Asymmetric Catalysis

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Asymmetric Alkaloid Synthesis: A One-Pot Organocatalytic Reaction to Quinolizidine Derivatives**

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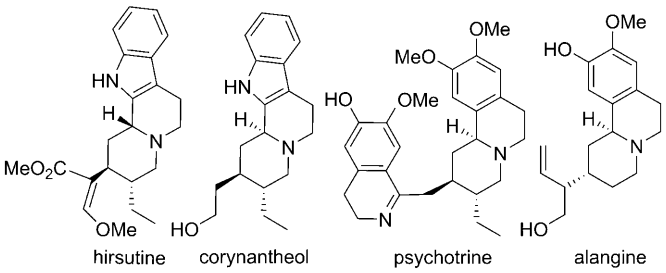
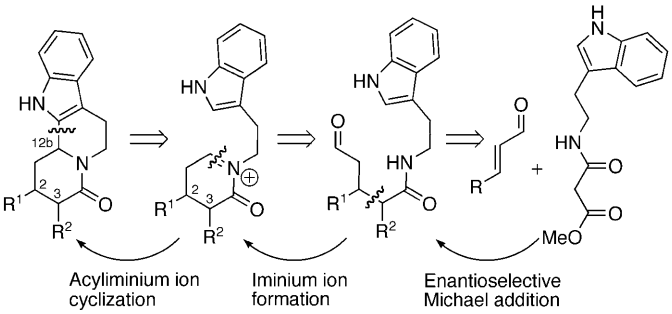
The quinolizidine skeleton is found in a large number of naturally occurring compounds and these alkaloids, together with non-natural derivatives thereof, have attracted much interest among both chemists and biologists because they are challenging synthetic targets and have diverse biological activity .[1]



Although several asymmetric methods for the construction of optically active quinolizidine derivatives have been developed, these strategies are in general target specific, multistep syntheses relying on starting material from the chiral pool.[2,3] In contrast to syntheses based on molecules from the chiral pool, only a few strategies that relay on asymmetric catalysis have been described.[4,5] The development of new stereoselective, efficient, and short routes to this class of compound would therefore open up new opportunities for natural product synthesis and medicinal chemistry.[6]

To devise such a method a retrosynthetic analysis of indolo[2,3*a*]quinolizidine skeleton was carried out, taking in account the selective formation of the three stereocenters indicated (C2, C3, and C12b; Scheme 1). It was anticipated that the stereocenter at C2 could be introduced in the first step through an enantioselective, organocatalytic conjugate addition.[7,8] The selective formation of the C2 center would control the formation of the two remaining stereocenters. The stereochemically labile stereocenter at C3 should adopt the



Scheme 1. Retrosynthetic analysis of the indolo[2,3*a*]quinolizidine skeleton.

thermodynamically stable *trans* configuration in the cyclic structure, and the stereocenter at C12b can be formed through a diastereoselective cyclization of the *N*-acyliminium ion.[9,10] Recently, highly efficient protocols for enantioselective secondary-amine-catalyzed conjugate addition of malonates, β-ketoesters, and enamides to α,β-unsaturated aldehydes[11] and ketones[12] have been developed. However, to the best of our knowledge, the asymmetric organocatalytic enol addition of activated amides to α,β-unsaturated aldehyde has not been previously reported. Herein we report the enantioselective organocatalytic C–C bond-forming reaction of activated amides and α,β-unsaturated aldehydes with the purpose of developing a fast and selective approach to give optically active indolo[2,3*a*]quinolizidine and benzo[*a*]quinolizidine derivatives.

The organocatalytic conjugate addition, for cinnamic aldehyde **1** and the indol substituted amide **2a** using the proline derivative (*S*)-**A** as the catalyst, was initially studied in different solvents (Table 1). After full conversion of amide **2a** (determined by ^{1}H NMR spectroscopy), excess trifluoroacetic acid (TFA) was added to the reaction mixture and after an additional 30 minutes, compounds **3a** and **4a** were isolated as a diastereomeric mixture. The screening of different solvents showed that the reaction performed best in CH_2Cl_2, and gave full conversion of amide **2a** within 2 days at room temperature (Table 1, compare entry 1 to entries 4–7). Although the conversion varied substantially, the enantioselectivity was more or less independent of the solvent. However, the enantioselectivity could be increased from 88% to 94% by lowering the reaction temperature to 3°C (Table 1, entry 2). If the temperature was further decreased to −20°C, less then 5% conversion was observed after 2 days (Table 1, entry 3). A series of catalysts was screened and evaluated with respect to the *ee* value and the conversion. The analogue, catalyst (*S*)-**B**, was less active and less selective for this reaction and required prolonged reaction time at an elevated temperature

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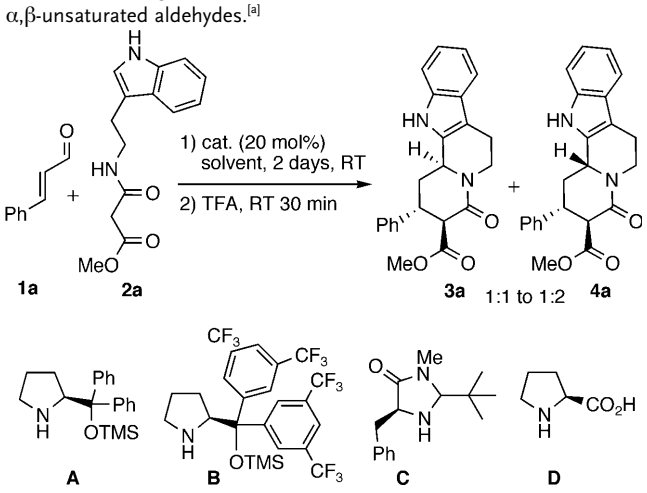
Table 1: Screening of the reaction conditions for the amide addition to α,β-unsaturated aldehydes.[a]



Entry	Cat.	Solvent	*T* [°C]	Conv. [%][b]	*ee* [%][d]
1	**A**	CH_2Cl_2	RT	full (57)	88
2	**A**	CH_2Cl_2	3	full (63)	94
3	**A**	CH_2Cl_2	−20	<5	–
4	**A**	CH_3CN	RT	33	92
5	**A**	toluene	RT	65	89
6	**A**	Et_2O	RT	–	–
7	**A**	DMF	RT	44	88
8[d]	**B**	CH_2Cl_2	39	45	54
9	**C**	CH_2Cl_2	RT	0	–
10	**D**	CH_2Cl_2	RT	0	–

[a] A solution of cinnamic aldehyde **1a** (1.5 equiv), amide **2a** (1 equiv) and catalyst (20 mol%) was stirred at the given temperature in the solvent (0.9 mM). After 2 days, TFA (10 equiv) was added to the reaction mixture and the products were isolated after 30 minutes. [b] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture before the addition of TFA. The value within the parentheses indicate the yield of the product upon isolation. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction time of 4 days. DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl.

(Table 1, entry 8). The imidazolidinone **C** and proline **D** were inactive as catalysts for this reaction, and only the starting materials were isolated (Table 1, entries 9 and 10).

After establishing the best reaction conditions for the conjugate addition, the acid-catalyzed cyclization of the acyliminium ion was investigated. When a catalytic amount of TFA (20 mol%) was added to the reaction mixture after full conversion of the amide **2a**, a non-selective reaction occurred to give **3a** and **4a** in a 1:1 ratio (Table 2, entry 1). However, when catalytic amounts of HCl were used some selectivity for **3a** over **4a** was observed, and cooling the reaction mixture prior to the addition of HCl increased the selectivity up to 85:15 (Table 2, entries 2 and 3). Similar selectivity was also observed for boron trifluoride etherate (Table 2, entries 4 and 5).

With the optimized reaction conditions in hand, a series of aromatic α,β-unsaturated aldehydes were employed in the one-pot, two-step reaction (Table 3). Good to excellent enantioselectivity were obtained for all the annulation products **3**, ranging from 87% to 95% *ee*. The diastereoselectivity ranged from ranged from 83:17 up to 90:10 (Table 3, entries 1, 2, 4, and 5) with the exception of the 4-acetoxy-3-methoxyphenyl substituent (**1c**) where the selectivity dropped to 74:26 (Table 3, entry 3).[13]

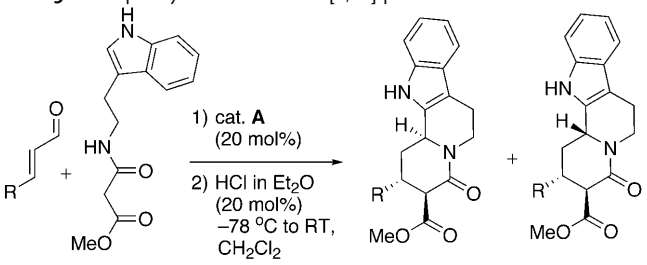
In the further development of this reaction, the 3-indolyl moiety of **2a** was replaced with an electron-rich phenyl group (3,4-dimethoxyphenyl) **2b**. The reaction of **2b** together with α,β-unsaturated aldehydes **1** in the presence of catalyst **A** and

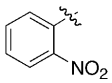
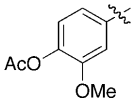
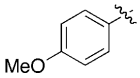
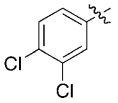
Table 2: Screening of acids for the formation of **3a** and **4a**.[a]

Entry	Acid	Equiv	*T* [°C]	**3a**/**4a**[b]
1	TFA	0.2	RT	50:50
2	HCl	0.2	RT	70:30
3	HCl	0.2	−78→RT	85:15
4	$BF_3{\cdot}OEt_2/MgSO_4$	0.4	RT	70:30
5	$BF_3{\cdot}OEt_2/MgSO_4$	0.2	−78→RT	83:17
6	amberlyst 15	–	−20	63:27

[a] A solution of cinnamic aldehyde **1a** (1.5 equiv), amide **2a** (1 equiv) and catalyst **A** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature for 2 days. After full conversion of **2a**, the given acid was added to the reaction mixture at the given temperature. [b] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

Table 3: One-pot synthesis of indolo[2,3*a*]quinolizidine.[a]

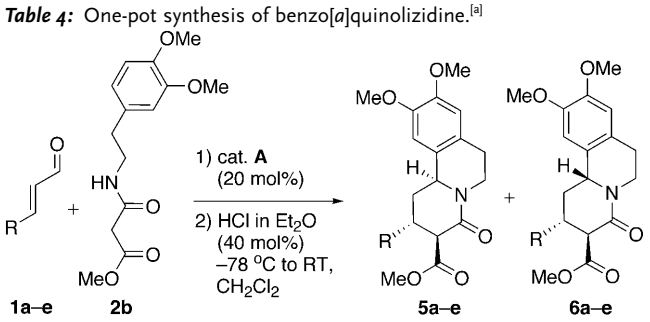


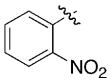
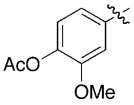
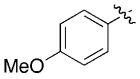
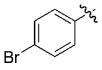
Entry	R		*t* [days]	*T* [°C]	Yield [%][b]	*ee* [%][c] of **3**	d.r.[d] of **3**/**4**
1		**1a**	3	3	69	94 (96)[e]	85:15
2		**1b**	5	RT	53	95	90:10
3		**1c**	2	RT	62	95	74:26
4		**1d**	1	3	71	87	83:17
5		**1e**	5	RT	56	89	83:17

[a] See the Supporting Information. [b] Total yield of **3** and **4**. [c] Determined by HPLC on a chiral stationary phase. [d] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [e] After single recrystallization from *i*PrOH.

subsequent addition of acid gave direct access to the benzo[*a*]quinolizidine skeleton with good to high enantioselectivity (Table 4). Although yields and enantioselectivities were compatible with the formation of indolo[2,3*a*]quinolizidine, the diastereoselectivity in the acid-catalyzed step was lower in all cases.[13] The formation of the benzo[*a*]quinolizidine required stronger acidic conditions (40 mol%) than for the indolo[2,3*a*]quinolizidine. This difference is believed to result from the poorer nucleophilicity of the phenyl ring compared to the 3-indolyl moiety.[14]

Table 4: One-pot synthesis of benzo[*a*]quinolizidine.[a]



Entry	R		*t* [days]	*T* [°C]	Yield [%][b]	*ee* [%][c] of **5**	d.r.[d] of **5**/**6**
1		**1a**	3	3	69	90	62:38
2		**1b**	5	RT	53	91	83:17
3		**1c**	2	RT	62	90	69:31
4		**1d**	1	3	71	89	76:24
5		**1f**	5	RT	56	98	72:28

[a] See the Supporting Information. [b] Total yield of **5** and **6**. [c] Determined by HPLC on a chiral stationary phase. [d] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

The annulation reactions of amides **2a**,**b** and α,β-unsaturated aldehydes **1** (Table 3 and 4) tolerate several functional groups in *ortho*, *m*eta, and *para* position on the aromatic ring of **1**. However, the reaction time was highly dependent on the electronic properties of the functional group. Electron-withdrawing groups increase the reaction time (Table 3, entries 2 and 5, and Table 4, entries 2 and 5) whereas electron-donating groups decrease the reaction time (Table 3, entries 3 and 4, and Table 4, entries 3 and 4). This observation is in accordance with the rate-determining step for the conjugate addition being the formation of the iminium ion and not the nucleophilic addition. Electron-donating groups on the phenyl ring of **1** will facilitate the elimination of water and therefore stabilize the cationic iminium ion intermediate.

The absolute configuration of the annulation products was established to be 2*R*,3*S*,11b*S* by single-crystal X-ray analysis of compound **5f** (Figure 1).[15]

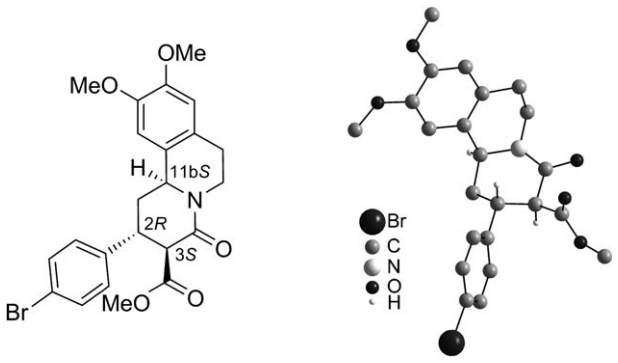
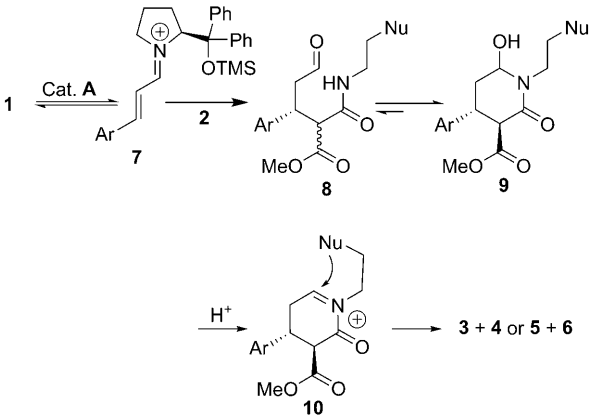


Figure 1. X-ray crystal structure of (2*R*,3*S*,11b*S*)-**5f**.

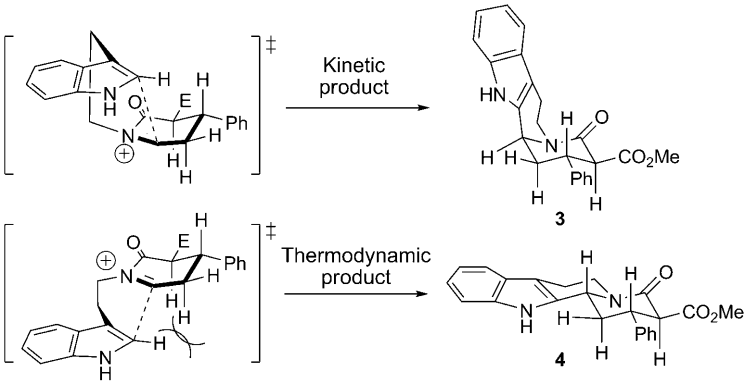
Thus, the *R* configuration at C2 is formed through efficient shielding of the *Re* face of the chiral iminium intermediate **7** by the aryl groups on catalyst **A**, thus leaving the *Si* face open for conjugate addition of amide **2** (Scheme 2). Next, intermediate **8** cyclizes spontaneously



Scheme 2. Proposed mechanism for the one-pot reaction (Nu = 3-indolyl or 3,4-dimethoxyphenyl).

under these reaction conditions to give hemiacetal **9**, then epimerization of the stereochemically labile stereocenter at C3 will establish the more thermodynamically stable 2*R*,3*S*-*trans* configuration. Treatment of **9** with catalytic amounts of acid will result in the formation of acyliminium ion **10**, which will undergo an electrophilic aromatic substitution with the aromatic moiety to give the quinolizidine products. The diastereoselectivity observed in the acid-catalyzed cyclization of the acyliminium ion is rationalized as being under kinetic control, as is exemplified by the formation indolo[2,3*a*]quinolizidine in Scheme 3.[16,17] Formation of **4** would give the thermodynamically more stable isomer owing to the equatorial orientation of the indol moiety. However, the formation of isomer **3** is rationalized as being faster under kinetic conditions (−78 °C) owing to less steric hindrance from the equatorial α proton in the transition state, as compared to the axial α proton in the transition state, which leads to isomer **4**.[18]

In summary, a short enantioselective one-pot, two-step synthesis to the indolo[2,3*a*]quinolizidine and the benzo[*a*]-



Scheme 3. Kinetic versus thermodynamic product formation in the cyclization of the acyliminium ion.

quinolizidine skeleton has been developed. The sequence, that involves an organocatalytic conjugate addition and subsequent acid-catalyzed cyclization of the acyliminium ion, gives direct access to the quinolizidine skeleton. The reaction sequence involves the formation of three new stereocenters with high to excellent enantioselectivity and moderate diastereoselectivity. Further investigation of the full scope and limitations of this one-pot reaction are under investigation and will be reported in due course.

Experimental Section

General Procedure for the one-pot synthesis of indolo-[2,3*a*]quinolizidine derivatives **3**: A solution of aldehyde **1** (0.42 mmol), catalyst **A** (18 mg, 0.05 mmol) and amide **2a** (80 mg, 0.28 mmol) in CH_2Cl_2 (0.3 mL) was stirred (see Tables for details). After full conversion of amide **2a** (determined by ^{1}H NMR spectroscopy), the reaction mixture was cooled to −78 °C and then HCl (50 μL, 0.05 mmol, 1 M in diethyl ether) was added. The mixture was stirred at −78 °C for 3 hours and slowly allowed to reach room temperature, and subsequently saturated aqueous $NaHCO_3$ (3 mL) and CH_2Cl_2 (3 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the crude product. The title compound was isolated as a single diastereoisomer after flash column chromatography (pentane/Et_2O).

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[13] The diastereomeric mixtures **3**/**4** and **5**/**6** could be separated by flash column chromatography (see the Supporting Information).
[14] When HCl (20 mol % in Et_2O) was used, only the corresponding hemiacetal **9** was isolated.
[15] CCDC 705562 (**5 f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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[18] The relative configuration of **3** and **4** was established by analysis of the ^3J couplings of the ^{1}H NMR spectra, see the Supporting Information.

