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Catalytic N-Acylation for Access to N−N Atropisomeric N-Aminoindoles: Choice of Acylation Reagents and Mechanistic Insights

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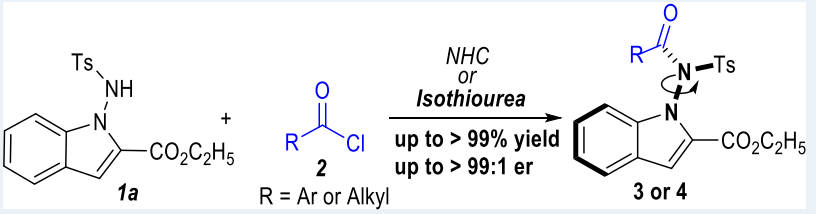

ABSTRACT: The synthesis of N−N axial compounds containing aromatic acyl amides using common acylation reagents remains challenging. We describe a highly atropenantioselective synthesis of N-aminoindoles containing N−N axes. A chiral cyclic isothiourea is used as the sole organic catalyst in the atropenantioselective transformation of the N-acylation reaction. Aroyl chlorides have been used as acylation reagents to construct atropisomeric compounds through N-acylation. The N-aminoindole products, which bear stereogenic N−N axes, were synthesized with high yields and enantioselectivities. Some of the enantiopure N-aminoindole products exhibited promising antibacterial activities against plant pathogens.

KEYWORDS: *stereogenic N−N axes, atropenantioselective reaction, chiral isothiourea, N-acylation, chiral N-aminoindole*

Chiral molecules that possess stereogenic axes are widespread in natural bioactive compounds, pharmaceutical molecules, and functional materials.[1] Over the last few decades, the field of atropenantioselective synthesis has experienced a significant expansion. Currently, numerous methods are used in the asymmetric synthesis of atropines, and the asymmetric preparation of C−C and C−N atropines has been widely reported.[1ac2] Early in 1931, Adamas and Chang proposed the existence of restricted rotations in N−N single bonds.[3] However, the development of enantioselective strategies for the synthesis of N−N atropisomers has been disclosed in recent years.[4]

Axially chiral compounds that possess N−N axes are widespread in natural products, bioactive compounds, and ligands (Figure 1a). The natural product dixiamycin A exhibited promising antibacterial activity toward *Bacillus thuringiensis* (MIC of 4 μg mL^{-1}).[5] The use of N,N-bisindophosphine ligands in a palladium-catalyzed enantioselective allylic alkylation reaction has resulted in excellent yields and enantioselectivities, which demonstrates the potential application of N,N-bisindole phosphine as a ligand.[6] Quinazolinone has exhibited significant anticonvulsant and hypnotic activity.[7] Heterocyclyluracils have been extensively studied in the development of novel pesticides as highly efficient herbicides.[8] Besipirdine is believed to enhance both cholinergic and adrenergic neurotransmission in the central nervous system and release the syndromes caused by Alzheimer's disease.[9] Binedaline has been investigated in clinical trials as a candidate antidepressant drug with fewer side effects than conventional tricyclic antidepressants.[10] Therefore, the development of efficient methods for access to novel N−N axially chiral derivatives holds interest and significance.

In the 3 years that followed the initial report of enantioselective synthesis of N−N atropisomers,[11] a significant amount of attention has been directed toward developing a variety of novel strategies for acquiring chiral N−N axes. These strategies encompass desymmetrization, cyclization, N-alkylation, and N-acylation. The fundamental strategy involves introducing sterically congested groups or cyclic structures to constrain the rotation of the N−N bond, thereby achieving stable chiral N−N axes. The group of Liu and You used copper-catalyzed alkylation[12] or arylation,[13] palladium-catalyzed C−H functionalization,[14] and iridium(I)-catalyzed C−H alkylation[15] for the desymmetrization preparation of N−N atropisomers. Researchers have recently constructed chiral N−N axes by using the ring formation strategy, for instance, palladium-catalyzed Buchwald−Hartwig amination,[16] 5-*endo* hydroaminocyclizations,[17] chiral phosphoric acid-catalyzed (3 + 2) cycloadditions

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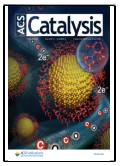

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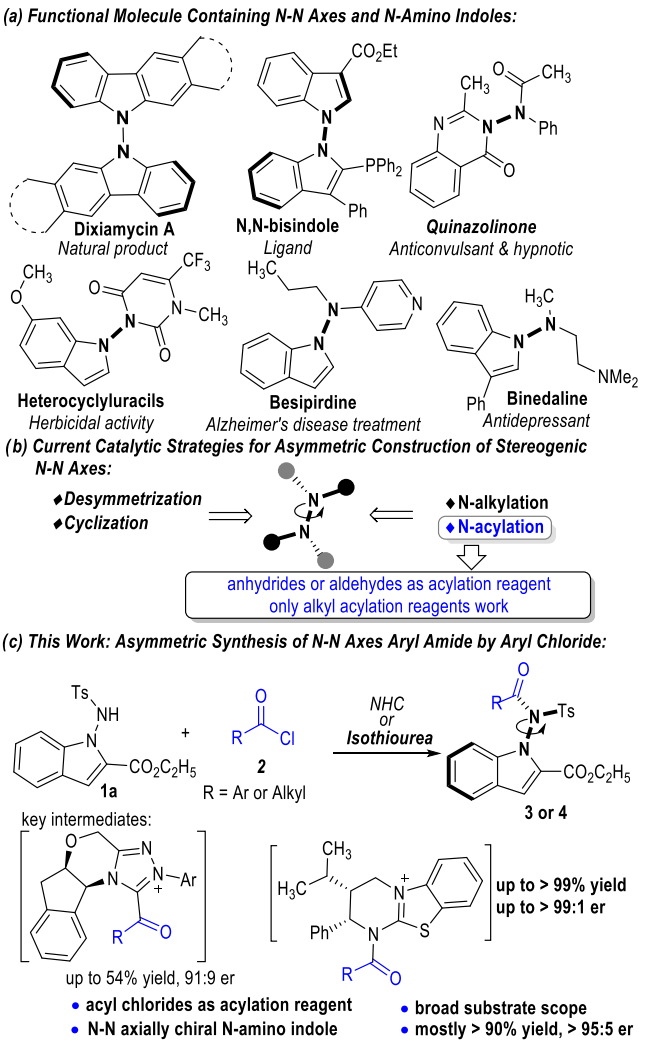

Figure 1. (a) Functional molecule containing N−N axes and N-aminoindoles. (b) Catalytic strategies for asymmetric construction of stereogenic N−N axes. (c) This work: asymmetric synthesis of N−N axes aryl amide by aryl chloride.

of indole-based enaminones,[6] dual-ring formation,[18] NHC (N-heterocyclic carbenes)-catalyzed (3 + 3) cycloaddition,[19] and Paal−Knorr reaction.[20] Another approach for obtaining N−N axes involves direct N−H functionalization, encompassing N-alkylation or N-acylation. For example, quinidine and phase-transfer catalysis achieved N-alkylation.[11,21] NHC[22] and chiral isothiourea[23] catalysts achieved N-acylation, in which chained anhydrides or chained aldehydes are used as acylation reagents (Figure 1b). Despite these advancements in obtaining chiral N−N axes, there remains an urgent need to develop potent enantioselective tools for the rapid and efficient synthesis of axially chiral N−N compounds. In particular, current methods are deficient in effective acylation reagents capable of aryl N-acylation.

We are committed to developing new molecules with axial and planar chirality and their synthetic methodologies. In recent years, we reported the asymmetric formation of C−C[24] and C−N axes[25] and planar chiral compounds.[26] The indole derivatives that we previously developed have achieved significant success as agricultural antimicrobial agents.[27] Our prior findings demonstrated that axially chiral molecules display configuration-dependent inhibitory effects against *Xanthomonas oryzae pv oryzae (Xoo)*.[24a] Expanding upon this groundwork, our present endeavors focus on synthesizing N−N axial chiral aminoindoles featuring aromatic amide structures through innovative and efficient methods. In this paper, we present a groundbreaking study introducing an isothiourea-catalyzed methodology for the highly atropenantioselective synthesis of N−N axially chiral aminoindoles bearing aromatic amide structures (Figure 1c). Acyl chlorides are highly reactive and readily available acylation reagents with good atom economy. It should be noted that acyl chlorides, due to their strong acylating ability, often lead to intense background reactions, making them unsuitable for the construction of chiral compounds. The present work adopted acyl chlorides as acylating reagents for the asymmetric construction of N−N axes. Both N-heterocyclic carbenes (NHCs) and chiral isothiourea can serve as chiral catalysts to yield axially chiral target products, although chiral isothiourea proves to be more suitable than NHCs in our system. The N-aminoindole products, bearing stereogenic N−N axes, are generally given in excellent yields and enantioselectivities. Moreover, we extend the frontiers of N−N axially chiral aminoindoles by exploring their potential as cutting-edge agricultural antibacterial agents.

RESULTS AND DISCUSSION

Toluenesulfonyl (Ts)-protected N-aminoindole **1a** bearing a 2-carboxylic ester group was selected to react with benzoyl chloride **2a** for the atroposelective acylation reaction (Table 1). NHCs are robust Lewis basic catalysts that have been extensively used in the activation of carboxylic acid derivatives for asymmetric acylation reactions.[28] Therefore, aminoindanol-derived NHC catalysts **A**, **B**, and **C** bearing different N-substituents were evaluated for this atropenantioselective N-acylation reaction (Table 1, entries 1−3). We were disappointed to find that N,N-atropisomeric N-aminoindole product **3a** could only be afforded in poor to moderate yields, although promising enantioselectivity was observed using NHC catalyst **C** bearing an electron-deficient N-pentafluorophenyl (N−C_6F_5) group (entry 3). Chiral isothioureas are also efficient Lewis basic organic catalysts in the activation of acyl halides, esters, and carboxylic anhydrides for asymmetric transformations.[29] We then turned our attention to the feasibility of using isothioureas in this atropenantioselective N-acylation reaction (entries 4−7). Chiral isothioureas **D** and **E** bearing chiral dihydroimidazole scaffolds could provide target N-aminoindole product **3a** in moderate to excellent yields with promising enantioselectivities (entries 4 and 5). Switching the chiral dihydroimidazole moiety to a chiral tetrahydropyrimidine structure resulted in significant improvements in both the product yield and enantioselectivity (entry 6). Introducing an isopropyl group to the *o*-cis-position to the phenyl group on the chiral structure of isothiourea **F** (to afford **G**) led to additional enhancements on both the reaction yield and enantioselectivity (entry 7). It is worth noting that the addition of a stoichiometric amount of a weak base is significant for this reaction, since only trace formation of target product **3a** was observed without the presence of any basic additive (entry 8). Switching Et_3N into a strong organic base such as DBU resulted in significant erosion of the reaction outcome (entry 9). A variety of inorganic bases can be used instead of Et_3N as additives for this transformation, although with slightly decreased reaction yields or enantioselectivities (entries 10 and 11). Nonpolar organic solvents were generally suitable for asymmetric N-acylation, with target axially chiral N-amino-indole product **3a** afforded in excellent yields and enantiose-

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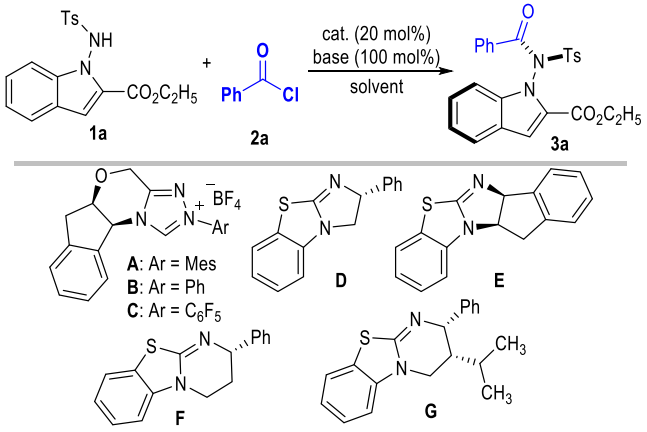
Table 1. Condition Optimization[a]



entry	cat.	base	solvent	yield [%][b]	er[c]
1	**A**	Et_3N	THF	58	50:50
2	**B**	Et_3N	THF	31	54:46
3	**C**	Et_3N	THF	54	91:9
4	**D**	Et_3N	THF	68	86:14
5	**E**	Et_3N	THF	90	60:40
6	**F**	Et_3N	THF	94	96:4
7	**G**	Et_3N	THF	>99	97:3
8	**G**		THF	<5	
9	**G**	DBU	THF	37	80:20
10	**G**	K_2CO_3	THF	>99	96:4
11	**G**	Cs_2CO_3	THF	95	94:6
12	**G**	Et_3N	EtOAc	96	98:2
13	**G**	Et_3N	Toluene	>99	>99:1
14	**G**	Et_3N	^{i}PrOH	50	98:2
15[d]	**G**	Et_3N	toluene	>99	>99:1
16[e]	**G**	Et_3N	toluene	96	>99:1

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.05 mmol), cat. (20 mol %), base (0.05 mmol), and solvent (1.0 mL) at r.t for 12 h. [b]Isolated yield of **3a**. [c]The er values were determined via HPLC on the chiral stationary phase. [d]5 mol % **G** was used. [e]1 mol % **G** was used.

lectivities (entries 12 and 13). Protic solvents such as isopropyl alcohol were not suitable for this catalytic process (entry 14). To our delight, chiral isothiourea **G** could be used in only 5 mol % for this transformation without any erosion on the reaction outcome (entry 15). Further shrinking the catalyst loading led to a drop in the product yield (entry 16).

Having identified an optimized reaction condition for the atroposelective N-acylation of N-aminoindole **1a** (Table 1, entry 15), we then examined the substrate scope of N-aminoindole **1** in the reaction with benzoyl chloride **2a** (Scheme 1). Substituents could be introduced onto the 3-, 4-, 5-, and 6-positions around the indole ring regardless of their electronic properties, with all of the corresponding N−N atropismeric products afforded in excellent yields and enantioselectivities (**3b** to **3k**). The ethyl ester group on the 2-position of the indole ring could be switched into methyl, *i*-propyl, *t*-butyl, and even substituted phenyl esters without obvious erosions on the reaction outcomes (**3l** to **3o**). Gratifyingly, the *p*-tolyl group on the sulfonamide moiety of substrate **1a** could be replaced with *p*-nitrophenyl, naphthyl, thiofuranyl, and benzyl groups without much loss on the product yields or optical purities (**3p** to **3s**). Noteworthily, the aryl group on the sulfonamide moiety of substrate **1a** could even be switched into alkyl and amino groups to give the optical pure N-aminoindole products in excellent yields. In addition, the indole 2-substituents are not limited to ester groups (**3y**). However, this strategy does not seem to work with pyrroles (**3z** and **3za**).

The scope of aroyl chloride **2** was also investigated (Scheme 2). Both electron-donating and electron-withdrawing substituents could be installed onto each position around the benzene ring of benzoyl chloride **2a**, with the N,N-atropisomeric N-aminoindole products afforded in excellent yields and optical purities (**4a** to **4p**). The benzene ring of **2a** could be switched into diverse heteroaromatic groups without obvious erosion on the enantioselectivity (**4q to 4t**), though the acyl chloride substrate bearing an electron-deficient pyridyl group provided a decreased reaction yield (**4q**). However, replacing the aromatic groups on the aroyl chloride substrates with alkyl (**4u** to **4v**) or alkenyl groups (**4w** to **4x**) resulted in significant drops in the reaction enantioselectivities. This might result from the uncontrollable side reactions that are triggered by the highly reactive aliphatic acyl chlorides. Therefore, we paid attention to the search for other suitable acylating reagents and reaction conditions for the atropenantioselective synthesis of axially chiral N-aminoindoles bearing aliphatic N-acyl groups.

The carboxylic anhydrides have proven to be efficient acylating reagents for the generation of chiral molecules bearing stereogenic centers or axes. It is pleasing to find that the carboxylic anhydride compounds were also highly efficient in the current isothiourea-catalyzed N-atropenantioselective amide formation process (Scheme 3). Both the yields and optical purities of N,N-atropisomeric N-aminoindoles **4u** to **4x** could be dramatically improved after switching the acyl chlorides into the corresponding anhydride substrates under slightly verified reaction conditions (Table S1, entry 12). Interestingly, when using anhydride as the acylation reagent, the yield and enantioselectivity of the target product are maintained even when no base is added (Table S1, entry 6). Carboxylic anhydride **5** could be linear anhydrides with different sizes, with all of the desired N−N atropisomeric N-aminoindole products afforded in quantitative yields with excellent er values (**6a** to **6d**). A phenyl group was also well tolerated at the b-position of the aliphatic chain (**6e**). Introducing either alkyl or aryl groups on the b-position of the a,b-unsaturated anhydride substrates did not affect the reaction outcome (**6f** and **6g**).

In addition, the aliphatic anhydrides could react smoothly with N-aminoindole substrates bearing different substituents around the indole rings. For instance, both electron-donating and electron-withdrawing groups could be introduced onto the 5-, 6-, and 4-positions of the indole scaffold without much erosion on either the product yields or enantioselectivities (**6h** to **6q**). The 4-toluene group of the N-Ts could be changed to a 4-nitrophenyl group, although the yield of optically pure product **6r** was slightly dropped. The phenyl group of the sulfonamide moiety could also be switched into thiofuranyl (**6s**), benzyl (**6t**), alkyl (**6u** to **6w**), and amino groups (**6x**) to give the enantioenriched N,N-atropisomeric products in almost quantitative yields.

It is also worth noting that the enantioselective N-acylation reaction between N-aminoindole substrate **1a** and benzoyl chlorides or linear acetic anhydrides can be carried out in gram scales without erosion on the product yields or enantioselectivities (e.g., **3a** and **4v** in Figure S1 in the Supporting Information). To further understand the conformational stability of atropisomers, the barriers to rotation for **4v** were measured experimentally ($\Delta G^{\ddagger}$ = 36.4 kcal/mol, see Table S2 in the Supporting Information for details).

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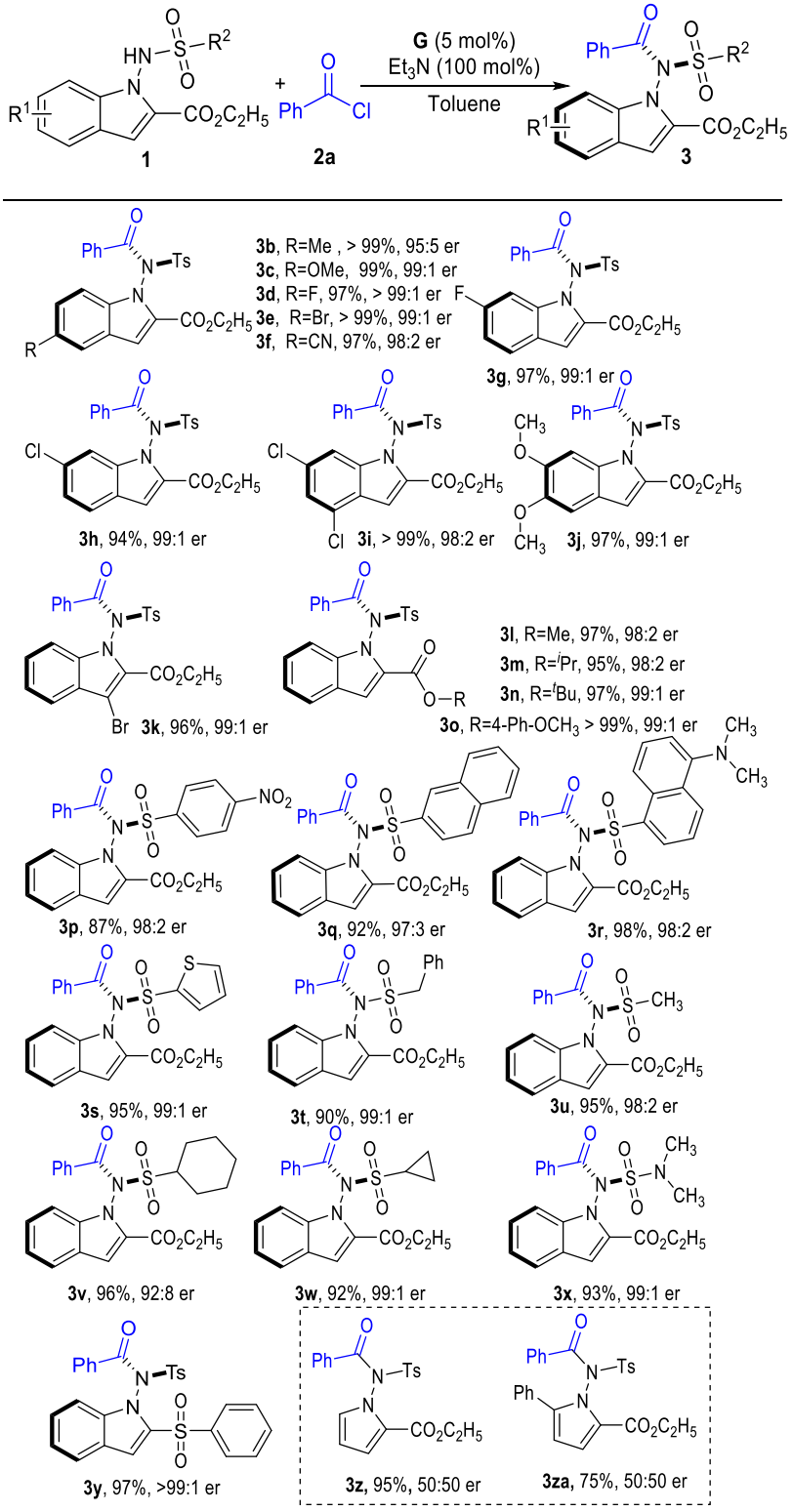
Scheme 1. Scope of N-Aminoindole Substrate 1[a]



[a]Reaction conditions as stated in Table 1, entry 15. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on the chiral stationary phase.

We conducted a series of control experiments to investigate the reaction mechanism. It is not a surprise that substrate **1a** reacts with 1 equiv of benzoyl chloride **2a** in the presence of Et_3N, leading to a pronounced background reaction (Figure 2eq 1). The addition of a catalytic amount of chiral isothiourea **G** (20%) to the reaction can effectively suppress the background reaction, resulting in the formation of product **3a** with exceptional optical purity (Figure 2 eq 2). The preparation of **3a** in optically pure form indicates that the chiral pathway was faster than the racemic pathway. In addition, when chiral

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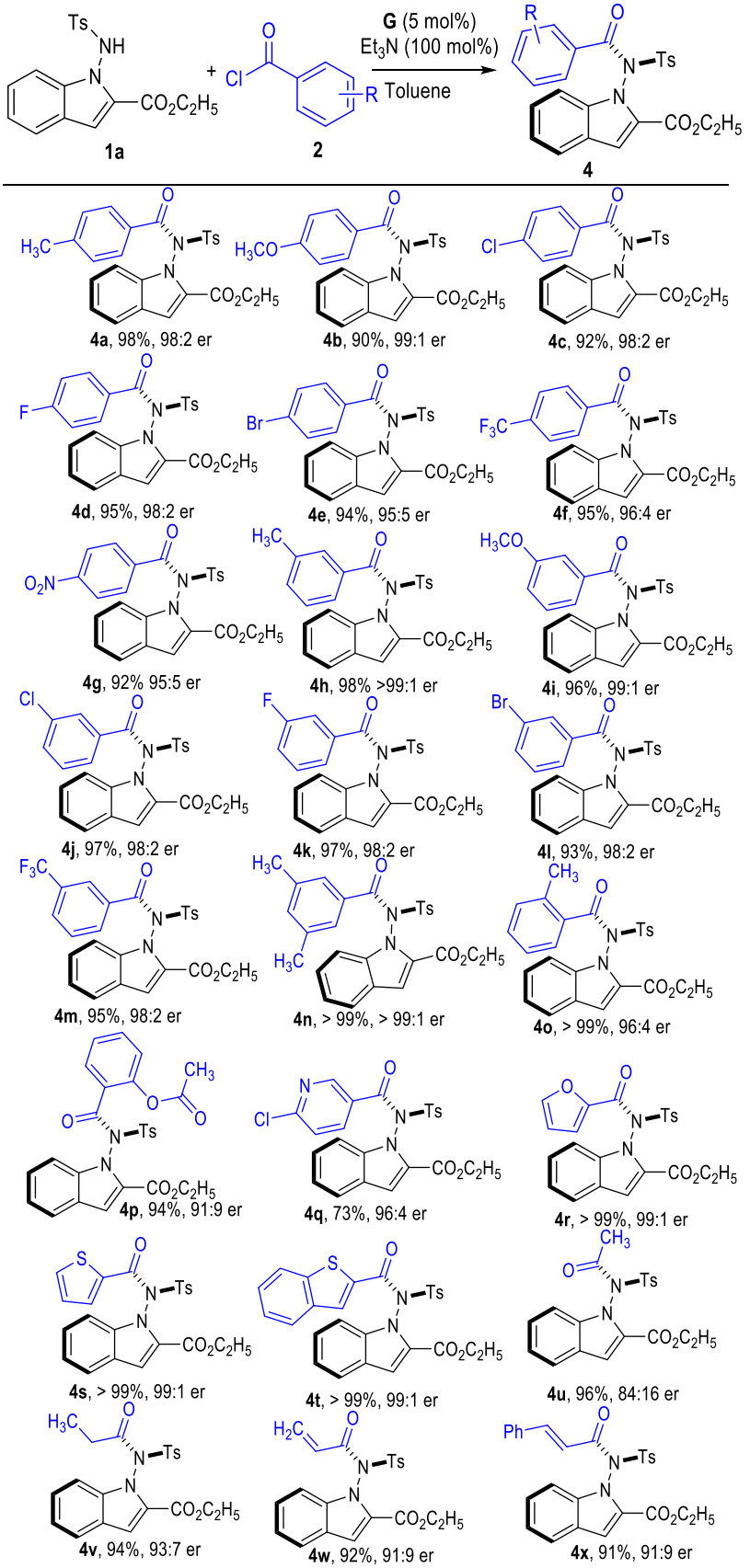
Scheme 2. Scope of Acyl Chloride Substrate 2[a]



[a]Reaction conditions as stated in Table 1, entry 15. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on the chiral stationary phase.

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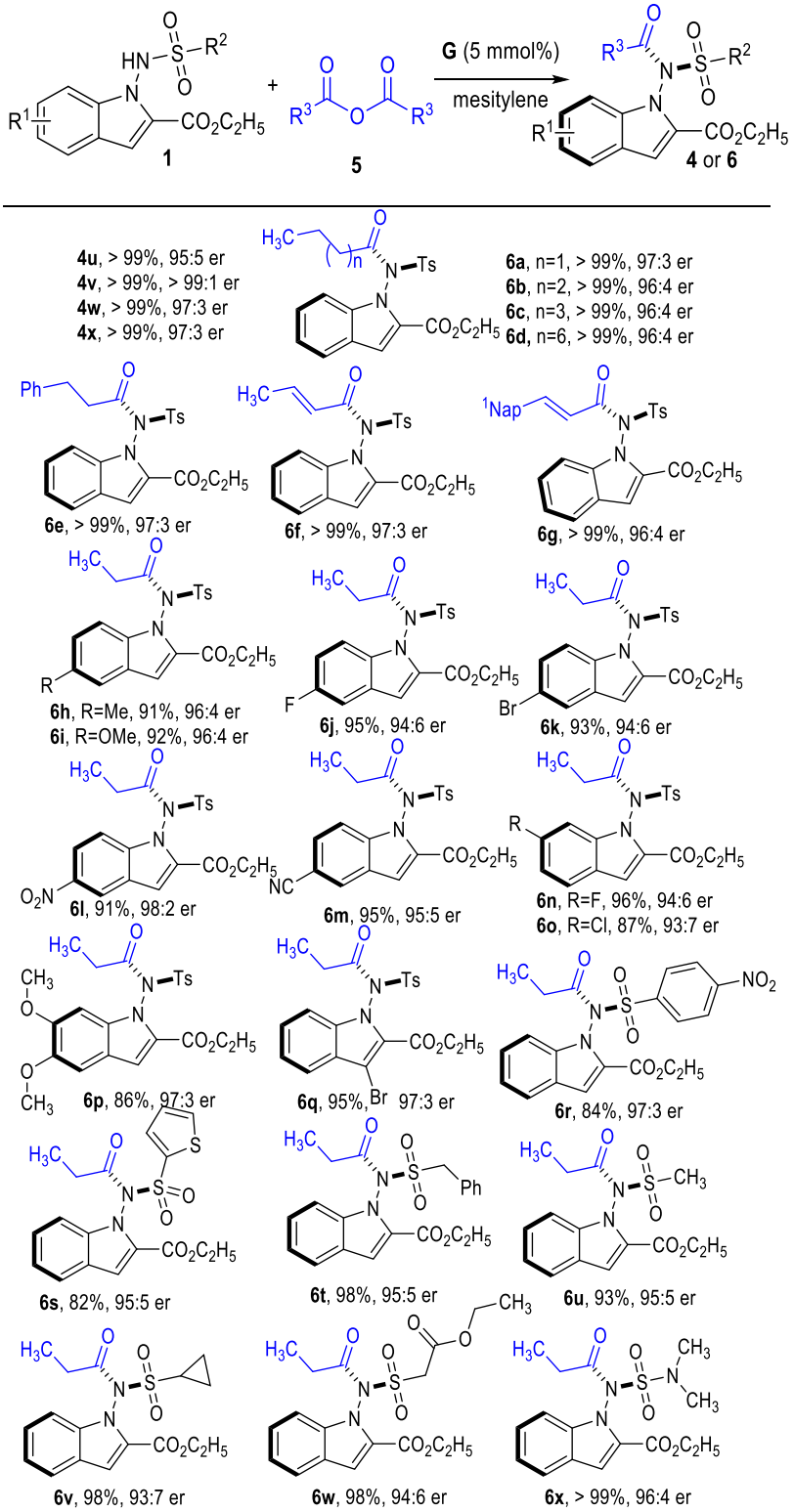
Scheme 3. Scope of the Reaction between N-Aminoindole 1 and Anhydride 5[a]



[a]Reaction conditions as stated in Table 1, entry 15. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on the chiral stationary phase.

isothiourea **G** (120 mmol %) was used as the base, target product **3a** was obtained in 65% yield and 99:1 er (Figure 2 eq 3). This implies that benzoyl chloride **2a** readily undergoes a reaction with **G** to produce intermediate **II** (chiral pathway B). Subsequently, we compared the reaction rates for the formation of intermediate **I** and intermediate **II** from **2a**. In the presence of Et_3N, intermediate **II** was not observed, indicating the preferential formation of intermediate **I** (Figure S2). Furthermore, in the presence of a catalytic amount of catalyst **G**, prepreparedintermediate **I** (Figure S3) still gave target product

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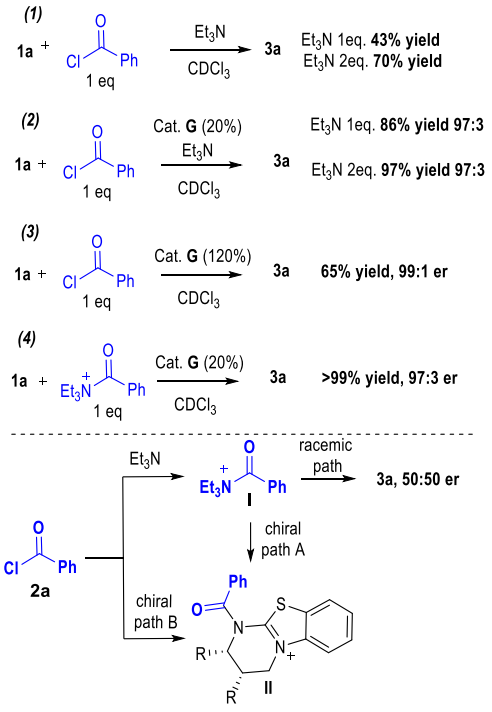

Figure 2. Control experiments.

3a with 97:3 er when reacted with **1a** (Figure 2 eq 4). This observation demonstrates that the reaction in this system prefers chiral path A.

Therefore, we propose the mechanism reaction, as depicted in Figure 3a. Benzoyl chloride substrate **2a** reacts with Et_3N to generate amide iminium cation **I**. Amide iminium cation **I** then rapidly forms intermediate **II** with catalyst **G**, accompanied by elimination of Et_3N. Although N-sulfonamide indole substrate **1a** is not nucleophilic enough for reaction with intermediate **II**, it can be deprotonated by the base (Et_3N) to give amide anion **III**, which can then react with cation **II** to give adduct **IV**. Atropisomeric N-aminoindole product **3a** can be afforded from adduct **IV** through the elimination of isothiourea catalyst **G**.

Based on previous studies[29d] and the crystal structure of product **3a**, a possible model of the transition state is proposed (Figure 3b). The conformation of acylisothiouronium intermediate **II** was fixed by no-α*C−S interaction.[29c30] The *Si* face of intermediate **II** could be attacked by deprotonated amide anion **III**. In addition, the oxygen atom on the sulfonyl group forms noncovalent interactions with the positively charged catalyst moiety on intermediate **II**,[31] which help bring the amide nucleophile close to acylisothiouronium intermediate **II** to give transition states A and B (**TS-A** and **TS-B**). Due to the steric repulsion between the 2-CO_2Et group on anion **III** and the catalyst scaffold of intermediate **II**, the acylation reaction is more favorable through transition state **TS-A** (rather than **TS-B**) to give (*S*)-**3a** as the final product.

The N−N atropisomeric N-aminoindole products obtained from this methodology exhibited interesting antibacterial activities against a variety of plant pathogens (Tables 2 and S3). For example, *Xanthomonas oryzae* pv *oryzae* (*Xoo*) can cause leaf blight in crops such as rice, zizania aquatica, and panicum maximum and shrink the crop harvests.[32] Both optically pure N-aminoindoles (*S*)-**4u** and (*S*)-**6e** showed good inhibition activities against *Xoo*, which were better than

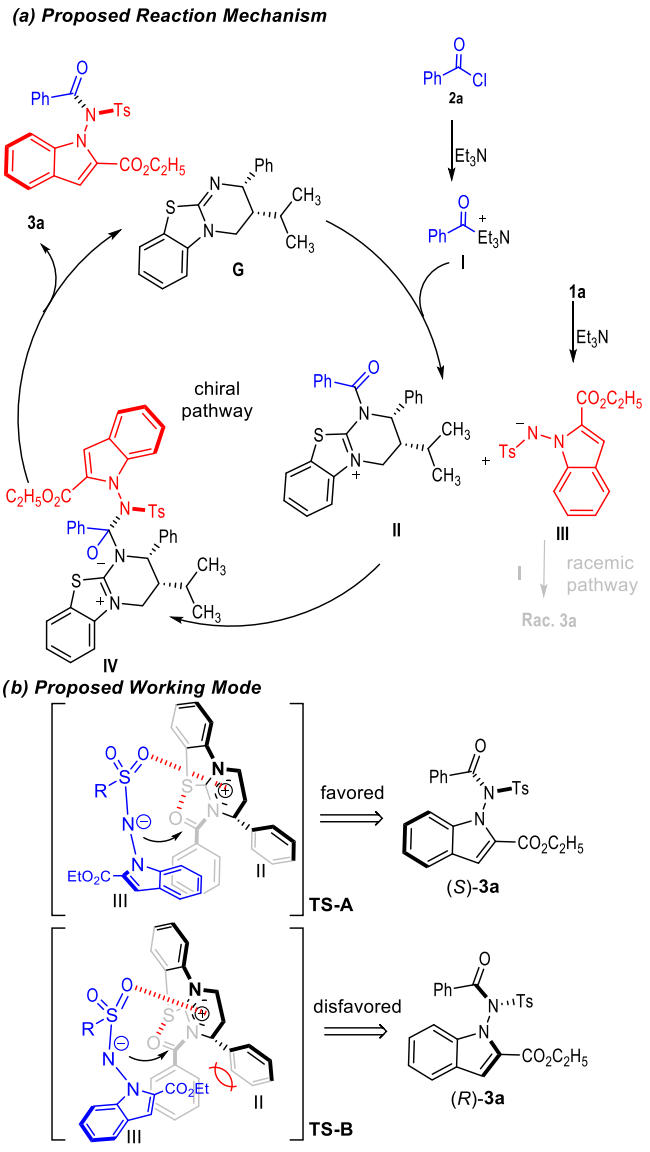

Figure 3. Proposed reaction mechanism and working mode.

their enantiomers, racemates, the commercial bactericides of thiodiazole copper (TC), and Bismerthiazol (BT). *Xanthomonas axonopodis* pv *citri* (*Xac*) is a disastrous and widespread bacteria that causes citrus canker in fruits such as lemons, oranges, and grapefruits.[33] Optically pure N-aminoindole product (*S*)-**4u** obtained from our approach exhibited promising and configuration-dependent inhibition activities against *Xac*.

CONCLUSIONS

In summary, we have developed an efficient and atropenantioselective method for facile access to N−N axially chiral aminoindoles with aromatic amide structures. For the first time, aroyl chlorides have been adopted as efficient acylation reagents for atroposelective transformations and asymmetric amide formation reactions. A structurally simple chiral isothiourea is used as the sole organic catalyst to activate aroyl chlorides and simple linear carboxylic anhydrides for asymmetric acylations with N-aminoindole substrates. All of the optically pure N-aminoindole products were obtained in good to excellent yields under mild conditions. The afforded chiral products exhibited promising and configuration-dependent

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Table 2. Antibacterial Activities of the Target Compounds against *Xac* and *Xoo*

	Xoo inhibition rate[a]
compounds	EC_{50} (μg/mL)
(±)-**4u**	107.31 ± 2.89
(*S*)-**4u**	80.54 ± 3.45
(*R*)-**4u**	124.98 ± 4.61
(±)-**6e**	95.73 ± 5.49
(*S*)-**6e**	82.39 ± 3.84
(*R*)-**6e**	112.86 ± 2.13
TC[b]	128.79 ± 4.56
BT[c]	92.28 ± 3.31
	Xac inhibition rate[a]
compounds	EC_{50} (μg/mL)
(±)-**4u**	68.53 ± 2.59
(*S*)-**4u**	60.20 ± 4.58
(*R*)-**4u**	85.81 ± 3.26
TC[b]	71.61 ± 2.94
BT[c]	75.19 ± 3.27

[a]Average of 3 replicates. [b]TC = thiodiazole copper. [c]BT = Bismerthiazol.

antibacterial activities against plant pathogens. In-depth investigations into the bioactivities of the N−N atropisomeric N-aminoindoles and the development of novel methods for access to challenging chiral molecules are in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c00720.

Crystallographic structure (**3a**) (CIF)
Crystallographic structure (**4v**) (CIF)
Experimental procedures and spectral data for all new compounds (PDF)

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Notes

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