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Diverse Asymmetric Quinolizidine Synthesis: A Stereodivergent One-Pot Approach

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Abstract: A diverse stereodivergent organocatalytic one-pot addition/cyclization/annulation sequence to optically active quinolizidine derivatives from easily available starting materials is presented. The one-pot sequence relies on a pyrrolidine-catalyzed enantioselective conjugate addition of electron-deficient amide α-carbons to α,β-unsaturated aldehydes, spontaneous hemiaminal formation and acid-catalyzed/mediated *N*-acyliminium ion cyclization to give the quinolizidine framework. Simple tuning of the reaction conditions in the *N*-acyliminuim ion cyclization step provides a diastereomeric switch, which gives access to both of the two bridgehead epimers through kinetic, thermodynamic or chelation control. The methodology display a broad substrate scope that is demonstrated by the stereoselective formation of indolo-, thieno-, benzofuro-, furo- and different benzoquinolizidine derivatives with high atom efficiency, up to >99% *ee* and up to >95:5 *dr*. Due to its efficiency, synthetic diversity and operational simplicity, this protocol has the potential to find important use as a key step in natural product synthesis, biochemistry and pharmaceutical science. The stereochemical outcome of the one-pot sequence was investigated, and the mechanism and origin of stereoselectivity of the different steps is discussed.

Keywords: *N*-acyliminuim ion cyclization; alkaloids; one-pot reaction; organocatalysis; quinolizidines; stereodivergent synthesis

Introduction

Over the last decades, the state of art in total synthesis has developed tremendously and today organic chemists can synthesize, in principle, any organic molecule no matter what its size or complexity.[1] However, as complexity and size increase, so does the number of chemical transformations required to assemble the desired molecule and each of these transformations usually involves tedious isolation and purification processes of synthetic intermediates. This makes the synthesis of complex molecules highly demanding with respect to resources and time. Furthermore, the loss of material in each transformation and purification step of a multi-step sequence dramatically decreases chemical efficiency, making larger scale synthesis on an industrial level almost impossible.[2] A solution to these problems is the recently increased interest for the development of asymmetric domino and one-pot reactions.[3] In these reactions, complex organic scaffolds are easily accessed from simple starting materials by combining two or more reaction steps, where at least one involves an asymmetric process, to take place in the same reaction vessel. This avoids time-consuming and costly processes, including the purification of intermediates and steps involving the protection and deprotection of functional groups. In addition to high efficiency, these processes are also environmentally friendly since the generation of chemical waste is reduced. In particular, organocatalytic reactions[4] have been found to be powerful participants to include in asymmetric one-pot and domino reactions.[5,6] This can mainly be accounted for by the robustness of the catalysts, insensitivity towards air and moisture and extensive functional group tolerance.

In an attempt to meet the challenge of efficient construction of complex organic molecules, we became interested in the development of novel strategies for the asymmetric synthesis of quinolizidine alkaloids. Although quinolizidine alkaloids are commonly found in nature and often show high biological

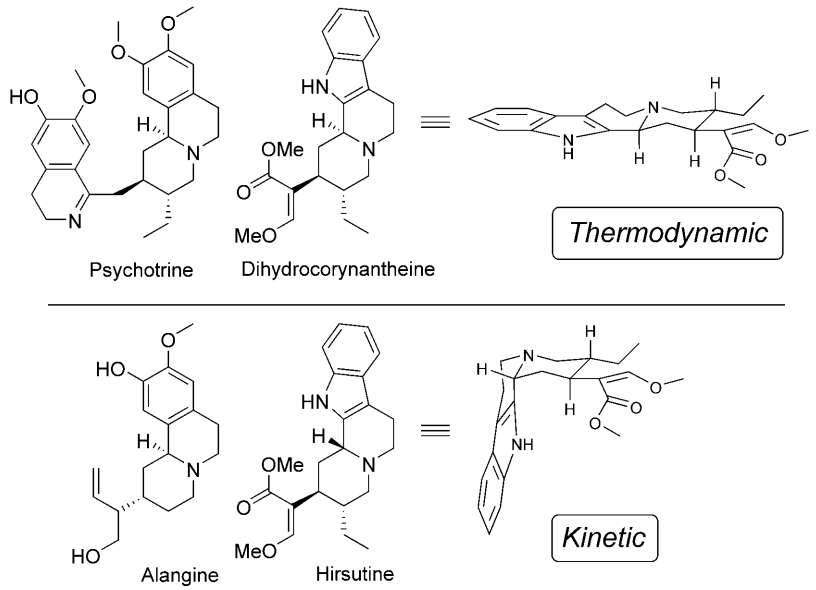


Figure 1. Representative quinolozidine alkaloids with "thermodynamic" and "kinetic" stereochemistry.

activity,[7] their enantioselective synthesis has been rather scarcely investigated and the strategies used are mainly *target-specific multistep synthesis* relying on starting material from the chiral pool.[8] Although, there are a few examples of target-specific strategies relying on asymmetric catalysis as one of the key steps,[9,10] efficient methodology based on asymmetric catalysis with *high synthetic diversity* of quiniolizidine derivatives have been scarcely reported.[11,12]

One of the key features to account for in the synthesis of quinolizidine frameworks is the configuration of the bridgehead carbon. This stereochemistry has a great impact on the conformation of the alkaloid that can be exemplified by the epimeric natural products dihydrocorynantheine and hirsutine (Figure 1).

Dihydrocorynantheine has a flat structure with all groups of the piperidine ring in equatorial positions. On the other hand, the epimer hirsutine has the indole moiety in an axial position giving this compound a V-shaped conformation that is very different in geometry compared to dihydrocorynantheine.[13] Furthermore, the axial indolo group will make hirsutine thermodynamically less stable compared to the all-equatorial epimer, dihydrocorynantheine. This means that special considerations have to be taken into account during the synthesis of the desired epimer.[8i]

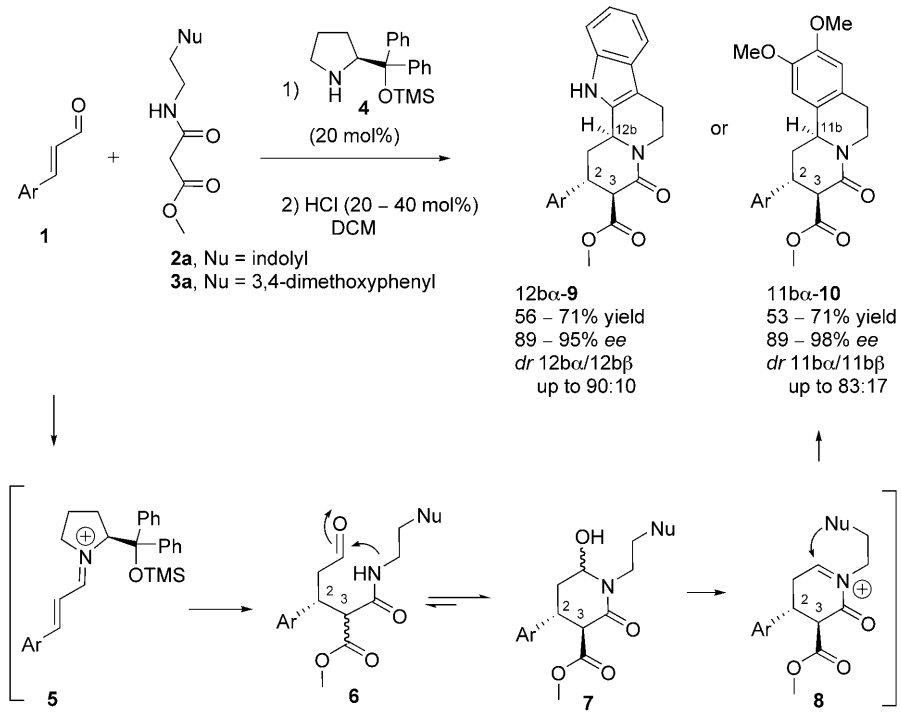
Recently in our group we developed an enantioselective one-pot reaction to the 12b**α**-indolo[2,3-*a*]quinolizidine **9** and the 11b**α**-benzo[*a*]quinolizidine **10** skeleton (Scheme 1).[14] The one-pot reaction sequence is based on a domino organocatalytic conjugate addition[15,16]/hemiaminal formation.[17] Acidification of the resulting reaction mixture initiates an intramolecular *N*-acyliminiumion cyclization[18,19] to give indolo[2,3-*a*]quinolizidines (**9**) and benzo[*a*]quinolizidines (**10**). The *N*-acyliminiumion cyclization was observed to be under kinetic control and gave the thermodynamically less stable epimers 12b**α**-**9** and 11b**α**-**10** as the major products.[20]

These quinolizidine derivatives can be regarded as stereochemical analogues to hirsutine and adapt the same V-shaped conformation (*cf.* Figure 1).

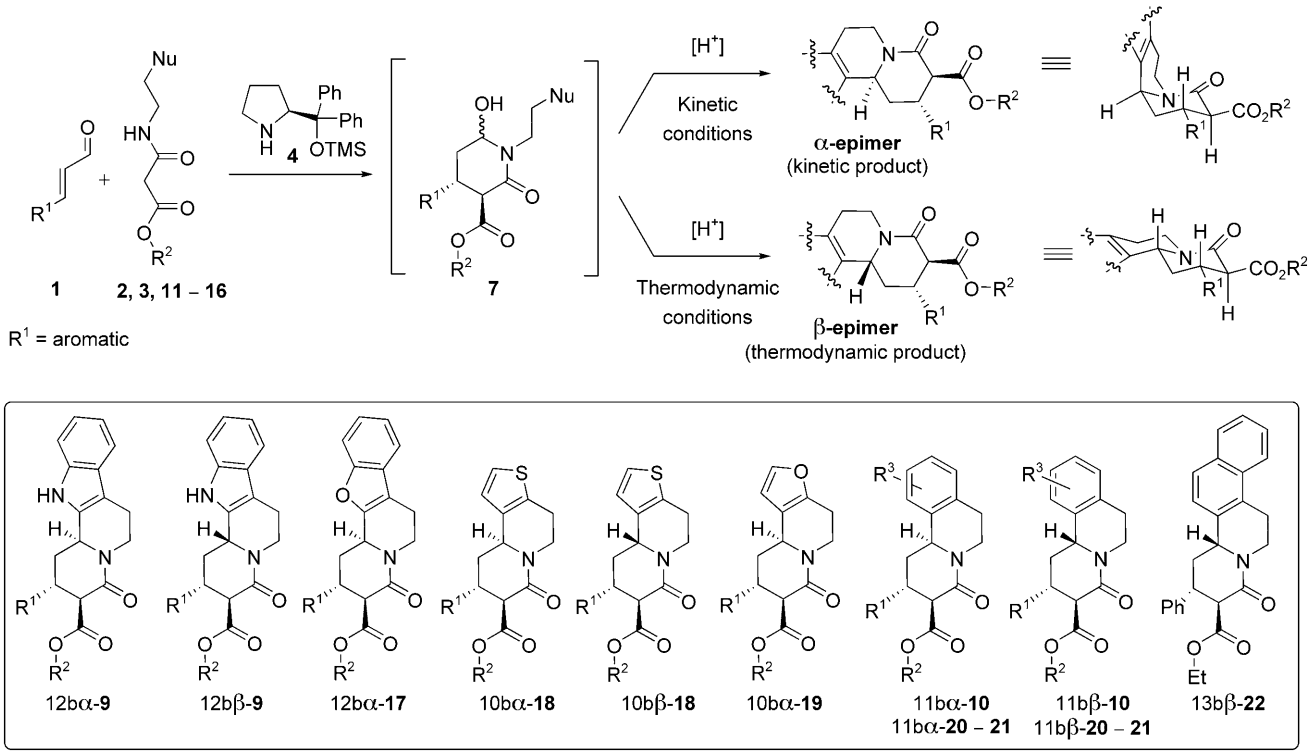
Taking into account the higher thermodynamic stability of the flat **β**-epimer compared to the V-shaped **α**-epimer and the fact that *N*-acyliminiumion cyclizations are under kinetic control, we envisioned that it could be possible to find *stereodivergent* one-pot reaction conditions that could selectively favor formation of either the **α**-epimer (kinetic reaction conditions) or the **β**-epimer (thermodynamic reaction conditions) (Scheme 2).

Such a *diastereomeric switch* will provide efficient protocols for the enantio- and diastereoselective synthesis of both the bridgehead epimers of the quinolizidine skeleton. Furthermore, we wanted to widen the scope of the one-pot sequence by using different aromatic and heteroatom aromatic groups on the amide. In this way, a wide variety of optically active quinolizidine derivatives can be easily accessed with high control of absolute and relative stereoselectivity.

Here we wish to present our result on the development of a *diverse*, *enantioselective* one-pot reaction with a *diastereomeric switch* that allows for the selective formation of both of the two bridgehead epimers of a vast number of quinolizidine derivatives from easily available starting materials. During the process



Scheme 1. Stereoselective one-pot reaction to 12b**α**-indolo[2,3-*a*]quinolizidines and 11b**α**-benzo[*a*]quinolizidines.



Scheme 2. A stereodivergent enantioselective one-pot cyclization/annulation.

we also disclose new findings and developments concerning the factors controlling reactivity and stereoselectivity in *N*-acyliminium ion cyclizations and organocatalytic conjugate additions.

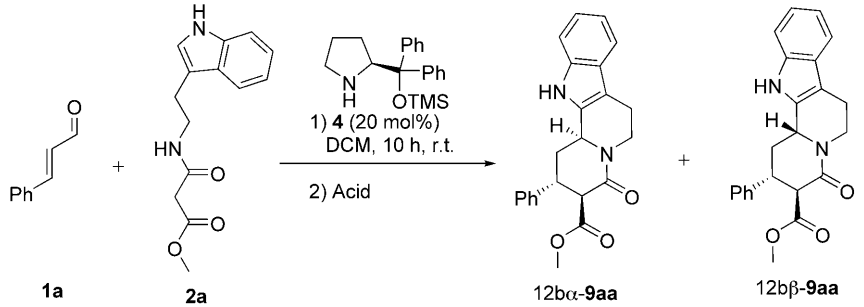
Results and Discussion

One-Pot Synthesis of Indolo[2,3-*a*]quinolizidine Derivatives

Recently, the asymmetric organocatalytic α-carbon addition of activated amides to α,β-unsaturated aldehydes was independently developed by our group[14] and Rios et al.[16g] In our study towards the one-pot reaction to quinolizidine derivatives, we found that conjugate addition of indole-substituted amide **2a** to cinnamaldehyde **1a** catalyzed by pyrrolidine derivative (*S*)-**4** preformed best in DCM at 3 °C to give the hemiaminal intermediate **7**. In the second step of the one-pot sequence, HCl (20 mol%) was added to the reaction mixture at low temperature to give the kinetically favored epimer 12bα-**9** (Table 1, entry 2). Although *N*-acyliminium cyclizations are known to occur under kinetic control[20] we observed that the diasterioselectivity is highly dependent on both the reaction temperature and the choice of acid. It was anticipated that the reaction conditions could be optimized in order to favor the thermodynamically more stable epimer 12bβ-**9**. When the previously established kinetic conditions (HCl, 20 mol%) were used at elevated temperature, a decrease in selectivity was observed for the epimer 12bα-**9**. The same trend was also observed for several acids, increasing temperature resulted in a decrease in selectivity. The first promising result was obtained using excess trifluoroacetic acid (TFA), which gave a 1:1 mixture of diastereoisomers at room temperature (Table 1, entry 4). Gratifyingly, when the reaction temperature was increased (refluxing TFA), high selectivity for the thermodynamic product was obtained (Table 1, entry 5). Prolonged reaction times resulted mainly in decomposition of the product; however, the diastereomeric ratio did not change (Table 1, entry 6). Interestingly, tin(IV) chloride also favored the thermodynamic product although with low selectivity (Table 1, entry 3).[21]

After having established methodology for the stereodivergent one-pot procedure, we wanted to investigate the effect of the ester moiety on the amide with respect to reactivity, enantio- and diastereoselectivity. A series of amides (**2a**–**d**) with different sterically demanding ester groups were tested and it was found that reactivity decreased with the steric bulk of the ester group. On the other hand, the enantioselectivity of the conjugate addition step increased substantially when going from methyl ester **2a** to ethyl ester **2b** (Table 2, entries 1 and 3). Further increases of steric bulk did not improve the enantioselectivity (Table 2, entries 5 and 7). The diastereoselectivity in the acid-catalyzed *N*-acyliminium ion cyclization was not affected when going from the methyl ester **2a** to the ethyl ester **2b** and good selectivity was obtained under both kinetic and thermodynamic reaction conditions to give 12bα-**9ab** and 12bβ-**9ab**, respectively, as the major epimers. (Table 2, entries 1–4). For the sterically more demanding *i*-Pr and *t*-Bu esters **2c**, **d** the selectivity decreased (Table 2, entries 5–7). The *t*-

Table 1. Screening of acids for the selective formation of 12bα-**9** and 12bβ-**9**.[a]



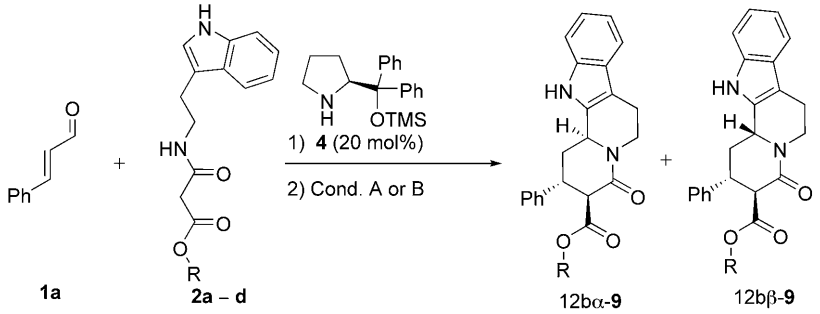
Entry	Acid	Equivalents	Temperature *T* [°C]	Time *t* [h]	*dr*[b]
1	HCl	0.2	r.t.	1	70:30
2	HCl	0.2	−78→r.t	O.N.	85:15
3	$SnCl_4$	1.2	r.t.	12	42:58
4	TFA	0.2	r.t.	1	50:50
5	TFA	0.1 M	70	2	18:82
6	TFA	0.1 M	70	18	trace (18:82)[c]

[a] A solution of cinnamaldehyde **1a** (1.2 equiv.), amide **2a** (1 equiv.) and catalyst **4** (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] 12bα-**9** and 12bβ-**9**, determined by ^1H NMR spectroscopy on the crude reaction mixture.

[c] Mainly decomposition of product/intermediate.

Table 2. Effect of ester group on enantioselectivity and diastereoselectivity.[a]



Entry	Amide	R	Time *t* [days]	Conditions	Product	*ee*[b]	*dr*[c]
1	**2a**	Me	1	A	12b**α-9aa**	88	85:15
2	**2a**	Me	1	B	12b**β-9aa**	–	18:82
3	**2b**	Et	1	A	12b**α-9ab**	93	82:18
4	**2b**	Et	1	B	12b**β-9ab**	–	19:81
5	**2c**	*i*-Pr	3	A	12b**α-9ac**	93	75:25
6	**2c**	*i*-Pr	3	B	12b**β-9ac**	–	22:78
7	**2d**	*t*-Bu	3	A	12b**α-9ad**	92	75:25
8	**2d**	*t*-Bu	3	B	–	–	–[d]

[a] A solution of cinnamaldehyde **1a** (1.2 equiv.), amide **2** (1 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature. After full conversion of **2**, acid was added to the reaction mixture according to conditions A or B. Conditions A: the reaction mixture was cold down to −78 °C and HCl (20 mol%, 1 M in Et_2O) was added. The mixture was stirred at −78 °C for 3 h and slowly allowed to reach room temperature overnight. Conditions B: to the reaction mixture was added TFA (0.5 mL mmol^{-1}) and the resulting mixture was heated at 70 °C in an open vessel for 5 min (to remove DCM) followed by further heating in a closed vessel for additional 1 h at 70 °C.

[b] Determined by chiral HPLC on the major diastereoisomer.

[c] 12b**α-9** and 12b**β-9**, determined by ^{1}H NMR on the crude reaction mixture.

[d] Decomposition.

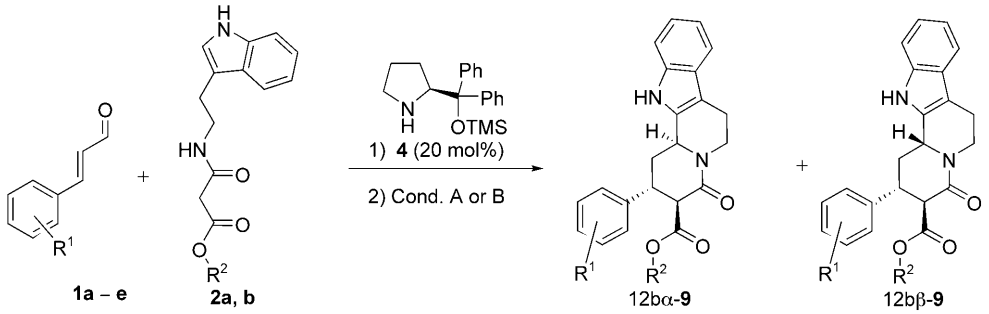
Bu ester derivative **2d** was not stable under the thermodynamic reaction conditions (reflux, TFA) and resulted in decomposition of the intermediate/product, most likely through cleaving of the *t*-Bu group and subsequent decarboxylation (Table 2, entry 8). Based on these results, the methyl and ethyl esters **2a**, **b** appeared to be the most promising substrates with respect to reactivity and selectivity.

Therefore, we decided to proceed with these two amides to investigate the substrate scope of the one-pot reaction. The reactions of cinnamaldehyde, *o/p*-nitrocinnamaldehyde and *p*-methoxycinnamaldehyde with both amides **2a**, **b** in the presence of catalyst **4** were studied. After full conversion of amide **2**, acid was added to the reaction mixture under kinetic (HCl, −78 °C→r.t.) and thermodynamic reaction conditions (TFA, reflux). The first observation we made was the pronounced difference in reaction rate between the different cinnamaldehydes, where electron-withdrawing groups tend to increase and electron-donating substituents tend to decrease the reaction time for the conjugate addition (Table 3, entries 1–14).

In general, the yields are all moderate to good, with a tendency to be somewhat higher for the kinetic reaction conditions than under the harsher thermodynamic reaction conditions. The reactions of cinnamaldehyde **1a** and *o/p*-nitrocinnamaldehydes **1b** and **1d** with both the methyl and ethyl esters **2a**, **b** were found to give similar results in terms of enantio- and diastereoselectivity and a series of both kinetic (12b**α-9**) and thermodynamic (12b**β-9**) products could be isolated in 93–96% *ee* with 78:22 to 90:10 *dr* (Table 3, entries 1–8 and 13, 14). Interestingly, for the pyrrolidine **4** catalyzed conjugate addition of amides **2a**, **b** to *p*-methoxycinnamaldehyde **1c**, the ester group turned out to be of crucial importance for the enantioselectivity of the reactions and after acidification under kinetic and thermodynamic conditions, the methyl ester derivatives 12b**α-9ca** and 12b**β-9ca** were isolated in 88–89% *ee*, whereas only one enantiomer could be detected for the corresponding ethyl esters 12b**α-9cb** and 12b**β-9cb** (Table 3, entries 9–12).

In contradiction to the cinnamaldehyde derivatives, 2-furylacrolein **1e** reacted much less selectively in the conjugate addition and gave only 50% enantiomeric excess with the methyl ester **2a** and 70% with the ethyl ester **2b**. Disappointingly, the reaction of 2-pentenal with amide **2a** in the presence of catalyst **4** resulted in decomposition of 2-pentenal and no hemiaminal intermediate could be observed.

Table 3. Stereoselective indolo[2,3-*a*]quinolizidine synthesis.[a]



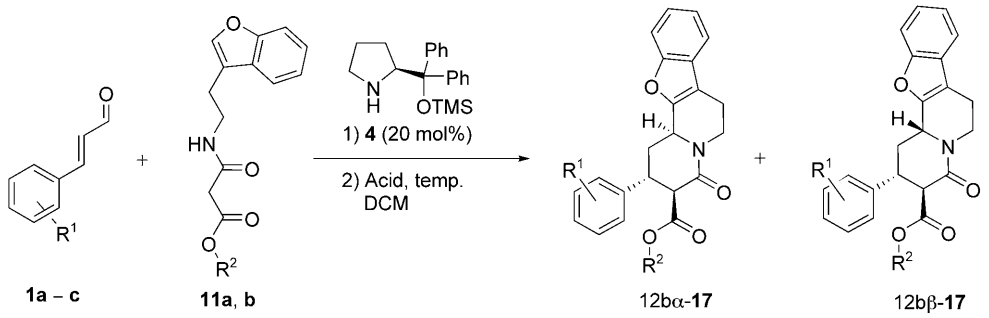
Entry		R^1	R^2	Time *t* [days]/Temperature *T* [°C]	Conditions	Product	Yield [%][b]	*ee*[c]	*dr*[d]
1	**1a**	H	Me	3/3	A	12bα-**9aa**	69	94	85:15
2	**1a**	H	Me	3/3	B	12bβ-**9aa**	64	94	18:82
3	**1a**	H	Et	4/3	A	12bα-**9ab**	53	95	82:18
4	**1a**	H	Et	4/3	B	12bβ-**9ab**	75	96	22:78
5	**1b**	*o*-NO_2	Me	5/r.t.	A	12bα-**9ba**	53	95	90:10
6	**1b**	*o*-NO_2	Me	5/r.t.	B	12bβ-**9ba**	36	94	17:83
7	**1b**	*o*-NO_2	Et	3/40	A	12bα-**9bb**	64	93	83:17
8	**1b**	*o*-NO_2	Et	3/40	B	12bβ-**9bb**	43	94	14:86
9	**1c**	*p*-MeO	Me	1/3	A	12bα-**9ca**	71	89	83:17
10	**1c**	*p*-MeO	Me	1/3	B	12bβ-**9ca**	38	88	18:82
11	**1c**	*p*-MeO	Et	3/r.t.	A	12bα-**9cb**	51	>99	91:9
12	**1c**	*p*-MeO	Et	3/r.t.	B	12bβ-**9cb**	71	>99	17:83
13	**1d**	*p*-NO_2	Me	3/40	A	12bα-**9da**	47	96	72:28
14	**1d**	*p*-NO_2	Et	5/40	A	12bα-**9db**	52	96	75:25
15	**1e**	Furyl	Me	3/r.t.	A	12bα-**9ea**	74	50	69:31[e]
16	**1e**	Furyl	Et	1/39	A	12bα-**9eb**	46	71	63:37
17	**1e**	Furyl	Et	1/39	B	12bβ-**9eb**	41	70	45:55

[a] For reaction conditions see Table 2 footnote[a].
[b] Total yield of 12bα-**9** and 12bβ-**9**.
[c] Determined by chiral HPLC on the major diastereoisomer.
[d] Determined by ^{1}H NMR on the crude reaction mixture.
[e] HCl (20 mol%, 1 M in Et_2O) was added at room termperature.

One-Pot Synthesis of Benzofuro[2,3-*a*]quinolizidine Derivatives

In contrast to the numerous reports on the synthesis and bioactivity of indolo[2,3-*a*]quinolizidine derivatives, very few examples are reported where the indole NH group has been substituted for oxygen to the analogous benzofuro[2,3-*a*]quinolizidines.[22] Furthermore, the benzofuran moiety has been rarely used as nucleophile in *N*-acyliminium ion cyclizations.[23] We therefore decided to investigate the compatibility of the benzofuran moiety in our one-pot cyclization/annulation reaction. Reaction of amide **11a** with cinnamaldehyde **1a** at 3 °C gave full conversion of amide **11a** in 3 days. The benzofuran moiety was expected to be less reactive in the second acyliminium cyclization and the kinetic reaction conditions (HCl 20 mol%, −78 °C→r.t) used for the 12bα-indolo[2,3-*a*]quinolizidine derivatives **9** gave no reaction. However, increasing the amount of HCl to 40 mol% gave full conversion to the kinetic 12bα-benzofuro[2,3-*a*]quinolizidine **17aa** in good diastereoselectivity (Table 4, entry 1). After further screening of acidic conditions we found that formic acid was the superior acid for the benzofuran moiety and the kinetic product 12bα-**17aa** could be isolated in excellent yield, diastereo- and enantioselectivity (Table 4, entry 5). Best selectivity was obtained from *o*-nitrocinnamaldehyde **1b** that gave the kinetic products 12bα-**17ba**, **bb** as the only observable diastereoisomers with excellent enantioselectivity. It is also interesting to point out that the methyl ester amide **11a** gave higher enantioselectivity than the ethyl ester amide **11b** for all cinnamaldehydes investigated (Table 4). Unfortunately, employing the thermodynamic reaction conditions (TFA, reflux) used for the synthesis 12bβ-indolo[2,3-*a*]quinolizidine derivatives **9** was not successful for the benzofuran derivatives and only the kinetic product 12bα-**17aa** was obtained in high *dr* (Table 4, entry 2). Several different Brøndsted

Table 4. Stereoselective benzofuro[2,3-*a*]quinolizidine synthesis.[a]



1a – c **11a, b** 12bα-**17** 12bβ-**17**

Entry	R^1	R^2	Time *t* [days]/Temperature *T* [°C]	Acid/*T* [°C]	Product	Yield [%][b]	*ee*[c]	*dr*[d]
1	H	Me	3/3	HCl/−78→r.t.	12bα-**17aa**	–	–	86:14
2	H	Me	3/3	TFA/70	12bα-**17aa**	–	–	84:16
3	H	Me	3/3	$SnCl_4$/r.t.	12bα-**17aa**	–	–	56:44
4	H	Me	3/3	$BF_3{\cdot}Et_2O$/−20	12bα-**17aa**	–	–	–[e]
5	H	Me	3/3	HCO_2H/r.t.	12bα-**17aa**	86	91	92:8
6	H	Et	3/r.t.	HCO_2H/r.t.	12bα-**17ab**	71	90	91:9
7	*o*-NO_2	Me	3/40	HCO_2H/r.t.	12bα-**17ba**	55	97	>95:5
8	*o*-NO_2	Et	3/40	HCO_2H/r.t.	12bα-**17bb**	57	92	>95:5
9	*p*-MeO	Me	4/3	HCO_2H/r.t.	12bα-**17ca**	87	96	93:7
10	*p*-MeO	Et	3/r.t.	HCO_2H/r.t.	12bα-**17cb**	70	86	90:10

[a] A solution of aldehyde **1** (1.2 equiv.), amide **11** (1 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature. After full conversion of **11**, formic acid (0.5 mL mmol^{-1}) was added and the resulting mixture was stirred at room temperature for 2 h.
[b] Total yield of 12bα-**17** and 12bβ-**17**.
[c] Determined by chiral HPLC on the major diastereoisomer.[d] 12bα-**17**/12bβ-**17**, determined by ^{1}H NMR on the crude reaction mixture.
[e] Decomposition of product/intermediate cinnamaldehyde.

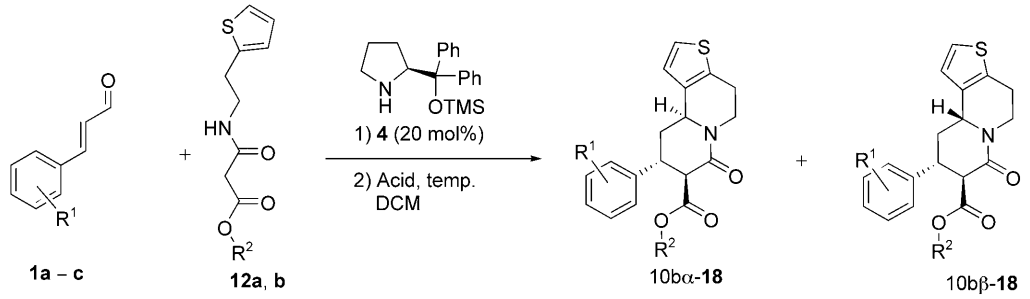
acid and Lewis acids were screened in order to obtain thermodynamic control.[21] The highest selectivity for the thermodynamic product was obtained with tin(IV) chloride which gave 12bα-**17aa** and 12bβ-**17aa** in 56:44 *dr* (Table 4, entry 3).

One-Pot Synthesis of Thieno[3,2-*a*]quinolizidine Derivatives

After investigating the nitrogen- and oxygen-containing heterocyclic compounds in the one-pot procedure, we turned our attention to the sulfur-containing heterocycles. The thiophene scaffolds are of interest in pharmaceutical chemistry due to the higher stability and structural chemical resemblance with the pyrrole and furan rings and specifically annulated thiophenes are becoming more and more interesting as therapeutic agents.[24,25] The thiophene substituted amide **12a** reacted smoothly with **1a** and gave, after full conversion of **12a** and subsequent treatment with acid under kinetic conditions, the corresponding 10bα-thieno[3,2-*a*]quinolizidine **18aa** as the major epimer although with moderate diastereoselectivity (Table 5, entry 1). However, applying the reaction conditions most suitable for the synthesis of 12bα-benzofuro[2,3-*a*]quinolizidine **17** (formic acid, room temperature), the selectivity could be increased to 74:26 in favor of the kinetic product 10bα-**18aa** (Table 5, entry 5).[21] In order to gain access to the thermodynamic product, an additional set of acids was screened. Interestingly, refluxing TFA gave the almost the same selectivity as hydrochloric acid at low temperature (Table 5, entries 1 and 2). Some success was met with $BF_3{\cdot}Et_2O$ and the thermodynamic product 10bβ-**18aa** was formed in low excess (Table 5, entry 3). When an excess of tin(IV) chloride (1.2 equiv.) was used a distinct improvement in selectivity towards the thermodynamic product was observed and epimer 10bβ-**18aa** could be isolated in good yield and enantioselectivity and in a diasteriomeric ratio of 75:25 (Table 5, entry 6).

However, when the amount of tin(IV) chloride was reduced to 40 mol% the selectivity dropped to give close to a 1:1 mixture of isomers (Table 5, entry 4). With those optimized condition in hand, the stereodivergent one-pot reaction was successfully employed in the synthesis of a series thieno[3,2-*a*]quinolizidine derivatives **18** having either the 10bα- or the 10bβ-configuration in high to excellent enantioselectivity, good yields and moderate to good diastereoselectivity

Table 5. Stereoselective thieno[3,2-*a*]quinolizidine synthesis.[a]



Entry	R^1	R^2	Time *t* [days]/Temperature *T* [°C]	Acid/*T* [°C]	Product	Yield [%][b]	*ee*[c]	*dr*[d]
1	H	Me	3/3	HCl/−78→r.t.	10b**α-18aa**	–	–	66:34
2	H	Me	3/3	TFA/70	10b**α-18aa**	–	–	61:39
3	H	Me	3/3	$BF_3{\cdot}Et_2O$/−78	10b**α-18aa**	–	–	40:60
4	H	Me	3/3	$SnCl_4$/r.t.[e]	10b**α-18aa**	–	–	55:45
5	H	Me	3/r.t.	HCO_2H/r.t.	10b**α-18aa**	65	92	74:26
6	H	Me	3/r.t.	$SnCl_4$/r.t.	10b**β-18aa**	72	92	25:75
7	H	Et	3/r.t.	HCO_2H/r.t.	10b**α-18ab**	79	95	75:25
8	H	Et	3/r.t.	$SnCl_4$/r.t.	10b**β-18ab**	79	95	33:67
9	*o*-NO_2	Me	3/39	HCO_2H/r.t.	10b**α-18ba**	69	89	83:17
10	*o*-NO_2	Me	3/39	$SnCl_4$/r.t.	10b**β-18ba**	20	–[f]	83:17
11	*o*-NO_2	Et	3/39	HCO_2H/r.t.	10b**α-18bb**	43	93	80:20
12	*o*-NO_2	Et	3/39	$SnCl_4$/r.t.	10b**β-18bb**	45	94	44:56
13	*p*-MeO	Me	3/r.t.	HCO_2H/r.t.	10b**α-18ca**	83	89	75:25
14	*p*-MeO	Me	3/r.t.	$SnCl_4$/r.t.	10b**β-18ca**	79	89	24:76
15	*p*-MeO	Et	3/r.t.	HCO_2H/r.t.	10b**α-18cb**	81	>99	68:32
16	*p*-MeO	Et	3/r.t.	$SnCl_4$/r.t.	10b**β-18cb**	84	>99	34:66

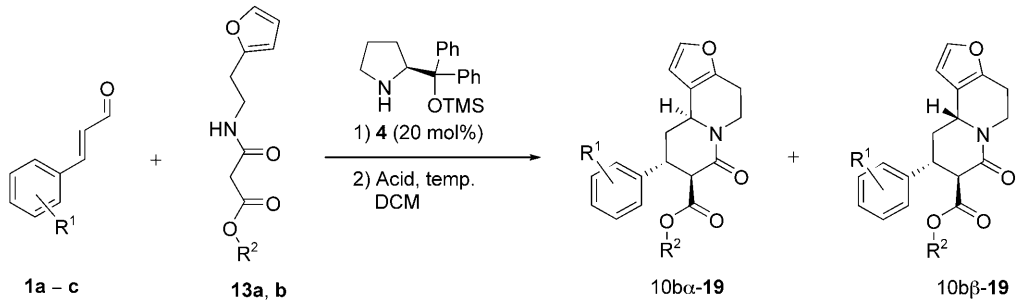
[a] A solution of aldehyde **1** (1.2 equiv.), amide **12** (1 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature. After full conversion of **12**, formic acid (0.5 mL mmol^{-1}) or $SnCl_4$ (1.2 equiv., 1 M in DCM) was added and the resulting mixture was stirred at room temperature for 5 and 1 h, respectively.
[b] Total yield of 10b**α-18** and 10b**β-18**.
[c] Determined by chiral HPLC on the major diastereoisomer.
[d] 10b**α-18**/10b**β-18**, determined by ^{1}H NMR on the crude reaction mixture.
[e] 0.4 equivalent of $SnCl_4$.[f] Decomposition of reaction intermediate/product.

(Table 5, entries 5–16). One exception was the *o*-nitro compound **12a**, **b** that reacted sluggish in the presence tin(IV) chloride. The methyl ester derivative **12a** mainly gave decomposition of the intermediate hemiacetal and/or the product and no selectivity for the thermodynamic product was observed (Table 5, entry 10). In the corresponding reaction with ethyl ester **12b**, the adduct 10b**β-18bb** could be isolated in low yield as a 1:1 mixture of diastereoisomers (Table 5, entry 12). For the combination of ethyl ester **12b** and *p*-methoxycinnamaldehyde **1c**, only one enantiomer could be observed, unfortunately, in moderate diastereoselectivity under both kinetic and thermodynamic reaction conditions (Table 5, entries 15 and 16). However, for the corresponding reactions with the methyl ester **12a** and *p*-methoxycinnamaldehyde **1c**, higher diastereoselectivity and lower enantioselectivity were observed (Table 5, entries 13 and 14).

One-Pot Synthesis of Furo[3,2-*a*]quinolizidine Derivatives

Furan derivatives have been rarely used in *N*-acyliminium ion cyclizations;[26] most likely as a result of the instability of the furan group under acidic conditions as well as the difficulties associated with the synthesis of the cyclization precursors. On the other hand, the furan moiety is a masked dicarbonyl moiety and a valuable handle for further transformations. The reaction of furan amide **13a** with cinnamaldehydes **1a** and **1c** went smoothly and full conversion was observed within 1–3 days at 3 °C. For *o*-nitrocinnamaldehyde a longer reaction time at elevated temperature was required to obtain full conversion. The instability of the furan moiety under acidic conditions turned out to be a serious problem and for most of the screened acids the major observation was decomposition of the conjugate addition adduct and/or the product (Table 6, entries 1–4).[21] Eventually, it was found that addition

Table 6. Stereoselective furo[3,2-*a*]quinolizidine synthesis.[a]



Entry	R^1	R^2	Time *t* [days]/Temperature *T* [°C]	Acid/*T* [°C]	Product	Yield [%][b]	*ee*[c]	*dr*[d]
1	H	Me	3/3	HCl/−78→r.t.	10b**α-19aa**	–	–	trace (50:50)[e]
2	H	Me	3/3	$SnCl_4$/r.t.	10b**α-19aa**	–	–	trace (50:50)[e]
3	H	Me	3/3	$BF_3{\cdot}Et_2O$/−78	10b**α-19aa**	–	–	–[e]
4	H	Me	3/3	HCO_2H/r.t.	10b**α-19aa**	–	–	–[e]
5	H	Me	3/3	TFA/−78	10b**α-19aa**	62	92	78:22
6	H	Et	4/3	TFA/−78	10b**α-19ab**	56	98	80:20
7	*o*-NO_2	Me	3/39	TFA/−78	10b**α-19ba**	21	98	83:17
8	*o*-NO_2	Et	3/39	TFA/−78	10b**α-19bb**	19	96	78:22
9	*p*-MeO	Me	6/3	TFA/−78	10b**α-19ca**	65	90	87:13
10	*p*-MeO	Et	6/3	TFA/−78	10b**α-19cb**	46	92	85:15

[a] A solution of aldehyde **1** (1.2 equiv.), amide **13** (1 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature. After full conversion of **13**, the reaction mixture was cooled to −78 °C followed by addition of TFA (5 equiv., 1 M in DCM). The mixture was stirred for at −78 °C for 3 h.
[b] Total yield of 10b**α**-**19** and 10b**β**-**19**.
[c] Determined by chiral HPLC on the major diastereoisomer.
[d] Determined by ^{1}H NMR on the crude reaction mixture.
[e] Mainly decomposition of product/intermediate.

of TFA diluted in DCM at −78 °C followed by careful quenching of the acid at ambient temperature gave the kinetically favored product 10b**α**-**19aa** in high selectivity (Table 6, entry 5). Considering the sensitivity of the furo group, the obtained yields are good for the phenyl derivative 10b**α**-**19aa**, **ab** and *p*-methoxycinnamaldehyde **19ca**, **cb** (Table 6, entries 5 and 6, 9 and 10). For the nitro compound **19ba**, **bb** the yields dropped to 21 and 19%, respectively. This is most likely the result of the low reactivity of the amide **13** and *o*-nitrocinnamaldehyde **1b** in the conjugate addition step and this favors the competing Knoevenagel condensation to give the corresponding dienes **23**, which was observed as the major product in these reactions (Figure 2).

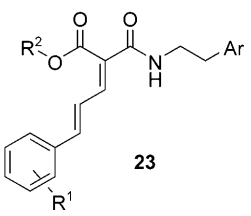


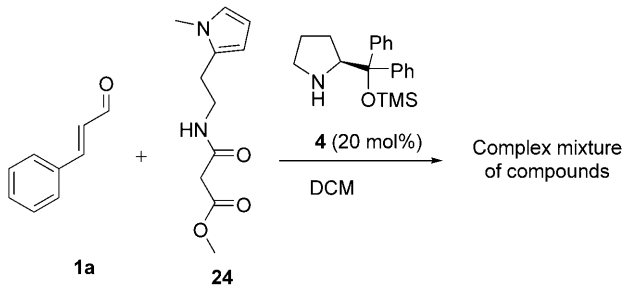
Figure 2.

As for the benzofuran derivatives, the furan derivatives failed to give the thermodynamic product and attempts to use thermodynamic reaction conditions only resulted in decomposition.

In order to complete the heterocylic five-mebered ring series, the *N*-methylpyrrole amide **24** was reacted with cinnamaldehyde in the presence of catalyst **4**. Although the amide **24** was consumed fast, only traces of product could be detected after addition of HCl (Scheme 3). Unfortunately, it is believed that the pyrrole moiety is more reactive as nucleophile than the amide α-carbon in the conjugate addition under these reaction conditions.[27]

One-Pot Synthesis of Benzo[*a*]quinolizidine Derivatives

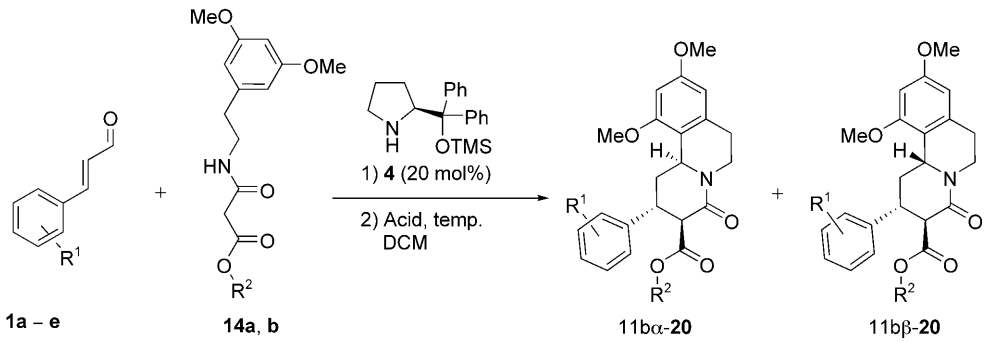
In order to further expand the scope of this reaction to the benzo[*a*]quinolizidine derivatives, we decided to investigate non-heteroatom aromatics as nucleophiles.[18] Since electron-rich aromatics are relatively strong nucleophiles we started our investigation with the 3,5-dimethoxyphenyl amide **14a**.[8a,d] This compound reacted smoothly with cinnamaldehyde **1a** in the presence of catalyst **4** to give full conversion of



Scheme 3. Attempted one-pot reaction with *N*-methylpyrrolamide **24** and cinnamaldehyde.

the amide **14a** in 3 days at 3 °C. By using the kinetic reaction conditions developed for the 12b**α**-indolo[2,3-*a*]quinolizidine derivatives **9** (20 mol% HCl, −78 °C→r.t.) no reaction occurred. However, when the acid loading was increased to 40 mol% under the same reaction conditions the kinetic product 11b**α**-**20aa** could be isolated in high yield, good *ee* and 90:10 *dr* (Table 7, entry 3). By further following the reaction conditions developed for 12b**β**-indolo[2,3-*a*]quinolizidines **9** in the synthesis of thermodynamic favored 11b**β**-benzo[*a*]quinolizidine derivatives, we changed the reaction conditions of the second step to refluxing TFA (Table 7, entry 4). Interestingly, if the reaction was quenched after 1 h reflux, full conversion to the product was observed, however, the *dr* was only 63:37 in favor of 11b**β**-**20aa** (Table 7, entry 1). Further reflux (18 h) resulted in mainly decomposition of the product and no further increase in *dr* could be observed (*vide infra*). It was also observed that, in the reaction of the 3,5-dimethoxy derivative with tin(IV) chloride, the kinetic product 11b**α**-**20aa** was obtained as the major isomer (Table 7, entry 2). The reaction with the corresponding ethyl ester **14b** turned out to be slower and required 3 days reaction time at room temperature to obtain full conversion of the amide. Subsequent acid treatment under kinetic and thermodynamic conditions gave 11b**α**-**20ab** and

Table 7. Stereoselective 9,11-dimethoxybenzo[*a*]quinolizidine synthesis.[a]



Entry	R^1	R^2	Time *t* [days]/Temperature *T* [°C]	Acid/*T* [°C]	Product	Yield [%][b]	*ee*[c]	*dr*[d]
1	H	Me	3/3	TFA/70	11b**β**-**20aa**	–	–	37:63
2	H	Me	3/3	$SnCl_4$/r.t.	11b**α**-**20aa**	–	–	66:34
3	H	Me	3/3	HCl/−78→r.t.	11b**α**-**20aa**	77	93	90:10
4	H	Me	3/3	TFA/70	11b**β**-**20aa**	73	93	28:72
5	H	Et	3/r.t.	HCl/−78→r.t.	11b**α**-**20ab**	78	95	91:9
6	H	Et	3/r.t.	TFA/70	11b**β**-**20ab**	83	95	24:76
7	*o*-NO_2	Me	5/39	HCl/−78→r.t.	11b**α**-**20ba**	69	92	>95:5[e]
8	*o*-NO_2	Me	5/39	TFA/70	11b**β**-**20ba**	–[f]	–	
9	*o*-NO_2	Et	5/39	HCl/−78→r.t.	11b**α**-**20bb**	77	93	>95:5[e]
10	*o*-NO_2	Et	5/39	TFA/70	11b**β**-**20bb**	–[f]	–	
11	*p*-MeO	Me	3/3	HCl/−78→r.t.	11b**α**-**20ca**	71	89	84:16
12	*p*-MeO	Me	3/3	TFA/70	11b**β**-**20ca**	77	87	23:27
13	*p*-MeO	Et	3/r.t.	HCl/−78→r.t.	11b**α**-**20cb**	64	94	92:8
14	*p*-MeO	Et	3/r.t	TFA/70	11b**β**-**20cb**	61	94	24:76

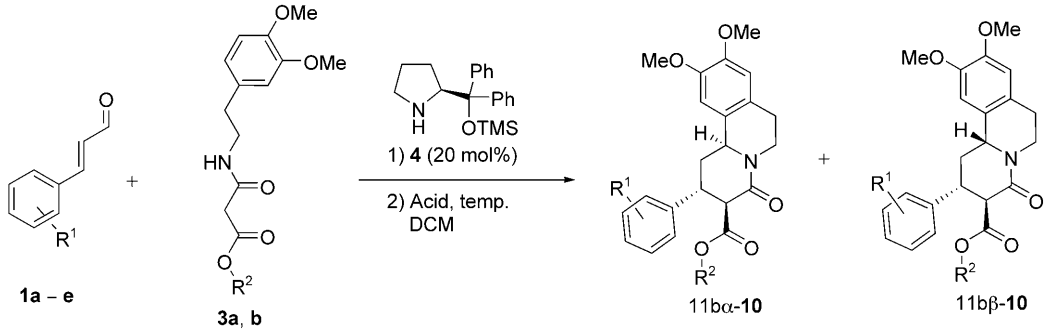
[a] A solution of cinnamic aldehyde **1a** (1.2 equiv.), amide **14a**–**d** (1 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature. After full conversion of **2**, HCl (0.4 equiv., 1 M in Et_2O) or TFA (0.5 mL mmol^{-1}) was added to the reaction mixture according to conditions A or B as described in Table 2, footnote[a].
[b] Total yield of 11b**α**-**20** and 11b**β**-**20**.
[c] Determined by chiral HPLC on the major diastereoisomer.
[d] Determined by ^{1}H NMR on the crude reaction mixture.
[e] Only one diastereoisomer could be observed by ^{1}H NMR.
[f] Mainly decomposition of product/intermediate.

11b**β**-**20ab**, respectively, in good yields and stereoselectivity (Table 7, entries 5 and 6). The reactions of *o*-nitrocinnamaldehyde **1b** with amides **14a**, **b** required 5 days in refluxing DCM to go to full conversion. Subsequent treatment of the reaction mixtures with acid under kinetic conditions gave the products 11b**α**-**20ba**, **bb** as single observable diastereoisomers in good yields and high *ee* (Table 7 entries 7 and 9). Unfortunately, when the harsher thermodynamic reaction condition was used only decomposition was observed (Table 7, entries 8 and 10). For the one-pot reaction of *p*-methoxycinnamaldehyde **1c** with the methyl and ethyl esters **14a**, **b** under kinetic and thermodynamic conditions gave 11b**α**-**20ca**, **cb** and 11b**β**-**20ca**, **cb**, respectively, in good diastereoselectivity. As been previously observed for the methoxy derivatives (*vide supra*), the methyl ester derivative 11b**α**-**20ca** was isolated in moderate enantioselectivity whereas the selectivity increased substantially for the corresponding ethyl ester derivative 11b**α**-**20cb** (Table 7, entries 11–14).

We then turned to the regioisomeric 3,4-dimethoxyphenyl compound. The catechol group is of special interest, since it is an often-occurring subunit in biologically active compounds, for example, emetine, the closely related psychotrine and alangine (Figure 1). The 3,4-dimethoxyphenyl amide **3a** and cinnamaldehyde **1a** in the presence of catalyst **4** gave full conversion to the intermediate hemiaminal in 3 days at 3 °C. To the reaction mixture was then added 40 mol% HCl and the kinetically favored product 11b**α**-**10aa** could be isolated in 90% *ee* and moderate *dr* (Table 8, entry 3).

Despite several attempts, the diasteroselectivity could not be improved for the kinetic product 11b**α**-**10aa**.[21] For the diastereoselective synthesis of the thermodynamic epimer 11b**β**-**10aa**, we first investigated the *N*-acyliminium ion cyclization in refluxing TFA, which gave moderate diastereoselectivity for the kinetic product 11b**α**-**10aa**. However, extensive screening of acid conditions revealed that using the thermodynamic conditions developed for the 10b**β**-

Table 8. Stereoselective 9,10-dimethoxybenzo[*a*]quinolizidine synthesis.[a]



Entry	R^1	R^2	Time *t* [days]/Temperature *T* [°C]	Acid/*T* [°C]	Product	Yield [%][b]	*ee*[c]	*dr*[d]
1	H	Me	3/3	TFA/70/0.1 M	11b**α**-**10aa**	–	–	62:38
2	H	Me	3/3	$SnCl_4$[e]/r.t.	11b**β**-**10aa**	–	–	26:74
3	H	Me	3/3	HCl/−78→r.t.	11b**α**-**10aa**	69	90	62:38
4	H	Me	3/3	$SnCl_4$/r.t.	11b**β**-**10aa**	72	90	26:74
5	H	Et	1/r.t.	HCl/−78→r.t.	11b**α**-**10ab**	41	95	67:33
6	H	Et	1/r.t.	$SnCl_4$/r.t.	11b**β**-**10ab**	66	94	23:77
7	*o*-NO_2	Me	5/39	HCl/−78→r.t.	11b**α**-**10ba**	53	91	83:17
8	*o*-NO_2	Me	5/39	$SnCl_4$/r.t.	11b**β**-**10ba**	52	91	50:50
9	*o*-NO_2	Et	5/39	HCl/−78→r.t.	11b**α**-**10bb**	42	94	73:27
10	*o*-NO_2	Et	5/39	$SnCl_4$/r.t.	11b**β**-**10bb**	39	95	25:75
11	*p*-MeO	Me	1/3	HCl/−78→r.t.	11b**α**-**10ca**	71	89	76:24
12	*p*-MeO	Me	1/3	$SnCl_4$/r.t.	11b**β**-**10ca**	75	89	24:76
13	*p*-MeO	Et	3/r.t.	HCl/−78→r.t.	11b**α**-**10cb**	63	94	67:33
14	*p*-MeO	Et	3/r.t.	$SnCl_4$/r.t.	11b**β**-**10cb**	72	95	25:75

[a] A solution of aldehyde **1** (1.2 equiv.), amide **3** (1 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature. After full conversion of **3**, HCl (40 mol%, 1 M in Et_2O) or $SnCl_4$ (40 mol%, 1 M in DCM) was added at the indicated temperature and stirred overnight and for 1 h, respectively.

[b] Total yield of 10b**α**-**10** and 10b**β**-**10**.

[c] Determined by chiral HPLC on the major diastereoisomer.

[d] 10b**α**-**10**/10b**β**-**10**, determined by ^{1}H NMR on the crude reaction mixture.

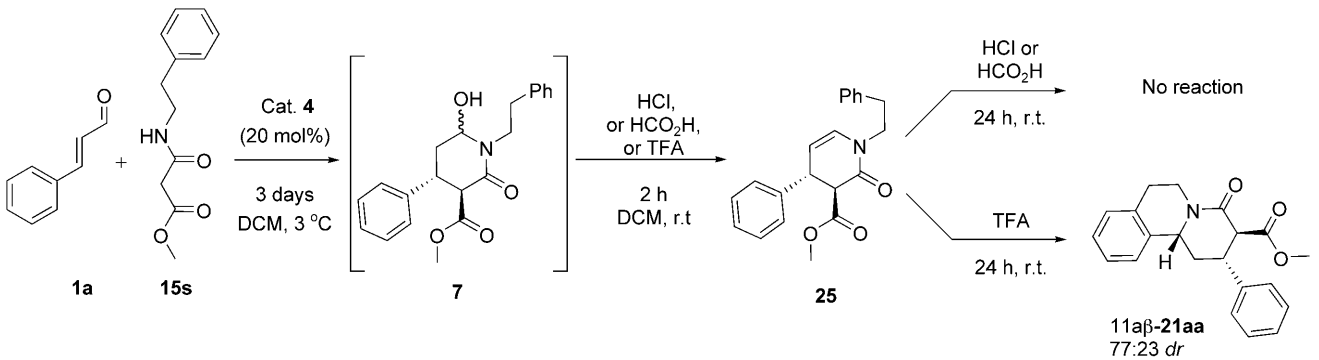
[e] 1.2 equivalents of $SnCl_4$.

thieno[3,2-*a*]quinolizidine derivatives **18** [tin(IV) chloride, 1.2 equiv.] gave the thermodynamically favored product 11b**β**-**10aa** in 74:26 *dr* (Table 8, entry 2). For the 3,4-dimethoxyphenyl amide **3a**, it was found that the tin(IV) chloride could be reduced to a catalytic amount (40 mol%) without affecting the diastereoselectivity of the reaction (Table 8, entry 4). The corresponding reactions of the ethyl ester **3b** and cinnamaldehyde **1a** gave similar yields and diastereoselectivity but a pronounced increase in enantioselectivity (Table 8, entries 5 and 6). The same trend of increased enantioselectivity was also observed for the corresponding reactions with *o*-nitrocinnamaldehyde **1b** and *p*-methoxycinnamaldehyde **1c** (Table 8, entries 7–14). The diastereoselectivity in the reaction with tin(IV) chloride turned out to be independent of which cinnamaldehyde was used and gave the thermodynamic product 11b**β**-**10** with approximately 75:25 diastereomeric ratio (Table 8) with the exception of the methyl ester **3a** in combination with *o*-nitrocinnamaldehyde **1b** that gave 11b**α**-**10ba** and 11b**β**-**10bb** in a 1:1 mixture (Table 8, entry 8).

The 3,5- and 3,4-dimethoxyphenyl groups are both relatively strong nucleophiles in aromatic substitution reactions so we wanted to evaluate if the less activated phenyl group could be used in the *N*-acyliminiumion cyclization. The initial conjugate addition step of phenyl amide **15a** and cinnamaldehyde **1a** in the presence of catalyst **4** went as expected with full conversion of amide **15a** in 3 days at 3 °C. The following acid promoted *N*-acyliminiumion cyclization turned out to be less feasible for the non-activate phenyl group compared to the more activated 3,4- and 3,5-dimethoxyphenyl groups and employing the previously optimized reaction conditions for kinetic control (*vide supra*) did not give any cyclization product.[21] For example, using HCl, formic acid or $SnCl_4$ only resulted in elimination of water to give the enamide derivative **25** (Scheme 4, Table 9, entries 1 and 2). The same result was also observed after 2 h reaction time when excess TFA was used. However, after a prolonged reaction time (24 h) it was observed that the enamide intermediate slowly cyclized to give the benzo[*a*]quinolizidine derivative. Surprisingly, examination of the stereochemistry revealed that the major product was the *thermodynamically favored* 11b**β**-**21aa** and *not the expected kinetic* 11b**α**-**21aa**. The thermodynamic reaction conditions (TFA, reflux) smoothly gave the benzo[*a*]quinolizidine derivative with a diastereoselectivity 73:27 in favor of 11b**β**-**21aa** (Table 9, entry 5). After further optimization it was found that the selectivity of the cyclization could be increased up to 83:17 in favor of 11b**β**-**21aa** by reducing the reaction temperature to 3 °C (Table 9, entry 6). The thermodynamically favored phenyl derivative 11b**β**-**21ab** and *p*-methoxyphenyl derivative 11b**β**-**21ca**, **cb** were also obtained in high diastereoselectivity and moderate to good enantioselectivity through the corresponding reactions (Table 9, entries 6 and 7, 10 and 11). The *o*-nitrophenyl derivative 11b**β**-**21ba**, **bb** gave good enantioselectivity but lower diasteroselectivity. For all acids used, the thermodynamic product 11b**β**-**21** was formed in good to high diastereoselectivity and all attempts to find reaction conditions favoring the kinetic product failed.[21] Furthermore, the 1-naphthyl amide **16** also worked smoothly in the one-pot reaction to give the thermodynamically favored tetracyclic compound 13b**β**-**22** in 57% yield, 92% *ee* and 87:13 *dr* (Scheme 5).

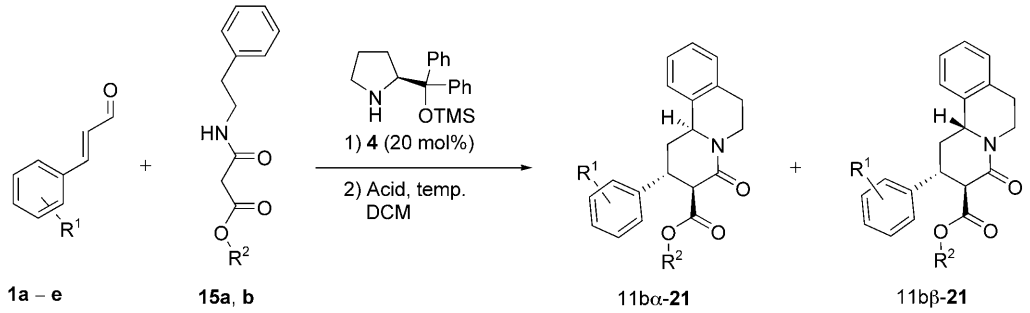
Mechanism/Origin of Selectivity

The stereochemistry of the three new stereocenters formed through this one-pot sequence is determined during three reaction steps. First; in the conjugate addition, the nucleophile is directed to the sterically less hindered *Si*-face by shielding of the *Re*-face of the iminium intermediate **5** by the bulky aryl groups on catalyst **4** (Scheme 6).[28] Spontaneous epimerization of the stereochemically labile stereocenter at C-3 to the thermodynamically more stabile *trans* conformation of hemiaminal **7** will establish the second stereocenter. Finally, addition of acid to the reaction mix-



Scheme 4.

Table 9. Stereoselective benzo[*a*]quinolizidine synthesis.[a]

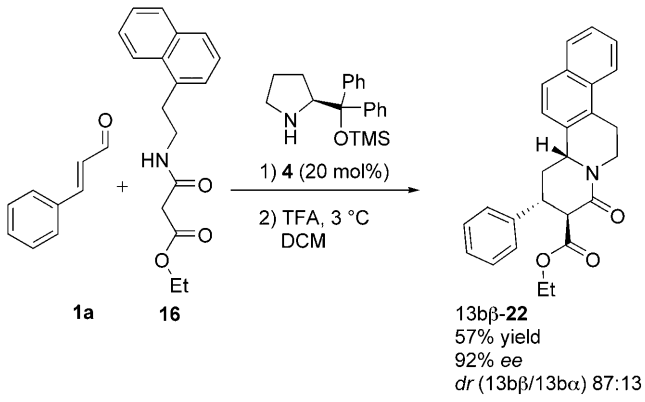


Entry	R^1	R^2	Time *t* [days]/Temperature *T* [°C]	Acid/*T* [°C]	Product	Yield [%][b]	*ee*[c]	*dr*[d]
1	H	Me	3/3	HCl/r.t.	11b**β**-**21aa**	–	–	–[e]
2	H	Me	3/3	$SnCl_4$/r.t.	11b**β**-**21aa**	–	–	–[e]
3	H	Me	3/3	H_2SO_4/r.t.	11b**β**-**21aa**	–	–	trace (39:61)[f]
4	H	Me	3/3	TFA/r.t.	11b**β**-**21aa**	–	–	23:77
5	H	Me	3/3	TFA/70	11b**β**-**21aa**	–	–	27:73
6	H	Me	3/3	TFA/3	11b**β**-**21aa**	78	89	17:83
7	H	Et	3/3	TFA/3	11b**β**-**21ab**	83	92	17:83
8	*o*-NO_2	Me	7/r.t.	TFA/3	11b**β**-**21ba**	67	93	37:63
9	*o*-NO_2	Et	5/40	TFA/3	11b**β**-**21bb**	78	92	31:69
10	*p*-MeO	Me	1/3	TFA/3	11b**β**-**21ca**	78	82	17:83
11	*p*-MeO	Et	1/3	TFA/3	11b**β**-**21cb**	73	91	17:83

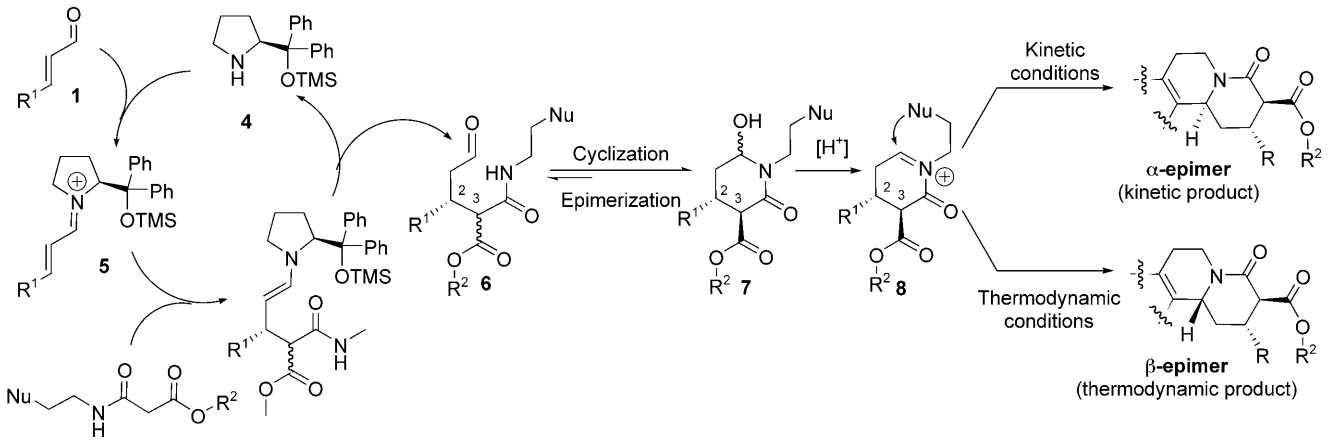
[a] A solution of aldehyde **1** (1.2 equiv.), amide **15** (1 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 (0.9 mM) was stirred at room temperature. After full conversion of **15**, TFA (0.5 mL mmol^{-1}) was added at −78 °C and the mixture was stirred at ambient temperature for 3 days.
[b] Total yield of 11b**α**-**21** and 11b**β**-**21**.
[c] Determined by chiral HPLC on the major diastereoisomer.
[d] 11b**α**-**21**/11b**β**-**21**, determined by ^{1}H NMR on the crude reaction mixture.
[e] Only **25** was observed.
[f] Mainly decomposition of product/intermediate.

ture leads to elimination of water and formation of the *N*-acyliminium ion **8**. Subsequent aromatic substitution gives the **α**- or **β**-epimer depending on the reaction conditions.

From the data obtained it is observed that the rate of the conjugate addition is mainly determined by the electronic properties of the cinnamaldehyde derivative, where electron-withdrawing groups increase and electron-donating groups decrease the reaction time. Interestingly, this is in contradiction with what can be expected, since electron-deficient cinnamaldehydes should be the better electrophiles and therefore react faster.These results rather imply that the rate-determining step is not the conjugate addition but the formation of the iminium ion, which should be facilitated by electron-donating groups. In an attempt to speed up the iminium ion formation, *p*-nitrobenzoic acid (20 mol%) was added to the reaction of indolyl amide **2a**, cinnamaldehyde **1a** and catalyst **4**; however, under these reaction conditions, formation of the corresponding Knoevenagel product **23** was favored (see Figure 2). The pyrrolidine **4** catalyzed conjugate addition turned out to be highly enantioselective for the reactions of cinnamaldehyde **1a** and *o*-nitrocinnamaldehyde **1b** with the methyl and the ethyl ester amides **2a**, **b** and both the kinetic and thermodynamic products could be isolated in 90–98% *ee*. In general, the ethyl esters gave somewhat higher enantioselectivity than the methyl esters in the corresponding conjugate additions, with the exception of the benzofuran amide **11**, where the methyl ester **11a** in all cases gave better



Scheme 5. One-pot reaction of 1-naphthyl amide **16** and cinnamaldehyde **1a**.



Scheme 6. Proposed mechanism for the one-pot reaction.

enantioselectivity than the corresponding reactions with ethyl ester **11b**. When comparing the reactions of *p*-methoxycinnamaldehyde **1c** with the methyl and ethyl esters **2**–**3** and **11**-**16**, a distinct increase in enantioselectivity was observed, for example, the indolo-[2,3-*a*]quinolizidine **9** was obtained in 89% *ee* from the methyl ester **2a** and in >99% *ee* from the ethyl ester **2b** (Table 3, entries 11–14).

The final, bridgehead, stereocenter is formed through an *N*-acyliminium ion cyclization. The *N*-acyliminium ion **8** is formed by acid-catalyzed elimination of water from the hemiaminal **7** and these species are strong electrophiles that readily react in electrophilic aromatic substitutions. Addition of the aromatic moiety to the *Si*-face of the iminium ion **8** would give the thermodynamically more stable **β**-epimer owing to the all-equatorial orientation of the substituents on the piperidine ring. However, under the kinetic reactions conditions used in this study (*vide supra*), the **α**-epimer is obtained as the major product, which is in agreement with addition of the aromatic moiety from the *Re*-face of the iminium ion (Figure 3). This due to the less steric hindrance from the equatorial α-proton of the iminium ion in the transition state leading to the **α**-epimer, as compared to the higher steric interactions between the aromatic moiety and the axial α-proton in the transition state leading to the **β**-epimer. This is in agreement with the observed increase in diastereoselectivity when going from 3,4-dimethoxyphenyl to the more sterically demanding 3,5-dimethoxyphenyl.

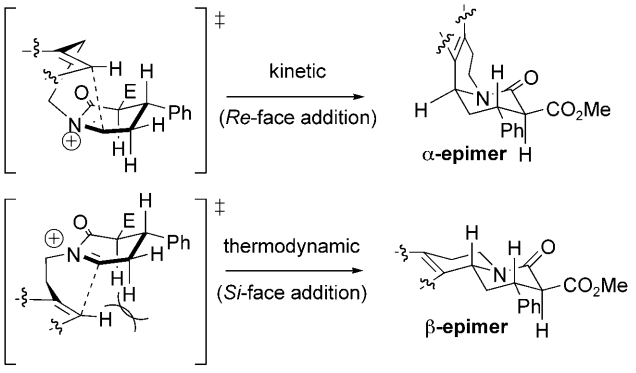
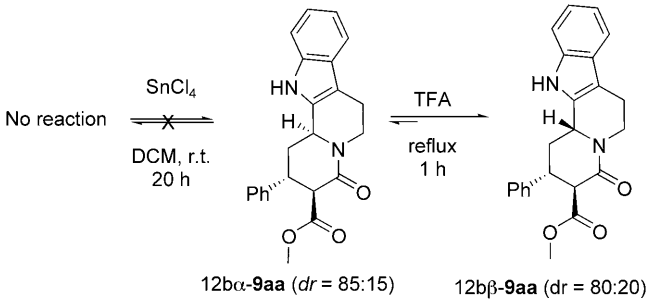


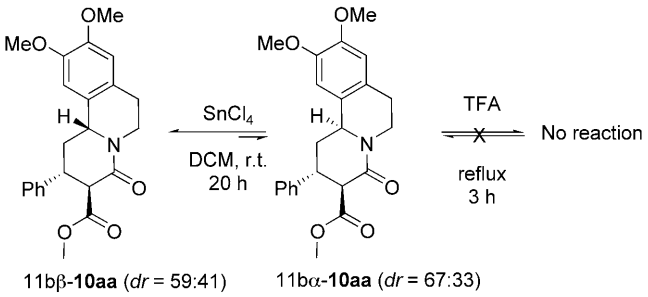
Figure 3. Kinetic *vs.* thermodynamic product formation in the *N*-acyliminium ion cyclization (E = CO_2R^2).

For the formation of 12b**β**-indolo[2,3-*a*]quinolizidine **9** and 11b**β**-9,11-dimethoxy-benzo[*a*]quinolizidine **20** under thermodynamic reaction conditions (TFA, reflux) it was found that the diastereomeric ratio varied with reaction temperature and reaction time (see Table 1, entries 10 and 11 and Table 7, entries 1 and 4). These results are in accordance with the initial formation of the kinetically favored **α**-epimer and subsequent epimerization to the thermodynamically more stable **β**-epimer. This was also supported by the epimerization of the kinetic products 12b**α**-indolo[2,3-*a*]quinolizidine **9aa** and 11b**α**-9,11-dimethoxybenzo[*a*]quinolizidine **20aa** in refluxing TFA which gave the thermodynamic compounds 12b**β**-**9** and 11b**β**-**20**, respectively (Scheme 7).

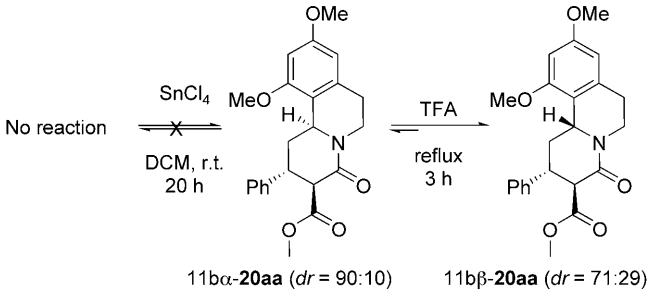
There are two plausible mechanisms to explain the epimerization: Through the reversed reaction, *that is,* protonation on the fused aromatic ring and subsequent ring opening/ring closing involving the intermediate *N*-acyliminium ion (Scheme 8). Or, by initial protonation of the amide and breaking of the carbon-nitrogen bond forming an intermediate ten-membered ring that will undergo intramolecular cyclization to the thermodynamic more stable product.[29]

In contrast to the indole and 3,5-dimethoxyphenyl amides **2a** and **14a**, the one-pot reaction of thiophene and 3,4-dimethoxy amides **12a** and **3a** using refluxing TFA for the *N*-acyliminium ion cyclization favored the *kinetic product* 10b**α**-thieno[3,2-*a*]quinolizidine **18aa** and 11b**α**-9,10-dimethoxybenzo[*a*]quinolizidine **10aa** in 61:39 *dr* and 62:38 *dr*, respectively, and *not the thermodynamic* product (Table 5, entry 2 and Table 8, entry 1). Furthermore, for the kinetic product



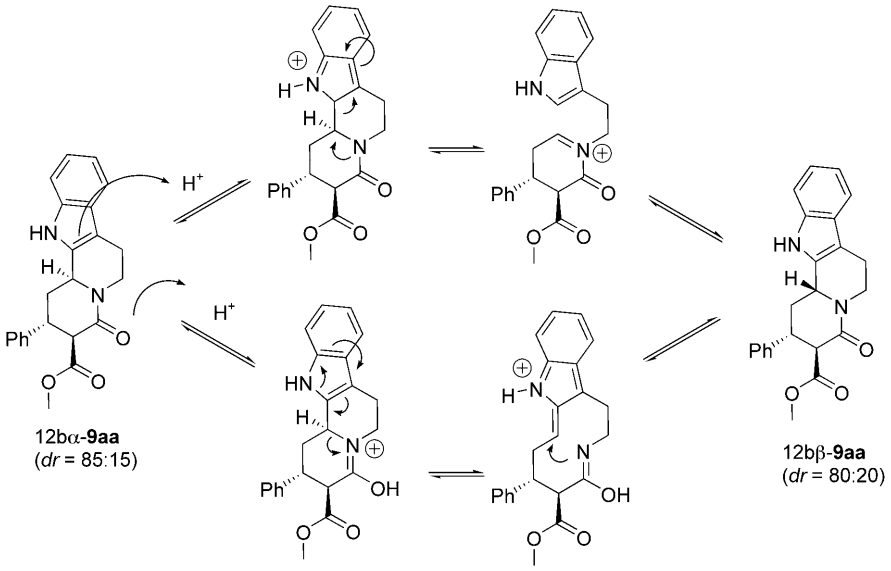


Scheme 9. Tin(IV) chloride-promoted epimerization of 9,10-dimethoxybenzo[*a*]quinolizidine.



Scheme 7. Trifluoroacetic acid-promoted epimerization of indolo[2,3-*a*]quinolizidine and 9,11-dimethoxybenzo[*a*]quinolizidine.

11b**α**-9,10-dimethoxybenzo[*a*]quinolizidine **10aa**, no epimerization was observed in refluxing TFA. However, a slow epimerization of 11b**α**-**10** was observed with tin(IV) chloride (1.1 equiv.) at room temperature giving 11b**β**-**10** in 59:41 *dr* after 18 h (Scheme 9). Comparing these results with the one-pot reaction starting from 3,4-dimethoxyphenyl amide **3a** and cinnamaldehyde **1a** with 40 mol% tin(IV) chloride, full conversion was obtained to the thermodynamic product 11b**β**-**10** in 74:26 *dr* after only 1 h (Table 8, entry 2). This indicate that the tin(IV) promoted reactions *do not* proceed through initial formation of the kinetic product 11b**α**-**10** followed by epimerization to the thermodynamically favored product 11b**β**-**10**. Thus, this reaction is rationalized to be under chelation control. It is proposed that the ester moiety interchanges from an equatorial position to an axial position by epimerization of the stereochemically labile stereocenter on C-3, thereby allowing for tin(IV) to coordinate between the ester oxygen and the two oxygen atoms on the 3,4-dimethoxyphenyl or to sulfur on the thiophene moiety. This will direct the aromatic addition to the sterically more hindered *Si*-face of the *N*-acyliminium ion giving the **β**-epimer. This is also consistent with the non or low chelation control observed for the reactions with the 3,5-dimethoxyphenyl, furan and benzofuran moieties. These aromatic compounds have weaker coordinating abilities compared to the 3,4-dimethoxyphenyl and the thiophene moieties and will react through kinetic control.



Scheme 8. Proposed mechanism for the epimerization indolo[2,3-*a*]quinolizidine in refluxing TFA.

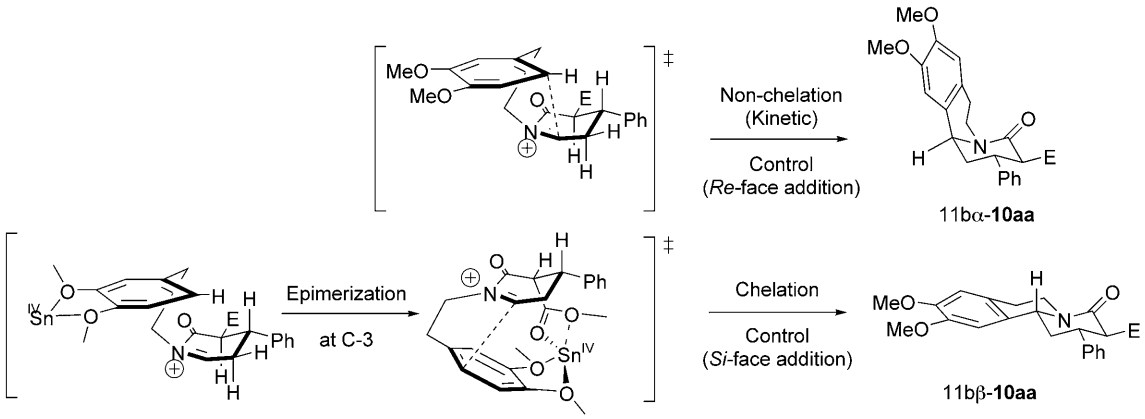


Figure 4. Chelation control *vs.* non-chelation (kinetic) control in the tin(IV) chloride-mediated *N*-acyliminium ion cyclization of 3,4-dimethoxyphenyl species (E = CO_2R^2).

The phenyl amides **15a**, **b** were found to be weak nucleophiles in the *N*-acyliminium ion cyclization and acid addition mainly resulted in elimination of water from the intermediate hemiaminal **7** to the corresponding enamide **25** (Scheme 4). Surprisingly, a prolonged reaction time resulted in slow conversion of the enamide **25** to the *thermodynamic* product 11b**β**-benzo[*a*]quinolizidine **21**. This is in contradiction to the preference for the kinetic product formation that was observed for the other aromatic nucleophiles used in this study (*vide supra*). The reason for this behavior is not established, although it is suggested that the addition of the phenyl group to the *N*-acyliminium ion occurs through an "*endo*" approach due to cation-π interactions of the electron-rich π-system of the phenyl group with the electron-deficient π-system of the *N*-acyliminium ion.[30] Through this "*endo*-transition state" addition to the *Re*-face of the iminium ion would encounter higher steric repulsion from the C-2 carbon then from the axial α-proton of the iminium ion and favor the *Si*-face addition (Figure 4). Due to the higher steric demands of the 3,4-dimethoxy and 3,5-dimethoxy groups and the lower aromatic character of the heteroatom aromatics, cation-π interactions would be diminished and these aromatics will react as outlined in Figure 3, Figure 4 and Figure 5.

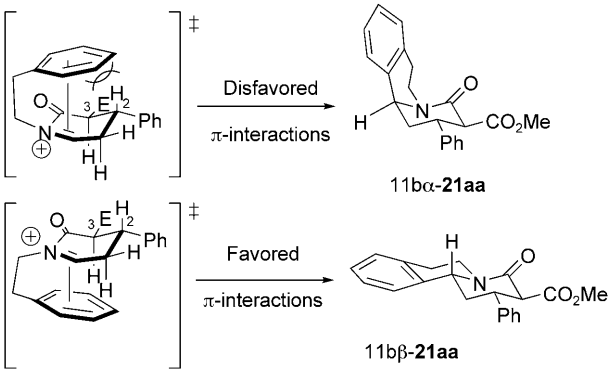


Figure 5. Selectivity control through cationic π-interactions (E = CO_2R^2).

The diastereoselectivity in the *N*-acyliminium ion cyclization is sensitive to the reaction conditions used and each amide required separate optimization in order to obtain the best selectivity. In general, the nitro compounds usually gave high diasteroselectivity under kinetic reaction conditions. However, the nitro group was found to be unstable under the harsher thermodynamic reaction conditions [TFA, reflux or tin(IV) chloride] resulting in poor yields and often also in low diastereoselectivity.

Conclusions

In summary, we have reported a fast and general one-pot protocol for construction of a wide number of quinolizidine derivates. This methodology relies on an enantioselective organocatalytic conjugate addition followed by hemiaminal formation and a diastereodivergent *N*-acyliminium ion annulation. The key advantages are the readily available starting materials, inexpensive and commercially available catalyst, broad substrate scope and easy operational protocol and direct access to structures that usually require multi-step processes with high stereoselectivity and yields. Beside this, for several substrates, the one-pot sequence also benefits from a diastereomeric switch that allows for the selective formation of either the **α**-epimer or the **β**-epimer by tuning of the reaction conditions of the *N*-acyliminium ion cyclization. The control of diastereoselectivity is obtained by taking advantage of kinetic, thermodynamic and chelation controlled reaction conditions. It is also interesting to point out the high *atom economy*[32] for this one-pot sequence, since the only waste product formed is water. For example; the major enantiomers of 12b**α**-benzofuro[2,3-*a*]quinolizidine **17ca** and 11b**α**-9,11-dimethoxybenzo[*a*]quinolizidine **20bb** were obtained

with 72% and 71% atom economy, respectively, from the corresponding amide and cinnamaldehyde derivative. The present study emphasizes the power of combining several reactions in a one-pot sequence for the efficient construction of complex organic scaffolds and further development of this one-pot reaction into applications for the synthesis of natural products is under investigation and will be reported in due course.

Experimental Section

Typical Procedure for the One pot Synthesis of 12bα-Indolo[2,3-*a*]quinolizidine Derivatives 9, Conditions A (Kinetic): Preparation of (2*R*,3*S*,12b*S*)-Ethyl 4-Oxo-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate 12bα-9ab

A solution of aldehyde **1a** (0.42 mmol), catalyst **4** (18 mg, 0.05 mmol) and amide **2b** (77 mg, 0.28 mmol) in DCM (0.3 mL) was stirred for 4 days at 3 °C. After full conversion of amide **2a** (determined by ^{1}H NMR), the reaction mixture was cooled to −78 °C followed by addition of HCl (50 μL, 0.05 mmol, 1 M in diethyl ether). The mixture was stirred for at −78 °C for 3 h and slowly allowed to reach room temperature. Saturated $NaHCO_3$ (3 mL) and DCM (3 mL) were added and the water phase was extracted with DCM (2× 3 mL). The combined organic phases 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 FC (pentane:EtOAc). Compound 12b**α-9ab** and 12b**β-9ab** was isolated in 53% total yield, *dr* 82:18 and 95% *ee*. Compound 12b**α-9ab**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (broad s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.36–7.32 (m, 3H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 7.22–7.18 (m, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 5.12 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.81 (t, *J* = 6.0 Hz, 1H), 4.12–4.02 (m, 2H), 3.76 (d, *J* = 7.5 Hz, 1H), 3.50 (td, *J* = 8.0, 4.5 Hz, 1H), 3.03 (tdd, *J* = 13.5, 5.0, 2.5 Hz, 1H), 2.95 (td, *J* = 12.0, 3.5 Hz, 1H), 2.77 (dt, *J* = 15.0, 2.0 Hz, 1H), 2.52–2.43 (m, 2H), 1.09 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 165.8, 140.9, 136.1, 132.2, 129.0, 127.5, 127.0, 122.3, 120.0, 118.4, 111.1, 61.4, 55.0, 52.3, 42.0, 38.8, 33.3, 21.0, 14.0; MS (APCI): *m*/*z* (%) = 389 (100) $[M+H]^+$. The enantiomers were separated by HPLC on a Chiralcel OJ-RH column (150 × 4.6 mm) with H_2O/acetonitrile as the eluent [70:30 to 20:80 (40 min gradient); 20:80 (isocratic 20 min); flow rate: 0.3 mL min^{-1}]: Rt (min) = 37.3 (minor enantiomer); 38.0 (major enantiomer).

Typical Procedure for the One-Pot Synthesis of 12bβ-Indolo[2,3-*a*]quinolizidine Derivatives 9, Conditions B (Thermodynamic): Preparation of (2*R*,3*S*,12b*R*)-Ethyl 4-Oxo-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate 12bβ-9ab

A solution of aldehyde **1a** (0.42 mmol), catalyst **4** (18 mg, 0.05 mmol) and amide **2b** (77 mg, 0.28 mmol) in DCM (0.3 mL) was stirred for 4 days at 3 °C. After full conversion of amide **2b** (determined by ^{1}H NMR), TFA (0.2 mL) was added and the resulting mixture was heated to 70 °C in an open vessel for 5 min (to remove DCM) and in a sealed vessel for one additional hour at 70 °C. Saturated $NaHCO_3$ (3 mL) and DCM (3 mL) were added and the water phase was extracted with DCM (2 × 3 mL). The combined organic phases 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 FC (pentane:EtOAc). Compound 12b**α-9ab** and 12b**β-9ab** was isolated in 75% total yield, *dr*. 22:78 and 96% *ee*. Compound 12b**β-9ab**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (broad s, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.32–7.30 (m, 3H), 7.26–7.24 (m, 1H), 7.21–7.17 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.97 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.05–4.00 (m, 2H), 3.57 (d, *J* = 5.0 Hz, 2H), 2.86 (td, *J* = 11.5, 4.5 Hz, 1H), 2.81–2.78 (m, 1H), 2.61 (ddd, *J* = 13.0, 4.0, 2.0 Hz, 1H), 2.10–2.02 (m, 1H), 1.03 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 165.2, 140.9, 136.4, 132.4, 129.0, 127.6, 126.9, 126.7, 122.4, 120.0, 118.5, 111.1, 109.6, 61.3, 57.1, 53.9, 40.9, 40.4, 35.6, 21.0, 14.0; MS (APCI): *m*/*z* (%) = 389 (100) $[M+H]^+$. The enantiomers were separated by HPLC on a Chiralcel OD-RH column (150 × 4.6 mm) with H_2O/acetonitrile as the eluent [70:30 to 20:80 (60 min gradient); 20:80 (isocratic 15 min); flow rate: 0.25 mL min^{-1}]: Rt (min) = 59.5 (minor enantiomer); 63.1 (major enantiomer).

Typical Procedure for the One-Pot Synthesis of 11bα-9,10-Dimethoxybenzo[*a*]quinolizidine Derivatives 10, Kinetic Conditions: Preparation of (2*R*,3*S*,11b*S*)-Ethyl 9,10-Dimethoxy-4-oxo-2-phenyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate 11bα-10ab

A solution of aldehyde **1a** (0.42 mmol), catalyst **4** (18 mg, 0.05 mmol) and amide **3b** (80 mg, 0.28 mmol) in DCM (0.3 mL) was stirred for 24 h at room temperature. After full conversion of amide **3b** (determined by ^{1}H NMR), the reaction mixture was cooled to −78 °C followed by addition of HCl (100 μL, 0.10 mmol, 1 M in diethyl ether). The mixture was stirred at −78 °C for 3 h and slowly allowed to reach room temperature. Saturated $NaHCO_3$ (3 mL) and DCM (3 mL) were added and the water phase was extracted with DCM (2 × 3 mL). The combined organic phases 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 FC (pentane:EtOAc). Compound 11b**α-10ab** and 11b**β-10ab** was isolated in 41% total yield, *dr*. 67:33 and 95% *ee*. Compound 11b**α-10ab**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (t, *J* = 7.5 Hz, 2H), 7.30–7.25 (m, 3H), 6.66 (s, 1H), 6.59 (s, 1H), 4.86 (ddd, *J* = 12.5, 4.5, 1.5 Hz, 1H), 4.61 (t, *J* = 6.0 Hz, 1H), 4.16–4.06 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.79 (d, *J* = 8.0 Hz, 1H), 3.52 (dt, *J* = 6.5, 6.0 Hz, 1H), 3.05 (ddd, *J* = 14.0, 14.0, 5.0 Hz, 1H), 2.93 (dt, *J* = 12.0, 3.0 Hz, 1H), 2.68 (broad d, *J* = 15.5 Hz, 1H), 2.48 (t, *J* = 6.5 Hz, 2H), 1.13 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 165.8, 148.1, 147.8, 141.7, 129.0, 128.1, 127.9, 127.3, 126.9, 112.0, 107.7, 61.3, 56.2, 56.0, 54.4, 54.1, 41.1, 38.8, 35.1, 28.4, 14.0; MS (APCI): *m*/*z* (%) = 410 (100) $[M+H]^+$. The enantiomers were separated by HPLC on a Chiralcel OJ-RH column (150 × 4.6 mm) with H_2O/acetonitrile as the eluent [70:30 to

20:80 (60 min gradient); 20:80 (isocratic 40 min); flow rate: 0.3 mL min^{-1}]: Rt (min) = 35.3 (major enantiomer); 36.4 (minor enantiomer).

Typical Procedure for the One-Pot Synthesis of 11bβ-9,10-Dimethoxybenzo[*a*]quinolizidine Derivatives 10, Thermodynamic Conditions: Preparation of (2*R*,3*S*,11b*R*)-Ethyl 2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-2-phenyl-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate 11bβ-10ab

A solution of aldehyde **1a** (0.42 mmol), catalyst **4** (18 mg, 0.05 mmol) and amide **3b** (80 mg, 0.28 mmol) in DCM (0.3 mL) was stirred for the given time at the given temperature (see Table 8). After full conversion of amide **3b** (determined by ^{1}H NMR), $SnCl_4$ (100 μL, 0.10 mmol, 1 M in DCM) was added and the resulting mixture was stirred at ambient temperature for 1 h. Saturated $NaHCO_3$ (3 mL) and DCM (3 mL) were added and the water phase was extracted with DCM (2 × 3 mL). The combined organic phases 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 FC (pentane:EtOAc). Compound 11b**α-10ab** and 11b**β-10ab** was isolated in 66% total yield, *dr*. 23:77 and 94% *ee*. Compound 11b**β-10ab**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.25 (s, 1H), 7.24 (s, 1H), 6.64 (s, 1H), 6.61 (s, 1H), 4.94–4.91 (m, 1H), 4.86 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.12–4.02 (m, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.57 (broad d, *J* = 5.0 Hz, 1H), 2.93 (td, *J* = 11.5, 4.0 Hz, 1H), 2.88 (td, *J* = 12.0, 2.0 Hz, 1H), 2.71–2.66 (m, 1H), 2.02–1.85 (m, 1H), 1.06 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 165.6, 148.5, 148.4, 141.8, 129.3, 128.6, 127.9, 127.4, 127.3, 112.0, 108.4, 61.5, 57.2, 56.7, 56.5, 56.4, 41.7, 40.3, 38.1, 28.8, 14.4; MS (APCI): *m*/*z* (%) = 410 (100) $[M+H]^+$. The enantiomers were separated by HPLC on a Chiralcel OJ-RH column (150 × 4.6 mm) with H_2O/acetonitrile as the eluent [70:30 to 20:80 (60 min gradient); 20:80 (isocratic 40 min); flow rate: 0.3 mL min^{-1}]: Rt (min) = 46.1 (major enantiomer); 47.1 (minor enantiomer).

Acknowledgements

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