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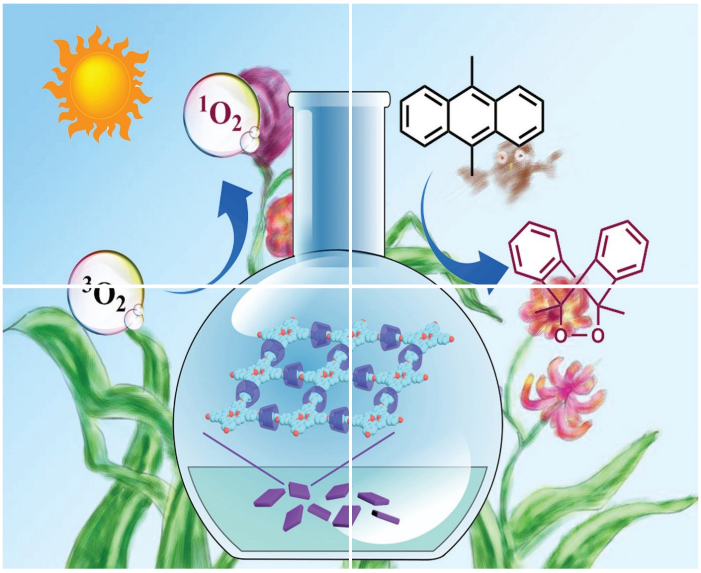

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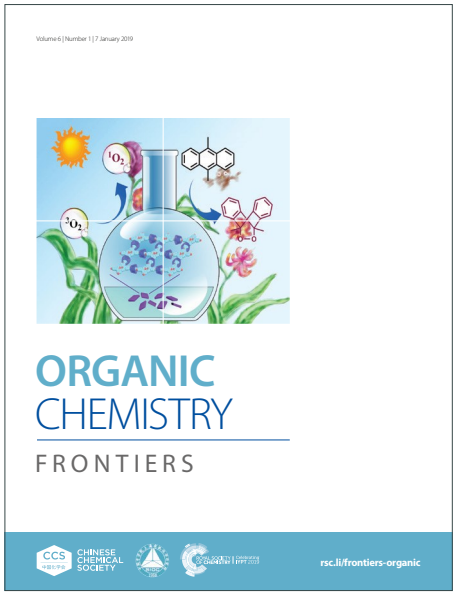

Organocatalytic atroposelective *N*-alkylation: divergent synthesis of axially chiral sulfonamides and biaryl amino phenols

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Xiao Xiao,[a] Yin-Jie Lu,[a] Hong-Yu Tian,[a] Hai-Jie Zhou,[a] Jia-Wei Li,[a] Yi-Ping Yao,[a] Miao-Lin Ke,[a] Fen-Er Chen* [a,b,c]

Axial chirality exists ubiquitously in numerous natural products and has been extensively recognized for decades in pharmaceuticals and enantioselective transformations. The development of efficient methodologies to obtain enantiopure structures bearing either a C-N or C–C axially chiral entity remains highly desired and sought after. Herein, a practical and universal organocatalytic atroposelective *N*-alkylation has been developed to efficiently access sulfonamides containing an allene or allyl entity. Furthermore, this process has also enabled a selective N–H activation in the subsequent transformation towards functionalized sulfonamides, and realized the kinetic resolution of NOBIN analogues to afford chiral catalyst precursors. The racemization experiments show that substituted allenoate-sulfonamides possess higher rotational barriers than corresponding acrylate-sulfonamides. This divergent synthetic procedure can be facilely scaled up and bode well for its wide applications in enantioselective synthesis.

Introduction

The significance of atropoisomerism as a chiral unit can be exemplified in its ubiquity in a variety of natural products and pharmaceuticals, together with its extensive use as chiral organocatalysts/ligands in asymmetric catalysis.[1] Since its discovery in 1922,[2] atropoisomerism has been a cutting-edge field and witnessed enormous advances in its construction. Among the different types of axially chiral compounds, biaryls possessing hindered rotation can be identified as the most recognized form. Notably, axially chiral 2-amino-2'-hydroxy binaphthyl (NOBIN) scaffolds have been extensively utilized as privileged catalysts and ligands in enantioselective catalysis,[3a-e] and can be found in natural products such as proteasome inhibitors TMC-95A–D[3f,g] (Fig. 1a). In comparison with the numerous methods developed for the construction of optically pure BINOL and its derivatives, asymmetric catalytic processes for the formation of chiral NOBIN-type biaryls are still underdeveloped. Existing procedures in the form of classical resolution[4], conventional oxidative coupling of two aryl synthons[5], kinetic resolution[6], and enantioselective transformation[7], often require either stoichiometric amounts of chiral reagents or extra steps for the preparation of the catalysts. In view of the importance of chiral NOBIN analogs and its limited synthetic routes, the development of both a general and practical methodology to access these enantiopure structures is highly desired.

Apart from the flourishing development of biaryls consisting of an atropoisomeric C–C bond, non-biaryl C–N axially chiral scaffolds which possess appealing medicinal and agricultural activities are also promising structural motifs that have attracted considerable attention from the chemistry and pharmaceutical communities.[8] Amongst them, efforts focused towards the construction of axially chiral sulfonamides have bloomed in recent years due to their utilities in the treatment of pain (Fig. 1b, left).[8d] Documented attempts include tertiary-amine-catalyzed *N*-alkylation,[6d] isothiourea-catalyzed *N*-acylation,[9] and Pd-catalyzed *N*-allylation[10]. Since the development of Pd-catalyzed *N*-allylation strategy to access chiral anilides pioneered by Taguchi[11] and Curran[12], the *N*-alkylation strategy has become a mainstream method to construct the C–N axially chiral entities.[6d,8e,13] Notably, Zhao and coworkers discovered an elegant asymmetric allylic alkylation (AAA) reaction to access chiral sulfonamides containing an allyl scaffold by utilizing sulfonamides and Morita–Baylis–Hillman (MBH) carbonates as substrates.[6d] Nevertheless, more efficient strategies such as reducing catalyst loadings for the synthesis of axially chiral sulfonamides is still in high demand (Fig. 1b, right). Allenes on the other hand, being geometrically unique and synthetically versatile substructures, occupy a prominent position in chemical synthesis.[14] At present, the construction of chiral allenic sulfonamides is unexplored despite its promising applications in many areas.

Morita–Baylis–Hillman (MBH) carbonates have been developed as effective synthons to access C–N axially chiral scaffolds *via* asymmetric organocatalysis (Fig. 1c).[6d,13f-i] Mechanistically, the basicity of the *tert*-butoxide anion released from the OBoc carbonate produced by the MBH carbonate is too strong to differentiate and selectively deprotonate different types of N–H bonds (Fig. 1d).[15] Therefore, this selective transformation to access axially chiral sulfonamides in compounds possessing different type of N–H bonds, such as the precursor for the formation of UK-240455, is much more difficult to realize. With reference to the pK_a value table, the N–H bond of sulfonamides is more acidic than those of

[a] Institute of Pharmaceutical Science and Technology, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China. Email: rfchen@fudan.edu,cn
[b] Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry
Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China.
[c] Shanghai Engineering Center of Industrial Asymmetric Catalysis for Chiral Drugs, Shanghai 200433, People's Republic of China

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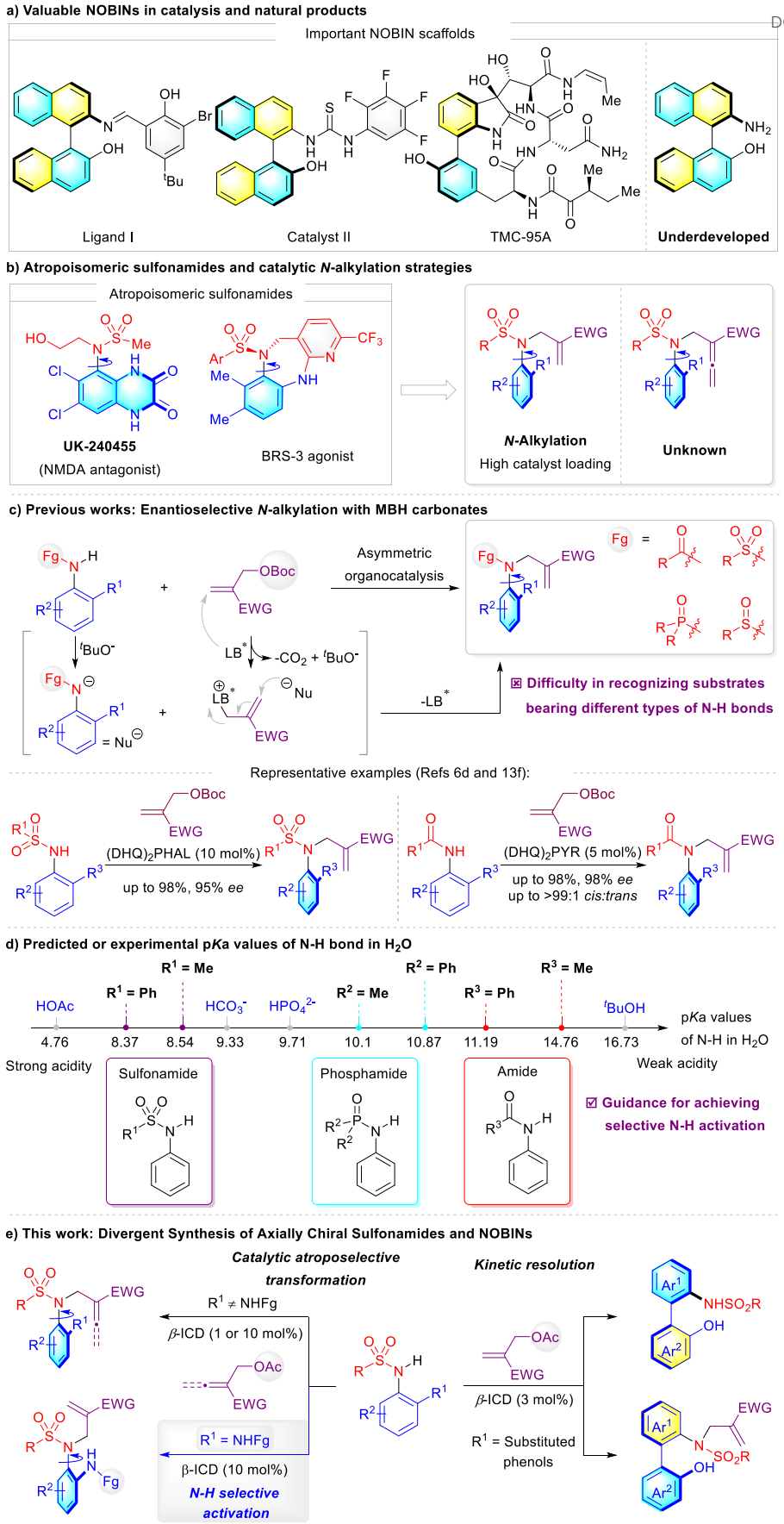
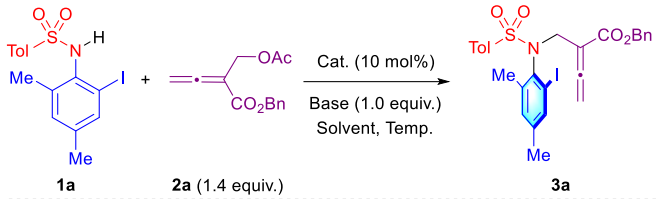
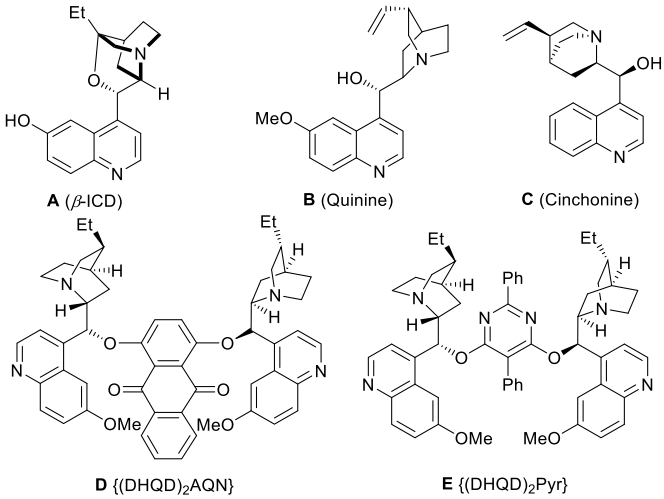


Figure 1. From inspiration to reaction design.

Table 1. Optimization of enantioselective *N*-alkylation[a]





Entry	Cat.	Base	Solvent	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	**A**	-	PhMe	24	71	51
2	**B**	-	PhMe	24	75	21
3	**C**	-	PhMe	24	63	15
4	**D**	-	PhMe	24	67	-27
5	**E**	-	PhMe	24	85	-17
6	**A**	-	Mesitylene	24	84	72
7[d]	**A**	-	Mesitylene	24	83	79
8[d]	**A**	-	Mesitylene	-20	9	88
9[d]	**A**	Cs_2CO_3	Mesitylene	-20	91	84
10[d]	**A**	Cs_2CO_3	Mesitylene	-40	92	89
11[d]	**A**	K_2CO_3	Mesitylene	-40	73	88
12[d]	**A**	Na_2CO_3	Mesitylene	-40	61	89
13[d]	**A**	$KHCO_3$	Mesitylene	-40	35	83
14[d]	**A**	K_3PO_4	Mesitylene	-40	31	89
15[d]	***A***	***Cs_2CO_3***	***Mesitylene***	***-50***	***92 (91)[e]***	***90***

[a]Unless noted otherwise, the reactions were performed with **1a** (0.05 mmol, 1.0 equiv.), **2a** (0.07 mmol, 1.4 equiv.), catalyst (10 mol%), and base (1.0 equiv.) in solvent (0.5 mL) at 24 to -50 °C for 12 h. [b]Yield was detected by ^{1}H-NMR. [c]The *ee* value was determined by chiral HPLC. [d]Mesitylene (4 mL) was added. [e]Isolated yield. Tol = 4-MeC_6H_4.

phosphamides and amides, which can enable selective N–H activation using appropriate substrates and base.[16] Therefore, to distinguish different N–H bonds and introduce selective deprotonation, a less basic acetate anion liberated from the corresponding MBH acetate under the catalytic conditions was hypothesized to be a better matched substrate. In particular, the N–H bond of sulfonamide can enable selective N–H activation using appropriate substrates and base.[16] Therefore, to distinguish different N–H bonds and introduce selective deprotonation, a less basic acetate anion liberated from the corresponding MBH acetate under the catalytic conditions was hypothesized to be a better matched substrate. In particular, the N–H bond of sulfonamide can be deprotonated by the carbonate/phosphate anion, while the N–H bond of phosphamides and amides would remain untouched. Therefore, the cooperation of MBH acetate with carbonate or phosphate anion could enable the selective N–H activation with the assistance of organocatalysis.[17]

Herein, we disclosed a universal and practical catalytic procedure to synthesize axially chiral sulfonamides bearing an allene or allyl unit, and achieved the kinetic resolution of NOBIN analogues to furnish chiral catalyst precursors (Fig. 1e). This highly efficient and practical method utilizes readily available reagents/catalysts, realizes selective N–H activation and be facilely scaled up.

Results and discussion

We commenced our development of an allene-functionalized *N*-alkylation process by exploring a range of organocatalyst in the presence of multi-substituted sulfonamide **1a**, 2-(acetoxymethyl)buta-2,3-dienoate **2a**, and in the presence of cesium carbonate base. In an effort to achieve this enantioselective transformation, a variety of phosphine catalysts were first screened, albeit with low *ee* values obtained (for details, please see the page 3 of SI).[15c,18] To our delight, further screening with the use of chiral amine catalysts afforded moderate enantioselectivities with toluene as the solvent at 24 °C (Table 1, entries 1-5), in which *β*-ICD was the best catalyst displaying the highest enantioselectivity (Table 1, entry 1). Solvent optimization conferred the desired product **3a** in 84% yield and with 72% *ee* in mesitylene (Table 1, entry 6; for details, please see the page 7 of SI). Decreasing the reaction concentration was found to increase the enantioselectivity (Table 1, entry 7). When the temperature was decreased to -20 °C, the *ee* value could be improved to 88%, but with a sharp decrease in yield (Table 1, entry 8). Subsequently, Cs_2CO_3 was loaded into the reaction and led to a much-improved reactivity and enantioselectivity (84% *ee*, 91% yield, Table 1, entry 9), which was utilized to promote the nucleophilicity of sulfonamide by deprotonating the N–H bond to generate the anionic species. A further decrease in temperature to -40 °C led to the product **3a** in 92% yield with 89% *ee*. Importantly, the base screening process demonstrated that Cs_2CO_3 was the best base to achieve the highest enantioselectivity and reactivity (Table 1, entries 10-14). Ultimately, when the temperature was decreased to -50 °C, the chiral compound **3a** was formed in 92% yield and 90% *ee* (Table 1, entry 15).

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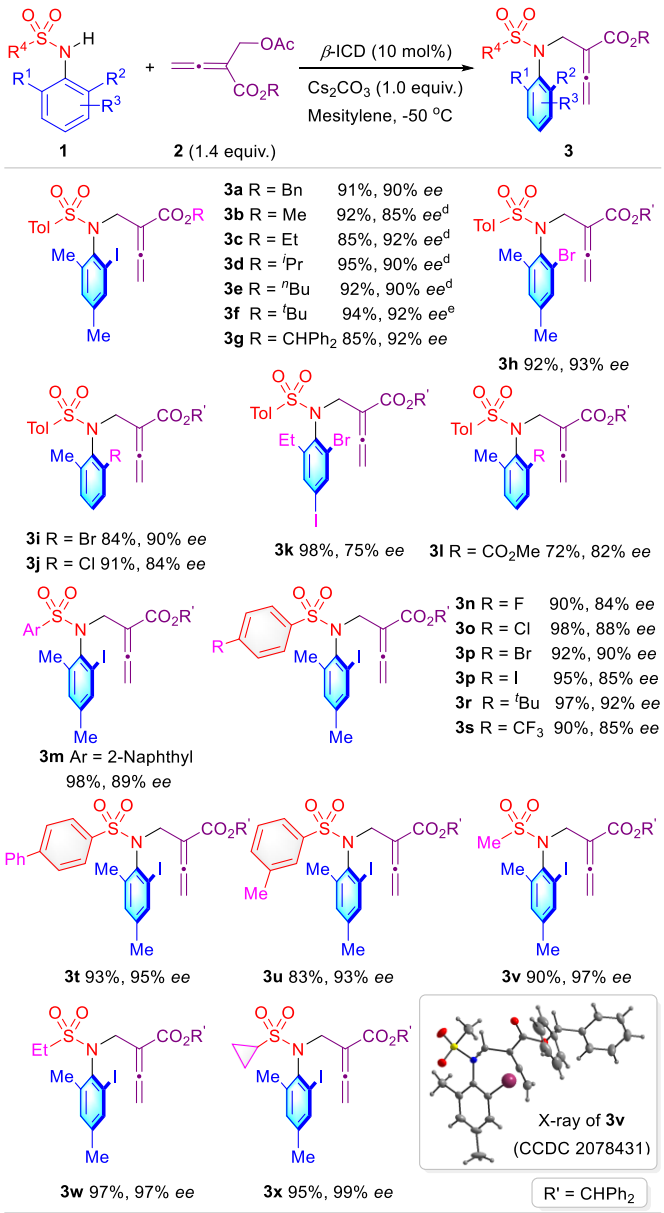
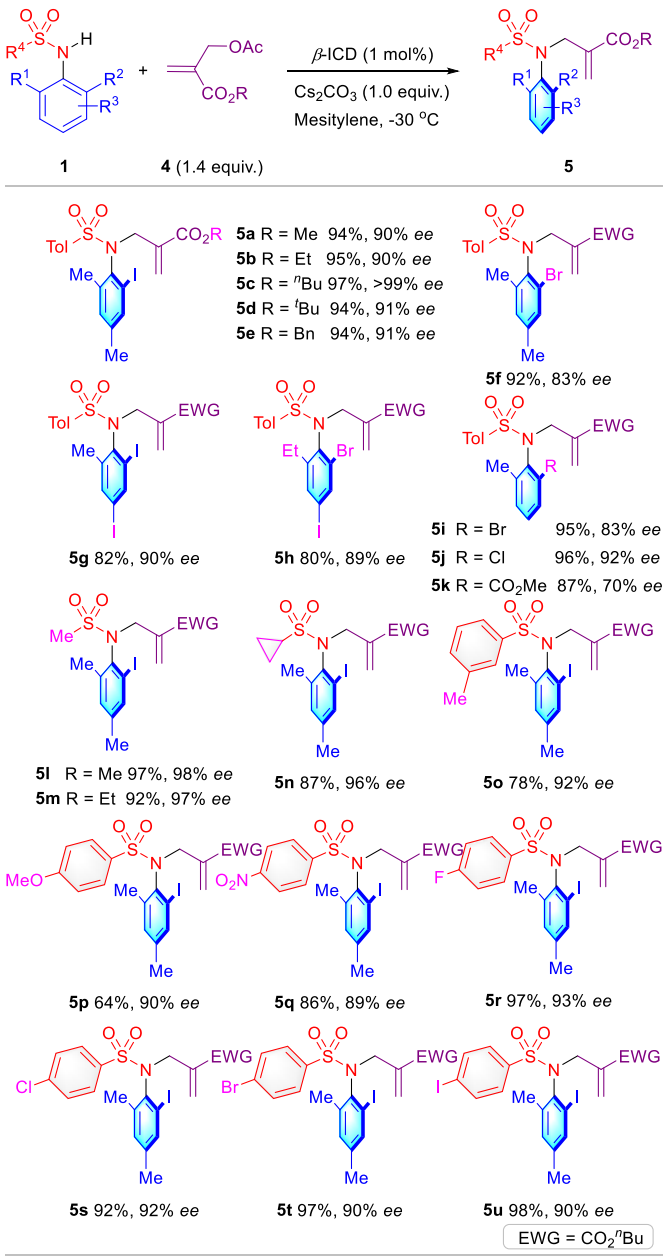
Table 2. Scope of axially chiral sulfonamides from allenoates[a,b,c]



[a]Unless noted otherwise, the reactions were performed with **1** (0.05 mmol), **2** (0.07 mmol, 1.4 equiv.), *β*-ICD (10 mol%), and Cs_2CO_3 (0.05 mmol, 1.0 equiv.) in mesitylene (4 mL) at -50 °C for 12-24 h. [b]Isolated yield. [c]The *ee* value was determined by chiral HPLC. [d]72 h. [e]7 d. Tol = 4-MeC_6H_4.

With the optimized conditions in hand, we examined the scope of this catalytic transformation (Table 2). The projected reaction was applicable to a wide range of 2,6-substituted arylsulfonamide **1** and 2-(acetoxymethyl)buta-2,3-dienoate adducts **2**. The ester group of 2-(acetoxymethyl)buta-2,3-dienoate **2** can be changed, from Bn (**3a**), Me (**3b**), Et (**3c**), *i*Pr (**3d**), *n*Bu (**3e**), and *t*Bu (**3f**), to benzhydryl (**3g**), with consistently excellent *ee* values and high yields. Apart from the small methyl allenoate **2b**, substrates **2** bearing increased steric hindrance on the ester group would promote the enantioselectivity of product **3** despite longer reaction times (**3f**). Next, the incorporation of halide substituent on the *N*-aryl group was well-tolerated to generate **3h**–**3k** in high yields with moderate to excellent enantioselectivities. The decrease in steric effect of the ortho halide substituent on *N*-phenyl ring from I to Cl led to a decrease in *ee* values (**3g**, **3i** and **3j**). The substrate possessing a halide atom (I) on the para-position obtained the product in moderate enantioselectivity (**3k**). An electron-poor aromatic substituent was also evaluated in this transformation and produced the desired product 3l in good yield and enantioselectivity. Lastly, the variation of the sulfonamide moiety was examined. It was found that substrates from the small mesyl group to a range of substituted aryl sulfonamides bearing both electron-withdrawing (EWG) and electron-donating group (EDG) could

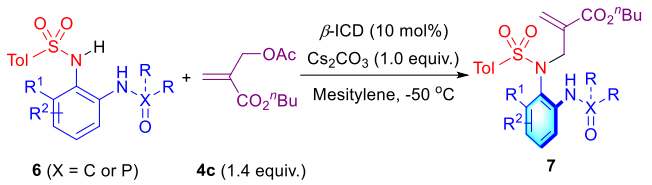
Table 3. Scope of axially chiral sulfonamides from MBH acetates[a,b,c]



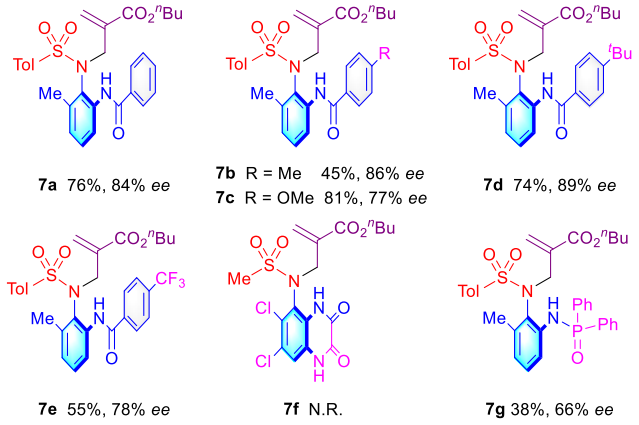
[a]Unless noted otherwise, the reactions were performed with **1** (0.1 mmol), **4** (0.14 mmol, 1.4 equiv.), *β*-ICD (1 mol%), and Cs_2CO_3 (0.1 mmol, 1.0 equiv.) in mesitylene (2 mL) at -30 °C for 72 h. [b]Isolated yield. [c]The *ee* value was determined by chiral HPLC. Tol = 4-MeC_6H_4.

afford the axially chiral N-aryl sulfonamides with uniformly high ees (**3m–3x**). The single crystal X-ray analysis of **3v** confirmed the absolute configuration of this class of compounds.[19]

Table 4. Scope of axially chiral sulfonamides via selective N-H activation[a,b,c]



6 (X = C or P) **4c** (1.4 equiv.) **7**

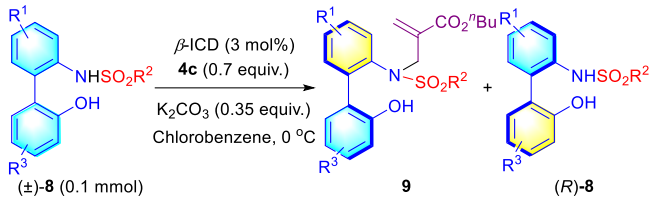


7a 76%, 84% *ee*
7b R = Me 45%, 86% *ee*
7c R = OMe 81%, 77% *ee*
7d 74%, 89% *ee*
7e 55%, 78% *ee*
7f N.R.
7g 38%, 66% *ee*

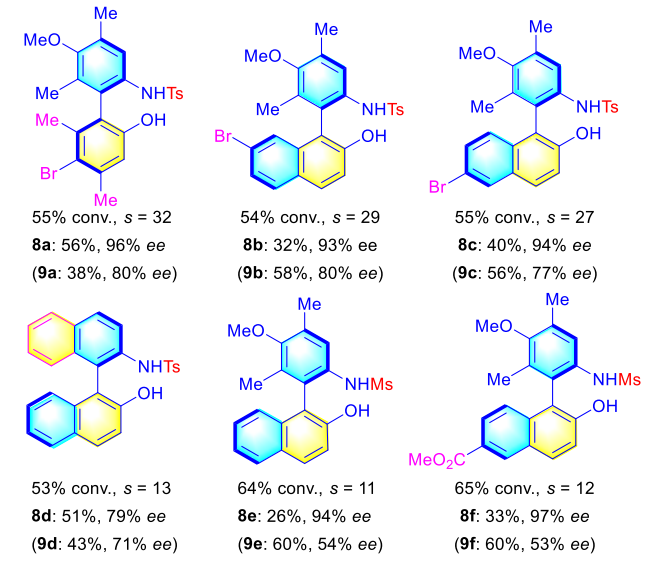
aUnless noted otherwise, the reactions were performed with 6 (0.05 mmol), 4c (0.07 mmol, 1.4 equiv.), β-ICD (10 mol%), Cs_2CO_3 (0.05 mmol, 1.0 equiv.) in mesitylene (3 mL) at -50 oC for 24 h. [b]Isolated yield. [c]The *ee* value was determined by chiral HPLC. Tol = 4-MeC_6H_4.

After the successful enantioselective construction of C–N axial chirality in allenoate-arylsulfonamides, we were then curious to find out if this methodology could be extended to acrylate-sulfonamides. The atroposelective *N*-alkylation of MBH carbonate and sulfonamide to synthesize the axially chiral acrylate-sulfonamide was reported by Zhao and required a relatively higher catalyst loading (10 mol%). The low catalyst loading (1 mol%) was utilized to treat this transformation from sulfonamide and MBH acetate (for details, please see the page 8 of SI). To our delight, controlling the enantioselectivity of atropisomeric acrylate-sulfonamides was relatively easier than the allenoate-sulfonamides at a higher temperature of -30 °C. The catalytic enantioselective *N*-allylic alkylation of sulfonamides for the atroposelective synthesis of acrylate-sulfonamide bearing a C–N bond was then explored, and the results are summarized in Table 3. Notably, a variety of C–N axially chiral acrylate-sulfonamides containing different ester substituents were synthesized, and all the products were formed in high yields with excellent enantioselectivities (**5a**-**5e**, 90-99% *ee*). Installing other halide substituents on the N-aryl ring did not show obvious influence on the enantioselectivity of the present transformation (**5f**-**5j**). The ortho substituent on N-phenyl ring possessing an EWG group resulted in access the product **5k** with moderate enantioselectivity. Next, several sulfonamide substrates were surveyed. Notably, the substituents on sulfonamide group could be varied, from aliphatic groups (**5l**-**5n**), to aromatic rings bearing both EWG and EDG groups (**5o**-**5u**), and the corresponding products could be obtained in high yields with excellent enantioselectivities (89-96% *ee*).

Table 5. Scope and structural exploration of NOBINs *via* kinetic resolution[a,b,c,d]



(±)-**8** (0.1 mmol) **9** (*R*)-**8**



55% conv., *s* = 32
8a: 56%, 96% *ee*
(**9a**: 38%, 80% *ee*)

54% conv., *s* = 29
8b: 32%, 93% ee
(**9b**: 58%, 80% *ee*)

55% conv., *s* = 27
8c: 40%, 94% *ee*
(**9c**: 56%, 77% *ee*)

53% conv., *s* = 13
8d: 51%, 79% *ee*
(**9d**: 43%, 71% *ee*)

64% conv., *s* = 11
8e: 26%, 94% *ee*
(**9e**: 60%, 54% *ee*)

65% conv., *s* = 12
8f: 33%, 97% *ee*
(**9f**: 60%, 53% *ee*)

[a]Unless noted otherwise, the reactions were performed with **10** (0.1 mmol), **4** (0.07 mmol, 0.7 equiv.), *β*-ICD (3 mol%), K_2CO_3 (0.035 mmol, 0.35 equiv.) in chlorobenzene (8 mL) at 0 °C for 32 h. [b]Isolated yield. [c]The *ee* value was determined by chiral HPLC. [d]Conversion (C) = $ee_8/(ee_8 + ee_9)$, s = ln[(1-C)(1-ee_8)]/ln(1-C)(1+ee_8)].

Important C–N axially chiral compounds, such as NMDA antagonist UK-240455, possess both sulfonamide and amide units which require selective N–H activation strategy to construct these entities. Taking reference from the p*K*a value table,[16] we envisioned that our method could potentially achieve this transformation, wherein the matched substrate and base could realize the selective N–H activation of the sulfonamide. To our delight, in the presence of a catalytic amount of *β*-ICD, amide **6a** reacted smoothly with MBH adduct **4c** to afford the single product **7a** bearing an axial C–N bond, albeit in 71% yield and 77% *ee*. This result demonstrated the difficulty in enantioselectivity control. The reaction temperature was then decreased to -50 °C and the *ee* value of the desired product was promoted. Notably, the ortho-substituted arylamides bearing both electron-donating and electron-withdrawing groups on *N*-aryl ring were well tolerated and the corresponding products could be afforded with moderate to high enantioselectivities (Table 4, **7a**-**7e**). The analogue of UK-240455 could not be obtained because of the extremely poor solubility of the

staring material (**7f**). The phosphamide group was also compatible in this conditions (**7g**). According to the foregoing experiments, controlling the enantioselectivity of allenoate-sulfonamide was more formidable than acrylate-sulfonamide. Predictably, the dienoate adduct **2** and functionalized sulfonamide **6** could transformed to the desired product with low efficiency and enantioselectivity (for details, please see the page 49 of SI, **7h** and **7i**).

Considering the significance and value of NOBINs, our catalytic process was further applied to realize the kinetic resolution of amino phenol scaffolds. To achieve a more efficient approach to access NOBIN and its derivatives, we sought to optimize this reaction using low catalyst loadings and successfully realized the reaction using only 3 mol% of *β*-ICD (for details, please see the page 9 of SI). Under the optimized reaction conditions, *N*-Ts substituted **8a** was recovered in 56% yield with 96% *ee* (Table 5). Examples **8b**–**8f** exemplified that substrates bearing numerous functional groups (i.e., halogens, esters, and condensed ring) in different positions, could afford good to high levels of enantioselectivity for the *N*-alkylation resolution as well. These scaffolds were recovered in excellent enantiopurity (79–96% *ee*). Similar to the Ts-protected anilines, the Ms-protected substrates (**8e**-**8f**) were also exhibited high compatibilities in this resolution route with the same level of enantioselectivity.

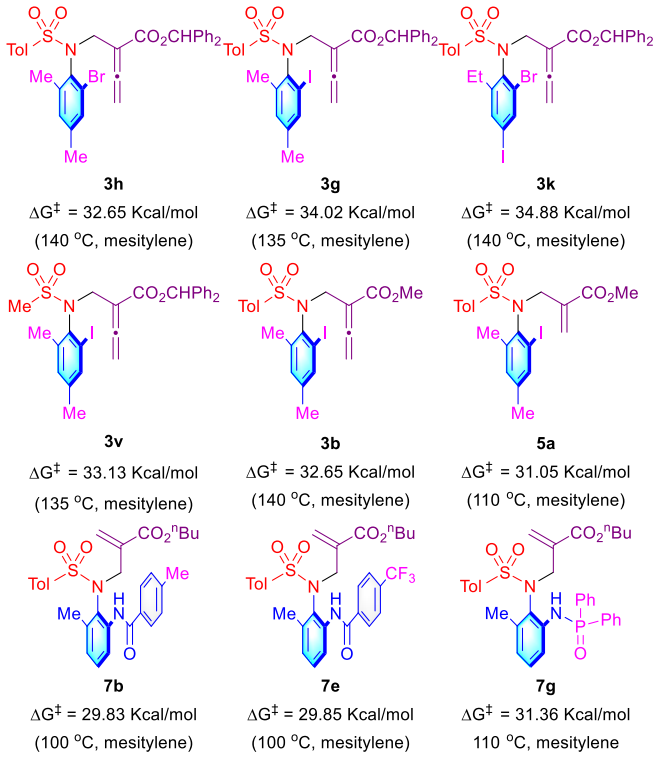


Figure 2. Examination of the stability of C–N axial chirality.

For the purpose of investigating the stereochemical stability, the racemization experiments of these atropisomeric compounds were performed to obtain rotational barriers (Fig. 2). At first, compound **3h** in mesitylene was heat to 110 °C and the *ee* value of **3h** remained unchanged in 5 hours. This indicated that allenoate-sulfonamide **3h** has a high stability. We then increased the temperature to 140 °C and the rotation barrier (ΔG‡) of **3h** was obtained as 32.65 kcal/mol.[20] We further tested the effect of the ortho-substituted group on stereochemical stability. The measured rotational energy barriers of **3g** and **3k** were 34.02 and 33.88 kcal/mol, respectively. These results reveal that the steric resistance of the substituent on the aromatic ring of aniline has a great influence on the rotation energy barrier. The chiral substrate **3v** possessing a small mesyl group obtained the lower rotational barrier and stability than the Ts-substituted product **3g**. Furthermore, the rotational barrier of **3b** was also experimentally determined. In general, compound **3g** appeared to be more configurationally stable than **3b**, which showed that the allenoate substrate bearing an ester group with bulky steric hinderance possessed high stability. The racemization experiments of acrylate-sulfonamide were subsequently carried out and the rotational barrier of **5a** was lower than **3b** because the size of vinyl was smaller than allenyl. Furthermore, the effect of ortho-substituted group bearing different types of amide on stereochemical stability was examined. The substituted acrylate-sulfonamide **7g** bearing a phosphamide possessed higher rotational barrier than the amide units **7b**/**7e**.

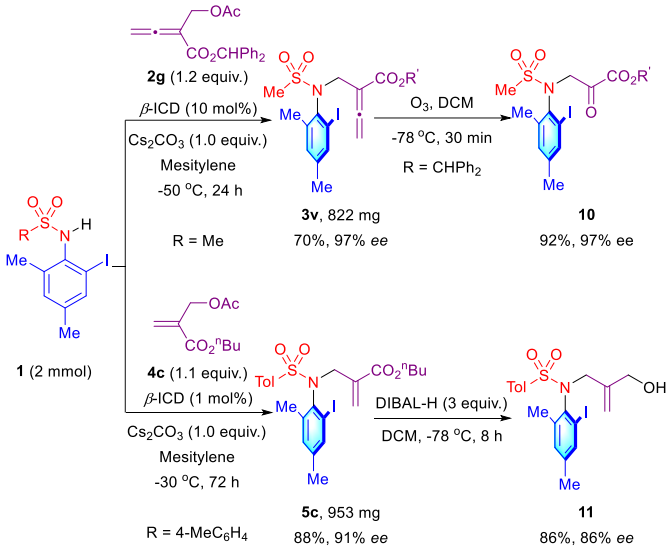


Figure 3. Further transformation.

To demonstrate the utility of our current method, the convenient gram-scale operations were performed to synthesize both the allenoate-sulfonamide **3v** and acrylate-sulfonamide **5c** in high yields with excellent enantioselectivities (Fig. 3). Subsequent ozonization of allenoate-sulfonamide **3v** furnished 1,2-dicarbonyl compound **10** in high efficiency. Alternatively, reduction of **5c** with DIBAL-H smoothly led to the alcohol product **11**. Notably, both the oxidative and reductive transformations occurred readily, with the high enantioselective retention. Furthermore, the synthesized axially chiral product **3v** and **5c** were tested as enantioselective iodine catalysts for the asymmetric oxidative spirolactonization of the phenol derivative, and the low catalytic efficiency was observed (for details, please see the page 71 of SI).

Conclusions

In conclusion, we have developed a versatile and efficient catalytic process that allows the synthesis of enantiopure compounds bearing either a C-N or C–C axially chiral entity. In the enantioselective construction of C-N axial chirality, both the allenoate-sulfonamide and acrylate-sulfonamide were achieved in high yields and excellent enantioselectivities in the presence of low catalyst loadings. Furthermore, we have achieved a selective N-H activation to synthesize functionalized compounds possessing different types of amide units. In addition to C-N axial chirality, optically pure NOBINs containing C-C axial chirality can be obtained *via* kinetic resolution. Successful gram-scale operation and further transformation opens a new avenue to drug and catalyst discovery. The racemization experiments were smoothly carried out to explore the stereochemical stability of these chiral units. The promising utility of these classes of scaffolds in drug delivery and asymmetric catalysis are currently under investigation in our laboratories and will be reported in due course.

Experimental

Representative procedure for synthesis of axially chiral allenoate-sulfonamide 3. To a Schlenk tube containing **1** (0.05 mmol), *β*-ICD (1.5 mg, 10 mol%) and Cs_2CO_3 (0.05 mmol, 1.0 equiv.) were added mesitylene (4 mL) and dienoate **2** (0.07 mmol, 1.4 equiv.). The reaction mixture was stirred at -50 °C for 24 hours to 7 days. The solvent was removed by silica gel column chromatography and the residue was then purified by silica gel column chromatography to afford the product **3**.

Representative procedure for synthesis of axially chiral acrylate-sulfonamide 5. To a Schlenk tube containing **1** (0.1 mmol), *β*-ICD (0.3 mg, 1 mol%) and Cs_2CO_3 (0.1 mmol, 1.0 equiv.) were added mesitylene (4 mL) and MBH acetate **4** (0.14 mmol, 1.4 equiv.). The reaction mixture was stirred at -30 °C for 32 h. The solvent was removed by silica gel column chromatography and the residue was then purified by silica gel column chromatography to afford the product **5**.

Representative procedure for synthesis of axially chiral sulfonamide 7 *via* selective N-H activation. To a Schlenk tube containing **6** (0.05 mmol), *β*-ICD (1.5 mg, 10 mol%) and Cs_2CO_3 (0.05 mmol, 1.0 equiv.) were added mesitylene (3 mL) and MBH acetate **4c** (0.14 mmol, 1.4 equiv.). The reaction mixture was stirred at -50 °C for 24 h. The solvent was removed by silica gel column chromatography and the residue was then purified by silica gel column chromatography to afford the product **7**.

Representative procedure for the kinetic resolution of NOBIN 8. To a Schlenk tube containing *rac*-**8** (0.1 mmol), *β*-ICD (1.0 mg, 3 mol%) and K_2CO_3 (0.035 mmol, 0.35 equiv.) were added chlorobenzene (8 mL) and MBH acetate **4c** (0.07 mmol, 0.7 equiv.). The reaction mixture was stirred at 0 °C for 72 h. The solvent was removed by silica gel column chromatography and the residue was then purified by silica gel column chromatography to afford the product **9** and unreacted starting material **8**.

Author Contributions

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X.X. and F.E.C. designed the project. X.X. and Y.J.L. designed and carried out the experiments. H.Y.T., H.J.Z., J.W.L., Y.P.Y., and M.L.K. contributed to part experiments. X.X. and F.E.C. discussed the results, contributed to writing the manuscript, and commented on the manuscript. All of the authors approved the final version of the manuscript for submission.

Conflicts of interest

There are no conflicts to declare.

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