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# Asymmetric total synthesis of (+)-indatraline via diastereoselective amination of chiral ethers using chlorosulfonyl isocyanate

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ABSTRACT

A concise asymmetric total synthesis of (+)-indatraline from readily available cinnamic acid is described. The key steps include Corey's oxazaborolidine-catalyzed asymmetric carbonyl reduction and a highly stereoselective amination of chiral benzylic ether with retention of stereochemistry using chlorosulfonyl isocyanate.



## 1. Introduction

The indane motif is a common scaffold found in several medical agents. In particular, compounds including the amine functionality on an indane framework have been used in drug candidates aiming at modulating a diverse group of target structures, such as dopamine,[1] serotonin[2] and neurokinin-2 receptors,[3] and monoamine transporters.[4] For example, (+)-indatraline (Lu-19005) is a non-selective monoamine transporter inhibitor to block the reuptake of dopamine, norepinephrine, and serotonin.[4] Rasagiline (Azilect) is a prescribed agent for the treatment of Parkinson's disease,[5] and irindalone displays antihypertensive properties via the selective blocking of 5-$HT_2$ receptor (Fig. 1).[6]

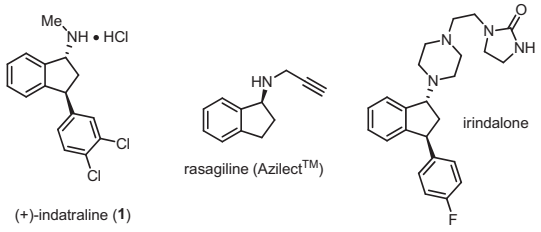


**Fig. 1.** Biologically active compounds containing 1-amino indane scaffold.

Cocaine is a non-selective monoamine reuptake inhibitor that blocks the reuptake of dopamine, norepinephrine and serotonin.[7] The illicit abuse of cocaine continues to be a serious public health problem throughout the world, but no uniformly effective medication for its treatment has been developed.[8] A possible treatment for cocaine dependence includes substitution medication that produces cocaine-like behavior, but with a slower onset and longer duration of action than cocaine.[9] (+)-Indatraline (**1**), is a potent long-acting monoamine reuptake inhibitor that has been investigated as a potential drug for the treatment of major depressive disorder and cocaine addiction. The (+)-enantiomer of indatraline is 20 times more potent than the (−)-enantiomer.[10,11a] Commercial production of (+)-indatraline relies on the chiral resolution of racemic indatraline. Due to its interesting pharmacological activity and unique structural features, several synthetic methods for indatraline have been developed. Most of these synthetic approaches rely on the preparation of 3-phenyl-1-indanone, which can be easily converted into *trans*-3-phenyl-1-indanamine through nucleophilic substitution reaction.[11,12] In a representative example of asymmetric synthesis, Davies reported an asymmetric total synthesis of (+)-indatraline based on rhodium-catalyzed enantioselective carbenoid C–H bond insertion into 1,4-cyclohexadiene.[12a] In another example, a diastereoselective total synthesis of (±)-indatraline was described via iodine-promoted oxidative ring contraction of 1,2-dihydronaphthalene followed by Hofmann rearrangement.[13] In a recent example, Juhl demonstrated a total synthesis of (+)-indatraline via enzymatic resolution of racemic *trans*-3-phenyl-1-indanol.[14]

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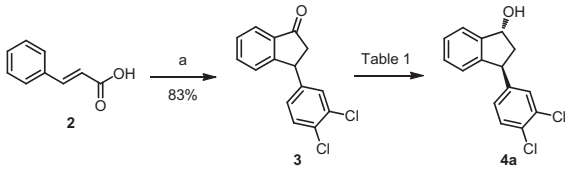
As part of an ongoing research program aimed at developing asymmetric total synthesis of biologically active compounds,[15] we recently described a facile strategy for the preparation of (+)-sertraline via stereoselective amination of various chiral benzylic ethers using chlorosulfonyl isocyanate (CSI).[16] In connection with our previous work on the regioselective and diastereoselective amination of cyclic benzylic ethers using CSI, we herein describe an asymmetric total synthesis of (+)-indatraline (**1**) starting from commercially available cinnamic acid (**2**) via highly stereoselective amination of chiral benzylic ether using chlorosulfonyl isocyanate as the key step.

## 2. Results and discussion

Our initial investigations focused on the efficient construction of indanone **3** and the formation of chiral indanol **4a** based on the reported literature (Scheme 1). First, cinnamic acid (**2**) was coupled with 1,2-dichlorobenzene in the presence of an excess amount of trifluoromethanesulfonic acid (TfOH) to afford our desired product **3** in 83% yield.[17]




**Scheme 1.** Reagents and conditions: (a) 1,2-dichlorobenzene, $CF_3SO_3H$, rt, 72 h.

The enantioselective reduction of **3** was achieved by Corey's oxazaborolidine-catalyzed asymmetric carbonyl reduction methodology (Table 1).[18] Treatment of the ketone **3** with (*S*)-(−)-2-methyl-CBS-oxazaborolidine catalyst (**5**) and catecholborane afforded a separable mixture of (1*R*,3*S*)-*trans*-indanol **4a** and its diastereoisomer **4b** with high enantioselectivities (Table 1, entry 1). The relative stereochemistry of **4a** and **4b** was confirmed by NOESY NMR analysis (see Supplementary data for further details). After optimization of the reaction conditions, we found that prochiral ketone **3** was converted into our desired compound **4a** in 45% yield with excellent enantioselectivity (>99% ee) by the use of **5** and *N*,*N*-diethylaniline borane (Table 1, entry 4).[19] The absolute configuration of **4a** was determined by comparison with a reported data via chiral HPLC analysis.[12e]

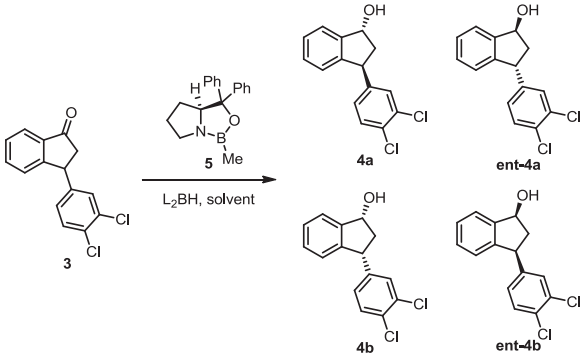
Benzylation of **4a** under standard conditions (benzyl bromide, NaH, THF/DMF) afforded benzyl ether **6** in 83% yield. Next, the diastereoselectivity of the reaction of **6** using chlorosulfonyl isocyanate (CSI) was examined under various reaction conditions, and the selected results are summarized in Table 2. As shown in entry 1, the reaction in methylene chloride at −40 °C gave the desired product **7** and its diastereomer with 92:8 of diastereomeric ratio. After screening of solvents under otherwise identical conditions, *n*-hexane was found to be most effective solvent in this reaction, affording exclusively compound **7** in 75% yield with an excellent diastereoselectivity (99>1). The observed stereochemistry can be explained by the competition between the $S_Ni$ mechanism leading to retention of stereochemistry through a four-centered transition state and the $S_N1$ mechanism through carbocation intermediate.[20] This result is consistent with the formation of a tight ion pair in nonpolar *n*-hexane solvent, compared to relatively polar methylene chloride solvent.

**Table 2**
Selected optimization for the diastereoselective amination of **6**[a]

| Entry | Solvent | Time (h) | Yield[b] (%) | dr[c] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 14 | 61 | 92:8 |
| 2 | Toluene | 40 | 70 | 96:4 |
| 3 | *n*-Hexane | 40 | 75 | 99>1 |

[a] Reaction conditions: (i) compound **6** (1 equiv), chlorosulfonyl isocyanate (3 equiv), $Na_2CO_3$ (3 equiv), solvent (0.06 M), −40 °C (ii) 25% $Na_2SO_3$, rt, 12 h.
[b] Isolated yield by flash column chromatography.
[c] Diastereomeric ratio was determined by $^1$H NMR analysis of a crude reaction mixture.

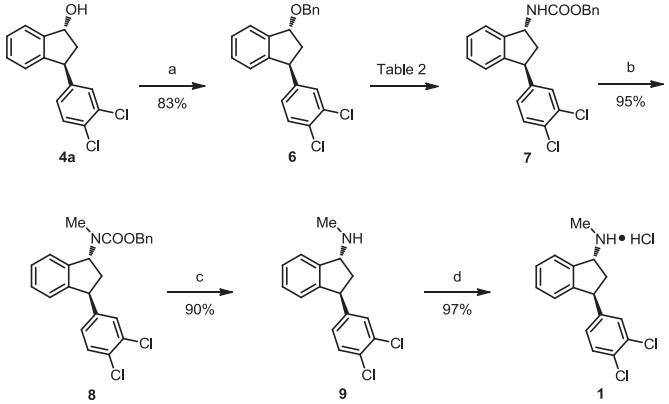
**Table 1**
Selected optimization for the asymmetric reduction of **3**[a]




| Entry | $L_2BH$ | Solvent (M) | Temp (°C) | Time (h) | **4a**+*ent*-**4a** | | **4b**+*ent*-**4b** | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Yield[b] (%) | ee (%)[c] | Yield[b] (%) | ee (%)[c] |
| 1 | Catecholborane | $CH_2Cl_2$ (0.5) | −78 | 12 | 31 | 95 | 50 | 85 |
| 2 | *N*,*N*-DEAB | Toluene (0.15) | −20 | 24 | No reaction | | | |
| 3 | *N*,*N*-DEAB | Toluene (0.15) | 0 | 24 | 5 | — | 5 | — |
| 4 | *N*,*N*-DEAB | Toluene (0.15) | rt | 4 | 45 | >99 | 46 | 91 |

[a] Reaction conditions: compound **3** (3.0 mmol), **5** (20 mol %), $L_2BH$ (6.0 mmol), solvent, under $N_2$.
[b] Isolated yields by flash column chromatography.
[c] Enantiomeric excess (ee) was determined by chiral stationary phase HPLC analysis.

To complete the synthesis of (+)-indatraline, the carbamate **7** was treated with MeI and NaH to afford the compound **8**, which was hydrogenated using the Raney Ni catalyst to afford indatraline free amine (**9**) in 90% yield (Scheme 2). The spectral data ($^1$H NMR and $^{13}$C NMR) and specific rotation of **8** were in full agreement with the reported values.[12e] Finally, indatraline free amine (**9**) was treated with HCl in diethyl ether to give (+)-indatraline hydrochloride salt in 97% yield.




**Scheme 2.** Reagents and conditions: (a) NaH, BnBr, THF/DMF (4:1), rt, 12 h; (b) NaH, MeI, THF/DMF (4:1), rt, 12 h; (c) Raney Ni, $H_2$, $CH_2Cl_2$/MeOH (1:4), rt, 6 h; (d) 1 M HCl, $Et_2O$, rt, 2 h.