed although this kind of chirality was realized and intensively studied by Adams and co-workers in the 1940s.[14, 23, 24] Atroposelective access to axially chiral styrenes, especially those bearing acyclic alkene units, is challenging due to low rotational barrier, weak configurational stability, and difficult control of the alkene *E*/*Z* selectivity (Fig. 1a).[23, 24] In the past, synthetic success were mainly limited to aryl-cycloalkene connections in which the alkene is trapped in a ring to imitate the rigidity of biaryls and increase conformational stability[25-32]. It is only till recent years that several approaches emerged for asymmetric access to axially chiral aryl-acyclic alkene scaffolds. These remarkable studies include chiral amines or Brønsted acids catalyzed addition of nucleophiles to ynals[33] and in situ generated allenes[34-43], transition metal-catalyzed cross coupling,[44-46] and desymmetrization/kinetic resolution strategies (Fig. 1b).[47-51] Despite of these progresses, it's still highly demanded to develop powerful atroposelective strategies for rapid access to axially chiral styrenes bearing acyclic alkenes.

Here we disclose an *N*-heterocyclic carbene (NHC)-catalytic approach for highly atroposelective and efficient synthesis of axially chiral styrenes bearing both a sulfone and a carboxylic ester units (Fig. 1c). In the confined arena of axially chiral molecule synthesis, NHC catalysis were previously used by us[52, 53] and others[30, 54-64] to mediate cycloaddition[30, 52, 54-58], desymmetrization[53, 59-61] or kinetic resolution[62-64] to construct molecules bearing the chiral axis between two rigid rings. In our present study, nucleophilic 1,4-addition of sulfur atom of sulfinic acid to an NHC-activated ynal set up the chiral axis. This nucleophilic addition is a chemo-selective process as another nucleophile (phenol) and an electronic

reactive site (the carbonyl carbon of the acyl azolium moiety) are simultaneously present in the same reaction system. The chiral axis is well controlled with up to >99:1 *e.r.*, and the alkene formation is also highly selective with exclusive formation of the *E*-alkene moiety in most of the cases. Both the sulfone and carboxylic ester groups in our axially chiral styrene products are common structural motifs in bioactive and other functional molecules.[65-66] This methodology opened a new gate for accessing axially chiral styrenes bearing acyclic alkenes.

Results

Optimization of reaction conditions. We initiated our studies by using ynal **1a** and sulfinic acid **2a** as model substrates with 3,3',5,5'-tetra-*tert*-butyldiphenylquinone (DQ) as an oxidant to search for suitable conditions. Preliminary results revealed that sodium acetate and diethyl ether are suitable base and solvent, respectively (Supplementary Table 1–3). Further optimization of conditions are summarized in Table 1. The use of aminoindanol-derived precatalyst with an *N*-mesityl substituent (*ent*-**A**) afforded the desired product with moderate yield (54%) and enantioselectivity (22:78 *e.r.*, entry 1). Switching the *N*-mesityl unit of catalyst **A** to electron-rich 2,6-dimethoxyphenyl group (to get catalyst **B**) didn't improve the enantioselectivity (entry 2). When NHC precatalyst **C** with an electron-deficient trichlorophenyl group was used, no desired product formed (entry 3). Examination of the steric hindrance of the *N*-substitutes on NHC catalyst showed that the introduction of a bulkier *N*-triisopropylphenyl (**D**) or *N*-tricyclohexylphenyl (**E**) substituent resulted in improved enantioselectivities (entries 4–5). We next chose NHC precatalyst **E** for further optimization and found that reducing the reaction temperature to 0 ^{o}C gave an apparent improvement in enantioselectivity (91:9 *e.r.*, entry 6). However, the yield of product was still moderate due to the competitive direct 1,2-addition of isopropanol to acetylenic acylazolium intermediates (**I**). Therefore, we further screened several nucleophiles to improve the results (entries 7–12) and delightfully found a sharp increase in yield when phenols were used (entries 8–12). Among the phenols, 2-methoxyphenol showed the best performance in the reaction, affording product **9a** in 97% yield with > 99:1 *e.r.* and *E*/*Z* 20:1 (entry 12). Further improvement in the *E*/*Z* value was observed by reducing the reaction temperature to -20 ^{o}C. The catalyst loading could also be reduced to 5 mol%, leading to the desired product (**9a**) in 94% yield with > 99:1 *e.r.* and *E*/*Z* > 20:1 (entry 13).

Substrate scope. With the optimal reaction conditions in hand (Table 1, entry 13), we next explored the generality of the reaction. Initially, we examined the scope of sulfinic acids (**2**) by using **1a** as model substrate (Table 2A). Both electron-donating (CH_3, OCH_3) and electron-withdrawing (CF_3, CN, halogens) groups were well tolerated, providing the desired axially chiral styrenes (**9b**-**9i**) in good to excellent yields with high optical purities and *E*/*Z* ratios. The steric effect of the substituents on the benzene ring has considerable influence on the reaction outcome. For example, introducing a methyl group at the *para*-position of the benzene ring gave the desired product **9b** in excellent results. However, when methyl group was installed at the *ortho*-position, the corresponding product (**9c**) was obtained in moderate yield (45%) with lower enantioselectivity (82.5:17.5 *e.r.*), which probably due to the steric repulsion between the methyl group and acetylenic acylazolium intermediate (**I**). The phenyl group of sulfinic acids could be

replaced with heteroaryl group (e.g. thiophenyl) without affection on the reaction efficiency, affording 9j in 99% yield with 98.5:1.5 *e.r.* and *E*/*Z* > 20:1. Moreover, aliphatic sulfinic acids were also compatible in our catalytic system providing the desired axially chiral styrenes (**9k**-**9l**) in good yields with high *e.r.* values, albeit with lower *E*/*Z* ratios than aromatic sulfinic acids.

The scope of ynals (**1**) was also investigated by using benzenesulfinic acid (**2a**) as the model substrate (Table 2B). The steric and electronic effects on the naphthalene ring of ynals were evaluated by tuning the substitution patterns. A wide range of electron-donating (OCH_3, OEt, OBn, OMOM, etc.) and electron withdrawing (CO_2CH_3, CN, halogens) substituents at different positions (2-, 3-, 6-, 7-) of naphthalene ring were well tolerated in our catalytic reaction, giving the corresponding axially chiral styrenes in good to excellent yields with high enatioselectivities and *E*/*Z* ratios. Notably, bulkier groups on the 2-position of naphthalene ring (**9p**-**9q**) and strong electron-withdrawing groups (**9p**,**9x**-**9y**) had a negative effect on both yield and enantioselectivity. To our delight, the β-naphthyl unit of **1a** can be replaced with heteroaryl substituents, such as quinoline (**9ab**), indole (**9ac**) and benzothiophene (**9ad**). In these cases, moderate to good yields and high *e.r.* values were regularly obtained, although the *E*/*Z* selectivity decreased for **9ad**. When the naphthalene ring in ynals was replaced with phenyl ring, high enantioselectivities could still be achieved, but the *E*/*Z* ratio dropped sharply (**9ae**-**9af**), which probably resulted from the less rigidity of the ynal skeleton.

Stability evaluation for the axially chiral products. The stereochemical stabilities of our axially chiral styrenes were evaluated via both experimental and computational methods.[67–70] We monitored the *ee* value of **9a** over 24 h at different temperatures in toluene, and found **9a** racemerized quickly at 100 ^oC, but much slower at 75 ^oC and 50 ^oC (Fig. 2a). Notably, a 2 month-term monitor showed no obvious *ee* drop of **9a** at room temperature. The experiment-based calculation (Supplementary Fig. 182) revealed that the rotational barrier of **9a** is $\Delta G^{‡}$ = 30.3 kcal/mol, which is in accordance with the value ($\Delta G^{‡}$ = 30.1 kcal/mol) resulted from the density functional theory (DFT) calculation (Fig. 2c). The computationally derived energy scan for **9a** over dihedral angles from − 180^o to 180^o also indicated the rotational barrier of **9a** is about 30 kcal/mol (Fig. 2b, Supplementary Table 5). Similarly, the rotational barriers for **9m** and **9n** were also measured experimentally at 100 ^oC in toluene (9m, $\Delta G^{‡}$ = 31.0 kcal/mol, $t_{1/2rac}$ = 18.1 h; 9n, $\Delta G^{‡}$ = 31.2 kcal/mol, $t_{1/2rac}$ = 25.1 h) with the racemization results shown in Fig. 2a. From these results, we can clearly see that our axially chiral products are stable at relatively low temperature, and the products bearing a bulker 2-substituent on the naphthalene ring would generally be more stable than that bearing a less bulky 2-substituent.

Scale-up synthesis and versatile transformations. Our NHC catalytic approach is amenable to gram-scale synthesis, with the formation of axially chiral styrene **9a** (1.24 g) in 87% yield with 98:2 *e.r.* and *E*/*Z* > 20:1. The optically enriched product could be further functionalized through simple protocols (Fig. 3). For example, our axially chiral styrenes were suitable for ester 1,2-addition reactions with Grignard reagents (**10a**-**10b**). The afforded alcohol (**10a**) could be further functionalized (e.g. silylation and alkylation, see the Supporting Information for details) without loss of *e.r.* and *E*/*Z* value. The ester unit of **9a** could

undergo a transesterification or aminolysis to afford different kinds of ester-containing styrenes (**11a**-**11c**), or amide-containing styrenes (**12**) in high yields without erosion of optical purity. It's worthy to note that even the extremely bulky *L*-menthol derived ester (**11c**) could be afforded efficiently as well. The alkyne-containing product (**11b**) can be used as coupling reagent in biorthogonal click chemistry[71–72] to form triazole linkages such as **14**. Additionally, our products could also be converted to oxazoline-containing axially chiral molecules (e.g. **13**) which could be potentially used as ligands in asymmetric catalysis. The halogen groups on our axially chiral products give opportunities for further functionalization via transition metal catalyzed cross-coupling reactions. For example, the Sonogashira coupling[73] between **9w** and phenylacetylene furnished **15** in 82% yield with > 99:1 *e.r.* and *E*/*Z* > 20:1. Further transformations based on sulfone unit[74–76] are also promising although several trials in our study was not successful. Actually, the sulfone unit in our products is a common moiety in pharmaceutically relevant compounds,[65, 66, 77–79] which indicates the potential utility of our methodology in pharmaceutical synthesis.

Discussion

In summary, we have developed an NHC catalytic strategy for atroposelective synthesis of the challenging axially chiral styrenes bearing acyclic alkenes. Our reaction involves ynals, sulfinic acids, and phenols as the substrates. Mild reaction conditions are used to provide a broad scope of products with moderate to high yields (up to 99%) and excellent stereoselectivities (up to > 99:1 *e.r.*, *E*/*Z* > 20:1). We have also evaluated the stabilities of the axially chiral styrenes via both experimental and computational methods and found that these molecules are quite stable at relatively low temperature. Both the sulfone and carboxylic ester groups in our axially chiral styrene products are common structural motifs in bioactive and other functional molecules, indicating the potential utility of our methodology in pharmaceutical synthesis. Our products bear functional groups that can be readily transformed to diverse axially chiral molecules, although there is a limit that the sulfone unit was not successfully functionalized in our study.

Despite that only sulfinic acids were employed to furnish the chemo- and enantio-selective 1,4-addition in the present research, other nucleophiles (e.g., phosphines, enol relevents, electron-rich aromatic units) are also potentially suitable in our catalytic system as related studies in our laboratories have shown encouraging results. Thus we believe our methodology would inspire a further study of axially chiral styrenes especially those bearing acyclic alkenes. Further studies on atroposelective synthesis of axially chiral molecules, especially those with potential applications in medicines and agricultural chemicals, are ongoing in our laboratories.

Methods

General information. All reactions were conducted in oven-dried glassware under an atmosphere of dry nitrogen or argon. All reaction solvents were purified before use: Tetrahydrofuran, diethyl ether were

distilled from Na/benzophenone. Dichloromethane, dimethylformamide, triethylamine were distilled from CaH_2. The procedures for preparation of NHC pre-catalysts, sulfinic acids and ynals are provided in supplementary materials. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker spectrometers using deuteriochloroform as solvent. High-resolution mass spectra (HRMS) were obtained on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation) and are reported as m/z (relative intensity). Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter. All the *e.r.* values were determined via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. All the *E*/*Z* ratios were determined via ^1H NMR analysis of the crude reaction mixture.

General procedure for the synthesis of axially chiral styrenes. To a 10 mL oven-dried Schlenk tube equipped with a magnetic stir bar, was added chiral aldehyde (0.1 mmol), NHC pre-catalyst **E** (2.9 mg, 0.005 mmol), 4 Å molecular sieves (150 mg), sulfinic acid (28.4 mg, 0.2 mmol), sodium acetate (24.6 mg, 0.3 mmol), 3,3',5,5'-tetra-*tert*-butyldiphenylquinone (81.8 mg, 0.2 mmol). The Schlenk tube was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). 2-Methoxyphenol (12 μL, 0.11 mmol) and diethyl ether (2 mL) were then added via syringe. The reaction mixture was stirred at -20°C for 6 days. After completion of the reaction, monitored by TLC plate, the reaction mixture was concentrated in *vacuo* and the residue was subjected to column chromatography directly using EtOAc/hexanes as eluent to afford the desired product.

The gram-scale synthesis of **9a** was performed according to the general procedure using **1a** (630.7 mg, 3.0 mmol), **2a** (853.0 mg, 6.0 mmol), NHC pre-catalyst **E** (86.0 mg, 0.15 mmol), sodium acetate (738.0 mg, 9.0 mmol), 3,3',5,5'-tetra-*tert*-butyldiphenylquinone (2.45 g, 6.0 mmol), 2-methoxyphenol (363.0 μL, 3.3 mmol) 4 Å molecular sieves (3.0 g) and diethyl ether (60 mL). After stirring at -20 °C for 6 days, the product **9a** (1.24 g, 87% yield, 98:2 *e.r.*, *E*/*Z* > 20:1) was afforded.

DFT calculations on the rotation barrier of the products. The energetic barriers of the racemization process of **9a** was investigated computationally by the density functional theory (DFT) calculation. All calculations were carried out using the Gaussian 16 C.01 program package. The geometry optimizations were performed using hybrid B3LYP exchange correlation. The 6-31G (d, p) basis set was used for C, H, O, and S atoms. Vibrational frequency calculations were performed (at 303.15 K) to characterize the nature of each stationary point. A tight convergence (10^{-12} au) criterion was employed, and the solvent toluene (ε = 2.40) was considered using the SMD continuum solvent model (UFF radii). Single-point calculations were carried out for each optimized structure by using M06-2X functional and Def2-TZVP basis sets. The ground-stage structure (**9a**) and two transition states (**TS9a**, **TS9a'**) corresponding to the rotation along two directions were located. The rotational barrier ($\Delta G^{\ddagger}$) for enantiomerization was obtained as the Gibbs free energy difference from the ground-state structure to the more stable transition state. The rate constants for enantiomerization (k_{ent}) and racemization (k_{rac}), and half-life for racemization ($t_{1/2}$) were calculated. Please see the supplementary materials for details.

Racemization studies of the products. The axially chiral product **9a**, **9m** and **9n** (0.005 mmol) were dissolved in toluene (100 mL) separately and heated at different temperatures for 24 h. The *ee* value was

tested every one hour *via* HPLC on chiral stationary phase. The detailed calculation of rotation barriers were provided in the supplementary materials.

Declarations

Data availability. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition number of CCDC 2033533. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. All other data is available from the authors upon reasonable request.

Acknowledgments:

We thank Dr. Yongxin Li (NTU) for assistance with X-ray structure analysis. We acknowledge financial supports from Singapore National Research Foundation under its NRF Investigatorship (NRF-NRFI2016-06) and Competitive Research Program (NRF-CRP22-2019-0002); the Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG7/20, RG5/19), MOE AcRF Tier 2 (MOE2019-T2-2-117), MOE AcRF Tier 3 Award (MOE2018-T3-1-003); Nanyang Research Award Grant, Chair Professorship Grant, Nanyang Technological University; the National Natural Science Foundation of China (21772029, 21801051, 21807019, 21961006, 22071036, 22061007, 82360589, 81360589), Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY number (2020)004]; The 10 Talent Plan (Shicengci) of Guizhou Province ([2016]5649); the Science and Technology Department of Guizhou Province ([2018]2802, [2019]1020); National Natural Science Foundation of China (No. 31960546); the Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University; the Guizhou Province First-Class Disciplines Project [(Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008], NSFC Grant (81360589), Guizhou University of Traditional Chinese Medicine (China); and Guizhou University.

Author contributions:

J.Y. designed and conducted the main experimental protocols, and wrote the initial draft. R.M conducted parts of the substrate scope experiments. S.R., J.X and B.M. synthesized the substrates. T.L. and Z.J contributed to the DFT calculations. W.T and Y.R.C supervised the research and revised the manuscript with comments from all authors.

Additional information

Supplementary Information accompanies this paper at http://www.nature.com/ naturecommunications

Competing interests: The authors declare no competing financial interests.

References

1. Brunel, J. M. Update 1 of: BINOL: a versatile chiral reagent. *Chem. Rev.* **107**, PR1-PR45 (2007).

2. Parmar, D., Sugiono, E., Raja, S. & Rueping, M. Complete field guide to asymmetric BINOL-phosphate derived Brønsted acid and metal catalysis: history and classification by mode of activation; Brønsted acidity, hydrogen bonding, ion pairing, and metal phosphates. *Chem. Rev.* **114**, 9047-9153 (2014).

3. Akiyama, T. & Mori, K. Stronger Brønsted acids: recent progress. *Chem. Rev.* **115**, 9277-9306 (2015).

4. Wang, J., *et al*. Discovery and assessment of atropisomers of (±)-lesinurad. *ACS Med. Chem. Lett.* **8**, 299-303 (2017).

5. Toenjes, S. T. & Gustafson, J. L. Atropisomerism in medicinal chemistry: challenges and opportunities. *Future Med. Chem.* **10**, 409-422 (2018).

6. Watterson, S.H. *et al.* Discovery of 6-fluoro-5-(R)-(3-(S)-(8-fluoro-1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)-2-methylphenyl)-2-(S)-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (BMS-986142): a reversible inhibitor of Bruton's tyrosine kinase (BTK) conformationally constrained by two locked atropisomers. *J. Med. Chem.* **59**, 9173-9200 (2016).

7. Beutner, G. *et al.* Adventures in atropisomerism: total synthesis of a complex active pharmaceutical ingredient with two chirality axes. *Org. Lett.* **20**, 3736-3740 (2018).

8. Dreikorn, B. A., Jourdan, G. P., Hall, H. R., Deeter, J. B. & Jones, N. Synthesis, separation, and fungicidal activity of the rotationally hindered isomers (atropisomers) of *N*-(methoxyacetyl)-*N*-[2-methyl-6-(methylthio)phenyl]-*D,L*-alanine methyl ester. *J. Agric. Food. Chem.* **38**, 549-552 (1990).

9. Smyth, J. E., Butler, N. M. & Keller, P. A. A twist of nature – the significance of atropisomers in biological systems. *Nat. Prod. Rep.* **32**, 1562-1583 (2015).

10. Bringmann, G. *et al.* Atroposelective synthesis of axially chiral biaryl compounds. *Angew. Chem. Int. Ed.* **44**, 5384-5427 (2005).

11. Wang, Y.-B. & Tan, B. Construction of axially chiral compounds via asymmetric organocatalysis. *Acc. Chem. Res.* **51**, 534-547 (2018).

12. Liao, G., Zhou, T., Yao, Q.-J. & Shi, B.-F. Recent advances in the synthesis of axially chiral biaryls via transition metal-catalysed asymmetric C–H functionalization. *Chem. Commun*. **55**, 8514-8523 (2019).

13. Carmona, J. A., Rodríguez-Franco, C., Fernández, R., Hornillos, V. & Lassaletta, J. M. Atroposelective transformation of axially chiral (hetero)biaryls. From desymmetrization to modern resolution strategies. *Chem. Soc. Rev.* **50**, 2968-2983 (2021).

14. Cheng, J. K., Xiang, S.-H., Li, S., Ye, L. & Tan, B. Recent advances in catalytic asymmetric construction of atropisomers. *Chem. Rev.* **121**, 4805-4902 (2021).

15. Barrett, K. T. & Miller, S. J. Enantioselective synthesis of atropisomeric benzamides through peptide-catalyzed bromination. *J. Am. Chem. Soc.* **135**, 2963-2966 (2013).

16. Barrett, K. T., Metrano, A. J., Rablen, P. R. & Miller, S. J. Spontaneous transfer of chirality in an atropisomerically enriched two-axis system *Nature* **509**, 71-75 (2014).

17. Fäseke, V. C. & Sparr, C. Stereoselective arene-forming aldol condensation: synthesis of axially chiral aromatic amides. *Angew. Chem. Int. Ed.* **55**, 7261-7264 (2016).

18. Tanaka, K., Takeishi, K. & Noguchi, K. Enantioselective synthesis of axially chiral anilides through rhodium-catalyzed [2+2+2] cycloaddition of 1,6-diynes with trimethylsilylynamides. *J. Am. Chem. Soc*. **128**, 4586-4587 (2006).

19. Kitagawa, O. *et al.* Highly enantioselective synthesis of atropisomeric anilide derivatives through catalytic asymmetric *N*-arylation: conformational analysis and application to asymmetric enolate chemistry. *J. Am. Chem. Soc.* **128**, 12923-12931 (2006).

20. Brandes, S., Bella, M., Kjærsgaard, A. & Jørgensen, K. A. Chirally aminated 2-naphthols—organocatalytic synthesis of non-biaryl atropisomers by asymmetric Friedel–Crafts amination. *Angew. Chem. Int. Ed.* **45**, 1147-1151 (2006).

21. Shirakawa, S., Liu, K. & Maruoka, K. Catalytic asymmetric synthesis of axially chiral *o*-iodoanilides by phase-transfer catalyzed alkylations *J. Am. Chem. Soc.* **134**, 916-919 (2012).

22. Li, S.-L. *et al.* Atroposelective catalytic asymmetric allylic alkylation reaction for axially chiral anilides with achiral Morita–Baylis–Hillman carbonates. *J. Am. Chem. Soc.* **140**, 12836-12843 (2018).

23. Adams, R. & Miller, M. W. Restricted rotation in aryl olefins. I. preparation and resolution of β-chloro-β-(2,4,6-trimethyl-3-bromophenyl)-α-methylacrylic acid. *J. Am. Chem. Soc.* **62**, 53-56 (1940).

24. Kumarasamy, E., Raghunathan, R., Sibi, M. P. & Sivaguru, J. Nonbiaryl and heterobiaryl atropisomers: molecular templates with promise for atropselective chemical transformations. *Chem. Rev.* **115**, 11239-11300 (2015).

25. Baker, R. W., Hambley, T. W., Turner, P. & Wallace, B. J. Central to axial chirality transfer via double bond migration: asymmetric synthesis and determination of the absolute configuration of axially chiral 1-(3'-indenyl)naphthalenes. *Chem. Commun.* 2571-2572 (1996).

26. Hattori, T. *et al.* Highly stereospecific conversion of C-centrochirality of a 3,4-dihydro-2H-1,1'-binaphthalen-1-ol into axial chirality of a 3,4-dihydro-1,1'-binaphthalene. *Tetrahedron Lett.* **42**, 8035-8038 (2001).

27. Feng, J., Li, B., He, Y. & Gu, Z. Enantioselective synthesis of atropisomeric vinyl arene compounds by palladium catalysis: a carbene strategy. *Angew. Chem. Int. Ed.* **55**, 2186-2190 (2016).

28. Pan, C., Zhu, Z., Zhang, M. & Gu, Z. Palladium-catalyzed enantioselective synthesis of 2-aryl cyclohex-2-enone atropisomers: platform molecules for the divergent synthesis of axially chiral biaryl compounds. *Angew. Chem. Int. Ed.* **56**, 4777-4781 (2017).

29. Jolliffe, J. D., Armstrong, R. J. & Smith, M. D. Catalytic enantioselective synthesis of atropisomeric biaryls by a cation-directed *O*-alkylation. *Nat. Chem.* **9**, 558-562 (2017).

30. Zhao, C. *et al.* Enantioselective [3+3] atroposelective annulation catalyzed by *N*-heterocyclic carbenes. *Nat. Commun.* **9**, 611 (2018).

31. Sun, Q.-Y. *et al.* Enantioselective synthesis of axially chiral vinyl arenes through palladium-catalyzed C–H olefination. *Chem. Commun.* **54**, 10706-10709 (2018).

32. Liang, Y. *et al.* Enantioselective construction of axially chiral amino sulfide vinyl arenes by chiral sulfide-catalyzed electrophilic carbothiolation of alkynes. *Angew. Chem. Int. Ed.* **59**, 4959-4964 (2020).

33. Zheng, S.-C. *et al.* Organocatalytic atroposelective synthesis of axially chiral styrenes. *Nat. Commun.* **8**, 15238 (2017).

34. Jia, S. *et al.* Organocatalytic enantioselective construction of axially chiral sulfone-containing styrenes. *J. Am. Chem. Soc.* **140**, 7056-7060 (2018).

35. Tan, Y. *et al.* Enantioselective construction of vicinal diaxial styrenes and multiaxis system via organocatalysis. *J. Am. Chem. Soc.* **140**, 16893-16898 (2018).

36. Li, D. *et al.* Asymmetric Mannich reaction and construction of axially chiral sulfone-containing styrenes in one pot from α-amido sulfones based on the waste–reuse strategy. *Org. Lett.* **20**, 4959-4963 (2018).

37. Li, S. *et al.* Organocatalytic asymmetric atroposelective construction of axially chiral 1,4-distyrene 2,3-naphthalene diols. *Org. Lett.* **20**, 7665-7669 (2018).

38. Wang, Y.-B. *et al.* Rational design, enantioselective synthesis and catalytic applications of axially chiral EBINOLs. *Nat. Catal.* **2**, 504-513 (2019).

39. Zhang, N. *et al.* Organocatalytic atropo- and *E*/*Z*-selective Michael addition reaction of ynones with α-amido sulfones as sulfone-type nucleophile. *Org. Chem. Front.* **6**, 451-455 (2019).

40. Li, Q.-Z. *et al.* Organocatalytic enantioselective construction of heterocycle-substituted styrenes with chiral atropisomerism. *Org. Lett.* **22**, 2448-2453 (2020).

41. Huang, A. *et al.* Asymmetric one-pot construction of three stereogenic elements: chiral carbon center, stereoisomeric alkenes, and chirality of axial styrenes. *Org. Lett.* **21**, 95-99 (2019).

42. Wang, C.-S. *et al.* Axially chiral aryl-alkene-indole framework: a nascent member of the atropisomeric family and its catalytic asymmetric construction. *Chin. J. Chem.* **38**, 543-552 (2020).

43. Zhang, W., Wei, S., Wang, W., Qu, J. & Wang, B. Catalytic asymmetric construction of C-4 alkenyl substituted pyrazolone derivatives bearing multiple stereoelements. *Chem. Commun.* **57**, 6550-6553 (2021).

44. Sun, C. *et al.* Asymmetric allylic substitution–isomerization to axially chiral enamides via hydrogen-bonding assisted central-to-axial chirality transfer. *Chem. Sci.* **11**, 10119-10126 (2020).

45. Kumar, P., Shirke, R. P., Yadav, S. & Ramasastry, S. S. V. Catalytic enantioselective synthesis of axially chiral diarylmethylidene indanones. *Org. Lett.* **23**, 4909-4914 (2021).

46. Wang, J. *et al.* Tandem iridium catalysis as a general strategy for atroposelective construction of axially chiral styrenes. *J. Am. Chem. Soc.*, 10.1021/jacs.1c04400 (2021).

47. Wang, Y.-B. *et al.* Asymmetric construction of axially chiral 2-arylpyrroles by chirality transfer of atropisomeric Alkenes. *Angew. Chem. Int. Ed.* **58**, 13443-13447 (2019).

48. Ma, C. *et al.* Atroposelective access to oxindole-based axially chiral styrenes via the strategy of catalytic kinetic resolution. *J. Am. Chem. Soc.* **142**, 15686-15696 (2020).

49. Jiang, M., Zhou, T. & Shi, B.-F. Construction of a new class of oxindole-based axially chiral styrenes via kinetic resolution. *Chinese J. Org. Chem.* **40**, 4364-4366 (2020).

50. Jin, L. *et al.* Atroposelective synthesis of axially chiral styrenes via an asymmetric C–H functionalization strategy. *Chem*. **6**, 497-511 (2020).

51. Song, H. *et al.* Synthesis of axially chiral styrenes through Pd-catalyzed asymmetric C–H olefination enabled by an amino amide transient directing group. *Angew. Chem. Int. Ed.* **59**, 6576-6580 (2020).

52. Li, T. *et al. N*-Heterocyclic carbene-catalyzed atroposelective annulation for access to thiazine derivatives with C–N axial chirality. *Angew. Chem. Int. Ed.* **60**, 9362-9367 (2021).

53. Jin, J. *et al.* Carbene-catalyzed atroposelective annulation and desymmetrization of urazoles. *Org. Lett.* **23**, 3991-3996 (2021).

54. Candish, L., Levens, A., & Lupton, D. W. *N*-Heterocyclic carbene catalysed redox isomerisation of esters to functionalised benzaldehydes. *Chem. Sci.* **6**, 2366-2370 (2015).

55. Xu, K., Li, W., Zhu, S. & Zhu, T. Atroposelective arene formation by carbene-catalyzed formal [4+2] cycloaddition. *Angew. Chem. Int. Ed.* **58**, 17625-17630 (2019).

56. Wu, Y.-T. *et al.* Access to dihydropyrano[3,2-b]pyrrol-5-ones skeletons by *N*-heterocyclic carbene-catalyzed [3+3] annulations. *Chem. Commun.* **56**, 9854-9857 (2020).

57. Zhang, C.-L., Gao, Y.-Y., Wang, H.-Y., Zhou, B.-A. & Ye, S. Enantioselective synthesis of axially chiral benzothiophene/benzofuran-fused biaryls by *N*-heterocyclic carbene catalyzed arene formation. *Angew. Chem. Int. Ed.* **60**, 13918-13922 (2021).

58. Ma, R. *et al.* Atroposelective synthesis of axially chiral 4-aryl α-carbolines via *N*-heterocyclic carbene catalysis. *Org. Lett.* **23**, 4267-4272 (2021).

59. Lu, S., Poh, S. B., Rong, Z.-Q. & Zhao, Y. NHC-catalyzed atroposelective acylation of phenols: access to enantiopure NOBIN analogs by desymmetrization. *Org. Lett.* **21**, 6169-6172 (2019).

60. Yang, G., Guo, D., Meng, D. & Wang, J. NHC-catalyzed atropoenantioselective synthesis of axially chiral biaryl amino alcohols via a cooperative strategy. *Nat. Commun.* **10**, 3062 (2019).

61. Barik, S. *et al.* NHC-catalyzed desymmetrization of *N*-aryl maleimides leading to the atroposelective synthesis of *N*-aryl succinimides. *Angew. Chem. Int. Ed.* **60**, 12264-12268 (2021).

62. Lu, S., Poh, S. B. & Zhao, Y. Kinetic resolution of 1,1'-biaryl-2,2'-diols and amino alcohols through NHC-catalyzed atroposelective acylation. *Angew. Chem. Int. Ed.* **53**, 11041-11045 (2014).

63. Bie, J., Lang, M. & Wang, J. *Org. Lett.* **20**, 5866 (2018)

64. Lu, S. *et al.* Diastereo- and atroposelective synthesis of bridged biaryls bearing an eight-membered lactone through an organocatalytic cascade. *J. Am. Chem. Soc.* **141**, 17062-17067 (2019).

65. Richard, E. O. & Charles, F. A. Recent progress in the medicinal chemistry of γ-secretase inhibitors. *Curr. Top. Med. Chem.* **8**, 17-33 (2008).

66. Alba, A.-N. R., Companyó, X. & Rios, R. Sulfones: new reagents in organocatalysis. *Chem. Soc. Rev.* **39**, 2018-2033 (2010).

67. Reist, M., Testa, B., Carrupt, P.-A., Jung, M. & Schurig, V. Racemization, enantiomerization, diastereomerization, and epimerization: their meaning and pharmacological significance. *Chirality* **7**, 396-400 (1995).

68. Curran, D. P., Liu W. & Chen, C. H.-T. Transfer of chirality in radical cyclizations. cyclization of *o*-haloacrylanilides to oxindoles with transfer of axial chirality to a newly formed stereocenter. *J. Am. Chem. Soc.* **121**, 11012-11013 (1999).

69. Shirakawa, S., Liu, K. & Maruoka, K. Catalytic asymmetric synthesis of axially chiral *o*-iodoanilides by phase-transfer catalyzed alkylations. *J. Am. Chem. Soc.* **134**, 916-919 (2012).

70. Wang, Q. *et al.* Rhodium-catalyzed atroposelective oxidative C–H/C–H cross-coupling reaction of 1-aryl isoquinoline derivatives with electron-rich heteroarenes. *J. Am. Chem. Soc.* **142**, 15678-15685 (2020).

71. Jia, Z. & Zhu, Q. ‘Click’ assembly of selective inhibitors for MAO-A. *Bioorg. Med. Chem. Lett.* **20**, 6222-6225 (2010).

72. Rodrigues, M. P. *et al.* Synthesis of cinnamic acid derivatives and leishmanicidal activity against Leishmania braziliensis. *Eur. J. Med. Chem.* **183**, 111688 (2019).

73. Finke, A. D., Elleby, E. C., Boyd, M. J., Weissman, H. & Moore, J. S. Zinc chloride-promoted aryl bromide–alkyne cross-coupling reactions at room temperature. *J. Org. Chem.* **74**, 8897-8900 (2009).

74. Denmark, S. E. & Cresswell, A. J. Iron-catalyzed cross-coupling of unactivated secondary alkyl thio ethers and sulfones with aryl Grignard reagents. *J. Org. Chem.* **78**, 12593-12628 (2013).

75. Zhang, H., Yu, Y., Huang, S. & Huang, X. Palladium-catalyzed cascade reaction of *o*-bromobenzaldehydes with *N*-sulfonylhydrazones: an efficient approach to the naphthalene skeleton. *Adv. Synth. Catal.* **361**, 1576-1581 (2019).

76. Gong, L. *et al.* Ni-catalyzed Suzuki–Miyaura cross-coupling of α-oxo-vinylsulfones to prepare C-aryl glycals and acyclic vinyl ethers. *J. Am. Chem. Soc.* **141**, 7680-7688 (2019).

77. Reck, F. *et al.* Identification of 4-substituted 1,2,3-triazoles as novel oxazolidinone antibacterial agents with reduced activity against monoamine oxidase A. *J. Med. Chem.* **48**, 499-506 (2005).

78. Scott, J. P. *et al*. A practical synthesis of a γ-secretase inhibitor. *J. Org. Chem.* **72**, 4149-4155 (2007).

79. Tang, H. *et al.* Combinatorial synthesis and biological evaluations of (*E*)-β-trifluoromethyl vinylsulfones as antitumor agents. *RSC Adv.* **9**, 31474-31482 (2019).

Figures

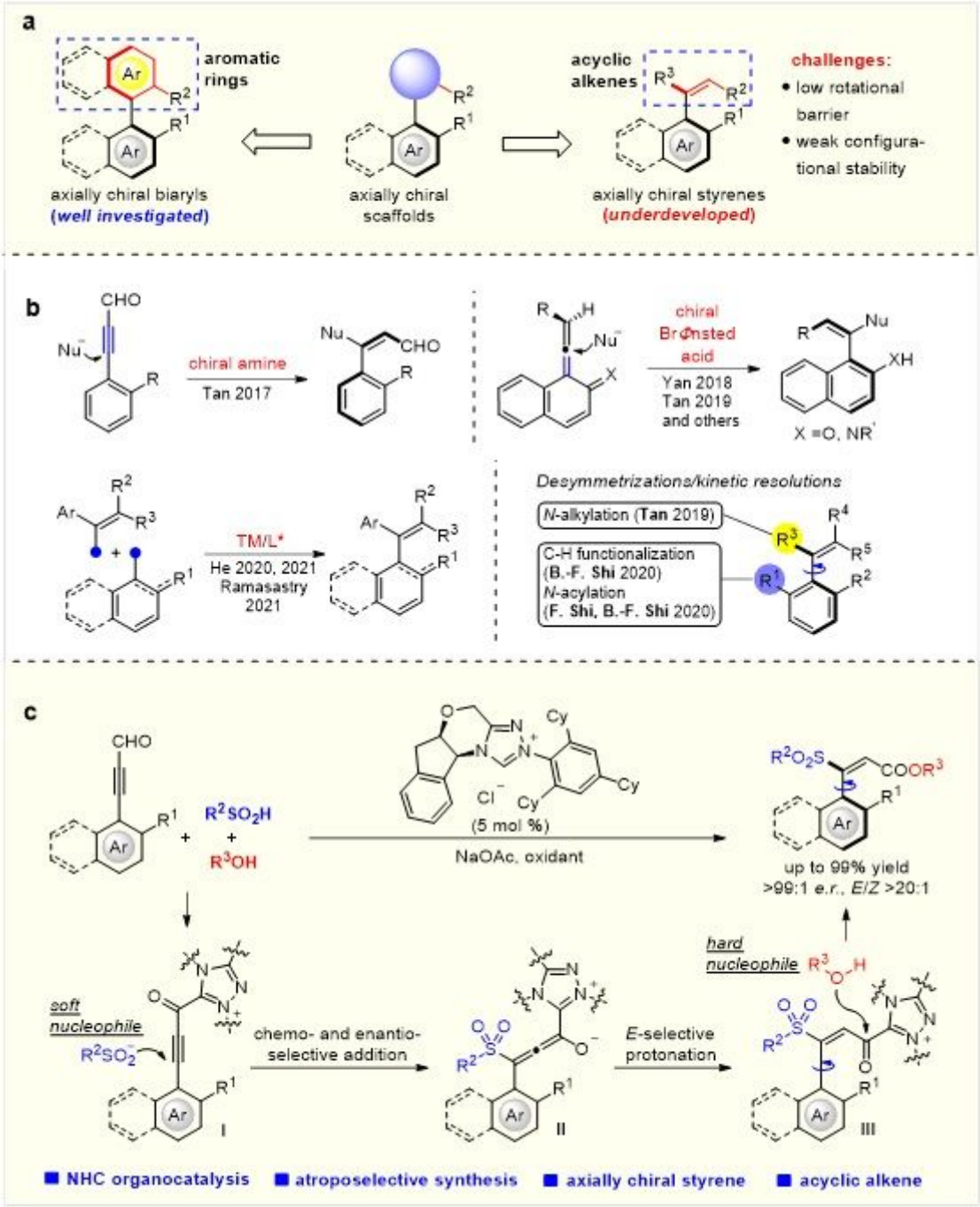

Figure 1

Challenges and strategies to access axially chiral styrenes bearing acyclic alkenes. (a) Challenges in synthesis of axially chiral styrenes bearing acyclic alkenes. (b) Previous methods for accessing axially chiral styrenes bearing acyclic alkenes. (c) Our Strategy: carbene-catalyzed chemo- and enantio-selective addition

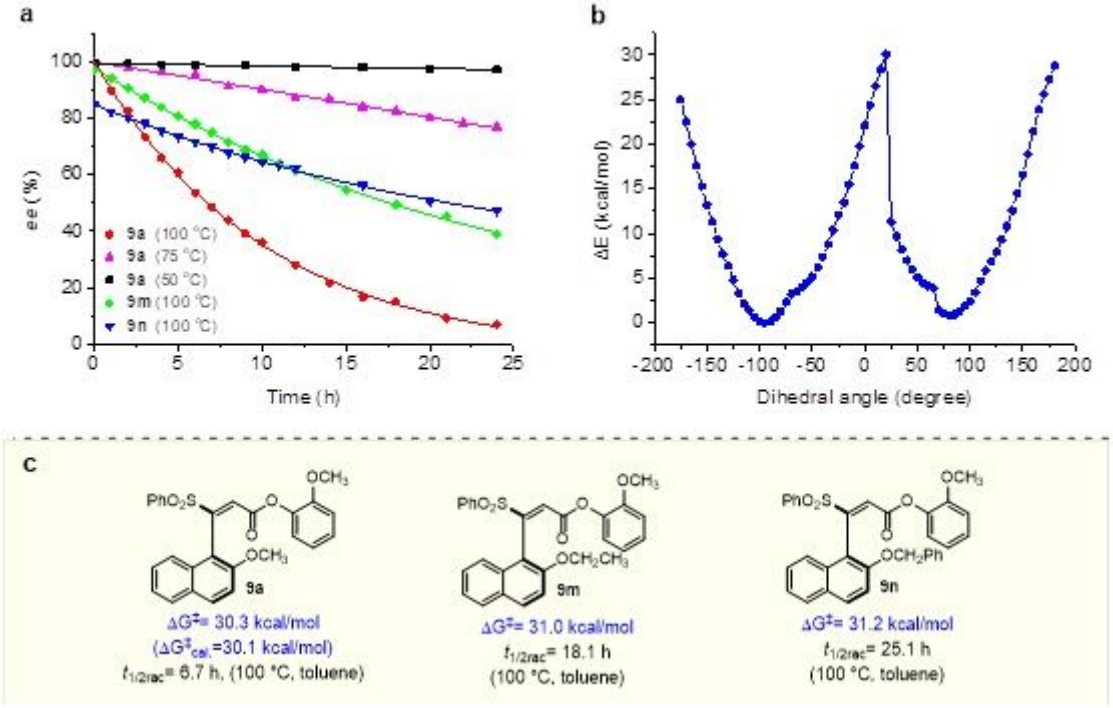

Figure 2

Stability evaluation for the axially chiral styrenes. (a) The racemization results of 9a and 9m-n over the time. (b) Computationally derived energy scan for 9a over dihedral angles from -180o to 180o. (c) The rotational barriers (△G‡) and half-lives (t1/2rac) of 9a, 9m-n.

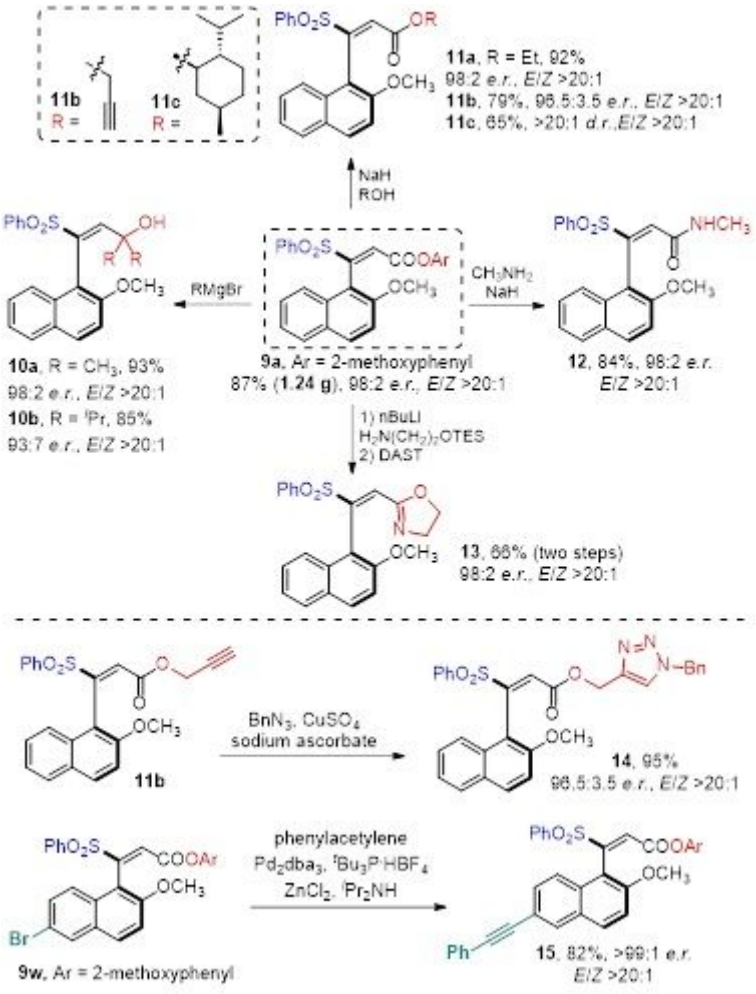

Figure 3

Synthetic transformations of the axially chiral products

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