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Atroposelective Nenitzescu Indole Synthesis

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In commemoration of Prof. C. D. Nenitzescu's 120th birthday.

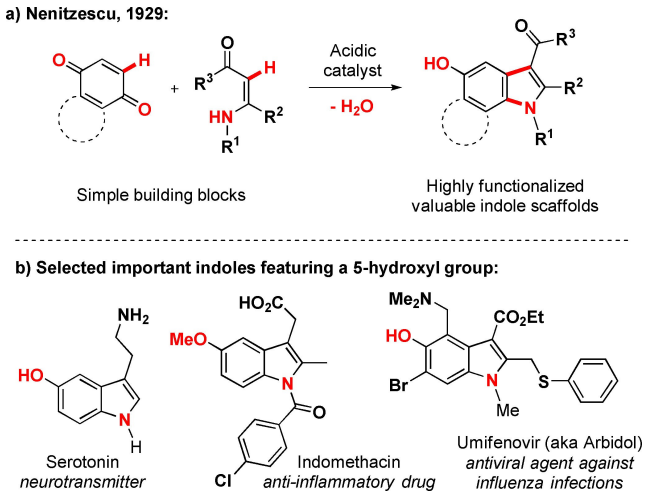
Abstract: In the past decade, compounds bearing a stereogenic C–N axis have gained significant attention in fields ranging from ligand to drug design. Yet, the atroposelective synthesis of these molecules remains a considerable challenge. In contrast to recent methods using more advanced chiral catalysts, a very simply accessed Jacobsen-type chromium(III)–salen complex was used here as a chiral enantiopure Lewis acid catalyst for a highly atroposelective Nenitzescu indole synthesis. Mild reaction conditions afforded various 5-hydroxybenzo[*g*]indoles in up to 97% yield. Moreover, through a simple work-up, very high enantiomeric excesses of up to 99% could be obtained.

Introduction

The Nenitzescu reaction, or Nenitzescu indole synthesis, is a versatile synthetic tool for accessing 5-hydroxyindole scaffolds of high value in a single step.[1] It moreover operates with trivial building blocks, usually simple benzoquinones with β-aminocrotonic derivatives. The Nenitzescu coupling reaction is then enabled by a Michael enamine addition and condensation cyclization sequence. Since its discovery in 1929,[2] no enantioselective solution of any kind was ever developed for this reaction (Scheme 1a), in spite of 5-hydroxyindoles being of great interest for their strong pharmacological activities (Scheme 1b).[3]

While C–C bond atropisomerism has been extensively studied and used in a wide range of chiral applications,[4] such as in the emblematic 2,2′-binaphthol case, C–N bond atropisomerism has been largely overlooked in spite of inspiring recent progress in this field.[5] This is regrettable because many C–N atropisomers are associated with divergent biological activity, or suspected thereof.[6] Moreover, many important and diverse organic scaffolds feature stable C–N atropisomers (Scheme 2a),[7] making the development of enantioselective methods both urgent and of paramount importance.

In this field, there are three main enantioselective routes to N-substituted indoles. The first method involves the functionalization of an already existing *N*-aryl indole.[8] The second strategy consists of the direct atroposelective N-arylation of an indole.[9] A third method would be to introduce enantioselectivity during the construction of the indole ring itself, although this strategy has been less documented. In 2010, an intramolecular, atroposelective construction of a *N*-aryl indole was reported by Kitagawa and co-workers,[10] utilizing a chiral enantiopure Pd^{II} catalyst achieving up to 83% enantiomeric excess (*ee*), which was later transposed to a chiral phosphoric acid (CPA) catalyzed reaction by Ye and co-workers.[11] This paved the way for further challenging intermolecular enantioselective approaches (Scheme 2b). Lin and co-workers reported an intermolecular enantioselective construction of an indole ring with excellent *ee* of up to 99%,[12] with a chiral phosphoric acid catalyst. Very recently, Li and co-workers performed a similar reaction as the group of Kitagawa, however using Rh-catalyzed C–H bond activation to generate an *ortho*-alkynylaniline in situ followed by a hydroaminocyclization.[13] In contrast, we propose here a very simple Lewis acid Cr^{III}-catalyzed enantioselective version of the illustrious Nenitzescu indole



Scheme 1. The Nenitzescu indole synthesis.

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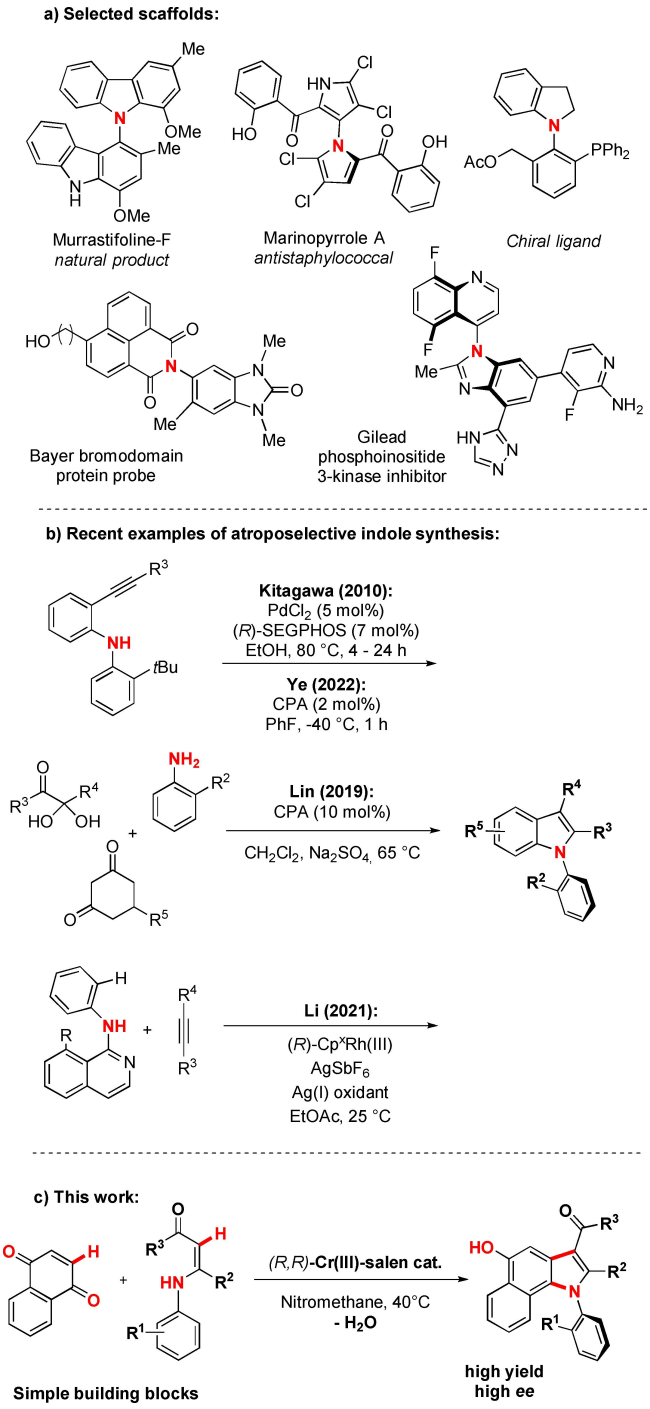


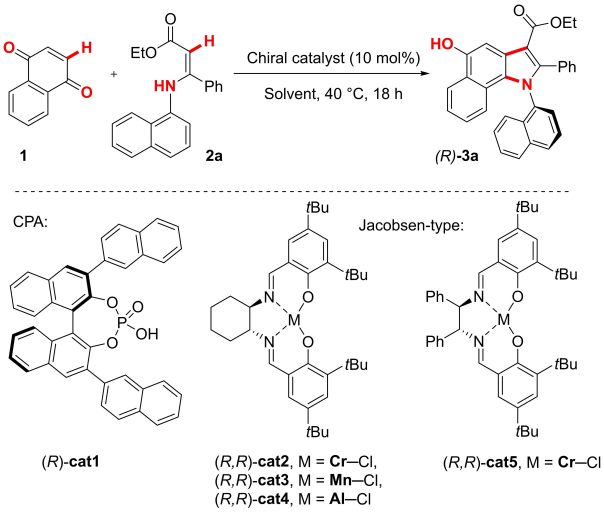
Scheme 2. Atropisomerism along a C–N bond.

synthesis. This is to our knowledge the first ever enantioselective Nenitzescu reaction (Scheme 2c).

Results and Discussion

Inspired by some of the leading works of Bin Tan and other groups with chiral phosphoric acid catalysts,[10,14] we started our investigations with CPA catalyst (*R*)-**cat1** (Table 1, entry 1,

Table 1. Optimization of reaction conditions.[a]

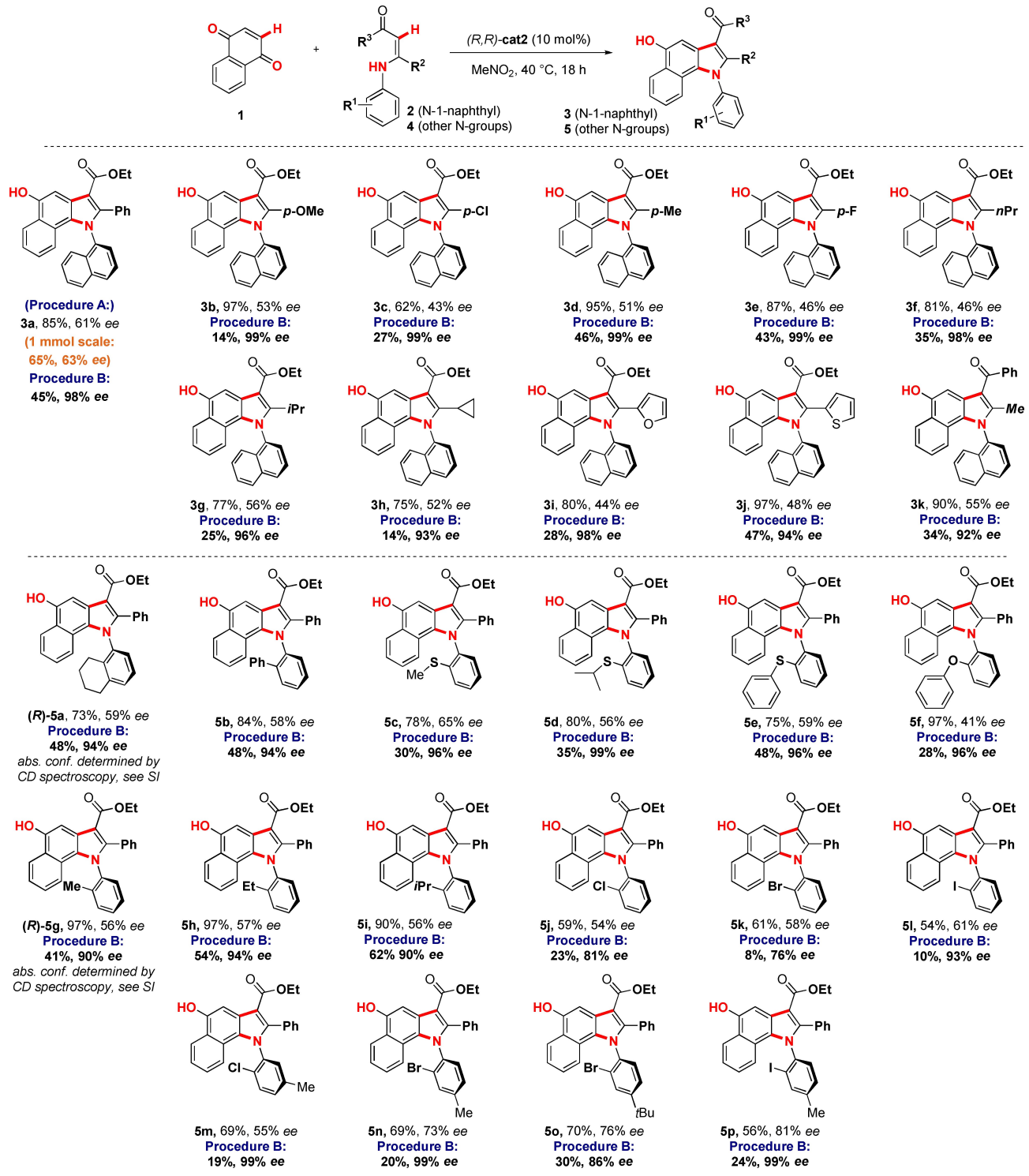


Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	(*R*)-**cat1**	DCM	traces	46
2	(*R,R*)-**cat2**	DCM	67	39
3	(*R,R*)-**cat2**	DCE	83	50
4	**(*R,R*)-cat2**	**$MeNO_2$**	**85**	**61**
5[d]	(*R,R*)-**cat2**	$MeNO_2$	12	60
6[e]	(*R,R*)-**cat2**	$MeNO_2$	81	38
7[f]	(*R,R*)-**cat2**	$MeNO_2$	81	45
8	(*R,R*)-**cat3**	$MeNO_2$	69	24
9	(*R,R*)-**cat4**	$MeNO_2$	68	32
10	(*R,R*)-**cat5**	$MeNO_2$	traces	0

[a] General reaction conditions: **1** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol) and catalyst (10 mol%) were stirred in 20 mL reaction vials with sealed aluminous headspace caps under air in 1 mL solvent at 40 °C for 18 h. [b] Isolated yields, determined after column chromatography. [c] Determined by chiral-phase analytical HPLC. [d] Reaction performed at 0 °C. [e] Reaction carried out under argon atm. [f] Reaction carried out under O_2 atm.

product **3a**, for more catalysts, see the Supporting Information). Unfortunately, none of the CPAs we explored delivered interesting conversion when coupling naphthoquinone **1** with **2a**, although some promising enantiomeric excesses (*ee*) were noted (entry 1).

In this context, we rapidly turned our attention to Jacobsen-type salen based Cr^{III} chiral complexes such as (*R,R*)-**cat2**. Indeed, these have proven to be exceptional enantioselective catalysts for a broad array of organic transformations, and they are moreover trivial to prepare from simple and low-cost building blocks.[15] This approach readily afforded higher conversion and *ee* (entries 2–4). Lowering the temperature (entry 5) or altering the overlaying atmosphere (entries 6 and 7) did not improve these results. Of all tested solvents (entries 2–4), nitromethane performed best in terms of both yield and *ee* (product **3a**, 85%, 61% *ee*, entry 4, thereafter referred to as procedure **A**). Utilizing alternative salen complexes based on Mn^{III} or Al^{III}, or altering the diamine stereogenic backbone led to significantly inferior results (entries 8–10). We next verified that the reaction could be scaled-up to 1 mmol. Although this decreased the yield somewhat (65%), 63% *ee* was thereby obtained (Scheme 3, product **3a**, see the Supporting Informa-



Scheme 3. Reaction scope, isolated yields. General reaction conditions: **1** (0.15 mmol, 1.5 equiv.), **2** or **4** (0.1 mmol) and catalyst (*R,R*)-**cat2** (10 mol%) were stirred in 20 mL reaction vials with sealed aluminous headspace caps under air in 1 mL $MeNO_2$ at 40 °C for 18 h. Procedure **A**: the product is taken in MeOH, and engaged on chiral analytical HPLC. Procedure **B**: the product is precipitated in hexane/iPrOH and filtered off, the enantio-enriched product remaining dissolved in the organic layer, see the Supporting Information.

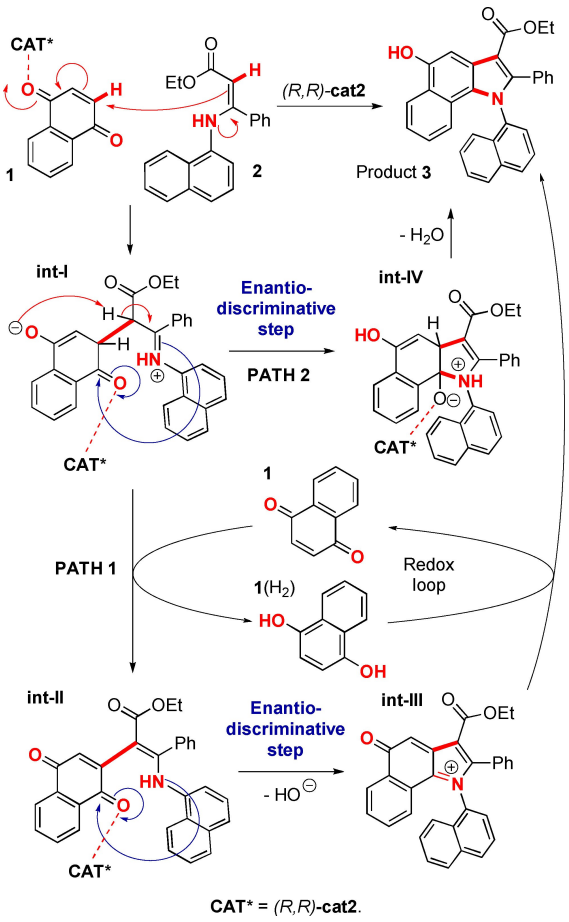
tion). This therefore demonstrates the synthetic utility of the method.

Importantly, the racemates of all products tend to be far less soluble than the corresponding enantiomers taken separately. This property presumably arises from the stronger intermolecular H-bonding networks involving 5-hydroxy-indoles of opposite handedness, compared to homo-chiral intermolecular H-bonding. This can be taken advantage of in order to

obtain very high *ee*, by purposely removing the minor enantiomer, associated with an equivalent sacrificial amount of the major enantiomer. Thus, with an alternative filtration-based work-up procedure **B**, product **3a** could be obtained with an impressive 98% *ee* (Scheme 3), albeit with a reduced 45% yield. In other words, the *ee* can easily be augmented by simple filtration. All herein displayed examples were first worked-up according to procedure **A** (Scheme 3), in order to provide an accurate picture of the entire product population. Work-up procedure **B** was likewise performed on all examples in order to maximize *ee* (Scheme 3, result in bold).

We then varied the β-amino-crotonic derivatives at positions R^1, R^2, and R^3 (Scheme 3). In general, excellent functional group and structural tolerance was observed in terms of yield, with both aromatic (**3a**–**3e**) and aliphatic substituents at the 2-position (**3f**–**3h**, **3k**). Even heterocyclic furane and thiophene were well tolerated (**3i** and **3j**), with high yields. In addition, the R^3 position tolerates phenones (**3k**). Next, we investigated substituent R^1, that is, with N-functionalization other than 1-naphthylamine (**5a**–**5p**). Indeed, the N-functional group is essential for both atropostability as well as for the enantiomeric induction process. Here too, good yields were generally obtained with a wide assortment of *N*-aryl groups. In particular, good to excellent yields were obtained with a broad selection of diverse *ortho* substituents (**5a**–**5p**), including alkyls, aryl, ethers, thioethers, and halides (X = Cl, Br and I), with encouraging *ee* values. Other *ortho* substituents however, such as hydroxyl or methoxy, deliver quasi-racemic products, possibly due to altered and competing interactions with the catalyst (see the Supporting Information). While the *ee* values arising from procedure **A** range otherwise from 41 to 81%, with **5p** delivering the best result, work-up procedure **B** afforded again impressive *ee* values of up to 99% in many cases. For an indicative list of less successful substrates on both the quinone as well as enamine side, see the Supporting Information (p. S22).

Next, we investigated the possibility of nonlinear effects occurring, by monitoring the *ee* of the product depending on the enantiopurity of the catalyst. No significant nonlinear effect was thus found (see the Supporting Information). A preliminary mechanism proposal is drawn in Scheme 4, which is based on precedent literature on the Nenitzescu reaction,[16] as well as on our observations (Table 1). The C–C bond formation step would occur first by enamine attack of the electrophilic naphthoquinone Michael acceptor towards intermediate **int-I**, followed in a second step by the intramolecular enantio-discriminative C–N bond formation (**PATH 1** and **2**, Scheme 4). In the latter step, the orientation of the 1-naphthyl or similar unsymmetrical bulky arene unit would be influenced by the proximity of the chiral salen complex, thus leading to an enantioselective condensation. Based on early intermediate isolation experiments, Nenitzescu himself as well as several other authors argued that the intramolecular C–N condensation must first be preceded by an oxidation step towards the more electrophilic naphthoquinone intermediate **int-II**, followed by condensation and then reduction of subsequent quinoid intermediate **int-III**. This is the so-called redox Nenitzescu-Allen mechanism[17] (**PATH 1**,

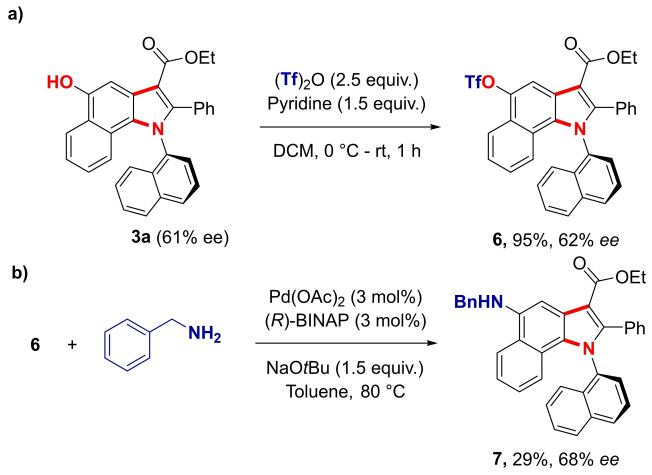


Scheme 4. Proposed reaction mechanism.

Scheme 4). Other authors have suggested that under Lewis acid catalysis, a direct condensation path might exist between **int-I** and **int-IV**, in a non-redox fashion (**PATH 2**).[18]

Next, the absolute configuration of the major enantiomeric product obtained from (*R*,*R*)-**cat2** was determined by means of CD spectroscopy and theoretical calculations for two different products. The obtained data is in excellent agreement with the (*R*)-**5a** configuration, as well as for the (*R*)-**5g** configuration (Scheme 3, see the Supporting Information for details). Moreover, the energy barrier for the rotation around the C–N bond was calculated at the B3LYP/6-31G* level to be about 50 and 42 kcal/mol for **5a** and **5g**, respectively (see the Supporting Information). These relatively high values arise in large part due to the bulky naphthol moiety, in spite of the small *ortho* methyl group in **5g**. No racemization was observed, even within days at 80 °C, at which temperature chemical decomposition typically becomes significant (see the Supporting Information).

Finally, it was found possible to activate the phenolic OH group of product **3a** towards triflate product **6** (95% yield, Scheme 5). Interestingly, however, work-up procedure **B** no longer allows to increase the *ee* of indole scaffold **6**, due to enhanced solubility. This indicates that the OH functional group and its H-bonding ability are critical to achieve high *ee* in work-up procedure **B** (Scheme 3). Subsequently, product **6** can then



Scheme 5. a) Trifluorosulfonation of product **3a**. b) Subsequent Buchwald-Hartwig amination.

be used in a Buchwald-Hartwig amination.[19] In this case, benzylamine was engaged to obtain product **7** in 29% yield and 68% *ee*.

Conclusion

In conclusion, we have developed an unprecedented atroposelective Nenitzescu indole synthesis. This method uses a simple and cheap Jacobsen-type Cr^{III}–salen complex as enantioselective catalyst, which contrasts with the advanced chiral catalysts furnishing atroposelective C–N bonds in the recent literature. Overall, a wide range of examples were documented with yields up to 97%. The strong H-bonding ability of the products allowed us to reach an *ee* of up to 99% through a precipitation work-up procedure (**B**). The practicality of this approach should open a new chapter for the atroposelective synthesis of indoles, and the study of their biological and physical properties.

Experimental Section

Typically: substrate **2** (0.1 mmol), naphthoquinone **1** (1.5 equiv., 0.15 mmol, 23.7 mg), (*R,R*)-**cat2** Cr–salen catalyst (10 mol%) and nitromethane (1 mL) are added to a 20 mL reaction vial in open air. The vial is sealed with an aluminous headspace cap and heated to 40 °C for 18 h (aluminium heating block). The reaction is then cooled to room temperature. The crude reaction mixture is directly purified by SiO_2 gel column chromatography.

Procedure **A**: Due to the often strong solubility differences between racemic and enantiopure products, the sample for HPLC analysis may not be filtered. Removing any precipitate may result in artificially high *ee* of the mother layer. It is therefore advised to dissolve the sample in hot methanol (HPLC grade), and if necessary treat it with an ultrasonic bath and heat. It is also advised to work with diluted samples.

Procedure **B**: It is often possible to obtain highly enantiopure products, even with an only moderate enantiomeric induction performance of the catalyst. This can be achieved by filtrating off the racemic precipitate. The product is first synthesized and purified according to the general procedure above. The solvent (hexane/*i*PrOH) is then added to the pure compound (ethyl acetate, ether or dichloromethane are not suitable). The suspension is filtered over cotton and the filtrate is concentrated in vacuo. The *ee* is then obtained by HPLC analysis. If the enantiopurity is not high enough the procedure can be repeated again. While this procedure reduces the isolated yields, very high *ee* can indeed be reached.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: atroposelective coupling · chromium catalysis · CN axial chirality · Nenitzescu indole synthesis · Nenitzescu reaction

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