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Aminocatalyzed Cascade Synthesis of Enantioenriched 1,7-Annulated Indoles from Indole-7-Carbaldehyde Derivatives and α,β-Unsaturated Aldehydes

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Abstract: We report herein a new cascade strategy for the enantioselective synthesis of 1,7-annulated indoles based on iminium-enamine activation. A careful study of the indole substitution pattern revealed that a chloro substituent at the C-3 position was important to the implementation of the reaction. Employing a diphenylprolinol silyl ether catalyst, a range of 3-chloro-1*H*-indole-7-carbaldehyde derivatives reacted with α,β-unsaturated aldehydes to afford the corresponding 1,7-annulated indoles in good yields (62–99%) and enantioselectivities (62–92%). Besides the fluorescence properties of the 1,7-ring fused indoles prepared following our methodology, these compounds contain a useful set of functional groups which undergo various synthetic transformations.

Keywords: asymmetric catalysis; domino reactions; fused-ring systems; indoles; organocatalysis

The selective functionalization of indole skeletons is a thriving field of research due to the ubiquity of this framework in natural products, pharmaceuticals and material science. The synthetic potential of asymmetric organocatalysis through the generation of various activation modes has fuelled the implementation of numerous methodologies towards the functionalization of indoles at the C-3 and C-2 positions while the organocatalytic alkylation of the nitrogen atom has been far less described.[1] The ever increasing power of new synthetic methodologies has enabled the selective synthesis of ring-fused indole architectures through the combination of asymmetric organocatalysis and cascade processes. Successful organocatalytic methods have been recently described for the preparation of chiral 1,2-, 2,3- and 3,4-annulated indoles.[2]

To the best of our knowledge, the asymmetric synthesis of 1,7-annulated indoles (or pyrrolo[3,2,1-*ij*]quinolines) through an organocatalytic cascade approach has not been reported although it is a key structural unit found in natural products, therapeutic agents and materials (Figure 1).[3] For instance, murrayazoline is an alkaloid isolated from the genus *Murraya* which shows a potent antiplatelet aggregation activity.[4] KC 11404 exhibits activities against histamine, platelet activating factor (PAF) and leukotrienes which are involved in chronic asthma.[5] In addition, the tricyclic structure pyrrolo[3,2,1-*ij*]quinoline is the central core of red-emitting dopants for organic light-emitting diodes (OLEDs) such as DCQTB.[6] From a synthetic standpoint, indoles bearing relevant functional groups at the C-7 and/or N-1 positions have emerged as powerful building blocks to reach 1,7-annulated indoles through metal-catalyzed intramolecular processes.[7] In sharp contrast, the synthesis of 1,7-ring fused in-

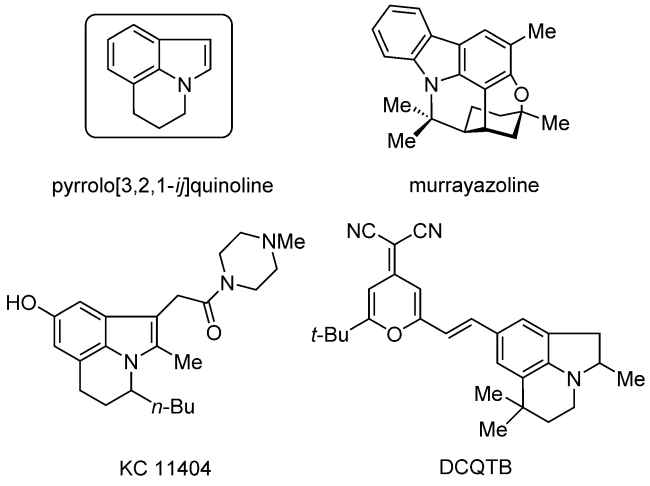
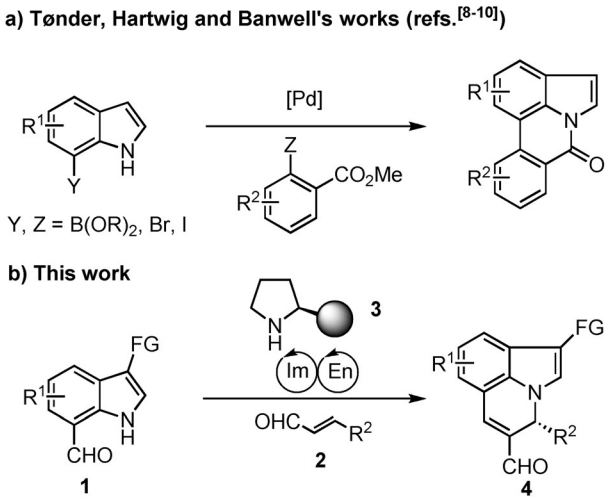


Figure 1. Importance of the pyrrolo[3,2,1-*ij*]quinoline framework.

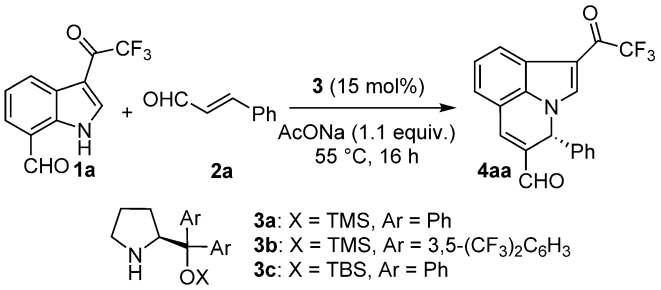
doles *via* bimolecular multi-bond forming processes starting from 1*H*-indoles has been scarcely reported in the literature. In an important contribution to this field, the group of Tønder reported in 2006 a tandem metallation/palladium-catalyzed cross-coupling/lactamization strategy starting from 7-bromoindoles and 2-halobenzoate derivatives (Scheme 1).[8]



Scheme 1. Catalyzed bimolecular strategies towards 1,7-annulated indoles.

Further to this work, the groups of Hartwig[9] and Banwell[10] extended the methodology to other targets by using, in particular, C-7 borolated indoles and 2-bromobenzoate derivatives. In this communication, we wish to report a new access to functionalized 1,7-annulated indoles. Central to the implementation of the methodology is the propensity of chiral secondary amines **3** to condense with α,β-unsaturated aldehydes **2** and to promote the cyclization reaction through iminium-enamine activation.[11] This novel cascade reaction lies in an aza-Michael addition starting from 1*H*-indole-7-carbaldehyde derivatives **1** followed by an intramolecular aldol condensation reaction to give the architectures **4**. Building upon previous works on organocatalytic alkylation of indoles,[2a–c] we surmised that the introduction of an electron-withdrawing group at the C-3 position could prevent a possible side reaction at this site and could reduce the pK_a value of the N–H proton which is a crucial point for the success of N-alkylation reaction.[12] To this aim, we chose the trifluoroacetyl group and subjected the indole derivative **1a** to the reaction with *trans*-cinnamaldehyde **2a** in the presence of an aminocatalyst **3**[13] and AcONa as base (Table 1). The reaction of **1a** with **2a** in the presence of the catalyst **3a** afforded **4aa** in 99% yield and 82% *ee* determined by chiral HPLC (entry 1).[14] The influence of the catalyst structure on the reaction was then investigated by using the 3,5-$(CF_3)_2C_6H_3$-derived catalyst **3b** and the catalyst **3c**

Table 1. Reaction optimization.[a]

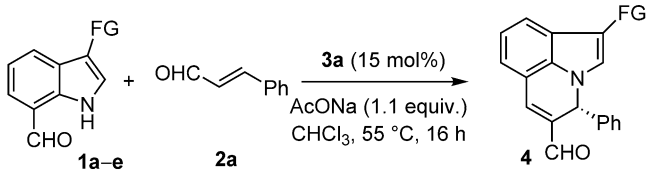


Entry	3	Solvent	Yield [%]	*ee* [%][b]
1	**3a**	$CHCl_3$	99	82
2	**3b**	$CHCl_3$	64	57
3	**3c**	$CHCl_3$	36	61
4[c]	**3a**	$CHCl_3$	98	30
5[d]	**3a**	$CHCl_3$	99	37
6	**3a**	MeCN	100	45
7	**3a**	toluene	82	26
8	**3a**	1,2-DCE	93	78

[a] Reactions were performed on a 0.3 mmol scale using 1 equiv. of **1a**, 1.5 equiv. of **2a**, 15 mol% of **3** and 1.1 equiv. of AcONa at 55 °C for 16 h unless otherwise noted.
[b] Enantiomeric excesses were determined by chiral HPLC.
[c] In this case, no AcONa was added to the reaction mixture.
[d] In this case, the reaction mixture was conducted at room temperature for 64 h.

possessing a bulkier silyl group (e.g., TBS) which could improve the stability and lifetime of the catalyst (entries 2 and 3).[11g] Both catalysts **3b** and **3c** resulted in a significant decrease of yields and enantioselectivities. The reaction carried out without sodium acetate gave rise to **4aa** in 98% yield with a dramatic decrease of the enantioselectivity (entry 4). A similar trend was observed by employing the reaction conditions at room temperature for 64 h. A brief solvent screening indicated that acetonitrile, toluene and 1,2-dichloroethane are suitable solvents for the transformation even if the best enantiomeric excess was obtained for chloroform (entries 1, 6–8). The decrease of the enantioselectivity for the reaction performed at room temperature for 64 h (*ee* = 37%, entry 5 *vs.* *ee* = 82%, entry 1) prompted us to study the configurational stability of **4aa** over time. A racemization of the chiral center (11% loss of *ee*) was observed after storage for 6 days at −5 °C. The racemization was even faster (40% loss of *ee*) by storing the compound **4aa** at room temperature as an isopropyl alcohol solution. Therefore, the use of indole **1a** was precluded as the resulting product **4aa** racemized upon storage. In light of these observations, we assumed that the trifluoroacetyl group could play a key role in the racemization process by increasing the acidity of the proton borne

Table 2. Influence of the functional group.[a]

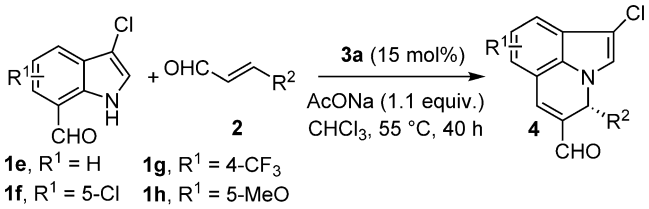


Entry	FG	4	Yield [%]	*ee* [%][b]
1	-$COCF_3$ (**1a**)	**4aa**	99	82
2	-CHO (**1b**)	**4ba**	76	78
3	-H (**1c**)	**4ca**	n.r.	n.d.
4[c]	-Br (**1d**)	**4da**	42	87
5	-Cl (**1e**)	**4ea**	49	91
6[c]	-Cl (**1e**)	**4ea**	87	92

[a] Reactions were performed on a 0.3 mmol scale using 1 equiv. of **1a–e**, 1.5 equiv. of **2a**, 15 mol% of **3a** and 1.1 equiv. of AcONa at 55 °C for 16 h in chloroform unless otherwise noted. n.r. = no reaction. n.d. = not determined.
[b] Enantiomeric excesses were determined by chiral HPLC.
[c] Reaction time was 40 h.

by the chiral center. As a result, the influence of the functional group at C-3 position was investigated (Table 2).[15] The introduction of a formyl group at C-3 position gave similar results to those obtained with the trifluoroacetyl group. The product **4ba** was produced in 76% yield and 78% *ee* (entry 2). It is worthwhile noting that no reaction occurred starting from 1*H*-indole-7-carbaldehyde under our reaction conditions (entry 3). We then turned our attention to halogen substituents because they are weakly electron-withdrawing due to inductive effects and the corresponding products **4da** and **4ea** could undergo cross-coupling reactions for further transformations (entries 4–6). While a dramatic decrease of reactivity was observed with **1d** (FG = Br, 40 h reaction time), the introduction of a chloro substituent gave rise to **4ea** in 49% yield and 91% *ee* after 16 h of reaction (entry 5). Extending the reaction time to 40 h increased the yield of **4ea** to 87% while maintaining a high enantioselectivity (*ee* = 92%). Regardless of the storage conditions, no racemization of **4ea** was observed, thus demonstrating the influence of the C-3 substituent on the racemization process. With the optimized conditions in hand (Table 2, entry 6), the scope and limitations with respect to the nature of R^1 and R^2 were assessed (Table 3). Initially, changes to the R^2 group on the α,β-unsaturated aldehydes **2** were investigated (**2a–k**). Regardless of the nature of R^2, good-to-excellent yields of the desired 1,7-annulated indoles **4** were obtained. The reaction with α,β-unsaturated aldehydes **2b–d** bearing a methoxy group on the aromatic ring gave the corresponding products in yields ranging from 62% to 84% with enantioselectivities slightly lower than the result obtained with *trans*-cinnamaldehyde (entries 1–4). The compound **4ee** was obtained in 87% yield and 72% *ee* (entry 5). Similar results were obtained for the compound **4ef** while an increase of both the yield and the enantioselectivity was observed starting from aldehydic compound **2g** (entries 6 and 7). The nitro substituent was well tolerated, leading to the compounds **4eh** and **4ei** in 76% yield, 81% *ee* and 71% yield, 84% *ee*, respectively (entries 8 and 9). A decrease of enantiomeric excess compared to the results obtained with *trans*-cinnamaldehyde was observed on reacting **1e** and **2j** (entry 10). The α,β-unsaturated aldehyde **2k** was amenable to the aza-Michael/cascade cyclization sequence by providing the compound **4ek** in 99% yield and 82% *ee* (entry 11). Unfortunately, no reaction took place between the indole **1e** and crotonaldehyde. Variations to the indole scaffold were next investigated (entries 12–14). The indoles **4fa** and **4ga** were produced in excellent yields and good enantioselectivities (entries 12 and 13). The reaction of **1h** with *trans*-cinnamaldehyde **2a** gave rise to **4ha** in 80% yield and 80% *ee* (entry 14). Based on the above results and literature reports, a plausible catalytic cycle is shown in Scheme 2.[2a–c]

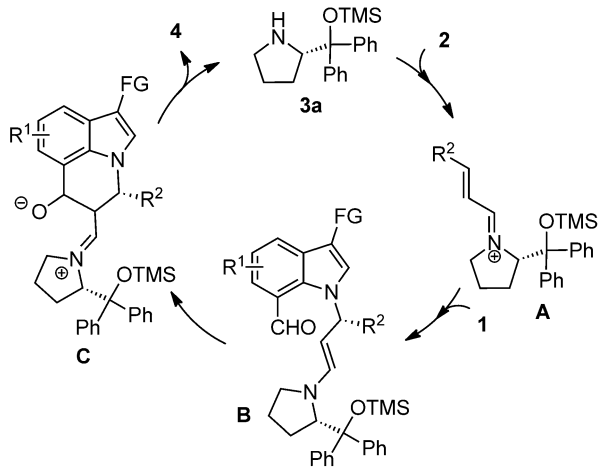
Table 3. Scope and limitations.[a]



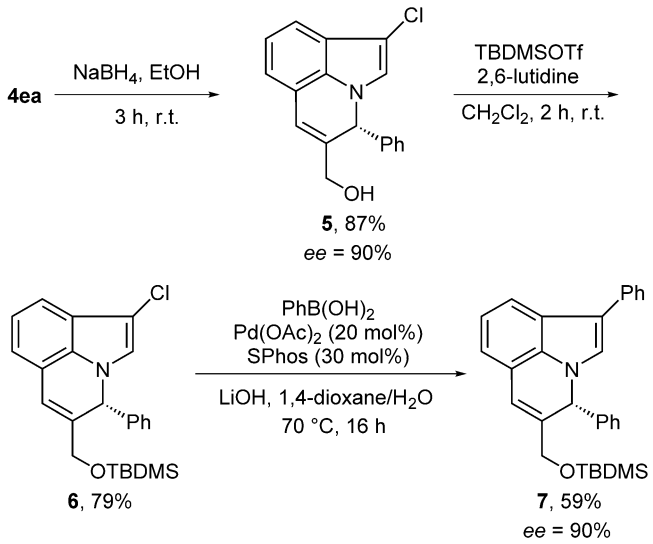
Entry	1	R^2	4	Yield [%]	*ee* [%][b]
1	**1e**	Ph (**2a**)	**4ea**	87	92
2	**1e**	4-$MeOC_6H_4$ (**2b**)	**4eb**	62	79
3	**1e**	3-$MeOC_6H_4$ (**2c**)	**4ec**	83	87
4	**1e**	2-$MeOC_6H_4$ (**2d**)	**4ed**	84	84
5	**1e**	4-MeC_6H_4 (**2e**)	**4ee**	87	72
6	**1e**	4-ClC_6H_4 (**2f**)	**4ef**	88	73
7	**1e**	3-ClC_6H_4 (**2g**)	**4eg**	95	88
8	**1e**	4-$NO_2C_6H_4$ (**2h**)	**4eh**	76	81
9	**1e**	2-$NO_2C_6H_4$ (**2i**)	**4ei**	71	84
10	**1e**	2-naphthyl (**2j**)	**4ej**	90	62
11	**1e**	2-thienyl (**2k**)	**4ek**	99	82
12	**1f**	Ph (**2a**)	**4fa**	95	82
13	**1g**	Ph (**2a**)	**4ga**	79	79
14	**1h**	Ph (**2a**)	**4ha**	80	80

[a] Reactions were performed on 0.3 mmol scale using 1 equiv. of **1**, 1.5 equiv. of **2**, 15 mol% of **3a** and 1.1 equiv. of AcONa at 55 °C for 40 h in chloroform.
[b] Enantiomeric excesses were determined by chiral HPLC.

The catalytic cycle would start by the formation of the iminium **A**. The attack of the indole **1** to the less hindered face of the iminium **A** would afford the en-



Scheme 2. Proposed catalytic cycle.



Scheme 3. Synthetic transformations.

amine intermediate **B** which would form **C** *via* an intramolecular aldol reaction. The hydrolysis of **C** to release the catalyst **3a** followed by a dehydration reaction would give rise to the desired target **4**.

An interesting feature is the fluorescence of the 1,7-annulated indoles **4** as shown with the absorption and fluorescence spectra of **4ea** (Figure 2).[16] The compound **4ea** presents a maximum of absorption at 400 nm and the fluorescence spectrum recorded at this wavelength exhibits a maximum at 500 nm. However, the alcohol **5** prepared by reduction of the aldehyde function of **4ea** had no fluorescent properties, demonstrating the importance of the enal moiety in the fluorescence process.

In addition to providing a tricyclic key structure motif, the compounds **4** contain a useful set of functional groups. In particular, the chloro substituent at the C-3 position is prone to cross-coupling reactions of the Suzuki–Miyaura type as exemplified in the Scheme 3.[17] The sequence started from **4ea** by the reduction of the aldehydic function in the presence of $NaBH_4$ in ethanol. Under these conditions, the alcohol **5** was obtained in 87% yield with a slight racemization of the chiral center (92% *ee* to 90% *ee*). Protection of the alcohol furnished the product **6** in 79% yield which underwent a cross-coupling reaction in the presence of $PhB(OH)_2$ and the catalytic system $Pd(OAc)_2$/SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl). This allowed the formation of **7** in 59% yield.

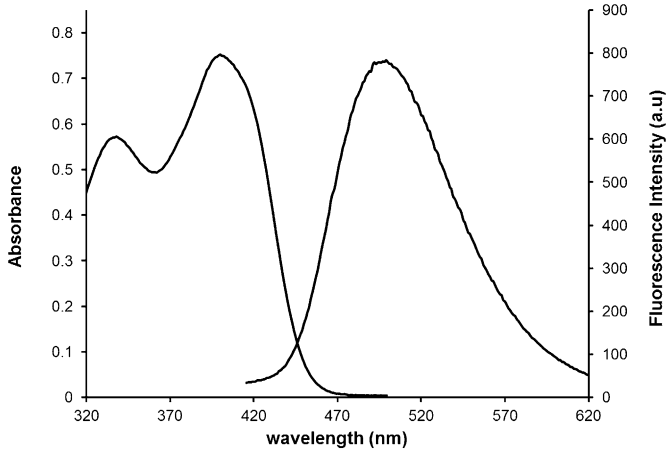


Figure 2. Absorption and fluorescence spectra of **4ea** in $CHCl_3$ (1×10^{-5} M).

In conclusion, we have described the implementation of an unprecedented strategy for the enantioselective synthesis of 1,7-annulated indoles which are key motifs found in biologically relevant compounds. This represents the first synthesis of enantioenriched 1,7-annulated indoles through an aminocatalyzed N-alkylation/cyclization cascade. Optimization studies performed on a range of C-3-functionalized indole-7-carbaldehydes revealed the influence of the C-3 functional group on the reaction outcome and the configurational stability of the products. Starting from 3-chloro-1*H*-indole-7-carbaldehyde derivatives and α,β-unsaturated aldehydes, a series of 1,7-ring fused indoles was prepared in yields ranging from 62% to 99% with good enantioselectivities (62–92%). In addition, the indole-containing target compounds which exhibit fluorescence properties include various functionalities which can undergo synthetic transformations.

Experimental Section

General Experimental Procedure of Table 3

Indole **1** (0.31 mmol, 1 equiv.), α,β-unsaturated aldehyde **2** (0.47 mmol, 1.5 equiv.), catalyst **3a** (15.1 mg, 0.047 mmol, 0.15 equiv.), AcONa (27.8 mg, 0.34 mmol, 1.1 equiv.) and

$CHCl_3$ (1.5 mL) filtered over alumina were introduced in a capped flask. The mixture was stirred for 40 h at 55 °C. The solvent was removed under reduced pressure. The crude compound was purified by column chromatography on silica gel.

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