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 axially compounds containing aromatic acyl amides using common acylation reagents remains challenging. We describe, for the first time, the 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. Unprecedentedly, aroyl chlorides have been used as the acylation reagents to construct atropisomeric compounds through N-acylation. The N-aminoindole products, which bears a stereogenic N-N axes, were synthesized with excellent yields and enantioselectivities. Some of the enantio-pure N-aminoindole products exhibited promising anti-bacterial activities against plant pathogens.

Keywords

Stereogenic N-N axes, Atropenantioselective reaction, Chiral isothiourea, Chiral N-amino indole

Introduction

Chiral molecules that possess a stereogenic axes are widespread in natural bioactive compounds and functional materials.[1-3] Over the last 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.[1, 3-7] Early in 1931, Adamas and Chang proposed the existence of restricted rotations in N-N single bonds.[8] However, the development of enantioselective strategies for the synthesis of N-N atropisomers has been disclosed in recent years.

Axially chiral compounds that possess N-N axes are widespread in natural products, bioactive compounds, and ligands (Fig. 1a). The natural product Schischkiniin exhibited moderate in vitro anticancer activity toward colon cancer cell line with an IC_{50} of 76 μM.[9] 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.[10] Quinazolinone has exhibited significant anticonvulsant and hypnotic activity.[11] Heterocyclyluracils have been extensively studied in the development of novel pesticides as highly efficient herbicides.[12] Besipirdine is believed to enhance both cholinergic and adrenergic neurotransmission in the central nervous system and release the syndromes caused by Alzheimer's disease.[13-15] Binedaline has been investigated in clinical trials as a candidate antidepressant drug with fewer side effects than the conventional tricyclic antidepressants.[16-18] Therefore, the development of efficient methods for access to novel N-N axially chiral derivatives holds interest and significance.

In the three years that followed the initial report of enantioselective synthesis of N-N atropisomers,[19] 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 a stable chiral N-N axes. The group of Liu and You used copper-catalyzed alkylation[20] or arylation,[21] palladium-catalyzed C-H functionalization[22] and iridium(I)-catalyzed C–H alkylation[23] for the desymmetrization preparation of N-N atropisomers. Researchers have recently constructed chiral N-N axes using the ring formation strategy. For instance, palladium-catalyzed Buchwald-Hartwig amination[24] and 5-*endo* hydroaminocyclizations,[25] chiral phosphoric acid catalyzed (3+2) cycloadditions of

indole-based enaminones,[10] dual-ring formation[26] and Paal-Knorr reaction.[27, 28] 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.[19, 29] N-Heterocyclic carbenes [30] and chiral isothiourea catalysts achieved N-acylation,[31] in which chained anhydrides or chained aldehydes are used as the acylation reagents (Fig. 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 N-N axially chiral 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,[32-35] C-N axes,[36, 37] and planar chiral compounds.[38] The indole derivatives that we previously developed have achieved significant success as agricultural antimicrobial agents.[39, 40] Our prior findings demonstrated that axially chiral molecules display configuration-dependent inhibitory effects against *Xanthomonas oryzae pv. oryzae (Xoo)*.[32] 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 (Fig. 1c). It should be noted that acyl chlorides, due to their strong acylating ability, often lead to intense background reactions, making them unsuitable for constructing chiral compounds. The present work unprecedentedly adopted the 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 a 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

The toluenesulfonyl (Ts)-protected N-aminoindole **1a** bearing a 2-carboxylic ester group was selected to react with the 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.[41-43] Therefore, the aminoindanol-derived NHC catalysts **A**, **B** and **C** bearing different N-substituents were evaluated for this atropenantioselective N-acylation reaction (Table 1, Entries 1 to 3). We were disappointed to find that the N,N-atropisomeric N-aminoindole product **3a** could only be afforded in poor to moderate yields, although promising enantioselectivity was observed using the 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.[44-48] We then turned our attention to the feasibility of using isothioureas in this atropenantioselective N-acylation reaction (Entries 4 to 7). The chiral isothioureas **D** and **E** bearing chiral dihydroimidazole scaffolds could provide the target N-aminoindole product **3a** in moderate to excellent yields with promising enantioselectivities (Entries 4 to 5). Switching the chiral dihydroimidazole moiety to a chiral tetrahydropyrimidine structure resulted in significant improvements on 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 the 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 weak base is significant for this reaction, since only trace formation of the target product **3a** was observed without the presence of any basic additive (Entry 8). Switching the Et_3N into a strong organic base such as DBU resulted in significant erosion on the reaction outcome (Entry 9). A variety of inorganic bases can be used instead of the Et_3N as the additives for this transformation, although with slightly decreased reaction yields or enantioselectivties (Entries 10 to 11). Non-polar organic solvents were generally suitable for the asymmetric N-acylation, with the target axially chiral N-aminoindole product **3a** afforded in excellent yields and

enantioselectivities (Entries 12 to 13). Protic solvents such as the isopropyl alcohol were not suitable for this catalytic process (Entry 14). To our delight, the 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 drop on the product yield (Entry 16).

Having identified an optimized reaction condition for the atroposelective N-acylation of the N-aminoindole **1a** (Table 1, Entry 15), we then examined the substrate scope of the N-aminoindole **1** in the reaction with the 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 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 the 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 the substrate **1a** could even be switched into alkyl and amino groups to give the optical pure N-aminoindole products in excellent yields.

The the scope of the 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 the 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 decreased reaction yield (**4q**). However, replacing the aromatic groups on the aroyl chloride substrates into alkyl (**4u** to **4v**) or alkenyl groups (**4w** to **4x**) resulted in significant drops in the reaction enantioselectivities. This might be resulted from the uncontrollable side reactions that triggered by the highly reactive aliphatic acyl chlorides. Therefore, we paied our 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 of the yields and optical purities of the 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 enantioselectivitie of the target product are maintained even when no base is added (Table S1 Entry 6). The carboxylic anhydride **5** could be linear anhydrides with different sizes, with all 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**, **6g**).

In addition, the aliphatic anhydrides could react smoothly with the 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 into a 4-nitrophenyl group, although the yield of the 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 enantio-enriched N,N-atropisomeric products in almost quantitative yields.

It is also worth noting that the enantioselective N-acylation reaction between the 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 Fig. S1).

We conducted a series of controll experiments to investigate the reaction mechanism. Under the optimal conditions, benzoyl anhydride did not react with model substrate 1a to yield the desired product **3a**. In contrast, acetic anhydride 5b readily produced the desired product 4w (Fig. 2 Eqs. 1, 2). This indicates that the steric hindrance could block, the formation of the intermediate **II**. This might result in the limited use of isothioureas as catalysts in the N-acylation with aromatic acid anhydrides for the synthesis of N-N axes chiral compounds. It is not surprise that, the substrate **1a** react with 1 eq. of benzoyl chloride **2a** in the presence of Et_3N, leading to a pronounced background reaction (Fig. 2 Eqs. 3). The addition of a catalytic amount of the chiral isothiourea **G** (20%) to the reaction can effectively suppress the background reaction, resulting in the formation of the product **3a** with exceptional optical purity (Fig. 2 Eqs. 4). The preparation of **3a** in optically pure form indicats that the chiral pathway was faster than the racemic pathway. In addition, when chiral isothiourea **G** (120 mmol%) was as the base, the target product **3a** was obtained in 65% yield and 99:1 er (Fig. 2 Eqs. 5). 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 the intermediate **I** and the intermediate **II** from **2a**. In presence of Et_3N, intermediate **II** was not observed, indicating the preferential formation of intermediate **I** (Fig. S2). Furthermore, in presence of a catalytic amount of the catalyst **G**, the pre-prepared intermediate **I** (Fig. S3) still gave the target product **3a** with 97:3 er when reacted with **1a** (Fig. 2 Eqs. 6). This observation demonstrates that the reaction in this system prefers the chiral pathway A.

Therefore, we propose the mechanism reaction as depicted in Fig. 3. The benzoyl chloride substrate 2a reacts with Et_3N to generate the amide iminium cation **I**. The amide iminium cation **I** then rapidly forms intermediate **II** with the catalyst G, accompanied by elimination of Et_3N. Although the 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 the

amide anion **III**, which can then react with the cation **II** to give the adduct **IV**. The atropisomeric N-aminoindole product **3a** can be afforded from the adduct **IV** through elimination of the isothiourea catalyst **G**.

The N-N atropisomeric N-aminoindole products obtained from this methodology exhibited interesting anti-bacterial activities against a variety of plant pathogens (Table 3). For example, the *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) can cause leaf blight in crops such as rice, zizania aquatica and panicum maximum and shrink the crop harvests.[49] Both of the optically pure N-aminoindoles (*S*)-**4u** and (*S*)-**6e** showed good inhibition activities against *Xoo*, which were better than their enantiomers, racemates, and the commercial bactericides of thiodiazole copper (TC) and Bismerthiazol (BT). The *Xanthomonas axonopodis* pv. *citri* (*Xac*) is a disastrous and vast-spread bacteria that causes citrus canker in fruits such as lemons, oranges and grapefruits.[50, 51] The optically pure N-aminoindole product (*S*)-**4u** obtained from our approach exhibited promising and configuration-dependant inhibition activities against *Xac*.

Conclusion

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 are 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 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 anti-bacterial 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.

Supporting Information

Supporting Information is available and includes experimental procedures and spectral data for all new

compounds.

Conflict of Interest (required)

There is no conflict of interest to report.

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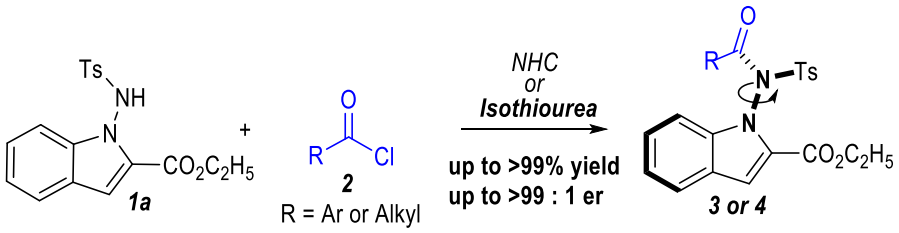
Table of Contents Graphic (required)



Illustrations:

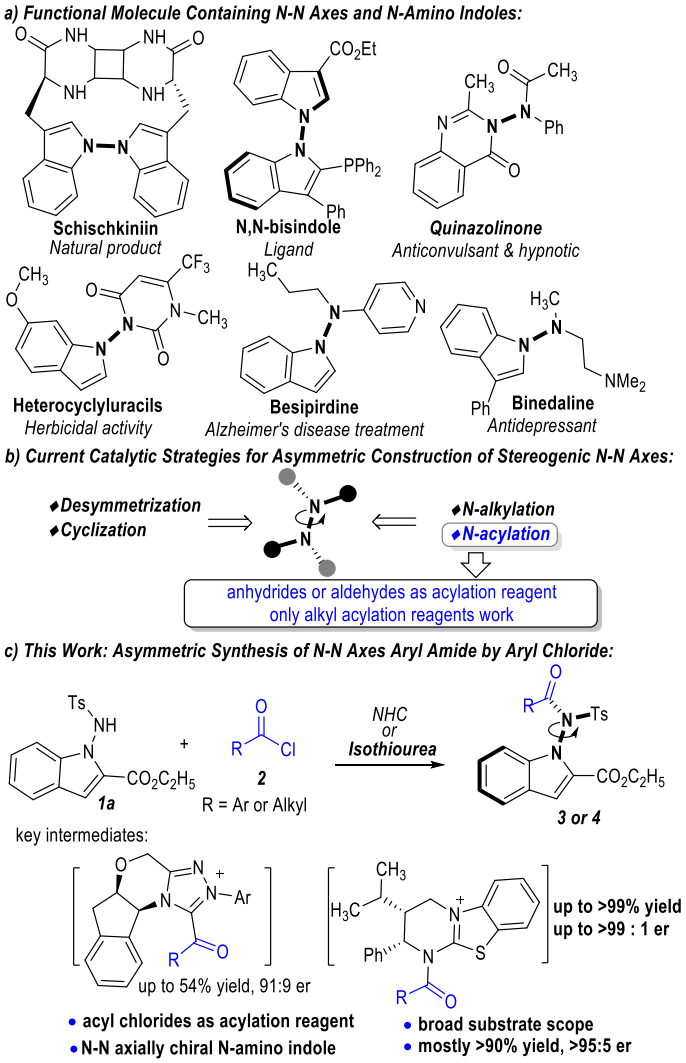
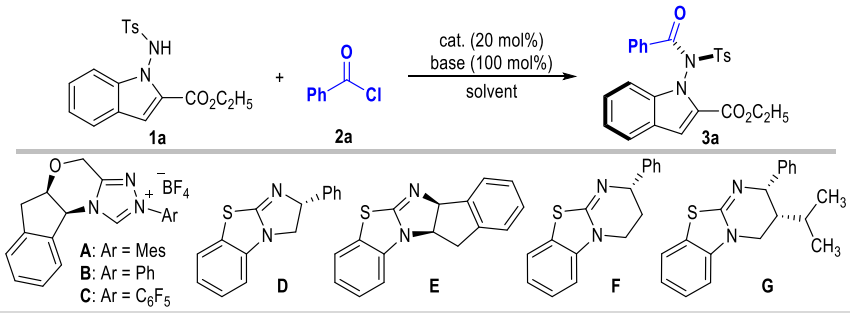


Fig. 1. a) Functional Molecule Containing N-N axes and N-Amino Indoles. b) Catalytic Strategies for Asymmetric Construction of Stereogenic N-N axes. c) This Work: Asymmetric Synthesis of N-N axes Aryl Amide by Aryl Chloride.

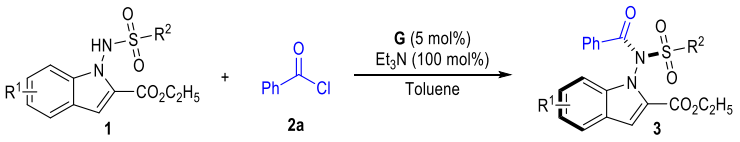
Table 1. Optimization of Reaction Conditions.[a]

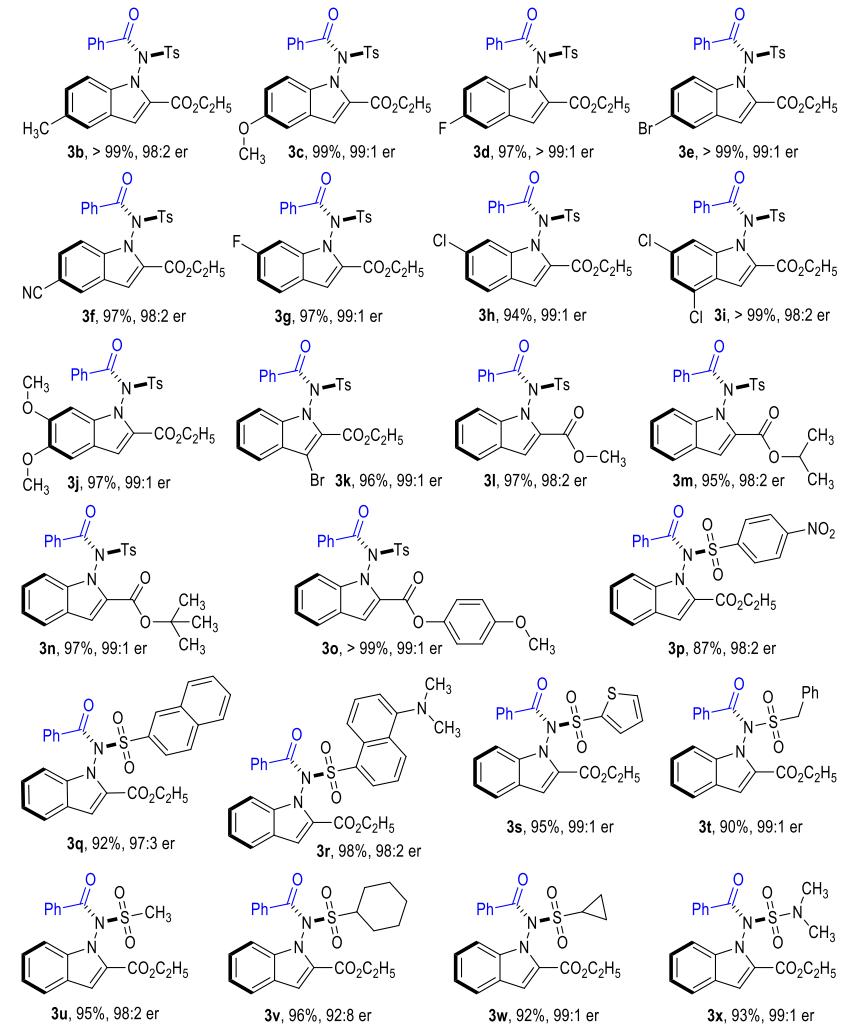


Entry	cat.	base	Solvent	Yield [%][b]	Er[c]
1	A	Et_3N	THF	58	50:50
2	B	Et_3N	THF	31	54:46
3	C	Et_3N	THF	54	91:9
4	D	Et_3N	THF	68	86:14
5	E	Et_3N	THF	90	60:40
6	F	Et_3N	THF	94	96:4
7	G	Et_3N	THF	> 99	97:3
8	G		THF	< 5	
9	G	DBU	THF	37	80:20
10	G	K_2CO_3	THF	> 99	96:4
11	G	Cs_2CO_3	THF	95	94:6
12	G	Et_3N	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 %), 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 chiral stationary phase. [d] 5 mol% of G was used. [e] 1 mol% of G was used.

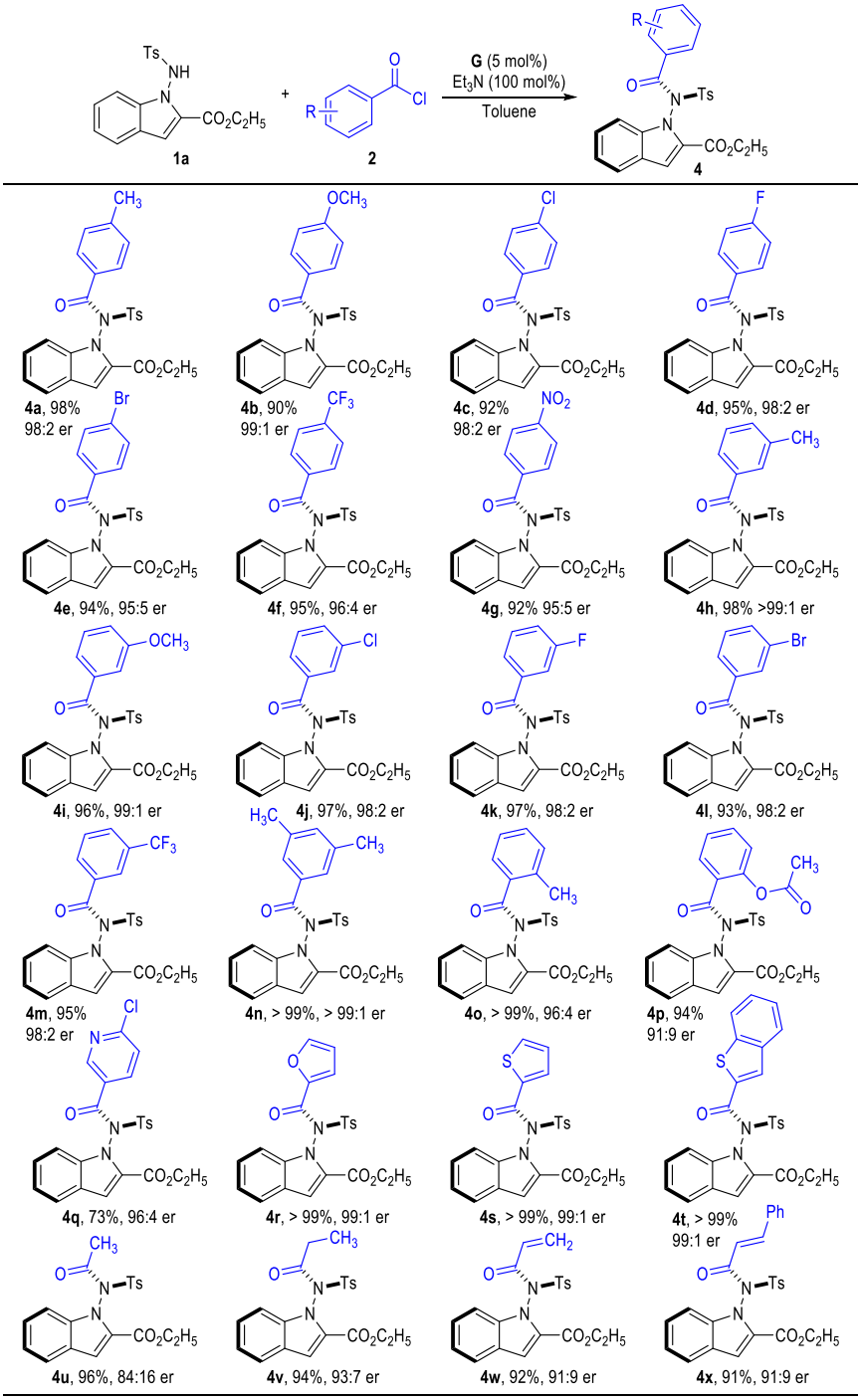
Scheme 1. Scope of the N-Aminoindole Substrate 1.[a]





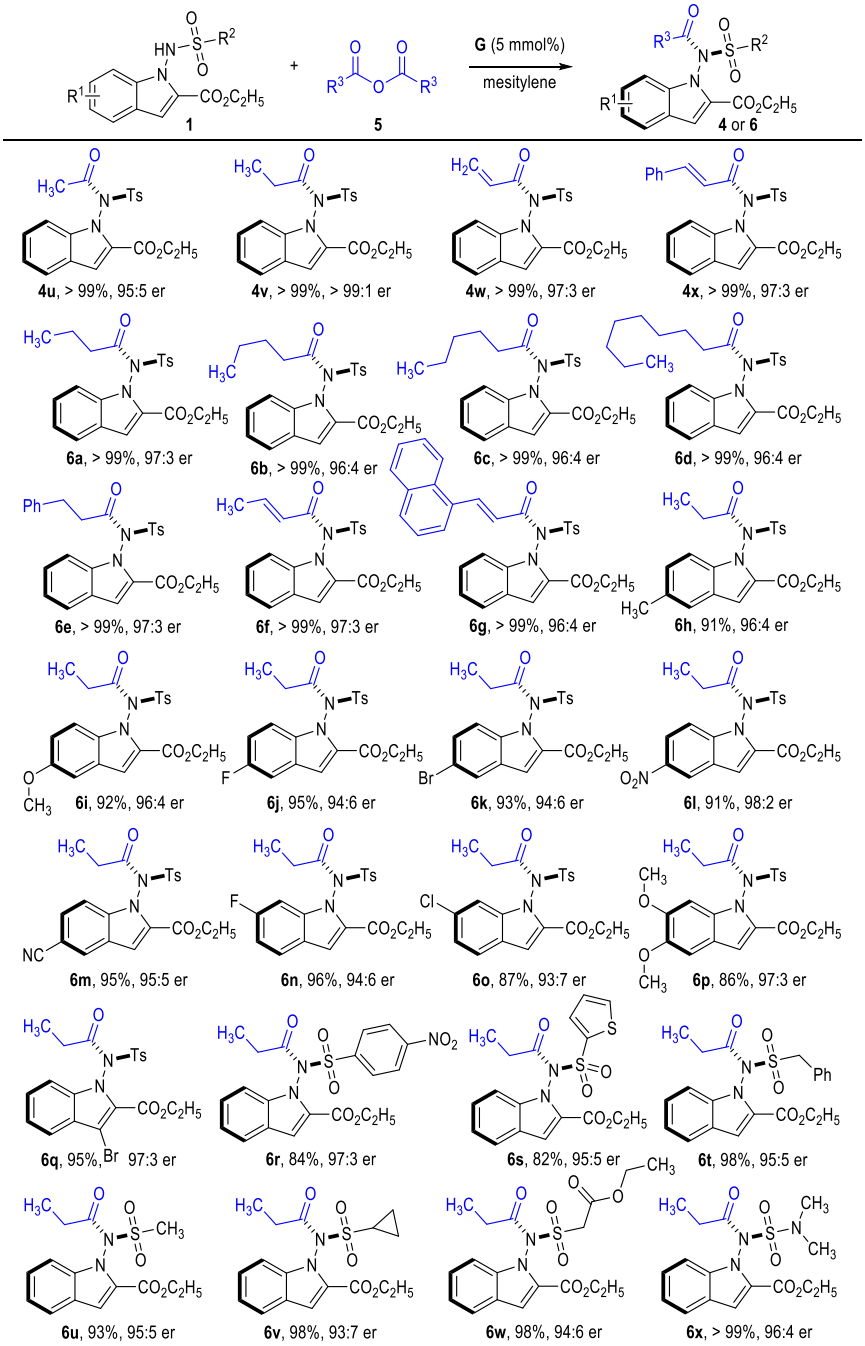
[a]Reaction conditions as stated in Table 1, entry 15. Yields are isolated yields after purification by column chromatography. Er values were determined *via* HPLC on chiral stationary phase.

Scheme 2. Scope of the 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 chiral stationary phase.

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



[a]The reactions as stated in table S1, Entry 12. Yields are isolated yields after purification by column chromatography. Er values were determined *via* HPLC on chiral stationary phase.

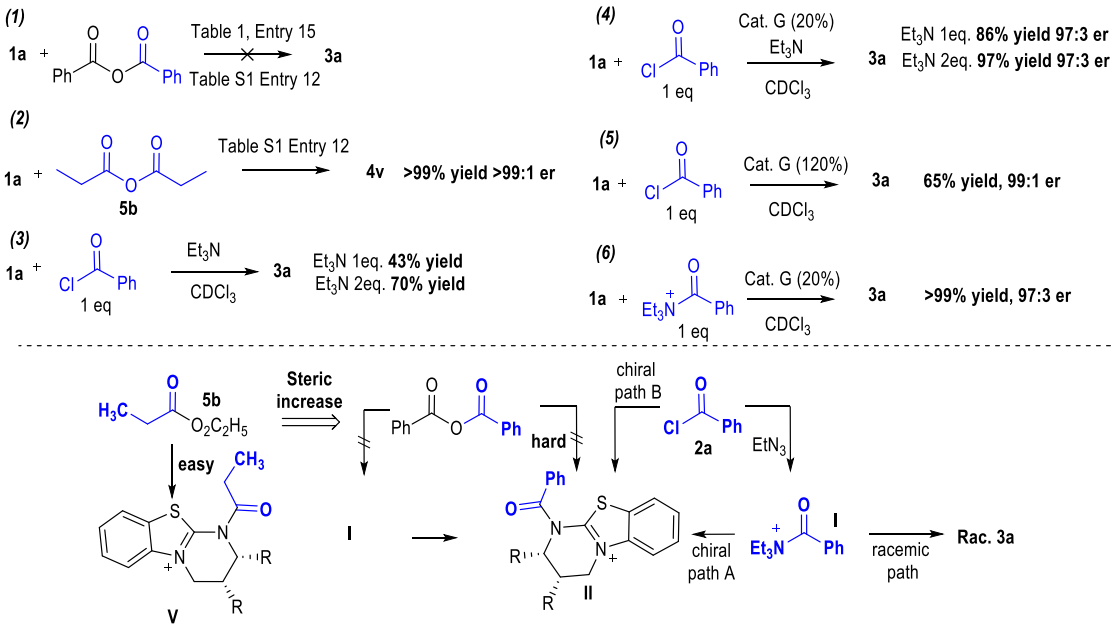


Fig. 2. control experiments.

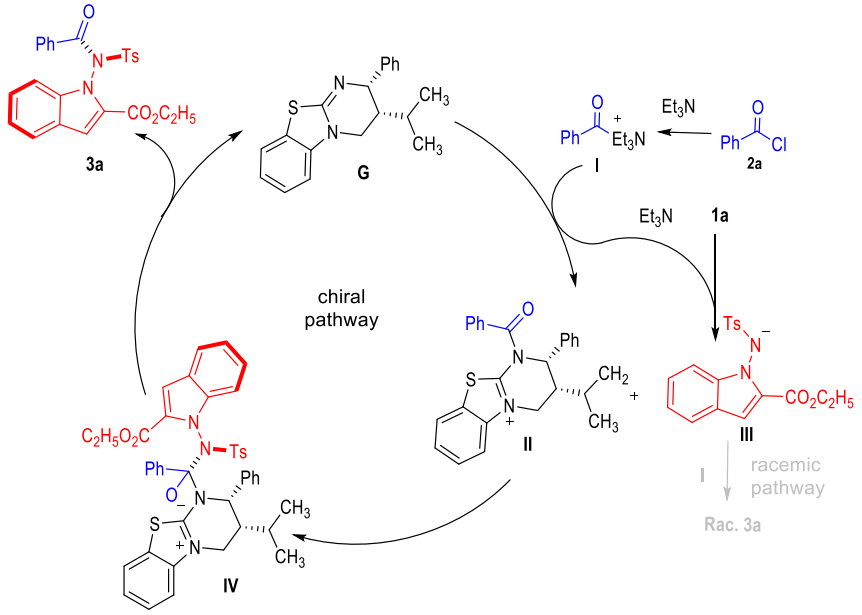


Fig. 3. Proposed Reaction Mechanism.

Table 3. Anti-bacterial Activities of the Target Compounds Against Xac and Xoo.

Compounds	*Xoo* Inhibition Rate (%)[a]		*Xac* Inhibition Rate (%)[a]	
	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL
(±)-4u	45.9 ± 3.7	35.8 ± 2.7	68.1 ± 2.6	46.8 ± 2.5
(S)-4u	59.6 ± 2.9	45.2 ± 3.1	70.4 ± 1.2	47.8 ± 1.8
(R)-4u	38.4 ± 2.2	27.0 ± 3.2	54.6 ± 3.0	35.9 ± 2.3
(±)-6e	48.5 ± 4.1	30.1 ± 5.4	47.2 ± 2.6	31.2 ± 2.0
(S)-6e	57.6 ± 3.0	39.0 ± 4.5	44.6 ± 3.1	33.7 ± 1.6
(R)-6e	32.9 ± 4.7	15.0 ± 2.8	45.9 ± 3.3	35.7 ± 2.2
TC[b]	32.1 ± 2.7	22.9 ± 2.3	54.7 ± 1.8	31.8 ± 2.6
BT[c]	41.9 ± 3.3	32.5 ± 2.4	43.5 ± 2.7	28.4 ± 3.1

[a] Average of 3 replicates. [b] TC = Thiodiazole coppers. [c] BT = Bismerthiazol.