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Chemo- and atroposelective Boc protection for asymmetric synthesis of NH_2-free axially chiral biaryl amino phenols

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Enantioselective protection strategies have emerged as powerful tools for creating high-value optically active compounds. Herein, we report an efficient and direct Lewis base-catalyzed enantioselective *tert*-butoxycarbonyl (Boc) protection strategy for the construction of axial chirality. Employing a chiral isothiourea (ITU) catalyst, a series of amino bisphenols undergo chemo- and atroposelective *O*-Boc protection with Boc anhydride (Boc_2O), delivering NH_2-free axially chiral biaryl amino phenols with moderate yields and high enantioselectivities. This desymmetrization protocol is scalable to gram level and enables facile downstream transformations of the chiral products. Computational studies reveal that the amino (NH_2) group on the naphthalene ring facilitates intramolecular proton transfer of the hydroxyl (OH) group. Moreover, an unprecedented S···C–NH_3^+ electrostatic interaction, in combination with π–π stacking, is identified as a key stabilizing factor in the transition states.

Introduction

The strategic use of protecting groups is essential for synthesizing complex molecules containing multiple reactive functionalities.[1] By integrating chiral catalysts with rationally designed substrates, conventional protection methods can be adapted for asymmetric transformations, opening new avenues for the construction of optically active compounds. In 2006, Snapper, Hoveyda, and co-workers pioneered an amino acid-derived imidazole-catalyzed asymmetric silylation of meso diols to afford secondary alcohols with high enantioselectivities (Scheme 1a).[2] Inspired by this elegant work, the research groups of Snapper and Hoveyda,[3a–c] Oestreich,[3d–g] Song,[3h] He,[3i] List,[3j] and Franz[3k] subsequently developed a range of Lewis base-, transition-metal-, and Brønsted acid-catalyzed enantioselective *O*-silyl protection protocols to generate carbon-, silicon-, and axial chirality. Despite these advances, there remains an urgent need for the development of versatile enantioselective protection systems. Boc anhydride (Boc_2O), also known as di-*tert*-butyl dicarbonate, is an easily available and synthetically versatile reagent that has been widely employed for amine protection in peptide, pharmaceutical, and natural product synthesis.[1,4] Occasionally, Boc_2O is also used for the protection of alcohols and thiols (Scheme 1b, left).[5] We envision that a chiral Lewis base could activate Boc_2O to form a reactive intermediate within a chiral environment, thereby enabling either the kinetic resolution of racemic substrates or the desymmetrization of prochiral substrates to establish new stereogenic centers (Scheme 1b, right). This approach could diversify catalytic asymmetric protection strategies beyond traditional silylation methods.

Atropisomeric 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) and its analogs are recognized as privileged scaffolds broadly utilized in the development of chiral ligands and catalysts (Scheme 1c).[6] Consequently, significant efforts have been devoted to the stereoselective preparation of these frameworks.[7–12] To date, there are four primary catalytic asymmetric strategies toward the synthesis of axially chiral NOBIN analogs (Scheme 1d): (i) transition-metal-catalyzed oxidative coupling of 2-naphthols and 2-naphthylamines;[8] (ii) Brønsted/Lewis acid-catalyzed nucleophilic addition of one aryl fragment to another;[9] (iii) organocatalytic kinetic resolution of racemic NOBINs;[10] and (iv) *N*-heterocyclic carbene (NHC)-catalyzed desymmetrization of prochiral amino bisphenols.[11] While those protocols are well-established, most of them lead to *N*-protected axially chiral biaryl amino phenols as final products, necessitating an additional deprotection step that limits their synthetic utility. Our group aims to advance catalytic systems for constructing synthetically valuable molecules.[13] We envisage that a Lewis base-catalyzed enantioselective *O*-Boc protection of unprotected biaryl amino bisphenols could offer a highly efficient and direct route to chiral NOBIN analogs.

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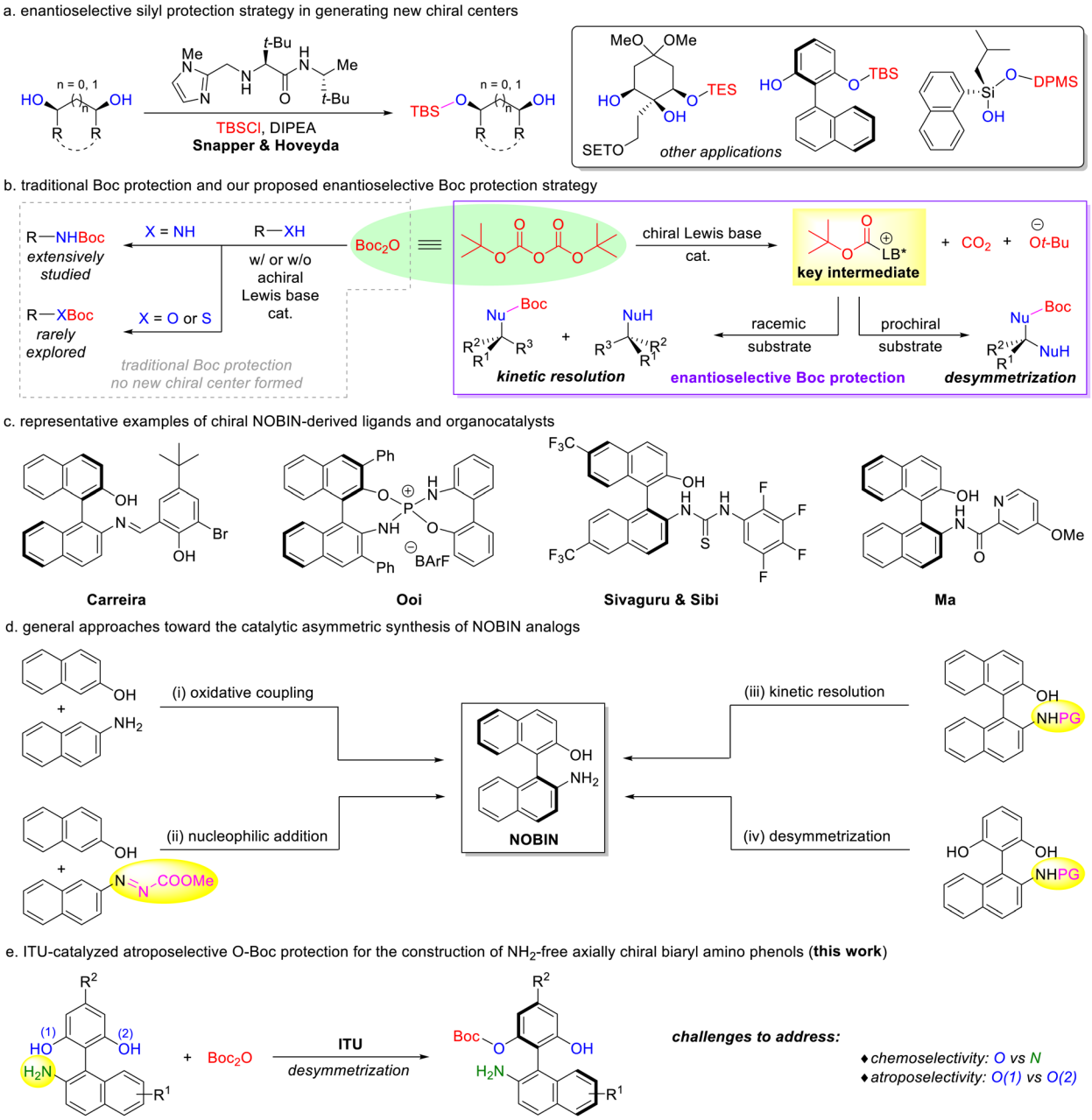


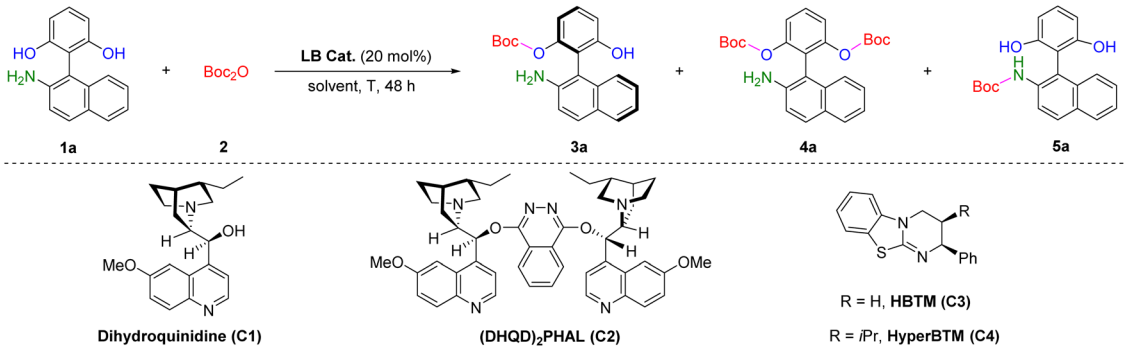
Scheme 1 Enantioselective protection strategy and our protocol to directly access NH_2-free NOBIN analogs.

Achieving such a transformation requires addressing two key challenges: chemoselectivity between *O*-Boc and *N*-Boc protection, and atroposelectivity between the two identical hydroxy groups. Herein, we disclose an isothiourea (ITU)-promoted chemo- and atroposelective Boc protection of amino bisphenols, allowing for the rapid access to NH_2-free axially chiral amino phenols with excellent enantiocontrol (Scheme 1e).

Results and discussion

We began our investigation by selecting amino bisphenol **1a** as the model substrate to react with Boc_2O **2** in dichloromethane (CH_2Cl_2) at 25 °C for 48 hours, with key results summarized in Table 1. The use of cinchona alkaloid-derived Lewis base catalysts **C1** and **C2** efficiently generated the desired *O*-Boc protected amino phenol **3a** in moderate yields and enantioselectivities, accompanied by side products including the di-*O*-Boc and *N*-Boc protected amino phenols (**4a** and **5a**) (entries 1 and 2). To our delight, when isothiourea (ITU) catalysts **C3** [14] and **C4** [15] were employed, formation of the undesired *N*-Boc product **5a** was completely suppressed. Under these conditions, **3a** was obtained in 35% yield with 56% ee and 53% yield with 69% ee, respectively (entries 3 and 4). Utilizing **C4** as the optimal catalyst, we next evaluated a variety of solvents (entries 5–9). Both polar and non-polar solvents were compatible, with diethyl ether (Et_2O) providing the best result,

Table 1 Optimization of reaction conditions[a]



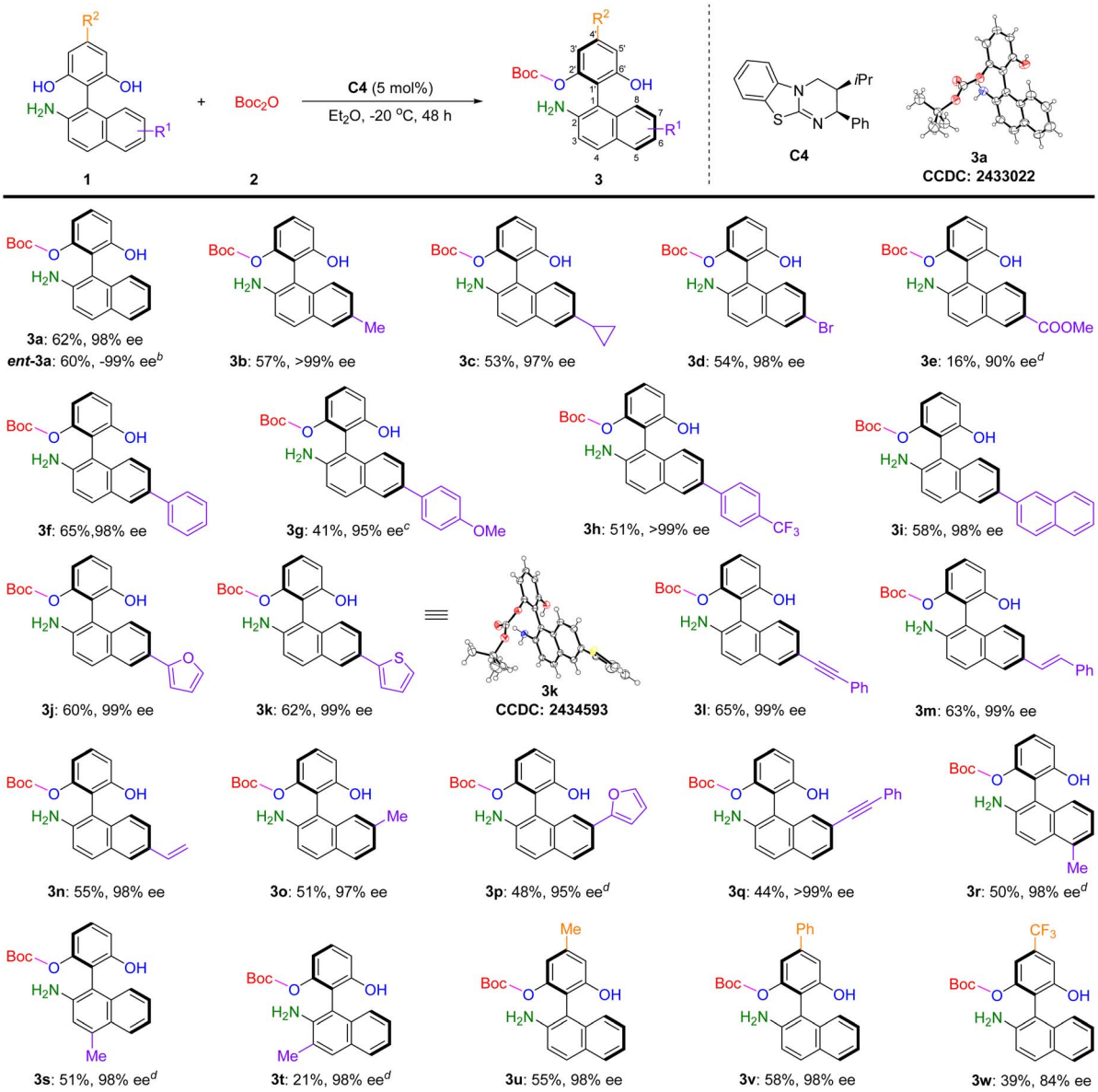
Entry	Lewis base cat.	Solvent	T (°C)	Yield of **3a** [b] (%)	Yield of **4a** [b] (%)	Yield of **5a** [b] (%)	ee of **3a** [c] (%)
1	**C1**	CH_2Cl_2	25	32	55	6	53
2	**C2**	CH_2Cl_2	25	39	40	4	66
3	**C3**	CH_2Cl_2	25	35	57	Trace	56
4	**C4**	CH_2Cl_2	25	53	40	Trace	69
5	**C4**	THF	25	49	47	Trace	69
6	**C4**	Et_2O	25	44	37	Trace	72
7	**C4**	EtOAc	25	46	42	Trace	63
8	**C4**	Toluene	25	35	21	Trace	67
9	**C4**	CH_3CN	25	43	34	Trace	20
10	**C4**	Et_2O	0	49	47	Trace	94
11	**C4**	Et_2O	−20	48	50	Trace	98
12[d]	**C4**	Et_2O	−40	48	50	Trace	98
13[e]	**C4**	Et_2O	−20	63	18	Trace	98
14[e,f]	**C4**	**Et_2O**	**−20**	**62**	**16**	**Trace**	**98**

[a] Reaction conditions are as follows: **1a** (0.2 mmol), **2** (0.3 mmol), Lewis base cat. (0.04 mmol), and solvent (2 mL) at a specific temperature for 48 h. [b] Isolated yield of product based on **1a**. [c] Enantiomeric excess of **3a**, determined *via* chiral-phase HPLC analysis. [d] 96 h. [e] 0.22 mmol of **2** was used. [f] 0.01 mmol of **C4** was used. THF = tetrahydrofuran.

affording **3a** in 44% yield and 72% ee (entry 6). Remarkably, lowering the reaction temperature to −20 °C significantly enhanced enantioselectivity, furnishing **3a** with excellent 98% ee (entries 10–12). Further optimization of stoichiometry and catalyst loading revealed that using 1.1 equiv. of **2** and 5 mol% of **C4** was sufficient to deliver the expected axially chiral biaryl amino phenol **3a** in 62% yield and 98% ee (entries 13 and 14).

Having established the optimized reaction conditions (Table 1, entry 14), we then explored the generality of this enantioselective protection strategy. As shown in Table 2, a series of amino bisphenols **1** bearing diverse substitution patterns were examined. Substrates containing 6-methyl and 6-cyclopropyl groups on the naphthyl ring delivered the corresponding *O*-Boc protected products **3b** and **3c** in 57% yield with >99% ee and 53% yield with 97% ee, respectively. Halogen substituent such as 6-bromo was accommodated to afford **3d** in 54% yield and 98% ee, indicating the potential for further elaboration of the axially chiral amino phenol scaffold. In contrast, the substrate bearing an electron-withdrawing COOMe group at the 6-position of the naphthyl ring formed the desired product **3e** in only 16% yield and 90% ee. When amino bisphenols possessing 6-aryl and 6-(2-naphthyl) groups were subjected to the reaction, the desired products **3f–3i** were obtained smoothly in 41–65% yields and 95 to >99% ee. Notably, replacing the aryl group with heteroaryl units had negligible effect on the reaction outcome, both 6-(2-furyl) and 6-(2-thienyl) substituted reactants efficiently furnished products **3j** and **3k** with moderate yields and outstanding enantioselectivities. Importantly, amino bisphenols comprising functional groups such as phenylethynyl, styryl, and vinyl were all competent substrates, providing the target axially chiral products **3l–3n** in 55–65% yields and 98–99% ee. Substitution at the 7-position of the naphthyl ring was equally compatible, giving rise to products **3o–3q** with decent yields and high enantioselectivities. Furthermore, when methyl groups were installed at the 5- or 4-position of the naphthyl ring, products **3r** and **3s** were isolated in approximately 50% yield with 98% ee. However, introducing a methyl group at the 3-position led to a significant drop in yield for product **3t**, although high enantioselectivity was retained. Substituents on the bisphenol moiety were also well-tolerated. Reactions of substrates featuring methyl or phenyl groups at the 4′-position offered products **3u** and **3v** in 55% yield with 98% ee and 58% yield with 98% ee, respectively. However, when a trifluoromethyl group was introduced at the 4′-position, both the yield and enantioselectivity of the resulting product **3w** decreased dramatically. Finally, the employment of ***ent*-C4** as the catalyst successfully delivered ***ent*-3a** in 60% yield and −99% ee, suggesting that both of the enantiomers were

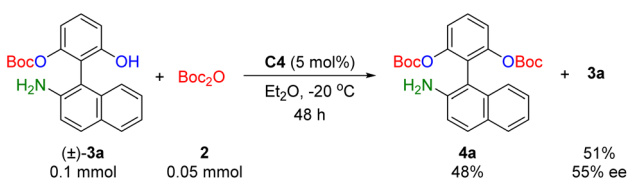
Table 2 Scope of reactions[a]



[a] Reaction conditions are as follows: **1** (0.2 mmol), **2** (0.22 mmol), **C4** (0.01 mmol), and Et_2O (2 mL) at −20 °C for 48 h. Isolated yield of product **3** based on **1**. The enantiomeric excess of **3** were determined *via* chiral-phase HPLC analysis. [b] ***ent*-C4** was used as the catalyst. [c] CH_2Cl_2 was used as the solvent. [d] 72 h.

readily accessible in our catalytic system. The absolute configurations of these axially chiral amino phenols were assigned as (*S*) by analogy to product **3a** and **3k**, whose structure was unequivocally confirmed through X-ray crystallographic analysis.[16]

Since for all the substrates examined in Table 2, the formation of di-*O*-Boc protected amino phenol **4** was consistently observed as a side product, which largely limited the yield of the desired product **3**, we sought to further investigate the role of the second *O*-Boc protection step. To this end, we conducted an additional experiment to determine whether this second protection event functions as a kinetic resolution (Scheme 2). Under the optimized reaction conditions, treatment of racemic **3a** with **2** (0.5 equiv.) led to the recovery of chiral **3a** in 51% yield (based on racemic **3a**) and 55% ee, along with the generation of di-*O*-Boc product **4a** in 48% yield. These results indicate that the high enantioselectivity observed in our catalytic system



Scheme 2 Kinetic resolution of racemic **3a**.

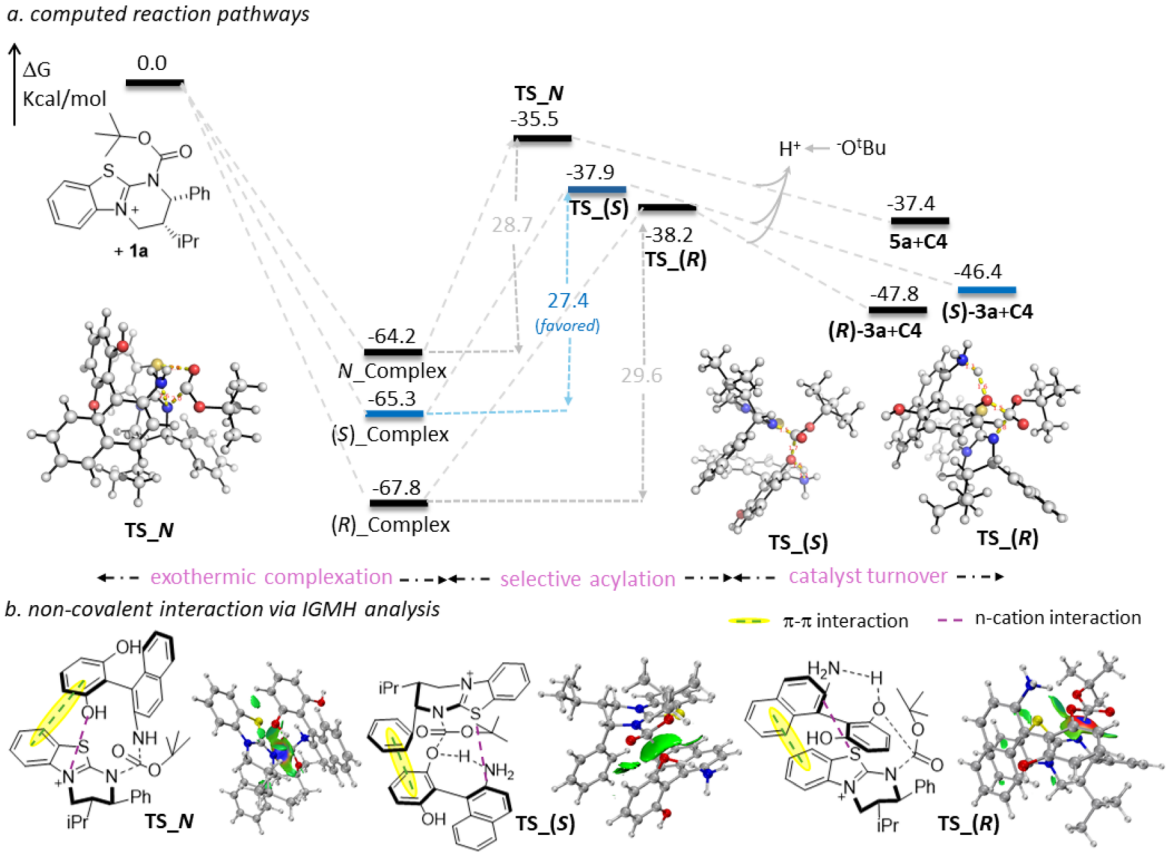


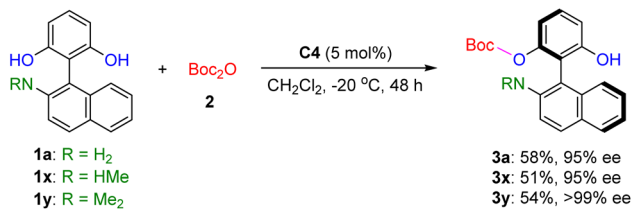
Fig. 1 Computational studies of chemo- and atroposelective Boc protection. (a) Reaction profile to form (*S*)-**3a**, (*R*)-**3a** and **5a**. Δ*G* at the level of SMD(Et_2O)-wB97M-V/def2-TZVP//IEFPCM (Et_2O)-B3LYP-D3(BJ)/def2-SVP in kcal mol^{-1}. (b) Non-covalent interaction analysis *via* IGMH with an isosurface of 0.01.

primarily originates from the initial desymmetrizing *O*-Boc protection step. Additionally, the second *O*-Boc protection may contribute positively to the final enantioselectivity outcome, albeit at the expense of product yield.

Experimentally, the asymmetric Boc protection of aminophenol **1a** using isothiourea catalyst **C4** predominantly yielded the *S*-configured product **3a**, without requiring additional bases. Notably, the phenol group was selectively acylated over the amino group. To gain further mechanistic insight into the origin of chemo- and atroposelectivity, density functional theory (DFT) calculations were performed, focusing on the key transition state. A simplified model was employed to probe the reaction pathway, highlighting the role of the amino group as an intramolecular base.

As depicted in Fig. 1, the most favorable transition state, **TS_(*S*)**, exhibited the lowest energy barrier (27.4 kcal mol^{-1}), which was 1.3 kcal mol^{-1} lower than **TS_*N*** (28.7 kcal mol^{-1}) and 2.2 kcal mol^{-1} lower than **TS_(*R*)** (29.6 kcal mol^{-1}). This energy difference is consistent with the experimentally observed high enantioselectivity (98% ee), although trace amounts of the *N*-acylated byproduct **5a** was detected. Interestingly, despite **TS_(*R*)** having a slightly lower relative Gibbs free energy—0.3 kcal mol^{-1} below **TS_(*S*)**—its corresponding starting substrate complex (*R*-complex) was 2.5 kcal mol^{-1} more stable than the *S*-complex. This energy landscape may help explain the minor formation of the di-*O*-Boc protected byproduct **4a**, even though the *S*-configured product **3a** remains predominant.

Non-covalent interactions were analyzed using the independent gradient model based on Hirshfeld partition (IGMH).[17] Contrary to previous reports,[18] no O···S chalcogen bonding (*n*O – σ*S–C) was identified in either **TS_(*S*)** or **TS_(*R*)**, both of which led to the *O*-acylated product (*S*)-**3a** and (*R*)-**3a**. Instead, the *S*-atom of the Boc-**C4** intermediate engaged in electrostatic interaction with the amino carbon of substrate **1a** (S···C–NH_3^+). This interaction is likely driven by intramolecular proton transfer from the OH group to the NH_2 group. In contrast, **TS_*N***, which leads to *N*-acylation, exhibited O···S chalcogen bonding, contributing to its conformational stability. Additionally, π–π

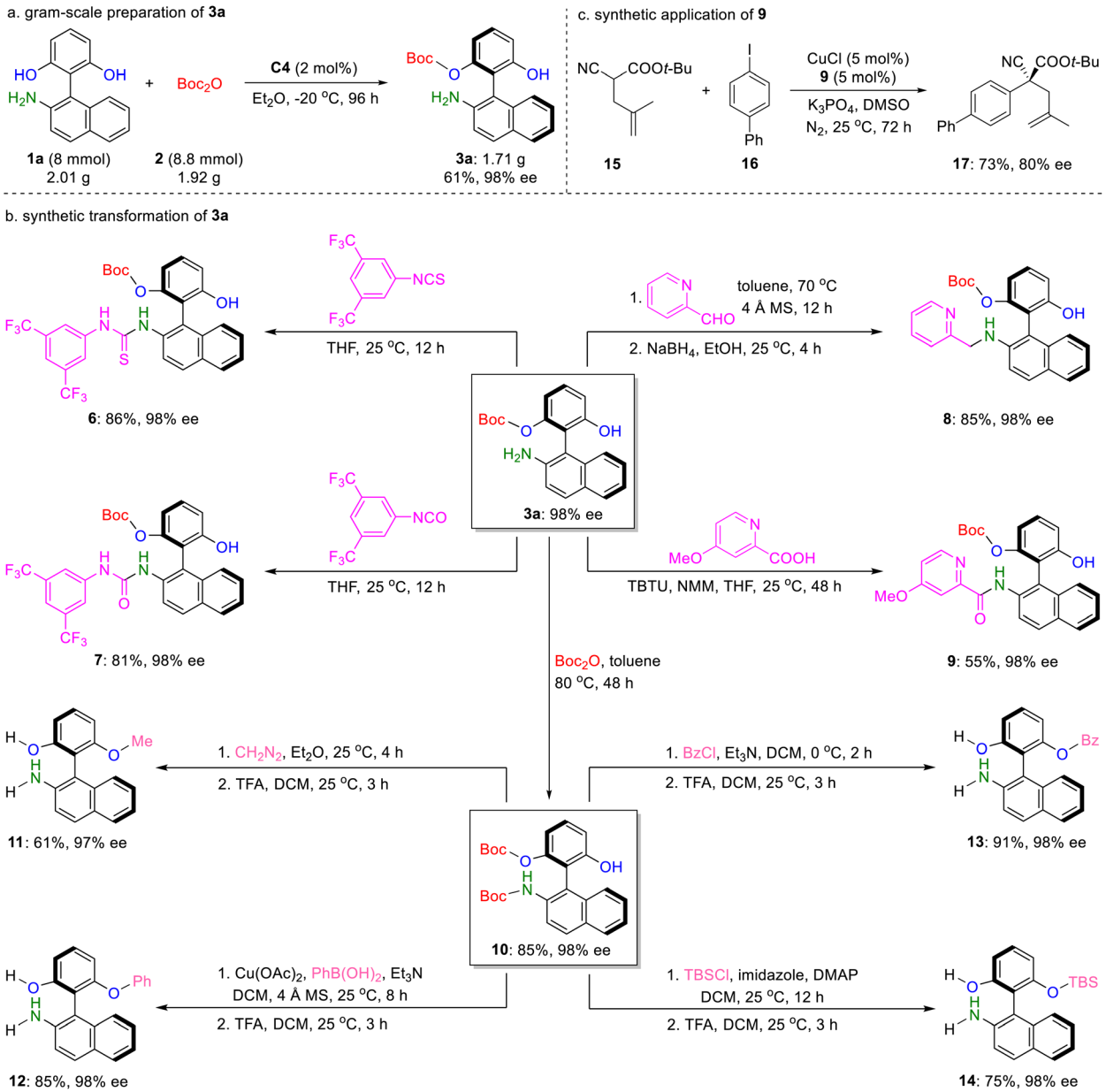


Scheme 3 Control experiments.

stacking interactions played a significant role in stabilizing all three key transition states.

To determine whether the NH_2 group is essential for maintaining a stable conformation and achieving high enantioselectivity, we conducted three control experiments. As illustrated in Scheme 3, the secondary (NHMe) and tertiary amine (NMe_2) substituted substrates afforded the corresponding products **3x** and **3y** in moderate yields with excellent enantioselectivities. These results indicate that protonation of the nitrogen atom facilitates electrostatic interactions between the sulfur and phenyl carbon, which are crucial regardless of whether the nitrogen substituent is NH_2, NHMe, or NMe_2. Further transition-state calculations for **3x** and **3y** also reveal the presence of such noncovalent interactions (please see SI for details). It is also noteworthy that, in the case of **3y**, the lower reaction energy barrier (21.0 kcal mol^{-1}) compared to **TS_(*S*)** may be attributed to its higher enantioselectivity (ee > 99%).

Finally, the practicality and applicability of the developed protocol were demonstrated by gram-scale preparation and downstream transformations of **3a**. Under the optimized catalytic conditions, the reaction was efficiently scaled up to an 8 mmol scale using only 2 mol% of **C4**, affording 1.71 g of **3a** without any loss in enantiopurity (Scheme 4a). The versatility of **3a** was showcased through various derivatizations. Treatment of enantioenriched **3a** with isothiocyanate and isocyanate smoothly delivered the corresponding thiourea **6** and urea **7** in 86% yield with 98% ee and 81% yield with 98% ee, respectively. Reactions of **3a** with pyridine derivatives provided the chiral amino phenol analogs **8** and **9** in acceptable yields with retention of the enantioselectivities. Moreover, condensation of **3a**



Scheme 4 Synthetic utility of the current protocol.

with Boc_2O **2** in the absence of a catalyst offered *N*-Boc protected amino phenol **10**. Subsequent *O*-functionalization of **10**, including *O*-methylation, *O*-phenylation, *O*-benzoylation, and *O*-silylation, followed by Boc deprotection, furnished the anticipated derivatives **11–14** in moderate to good yields and excellent enantioselectivities, thereby significantly enriching the library of axially chiral amino phenols (Scheme 4b). To further highlight the synthetic potential of this methodology, a Cu-catalyzed enantioselective coupling reaction of α-substituted cyanoacetate **15** with aryl iodide **16** was carried out utilizing the previously synthesized amino phenol derivative **9** as a chiral ligand (Scheme 4c).[6d] Gratifyingly, preliminary result showed that the corresponding product **17** bearing an all carbon quaternary stereocenter could be obtained in 73% yield with a promising 80% ee, revealing the utility of these axially chiral amino phenols in asymmetric catalysis.

Conclusions

In summary, we have developed the first enantioselective Boc protection strategy for the construction of optically pure compounds. In the presence of a chiral isothiourea catalyst, a broad range of bisphenols featuring diverse substitution patterns undergo reaction with Boc anhydride to afford NH_2-free axially chiral biaryl amino phenols with excellent enantiocontrol. This operationally simple and efficient method shows strong potential for application in preparative synthesis, and the resulting chiral products can be readily derivatized into valuable functional molecules. Complementary DFT studies provide mechanistic insight into the origins of the observed chemo- and atroposelectivities. Further investigations aimed at extending this enantioselective Boc protection strategy to the synthesis of additional types of chiral elements are currently underway in our laboratory.

Author contributions

Y. W. performed and analysed the experiments. Y. W., Z. X. and K. C. contributed to the data analysis. Y.-G. L. conducted the DFT calculations. X. C. and J. X. conceptualized and directed the project. H. Z. and J. X. drafted the manuscript. All authors contributed to the discussions.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures and characterization data. See DOI: **https://doi.org/10.1039/d5sc06233k**.

CCDC 2433022 and 2434593 contain the supplementary crystallographic data for this paper.[16a,b]

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