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General and Efficient Organocatalytic Synthesis of Indoloquinolizidines, Pyridoquinazolines and Quinazolinones through a One-Pot Domino Michael Addition-Cyclization-Pictet–Spengler or 1,2-Amine Addition Reaction

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Abstract: An asymmetric organocatalyzed reaction sequence involving a Michael addition of various 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes with subsequent diastereoselective Pictet–Spengler cyclization has been developed. The substrate scope was found to be general and optically active indoloquinolizidines were isolated as single diastereomers in high yields with high to excellent enantioselectivites. In addition to tryptamine, the reaction has also been successfully applied to other nucleophiles including *o*-aminobenzylamine and anthranilamide giving rise to pyridoquinauolines and quinazolinones.

Keywords: Brønsted acids; diarylprolinol ethers; Lewis base catalyis; Mannich reaction; multicomponent reaction

Introduction

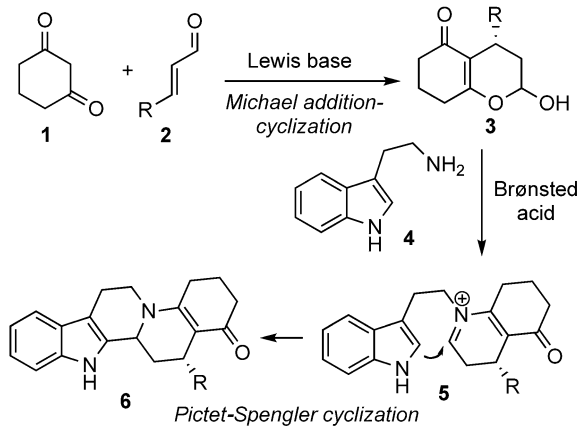
The indoloquinolizidine skeleton is a common structural motif, found in a wide range of naturally occurring indole alkaloids.[1,2] These compounds have attracted great attention due to their various biological and medicinal properties[3] and several methods are now available for the construction of their key structural unit. However, most of the developed methods involve multiple steps and are generally based on the chiral pool approach.[4] Recently, Franzén and coworkers reported an organocatalytic reaction cascade for the synthesis of quinolizidine derivatives.[5] The demand for the development of new and efficient methodologies for the synthesis of this class of compounds[6] led us to investigate an easy and useful asymmetric one-pot reaction sequence involving simple and readily available starting materials. Asymmetric cascade reactions have gained a lot of interest in recent years because of the notable advantages associated with them, including no need for time-consuming protection/deprotections steps or purification of the intermediates.[7,8]

We have previously reported a general and practical enantioselective organocatalytic addition-cyclization cascade of 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes.[9] In the presence of a catalytic amount of diarylprolinol ether as Lewis base, diketone **1** reacted with unsaturated aldehydes **2** to give chromenones **3**.[9c] We now report our full studies employing this strategy in the first fast and efficient synthesis of indoloquinolizidines, pyridoquinazolines and quinazolinones.

We envisioned that subsequent to the formation of chromenone **3**, a Brønsted acid-catalyzed reaction of the hemiacetal with tryptamine (**4**) generates the iminium ion **5**. This could then undergo a diastereoselective Pictet–Spengler cyclization[10–12] to provide the indoloquinolizidines **6** which are typically more difficult to prepare by other methods (Scheme 1).

Results and Discussion

Our initial investigations were carried out with 1,3-cyclohexanedione (**1**) and 2-hexenal (**2c**) in the presence of catalytic amounts of TMS-protected prolinols **7a**/

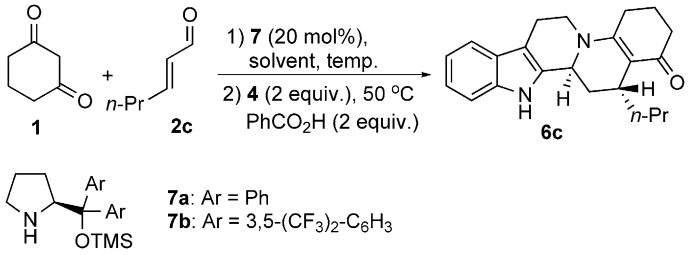


Scheme 1. Reaction of cyclic 1,3-diketone **1** with unsaturated aldehydes **2** and tryptamine **4**.

7b. A series of optimization studies were conducted and the results are summarized in Table 1. The hemiacetal intermediate formed after the first step was reacted in the same pot with 2 equivalents of tryptamine (**4**) and 2 equivalents of benzoic acid. A clean reaction was observed and only one diastereomer of the desired product was formed. The product **6c** was isolated in 73% yield with 94% enantiomeric excess (Table 1, entry 1). In an attempt to improve the enantioselectivity, other solvents were evaluated in the sequence by applying the same conditions for the second step (Pictet–Spengler cyclization). Apart from chloroform (entry 5), all other solvents afforded the product with lower enantioselectivity (Table 1, entries 2–4). Whereas no noticeable impact on the enantioselectivity was observed, an increase in the rate of the reaction was noted when changing the temperature from −20 °C to 0 °C (Table 1, entry 6). With 10 mol% of catalyst **7b**, high enantioselectivity was achieved when the reaction was performed at 0 °C in dichloromethane (DCM) (Table 1, entry 10). The product was isolated in 67% yield with 96% *ee*. The yield and the enantioselectivity were slightly improved when using 2 equivalents of acetic acid instead of benzoic acid (Table 1, entry 11 *vs.* 10).

With the optimized conditions for the reaction of 1,3-cyclohexanedione (**1**) with 2-hexenal (**2c**) in hand, we decided to explore the scope of this organocatalyzed reaction by employing a wide range of aliphatic, aromatic and heteroaromatic α,β-unsaturated aldehydes. As depicted in Table 2, the enantioselectivity gradually increased with increasing the chain length of the substituent on the aldehyde. Accordingly, the selectivities for the methyl-, ethyl- and propyl-substituted derivatives were 93, 95 and 97%, respectively (Table 1, entries 1–3). The enantioselectivity further increased with increasing branching of the substituent (*i*-Pr *vs.* *n*-Pr). In this case (R = *i*-Pr, Table 2, entry 4),

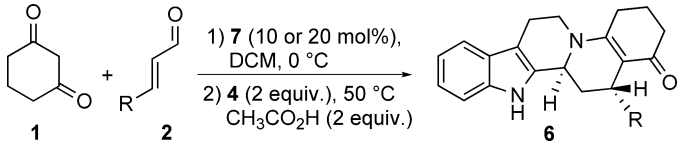
Table 1. Evaluation of solvents and catalysts in the Lewis Base-Brønsted acid catalyzed reaction sequence.[a]



Entry	Catalyst	Solvent	Temperature [°C]	Yield[b] [%]	*ee*[c] [%]
1	**7a**	DCM	−20	73	94
2	**7a**	toluene	−20	–	92
3	**7a**	DCE	−20	–	89
4	**7a**	CH_3CN	−20	–	87
5	**7a**	$CHCl_3$	−20	–	94
6	**7a**	DCM	0	62	94
7[d]	**7a**	DCM	0	71	94
8[d]	**7b**	DCM	0	75	96
9	**7b**	toluene	0	74	94
10	**7b**[e]	DCM	0	67	96
11[d]	**7b**[e]	DCM	0	79	97

[a] *General conditions:* 1) 0.2 mmol **1**, 1.5 equiv. **2c**, 20 mol% **7** in 1 mL solvent at the indicated temperature; 2) 0.4 mmol **4** and 0.4 mmol $PhCO_2H$.
[b] Yield after column chromatography.
[c] Determined by chiral HPLC analysis.
[d] Acetic acid was used.
[e] 10 mol% of catalyst was used.

Table 2. Scope of different α,β-unsaturated aldehydes in the sequential reaction.[a]



1 2 6

Entry	Catalyst	Mol [%]	6	R	Yield[b] [%]	*ee*[c] [%]
1	**7b**	10	**6a**	Me	68	93
2	**7b**	10	**6b**	Et	82	95
3	**7b**	10	**6c**	*n*-Pr	79	97
4	**7b**	10	**6d**	*i*-Pr	84	>99
5	**7b**	10	**6e**	*n*-heptyl	85	95
6[d]	**7b**	10	**6f**	*o*-Br-C_6H_4	76	92
7[d]	**7a**	20	**6f**	*o*-Br-C_6H_4	84	98
8[d]	**7a**	20	**6g**	*o*-Cl-C_6H_4	73	96
9[d]	**7a**	20	**6h**	*p*-Br-C_6H_4	81	90
10[d]	**7a**	20	**6i**	*p*-(Me_2N)-C_6H_4	82	90
11[d]	**7a**	20	**6j**	*p*-MeO-C_6H_4	83	86
12[d]	**7a**	20	**6k**	2-furyl	76	85

[a] *General conditions:* 1) 0.2 mmol **1**, 1.5 equiv. **2**, catalyst **7** in 1 mL of DCM; 2) 0.4 mmol **4** and 0.4 mmol acetic acid in 1 mL of DCM.
[b] Yield after column chromatography.
[c] Determined by chiral HPLC analysis.
[d] Product was isolated after the first step.

an excellent selectivity of >99% was achieved and the product was isolated in 84% yield.

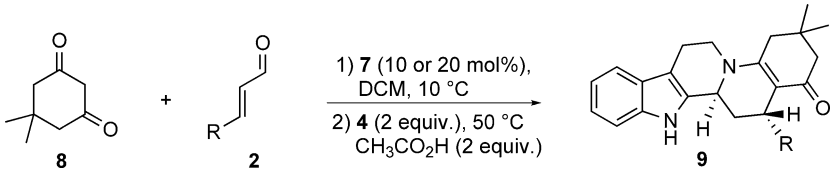
When using *o*-bromocinnamaldehyde under the optimized conditions, the product **6f** was isolated in 76% yield with 92% *ee* (Table 2, entry 6). To our delight, we found that use of 20 mol% of catalyst **7a** has a beneficial effect on both rate and selectivity, the product being isolated in 84% yield with an improved *ee* of 98% (Table 2, entry 7). Other substituted cinnamaldehydes were also employed and the products **6g–j** were isolated in good yields with high enantioselectivities (Table 2, entries 8–11). However, in the case of aromatic and heteroaromatic substituted aldehydes, purification of the products after the first step was crucial in order to obtain good yields for the final products **6f–k**. A simple filtration was enough to purify the compound for the second step. In general, electron-donating groups on the aromatic ring gave the products with slightly reduced enantioselectivities (Table 2, entries 10 and 11). Using 2-furylacrolein as aldehyde gave the final key assembly in 76% yield with 85% *ee* (Table 2, entry 12).

To further enhance the applicability of this enantioselective organocatalyzed addition-cyclization reaction, we tested another cyclic 1,3-dicarbonyl compound and our results are shown in Table 3. Dimedone **8** proved to be an excellent substrate for this reaction sequence and gave the desired products in high yields and excellent selectivities. Due to the low solubility of dimedone in DCM at 0°C, the reactions required longer times and yields were unsatisfactory. However, increasing the reaction temperature from 0°C to 10°C improved the yields and shortened the reaction time without a substantial decrease in enantioselectivity. Dimedone reacted with aliphatic substituted aldehydes **2a–e** in the same manner 1,3-cyclohexanedione and provided the corresponding products **9a–e** with good enantioselectivities (Table 3, entries 1–5). Aromatic aldehydes resulted in products with higher ee's when using 20 mol% of less sterically hindered catalyst **7a** instead of 10 mol% of catalyst **7b** (Table 3, entries 6 and 7).[13] Heteroaromatic substituted aldehydes were also found to be good substrates for the reaction (Table 3, entry 8).

The absolute configuration of the indoloquinolizidines was determined by the X-ray analysis of **6f** (Figure 1). The product has a 1,3-*anti* relationship between the C-12b and C-14 protons and the configuration at these positions was assigned as *S* and *R* respectively. The high diastereoselectivity occurring in the Pictet–Spengler cyclization is most likely due to steric repulsion taking place between the incoming indole nucleophile and the axial proton of C-13.

Pyridoquinazolines and quinazolinones are important synthetic intermediates for the preparation of biologically active compounds. The generality of this three-component reaction together with the importance of nitrogen-containing heterocycles stimulated us to investigate other binucleophiles in the second part of this sequence. For this purpose, the hemiacetal formed by the reaction of 1,3-cyclohexanedione (**1**) and 4-methylpentenal (**2d**) in the presence of 10

Table 3. Scope of different α,β-unsaturated aldehydes in the reaction with dimedone and tryptamine.[a]



8 2 9

Entry	Catalyst	Mol [%]	9	R	Yield[b] [%]	*ee*[c] [%]
1	**7b**	10	**9a**	Me	72	91
2	**7b**	10	**9b**	Et	79	98
3	**7b**	10	**9c**	*n*-Pr	81	93
4	**7b**	10	**9d**	*i*-Pr	85	98
5	**7b**	10	**9e**	*n*-heptyl	83	94
6	**7a**[d]	20	**9f**	*o*-Br-C_6H_4[d]	64	94 (90)[e]
7	**7a**[d]	20	**9j**	*p*-MeO-C_6H_4	81	78 (76)[e]
8	**7a**[d]	20	**9k**	2-furyl	78	90

[a] *General conditions:* 1) 0.2 mmol of dimedone, 1.5 equiv. **2**, catalyst **7** in 1 mL of DCM; 2) 0.4 mmol **4** and 0.4 mmol acetic acid in 1 mL of DCM.
[b] Yield after column chromatography.
[c] Determined by chiral HPLC analysis.
[d] Product was isolated after the first step.
[e] Number in brackets refers to the enantiomeric excess of the reaction conducted with 10 mol% of catalyst **7b**.

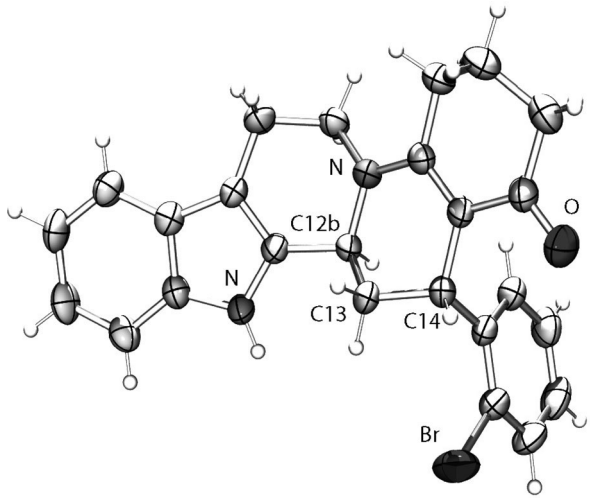


Figure 1. Crystal structure of **6f**.[14]

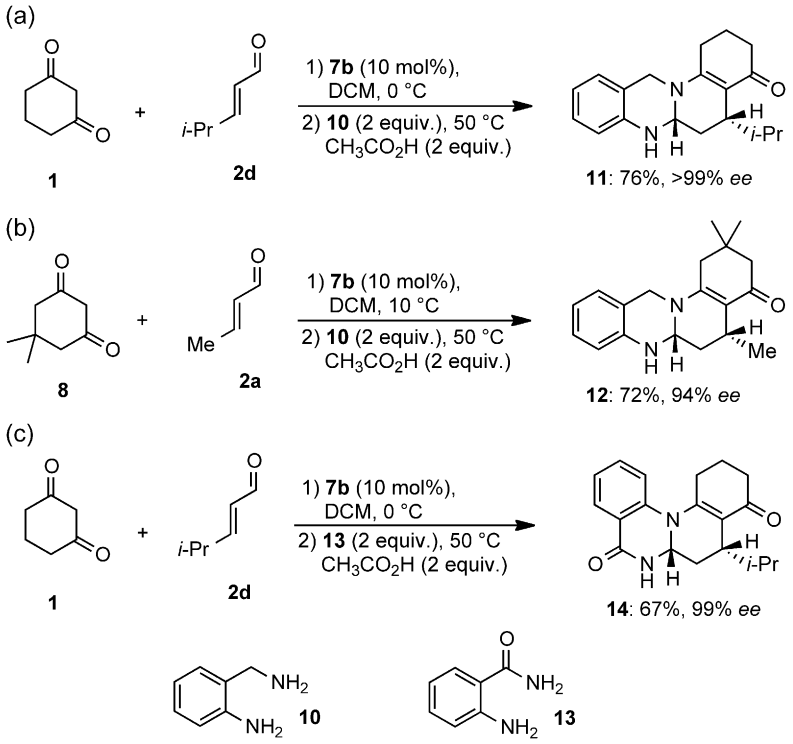
mol% **7b** was treated with *o*-aminobenzylamine **10** and 2 equivalents of acetic acid. The reaction proceeded smoothly and the hemiacetal selectively reacted with the primary benzylamine moiety. Ring closure *via* a diasteroselective aza-Mannich reaction provided compound **11** in 76% yield with >99% *ee* [Scheme 2 (a)]. Under the previously optimized conditions, the same sequence has been applied to dimedone **8** to get the analogue **12** in 72% yield with 94% *ee* [Scheme 2 (b)].

Using *o*-aminobenzamide **13** as nucleophile gave an interesting pyridoquinazolinone **14** as product. We were pleased to find that only one regioisomer was formed during the reaction. In contrast to *o*-aminobenzylamine **10**, anthranilamide **13** reacted with the aromatic nitrogen with the hemiacetal and the ring was closed by the nitrogen of the amide group. The product was isolated in 67% yield with an excellent *ee* of 99% [Scheme 2 (c)]. These reactions not only provide the first enantioselective access to this class of heterocycles but show that in principle all types of amine containing bis-nucleophiles can be employed in this reaction.

The regioselectivity and the configuration of the cyclization product **14** were determined from the single-crystal X-ray analysis (Figure 2). Unlike the case of indoloquinalizidones, the protons at C-6a and C-8 are on the same side showing that the product arises from the thermodynamic control rather than the kinetic control. Product **14** was thermodynamically more stable because of the equatorial orientation of the amide nitrogen.

Conclusions

In summary, we have developed a new efficient and general enantioselective multicomponent addition-cyclization sequence using simple and commercially available starting materials such as cyclic 1,3-dicarbonyl compounds, unsaturated aldehydes and tryptamine. A sophisticated indoloquinolzidine moiety was prepared in a one-pot two-step procedure which involves the creation of four new bonds and two chiral centers. A range of aliphatic, aromatic and heteroaromatic aldehydes was tolerated in the cyclization,



Scheme 2. Sequential reaction of 1,3-diketones, unsaturated aldehydes and aminobenzylamine (a), (b) or anthranilamide (c).

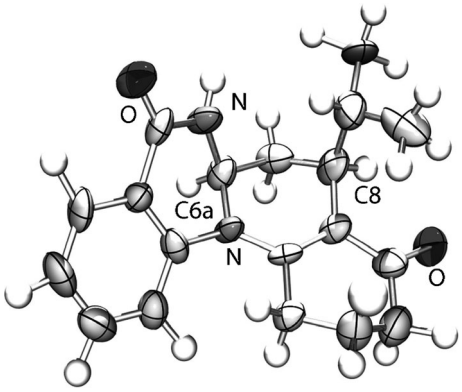


Figure 2. Crystal structure of **14**.[14]

yielding products in high yields with excellent enantioselectivity. The high diastereoselectivity for the Pictet-Spengler cyclization further increases the value of this sequential reaction process. Furthermore, we were for the first time able to extend this methodology to amine containing bis-nucleophiles which allowed fast access to valuable pyridoquinazolines and quinazolinones in a highly enantioselective manner. The method presented opens up a new perspective regarding the exploitation of sequential reactions to synthesize various heterocycles as principally all kinds of nitrogen containing bis-nucleophiles can be employed in this reaction sequence.

Experimental Section

General Experimental Procedure

In a screw-cap tube were placed 26 μL (1.5 equiv., 0.3 mmol) of crotonaldehyde **2a** and 12 mg (0.1 equiv., 0.02 mmol) of the catalyst **7b** in 1.0 mL of dry DCM and the contents were stirred at 0 °C for 10 min. 24 mg (1.0 equiv., 0.2 mmol) of 1,3-cyclohexanedione **1** were added to the reaction and stirring was continued until the complete disappearance of the diketone. The reaction mixture was allowed to warm to room temperature and diluted with 1 mL of DCM. 64 mg (2 equiv., 0.4 mmol) of tryptamine and 20 μL (2 equiv., 0.4 mmol) of acetic acid were added to the tube and heated at 50 °C for overnight. The crude reaction mixture was directly loaded for the column chromatography on silica gel to get the product **6a**; yield: 42 mg (0.14 mmol, 68%).

14-Methyl-3,4,6,7,12,12b,13,14-octahydroindolo-[2′,3′:3,4]pyrido[1,2-*a*]quinolin-1(2*H*)-one (6a): IR (film): $\nu = 3826, 3188, 2963, 2925, 2867, 1578, 1524, 1441, 1359, 1302, 1251, 1184, 1109, 1036, 952, 819, 742\ cm^{-1}$; ^1H NMR (600 MHz, CD_2Cl_2): $\delta = 1.09$ (d, $J = 6.9$ Hz, 3H), 1.65 (td, $J = 12.7$, 4.9 Hz, 1H), 1.80–1.90 (m, 1H), 1.93–1.98 (m, 1H), 2.22–2.27 (m, 2H), 2.30 (ddd, $J = 13.0$, 4.1, 2.1 Hz, 1H), 2.48 −2.52 (m, 2H), 2.72 (ddd, $J = 5.3$, 3.8, 1.9 Hz, 1H), 2.79 (dddd, $J = 14.4$, 11.8, 4.7, 2.4 Hz, 1H), 3.09–3.03 (m, 1H), 3.17 (ddd, $J = 13.5$, 12.0, 3.8 Hz, 1H), 4.16 (dd, $J = 13.6$, 3.4 Hz, 1H), 4.66 (d, $J = 12.3$ Hz, 1H), 6.98 (t, $J = 7.4$ Hz, 1H), 7.04 (t, $J = 7.5$ Hz, 1H), 7.39 (d, $J = 7.8$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (150.9 MHz, CD_2Cl_2): $\delta = 20.37, 22.21, 22.29, 23.11, 27.38, 34.34, 35.87, 45.05, 50.12, 63.76, 107.99, 111.05, 111.42, 117.75, 119.17,$

121.43, 126.72, 134.40, 136.38, 159.09, 193.80; LC-MS (ESI): $m/z = 307.25$, calcd. for $C_{20}H_{23}N_2O$: 307.41; $[\alpha]_D$: −50.9 (*c* 2.7, $CHCl_3$, 93% *ee*); HPLC (AD-H column, *n*-hexane/2-propanol = 85/15, flow rate = 1 mL min^{-1}): major enantiomer: $t_R = 9.97$ min, minor enantiomer: $t_R = 13.26$ min.

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[14] The CCDC number for compound **6f** is CCDC 829655 and that for compound **14** is CCDC 829654. Copies of these supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

