Asymmetric Catalysis

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Enantioselective Phase-Transfer-Catalyzed Intramolecular Aza-Michael Reaction: Effective Route to Pyrazino-Indole Compounds**

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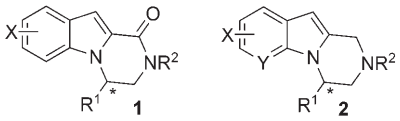
The preparation of enantiomerically pure compounds has become a stringent requirement for pharmaceutical synthesis.[1] In this context, asymmetric catalysis is probably the most attractive procedure for the synthesis of active pharmaceutical ingredients (APIs) due to environmental, operational, and economic benefits.

3,4-Dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones **1** (see Scheme 1) have attracted much attention due to the broad scope of their biological activities (that is, their antifungal properties, noncompetitive antihistamine activity, and specific inhibition of serotonergic receptors).[2] Moreover, recent patents reported the effectiveness of the corresponding 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **2** (Scheme 1) as anti-obesity agents and in the treatment and prevention of non-insulin-dependent diabetes.[3]

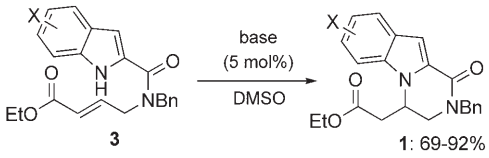


Scheme 1. Examples of polycyclic indolyl-based scaffolds. R^1 = alkyl, hydroxyalkyl; R^2 = H, Me, Bu; X = H, halogen, alkyl; Y = CH, N.

From these studies, the importance of the absolute configuration of the stereocenters on the pharmacological activity emerged clearly. Moreover, since the piperazine compounds **2** are readily obtainable from **1**,[3] the development of an effective stereoselective synthetic route to pyrazino-indol-1-ones **1** would be extremely valuable. The use of chiral pools and the resolution of racemates are the only synthetic routes to **1** and **2** to date.[3–5]

During our ongoing research addressing the functionalization of polycyclic indoles,[6] we recently communicated an efficient Pd-catalyzed approach to tetrahydro-β-carbolines through regio- and enantioselective C3-allylic nucleophilic alkylation (up to 97% *ee*).[7] Unfortunately, all our attempts to exploit such an approach to perform enantioselective indolyl-N1 ring-closing reactions were unsuccessful. Herein, we describe the first highly enantioselective synthesis of molecular motifs of type **1** through a phase-transfer-catalyzed[8] aza-Michael addition.[9]

The employment of a metal-free approach[10] stems from our recent findings on the intramolecular base-catalyzed synthesis of **1**, from readily available precursors **3** (Scheme 2).[11] However, the use of Lewis acid catalysis in the present ring-closing reaction failed, probably due to the poor electrophilic character of the α,β-unsaturated ester and to low catalyst turnover as a result of starting material/product inhibition (that is, a metallo-poisoning effect exerted by the strongly coordinating amide group).



Scheme 2. Base-catalyzed synthesis of **1**. Bn: benzyl; DMSO: dimethylsulfoxide.

Searching for an enantioselective variant, we firstly turned our attention to chiral organic bases such as the *Cinchona* alkaloids and sparteine, which gave disappointing results in the cyclizations of **3a** (X = H; toluene, reflux, 48 h, 0% *ee*). We reasoned that the unsatisfactory stereoinduction could be ascribable to the formation of flexible and not sufficiently tight ion pairs between the ammonium salt of the quinuclidine ring and the nucleophilic indolate intermediate (Figure 1a).

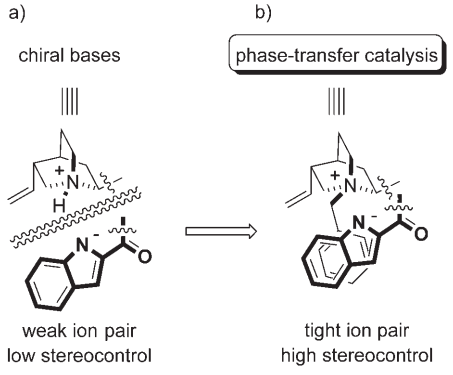


Figure 1. Chiral organic bases versus phase-transfer catalysis in the enantioselective ring closure of **3**.

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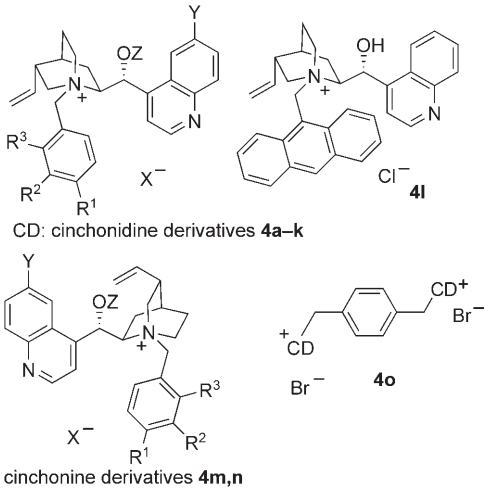
In light of this consideration, we envisioned that the use of more rigid chiral ammonium salts would guarantee higher enantioselection (Figure 1b).

The employment of *N*-benzylcinchonidinium bromide **4a** (10 mol%), in combination with KOH (25% aq; 0.5 equiv) under a phase-transfer regime, furnished **1a** in 84% yield and



with a promising 36% *ee* (toluene, 30 min, 0°C; Table 1, entry 1). Prompted by this result, we undertook a survey of chiral *Cinchona* ammonium salts (**4b–o**) in the cyclization of the model substrate **3a**; the corresponding outcomes are summarized in Table 1. Interestingly, the free hydroxy group at the C9 position proved to be crucial to guarantee reasonable *ee* values. In fact, the use of the C9-*O*-allyl catalyst **4c** gave **1a** in nearly racemic form (Table 1, entry 3). The inversion of stereoinduction observed with **4c** suggests an active role for the OH group during the enantiodiscrimination step of the process.[12] A steady improvement in enantiocontrol was obtained by introducing electron-withdrawing substituents on the benzyl group; these are known to favor tighter contact ion pairing with consequent strengthening of the substrate–catalyst interaction.[13] In particular, while a *para*-methoxy group (in **4b**) causes a marked drop in enantiocontrol (21% *ee*; Table 1, entry 2), the introduction of *para*-nitro, *para*-fluoro, and *para*-CF_3 moieties (in **4f**, **4i**, and **4j**, respectively) gave **1a** with comparable yields (89–90%) and *ee* values of 60–61% (Table 1, entries 6, 9, and 10). Mechanistically, the present intramolecular aza-Michael addition seems to work quite differently from most of the described phase-transfer-catalyzed alkylation reactions, in which a templating effect of molecules of water or cations is used to rationalize high levels of stereoinduction.[14] In fact, in our system, comparable enantiomeric excesses were recorded with several inorganic bases (LiOH, NaOH, and CsOH; solid and in aqueous solution), and the presence of coordinating groups at the *ortho* position of the phenyl ring (in **4e**; known to favor rigid catalyst conformations) led to a marked drop in induction (Table 1, entry 5). Remarkably, lowering of the reaction temperature to −20 and −45°C caused an increase of stereoinduction to 72 and 91%, respectively (Table 1, entries 16 and 17), with no significant variation in the chemical yield (91–93%).

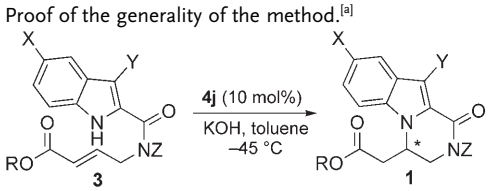
With the optimal reaction conditions established, the substrate scope of the reaction was investigated; the results are summarized in Table 2. Tolerance toward both electron-withdrawing and electron-donating groups on the indolyl scaffold (C5 position) is highlighted by entries 1–4 in Table 2. Under optimal conditions (**4j**, 10 mol%), the desired pyrazino-indol-1-ones **1b–e** were isolated in 85–93% yield and with enantiomeric excess values of up to 89%. The indolyl esters bearing electron-donating substituents (Me, OMe) at

Table 1: Screening of chiral catalysts (Cat*: **4a–o**) for the enantioselective ring closure of **3a**.[a]

Entry	Cat.*	$R^1/R^2/R^3$	$X^-/Y/Z$	Yield [%][b]	*ee* [%][c]
1	**4a**	H/H/H	Br/H/H	84	36
2	**4b**	OMe/H/H	Cl/H/H	82	21
3	**4c**	H/H/H	Cl/H/allyl	85	−5
4	**4d**	H/NO_2/H	Br/H/H	80	52
5	**4e**	H/H/NO_2	Br/H/H	81	−6
6	**4f**	NO_2/H/H	Br/H/H	89	60
7	**4g**	NO_2/H/H	Br/OMe/H	75	45
8	**4h**	F/F/F	Br/H/H	90	33
9	**4i**	F/H/H	Br/H/H	89	60
10	**4j**	CF_3/H/H	Br/H/H	90	61
11	**4k**	CF_3/H/H	Br/OH/H	75	25
12	**4l**	see structure		80	−8
13	**4m**	NO_2/H/H	Br/OMe/H	85	−30
14	**4n**	CF_3/H/H	Br/H/H	90	−25
15	**4o**	see structure		55	−7
16[d]	**4j**	CF_3/H/H	Br/H/H	91	72
17[e]	**4j**	CF_3/H/H	Br/H/H	93	91

[a] All reactions were carried out in open-air vials with reagent-grade toluene and 10 mol% of catalyst (0°C, 16 h, 0.5 equiv of KOH). [b] Yields after isolation by flash chromatography. [c] Determined by HPLC on a chiral stationary phase (DAICEL Chiralcel AD). [d] $T = -20$°C. [e] $T = -45$°C.

Table 2: Proof of the generality of the method.[a]

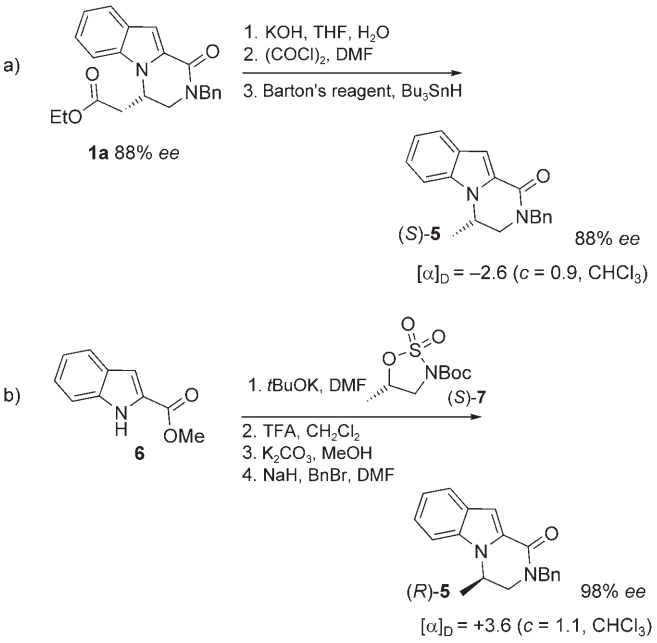


Entry	**1**	X/Y/Z/R	Yield [%][b]	*ee* [%][c]	Conf.
1	**1b**	F/H/Bn/Et	93	82	*S*
2	**1c**	Cl/H/Bn/Et	88	84	*S*
3[d]	**1d**	OMe/H/Bn/Et	85	89 (98)	*S*
4[e]	**1e**	Me/H/Bn/Et	85	89 (96)	*S*
5	**1f**	H/C_6H_5/Bn/Et	90	75	–
6	**1g**	H/β-naphth[f]/Bn/Et	55	80	–
7	**1h**	H/H/PMP[f]/Et	75	82	*S*
8[d]	**1i**	H/H/Bn/Me	90	90 (92)	*S*
9[d]	**1j**	H/H/Bn/*t*Bu	61	53	*S*

[a] All reactions were carried out in open-air vials with reagent-grade toluene with KOH (25% aq; 0.5 equiv) at −45°C for 16 h, unless otherwise specified. [b] Yields after isolation by flash chromatography. [c] Determined by HPLC on a chiral stationary phase. The values given in brackets are *ee* values after crystallization (boiling Et_2O for **1d** and **1e**; cyclohexane for **1i**). [d] Reaction time of 48 h. [e] Reaction time of 36 h. [f] Naphth: naphthalene; PMP: *para*-methoxyphenyl.

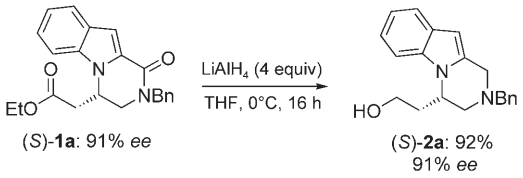
the C5 position (**3d** and **e**; Table 2, entries 3 and 4) underwent the cyclization with good stereocontrol but prolonged reaction times were needed to ensure complete conversion (36 and 48 h, respectively). Remarkably, nearly enantiomerically pure compounds can be readily obtained by recrystallization from boiling Et_2O (**3d**, 98% *ee*; **3e**, 96% *ee*). 3-Aryl indole derivatives **3f** and **3g** also smoothly cyclized under the optimal conditions to afford the corresponding functionalized pyrazino-indol-1-ones **1f** and **1g** in good yields (90 and 55%, respectively) and with good enantiomeric excess values (75 and 80%, respectively; Table 2, entries 5 and 6). Limitation on the scope of the reaction lies in the presence of sterically demanding groups (for example, *t*Bu) at the ester moiety. In fact, while methyl ester **1i** (yield 90%, 90% *ee*, 92% *ee* after crystallization; Table 2, entry 8) confirmed the result obtained with the model substrate **1a** (Table 1, entry 17), *tert*-butyl derivative **3j** underwent cyclization with only modest stereodiscrimination (53% *ee*; Table 2, entry 9).[15] To the best of our knowledge, only a handful of examples of asymmetric organocatalyzed intramolecular C–N bond-forming processes, through Michael addition, have been described to date.[16]

The absolute configuration of **1a** was determined to be *S* by chemical correlation to the pyrazino-indol-1-one (*R*)-**5** (Scheme 3). In particular, from enantiomerically enriched **1a** (88% *ee*), the saponification of the ester moiety followed by a radical decarboxylation reaction (with Barton's reagent[17]) of the corresponding acid chloride led to compound (*S*)-**5** with 88% *ee* in three steps (Scheme 3a). The chemical correlation (specific optical rotation and chiral HPLC retention times; see the Supporting Information) was carried out by exploiting the known multistep approach for the synthesis of pyrazino-indol-1-ones from enantiomerically pure cyclic sulfamidate (*S*)-**7** (Scheme 3b).[3] The absolute configuration of the polycyclic compounds **1b–e** and **1h–j** was assigned as *S* by analogy.



Scheme 3. Determination of the absolute configuration of product **1a**. THF: tetrahydrofuran; DMF: *N*,*N*-dimethylformamide; Boc: *tert*-butoxycarbonyl; TFA: trifluoroacetic acid.

The initial statement concerning the ready interconversion of **1** into 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **2** has been verified by treating (*S*)-**1a** with an excess of $LiAlH_4$ (4 equiv) at 0°C. Under these conditions, the corresponding pyrazino-indole (*S*)-**2a** was isolated in 92% yield without any appreciable racemization (91% *ee*, Scheme 4).



Scheme 4. Stereoretentive synthesis of pyrazino-indole **2a** from pyrazino-indol-1-one **1a**.

In conclusion, we have presented a flexible, mild, and highly enantioselective approach to 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones through phase-transfer catalysis. The ready availability of the acyclic precursors and the broadness of scope make the method a general and useful shortcut for the preparation of a plethora of enantioenriched polycyclic indolyl-based compounds, even for large-scale productions.

Experimental Section

Representative procedure for the synthesis of **1a**: A sample vial was charged with reagent-grade toluene (6 mL), the indolyl ester **3a** (20 mg, 50 μmol), and the phase-transfer catalyst **4j** (3 mg, 5 μmol). An aqueous solution of KOH (25%, 6 μL, 0.5 equiv) was added through a syringe, and the mixture was immediately cooled to −45°C. The reaction was stirred at the same temperature for 16 h, then the solvent was evaporated under reduced pressure. The crude product was directly purified through a pad of silica (cyclohexane/EtOAc 80:20) to give (*S*)-**1a** as a white solid in 93% yield and 91% *ee* (see the Supporting Information).

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