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Asymmetric Organocatalytic N-Alkylation of Indole-2-carbaldehydes with α,β-Unsaturated Aldehydes: One-Pot Synthesis of Chiral Pyrrolo[1,2-*a*]indole-2-carbaldehydes

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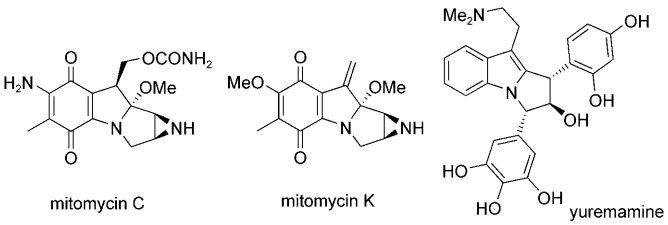
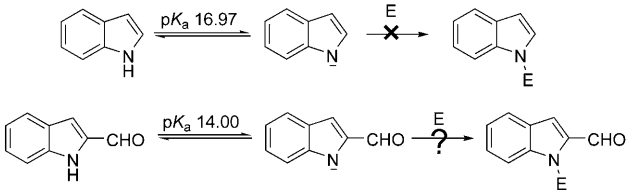
The pyrrolo[1,2-*a*]indole tricyclic ring structures are widely presented in a number of naturally occurring products and have attracted much attention due to the broad scope of their biological activities.[1] Representative examples are mitomycins,[1b] some of the most effective antitumor agents, and yuremamine,[1f] a new phytoindole recently isolated from the stem bark of *Mimosa hostilis*, which shows hallucinogenic and psychoactive effects. In addition to being an important motif in many biologically and pharmaceutically interesting compounds, they are also useful intermediates for the synthesis of polyheterocycles.[2] Although several approaches for the synthesis of this system have been explored, they usually require several steps and expensive reagents.[3] Thus, the exploration of novel, concise methodologies that allow the rapid establishment of these polycyclic indole skeletons in a single operation is highly desired.[4]



On the other hand, modifications of the indole structure mainly focus on enantioselective alkylation at the C3-position,[5] probably because of the privileged C3-chemoselectivity of indole compounds. Recently, the enantioselective synthesis of C2-substituted indoles has also been realized through the asymmetric alkylation of 4,7-dihydroindoles and subsequent oxidation.[6] In sharp contrast, the enantioselective N-alkylation of indoles has rarely been explored, probably due to the reduced nucleophilicity of the N–H functionality of indoles.[7]

As noted above, the use of indoles in direct catalytic asymmetric N-alkylation is challenging because the N–H proton of indoles, which must be removed to generate the nucleophile, has a relatively high pK_a value of 16.97 (Scheme 1).[8b] Direct organocatalytic methods based on amine



Scheme 1. N-Alkylation of indole or indole-2-carbaldehyde.

catalysis have a functional pK_a barrier for nucleophile activation that lies between the pK_a values of 16 and 17.[9] Based on this concept, we sought to activate the removal of the N–H proton by introducing an electron-withdrawing substituent at the C2-position; this may reduce the pK_a value of the N–H proton. We attempted to introduce an aldehydic group because the indole-2-carbaldehyde has a reduced pK_a value of 14.00,[8c] making it a candidate nucleophile in catalytic direct asymmetric N-alkylation, and furthermore, the aldehydic group allows many further transformations (Scheme 1).

As part of our continuing interest in asymmetric organocatalysis,[6g–h,10] we envisaged indole-2-carbaldehydes **1** and

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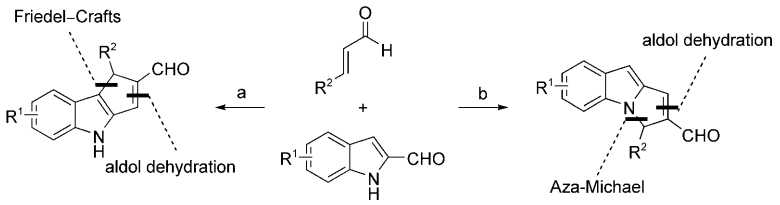
α,β-unsaturated aldehydes **2** as potential substrates for a cascade reaction made up of a Michael addition and an aldol reaction.[12] In planning our investigation of the reaction, the question arose as to whether the reaction of an indole-2-carbaldehyde with an α,β-unsaturated aldehyde leads to the classical Friedel–Crafts/aldol/dehydration products (Scheme 2, path a) or whether, after the aza-Michael addition, an intramolecular aldol reaction would occur, leading to pyrrolo[1,2-*a*]indole-2-carbaldehydes (Scheme 2, path b).



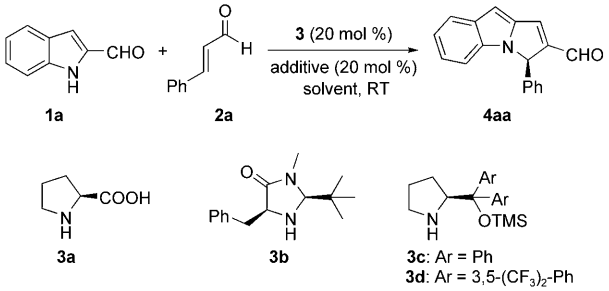
Scheme 2. Proposed C3- or N-selective alkylation of indole-2-carbaldehydes with α,β-unsaturated aldehydes.

To test our hypothesis, our experiments began with the addition of indole-2-carbaldehyde (**1a**) to cinnamaldehyde (**2a**) by the readily available diphenylprolinol TMS ether **3c** (TMS = trimethylsilyl). Indeed, the initial experiments showed that the use of catalytic amounts of a secondary amine enabled a reaction that resulted in the formation of the pyrrolo[1,2-*a*]indole-2-carbaldehyde **4aa**. On the basis of these observations, we decided to develop an asymmetric version of this domino reaction. Next, chiral pyrrolidines **3a–d** were screened for promoting the cascade reactions because they can activate α,β-unsaturated aldehydes by the formation of active iminium species.[13] The results showed that the catalysts probed exhibited significantly different catalytic activity toward the process. Poor catalytic activities were observed for L-proline (**3a**) and the MacMillan catalyst, **3b**[14] (Table 1, entries 1 and 2). Fortunately, the diphenylprolinol ether **3c** catalyzed the reaction efficiently to afford **4aa** in moderate yield and promising enantiomeric excess (*ee*) (Table 1, entry 3). To our surprise, catalyst **3d**, a general catalyst for the Michael addition of α,β-unsaturated aldehydes, was not active in this reaction (Table 1, entry 4). To optimize the reaction conditions further, the additives and solvents were varied. We found that the use of 4 Å molecular sieves (MS) as an additive and toluene as the solvent gave the best results (Table 1, entry 11). Experiments run at 0 °C showed similar results to those conducted at room temperature; however, a longer reaction time was required (Table 1, entry 16).

Having established optimal reaction conditions, we next examined the scope and limitations of this methodology with regard to the α,β-unsaturated aldehyde and indole-2-carbaldehyde substrates. The results showed that, in general, the reactions took place efficiently in moderate to good yields with good to excellent levels of enantioselectivity (Table 2). Aromatic α,β-unsaturated aldehydes, regardless of electron-donating or -withdrawing substituents on the phenyl ring or the substitution pattern, participated in this process in high efficiency (Table 2, entries 1–9). Unfortunately, when 2-furyl enal (**2j**) was used, the major product was the isomeric product **5aj** (Table 2, entry 10 and Scheme 3a).[15] For less reactive alkyl α,β-unsaturated aldehydes, the reaction showed much lower reactivity. This phenomenon was observed in the asymmetric N-allylic alkylation of indoles with Morita–Baylis–Hillman carbonates.[7c] The indole-2-carbaldehydes with electron-donating or -withdrawing substituents at the C5-position underwent the reaction with good yields and stereocontrol (Table 2, entries 11–13). Remarkably, nearly enantiomerically pure compounds can be readily obtained by a single recrystallization (Table 2, entries 1 and 9).

Furthermore, we found that all pyrrolo[1,2-*a*]indole-2-carbaldehyde derivatives **4** were stable in the air at room temperature. However, conversion of compound **4aa** into the tautomeric form **5aa** took place spontaneously and was complete within 24 h in a solution in $CDCl_3$ at room temper-

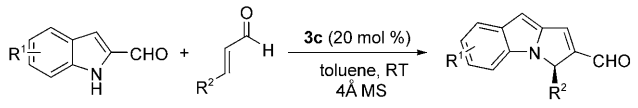
Table 1. Catalyst screening and reaction optimization.[a]



Entry	Catalyst	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	**3a**	THF	none	<10	n.d.[d]
2	**3b**	THF	none	<10	n.d.[d]
3	**3c**	THF	none	47	83
4	**3d**	THF	none	<10	n.d.[d]
5	**3c**	THF	$PhCO_2H$	38	84
6	**3c**	THF	CH_3CO_2H	40	76
7	**3c**	THF	CF_3CO_2H	<10	n.d.[d]
8	**3c**	THF	Et_3N	48	66
9	**3c**	THF	CH_3CO_2Na	45	83
10	**3c**	THF	4 Å MS[e]	62	83
11	**3c**	toluene	4 Å MS[e]	67	92
12	**3c**	$CHCl_3$	4 Å MS[e]	81	53
13	**3c**	CH_2Cl_2	4 Å MS[e]	77	42
14	**3c**	ether	4 Å MS[e]	43	35
15	**3c**	MTBE	4 Å MS[e]	71	60
16[f]	**3c**	toluene	4 Å MS[e]	58	93

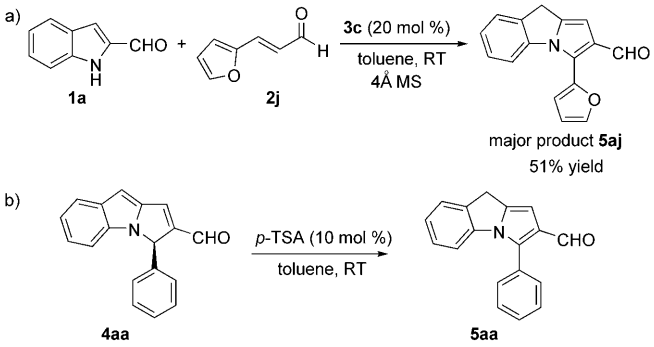
[a] Unless otherwise specified, the reaction was carried out with **1a** (0.24 mmol) and **2a** (0.20 mmol) in the presence of an organocatalyst **3** (0.04 mmol), additive (0.04 mmol), and solvent (1.0 mL) for 72 h. [b] Yield of the isolated product. [c] Determined by chiral HPLC on a Chiralpak AD column. [d] Not determined. [e] 4 Å MS (100 mg) were used. [f] The reaction was performed at 0 °C for 120 h. MTBE = methyl *tert*-butyl ether.

Table 2. Scope of domino aza-Michael/aldol reaction.[a]



Entry	**1**, R^1	**2**, R^2	Product	Yield [%][b]	*ee* [%][c]
1	**1a**, H	**2a**, Ph	**4aa**	67	92 (>99)[d]
2	**1a**, H	**2b**, 2-MeOPh	**4ab**	61	88
3	**1a**, H	**2c**, 2-FPh	**4ac**	75	90
4	**1a**, H	**2d**, 2-ClPh	**4ad**	70	96
5	**1a**, H	**2e**, 3-MeOPh	**4ae**	66	86
6	**1a**, H	**2f**, 4-MeOPh	**4af**	63	81
7	**1a**, H	**2g**, 4-FPh	**4ag**	81	90
8	**1a**, H	**2h**, 4-ClPh	**4ah**	75	90
9	**1a**, H	**2i**, 4-BrPh	**4ai**	74	91 (>99)[d]
10	**1a**, H	**2j**, 2-furyl	**4aj**	trace	71
11	**1b**, 5-MeO	**2a**, Ph	**4ba**	71	89
12	**1c**, 5-F	**2a**, Ph	**4ca**	84	83
13	**1d**, 5-Cl	**2a**, Ph	**4da**	57	86

[a] Unless otherwise specified, the reactions were carried out with **2** (0.20 mmol) and **1** (1.2 equiv) in toluene at room temperature for 72 h in the presence of **3c** (20 mol %) and 4 Å MS (100 mg). [b] Yield of the isolated product. [c] For analysis of the *ee* values of the products, see the Supporting Information. [d] After a single recrystallization.



Scheme 3. Synthesis of 9*H*-pyrrolo[1,2-*a*]indole-2-carbaldehydes **5**.

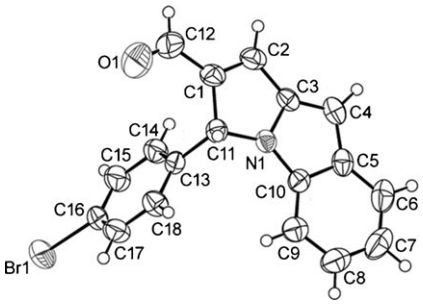
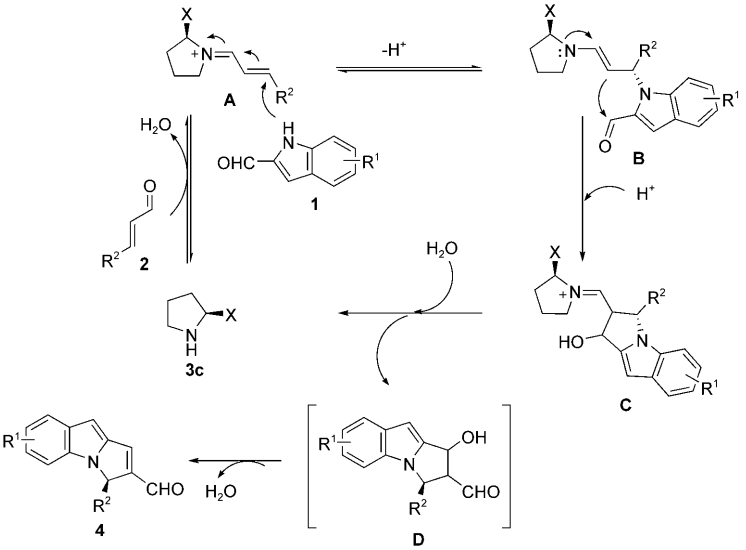


Figure 1. X-ray structure of (*R*)-**4ai**. Thermal ellipsoids are given at the 20 % probability level.



Scheme 4. Iminium/enamine activation: a proposed catalytic cycle for the asymmetric cascade aza-Michael/aldol reaction.

ature in the NMR tube.[3b,6c] The same result was obtained by stirring a solution of **4aa** in toluene for 1 h in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA; Scheme 3b).

Finally, the absolute configuration of the products was determined by X-ray analysis. Suitable crystals of compound **4ai** that enabled assignment of the absolute configuration were obtained and single-crystal analysis revealed the configuration to be *R* (Figure 1).[16]

With regard to the reaction mechanism, we assume that the diphenylprolinol ether **3c** forms the intermediate iminium ion **A** (Scheme 4) from reaction with the α,β-unsaturated aldehyde **2**.[17] The efficient shielding of the *Si* face of the chiral iminium intermediate by the bulky aryl groups results in a stereoselective *Re*-facial nucleophilic conjugate attack on the β-carbon by the indole-2-carbaldehyde **1**, resulting in a chiral enamine intermediate **B** (Scheme 4). Next, the activated enamine undergoes an intramolecular aldol reaction. Hydrolysis then releases the intermediate **D** (Scheme 4) from the catalytic cycle and the catalyst **3c** is regenerated. Finally, the elimination of water results in the formation of product **4**.

In summary, we have developed a highly useful method for the construction of pyrrolo[1,2-*a*]indole-2-carbaldehydes through a cascade aza-Michael/aldol reaction of indole-2-carbaldehydes with α,β-unsaturated aldehydes. This method provides easy access to pyrrolo[1,2-*a*]indole-2-carbaldehydes, which are generally difficult to access synthetically and can be used in the future synthesis of natural products, in a single operation with moderate to excellent enantioselectivities. The notable features of the process include 1) the use of easily accessible building blocks; 2) the cheapness of the reagents involved; 3) the capability to obtain optically active pyrrolo[1,2-*a*]indole tricyclic ring structures in a single step that are otherwise difficult to prepare by asymmetric catalysis; and 4) the generation of chiral products possessing different substituents and containing a synthetically useful aldehyde functionality, which is susceptible to further transformations. Further applications of the current methodology are ongoing in our laboratory.

Experimental Section

General procedure: Indole-2-carbaldehyde **1a** (0.24 mmol) was added to a solution of α,β-unsaturated aldehyde **2a** (0.20 mmol) in the presence of catalyst **3c** (20 mol%) and 4 Å MS (100 mg) in toluene (1.0 mL) and the resulting solution was stirred for 72 h at room temperature. The reaction mixture was directly purified by silica gel chromatography without work up and fractions were collected and concentrated in vacuo to provide the pure desired product **4aa**.

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Keywords: aldehydes · alkylation · domino reactions · indoles · organocatalysis

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