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Organocatalytic asymmetric synthesis of highly functionalized pyrrolizidines via cascade Michael/hemi-aminalization reactions of isoindolinones

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ABSTRACT

This Letter describes the first application of activated 3-substituted isoindolinones in asymmetric synthesis of aza-tricyclic heterocycles, belonging to the class of pyrrolizidines. It was found that diphenylprolinol trimethylsilyl (TMS) ether was particularly effective, allowing the obtaining of adducts in good yields and up to 96% ee via iminium ion catalysis in the reaction of unsaturated aldehydes.

Introduction

The development of new methods for the synthesis of the isoindolinone heterocyclic compounds **1** is a subject of great interest due to their wide range of biological activities.[1,2] In addition, related pyrrolizidine are commonly observed structural units of many alkaloids and bioactive compounds,[2–6] as for example for cyclin dependent kinase inhibitors.[7] Although several synthesis leading to the racemic analogs **2** have been reported,[7–9] no attention has been paid to the asymmetric synthesis of these aza-polycyclic compounds (Fig. 1).

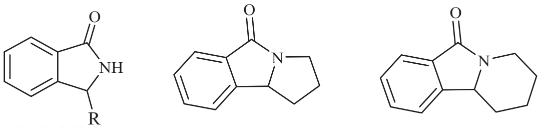
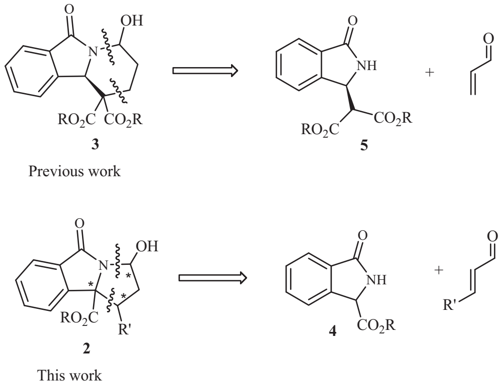

1 isoindolinone **2** benzopyrrolizidine **3** benzoindolizidine

Figure 1. Isoindolinone, indolizidine and pyrrolizidine scaffolds.

In our recent works we have developed a convenient approach to tricyclic indolizidines **3** via a K_2CO_3-catalyzed cascade Michael conjugated addition/hemi-aminalization reaction of isoindolinones with unsaturated aldehydes for the construction of the six membered ring (Scheme 1).[10–13] In connection with those works, we envisioned that a related Michael reaction might occur at the activated 3-position of alkyl-2-(1-oxoisoindolin-3-yl) carboxylates **4**, while the NH group of the lactam should guarantee the closure for the five membered ring. However, the success in the asymmetric synthesis of **3** was related to availability of the highly enantioenriched dialkyl-2-(1-oxoisoindolin-3-yl)malonates **5**, previously obtained in organocatalyzed tandem reactions.[13,14] In the case of **2**, the formation of the new stereocenters and the



Scheme 1. Retrosynthetic analysis for indolizidine (previous work) and pyrrolizidine (this work).

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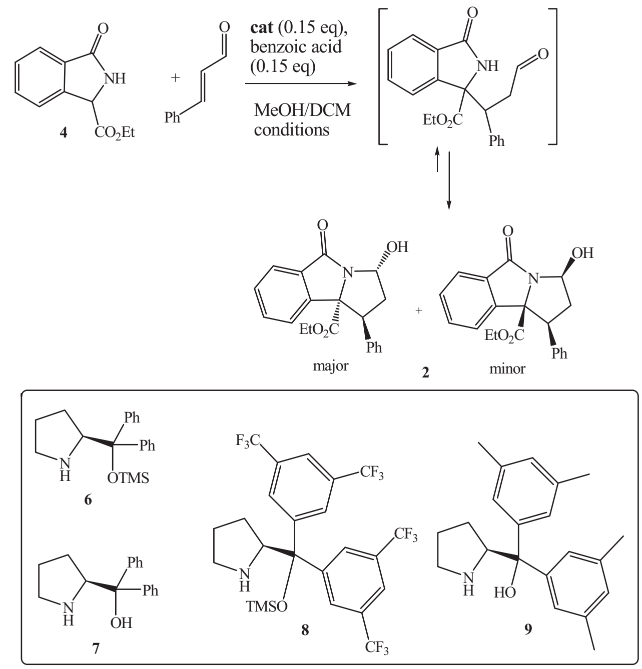


Scheme 2. Synthesis of aza-polycyclic compounds.

Table 1
Preliminary investigation

Entry	cat	*T* (°C)	*t* (h)	Yield[a] (%)	Dr[b]	ee[c] (%)
1	**6**	rt	1	**2a**: 71%	60/40	57/63
2	**7**	rt	2	**2a**: 58%	60/40	27/48
3	**8**	rt	8	No reac.		
4	**9**	rt	8	No reac.		
5	**6**	0	3	**2a**: 81%	56/44	80/83
6[d]	**6**	−10	5	**2a**: 80%	55/45	84/90
7	**6**	−15	24	**2a**: 62%	54/46	86/95
8[d]	**6**	−15	18	**2a**: 85%	53/47	87/96
9[d]	**6**	−20	24	**2a**: 87%	60/40	85/91

[a] Isolated yield.
[b] Determined by ^{1}H NMR on the crude.
[c] Determined by HPLC on chiral column.
[d] Reaction performed in MeOH/DCM mixture (10/1). All the other experiments were performed in MeOH only.

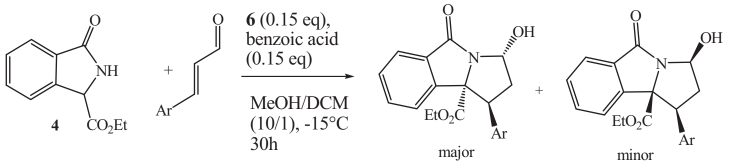
construction of the five membered ring should occur in a unique process employing isoindolinones **4** as pro-nucleophiles.

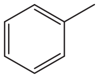
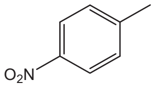
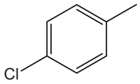
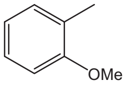
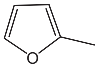
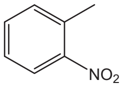
Results and discussion

In this Letter, we have focused on proline-based organocatalysts, since iminium catalysis has proved to be a powerful tool in asymmetric Michael reactions of unsaturated aldehydes,[15–24] and in cascade reactions for the synthesis of nitrogen heterocycles.[22,23] Therefore, we investigated the reaction of cinnamaldehyde with the readily available isoindolinone **4**[25] activated by an ester group, testing different organocatalysts (Scheme 2). To our delight, the diphenylprolinol trimethylsilyl (TMS) ether **6** led to the expected tricyclic adduct **2a** in good yield, but with moderate enantioselectivity, while the other catalysts were less effective (Table 1, entries 1–4).

A notable increase of the enantioselectivity, up to 96% ee, was achieved after the optimization of the reaction conditions, performing the reaction in a 10:1 mixture of MeOH/DCM, used to improve the solubility of **4** at −15 °C (entry 8). Under these conditions, the scope was briefly analyzed reacting differently substituted unsaturated aldehydes (Table 2). Good results in terms of yields and enantioselectivity were obtained, except for the 2-furyl

Table 2
Scope of asymmetric Michael/hemi-aminalization reaction



Entry	Ar	Yield[a] (%)	Dr[b]	ee[c] (%)
1		**2a**: 85%	53/47	87/96
2		**2b**: 78%	80/20	93/n.d.
3		**2c**: 82%	66/34	88/91
4		**2d**: 80%	75/25	81/62
5		**2e**: 81%	60/40	73/55
6		**2f**: 75%	63/37	87/85

[a] Isolated yield.
[b] Determined by ^{1}H NMR on the crude.
[c] Determined by HPLC on chiral column.

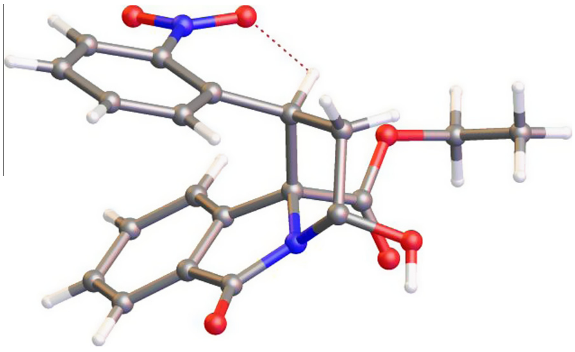
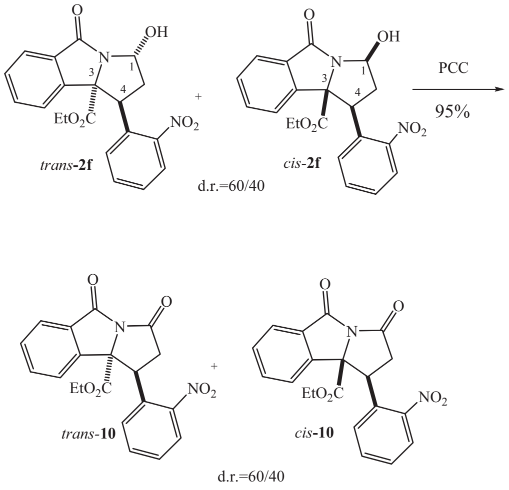


Figure 2. X-ray structure of the major diastereomer of *rac*-**2f** (CCDC 1047317).[26]



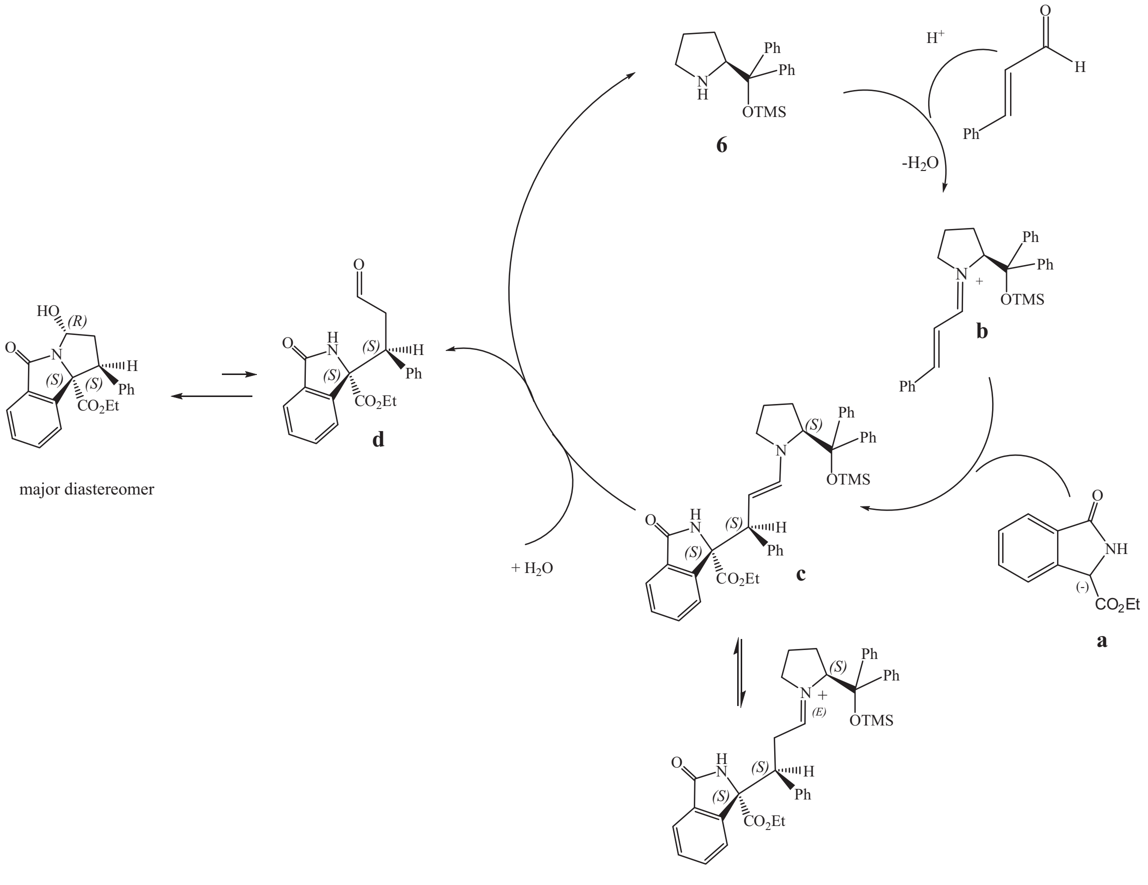
Scheme 3. PCC oxidation of *rac*-**2f**.

acrolein, for which a moderate enantiomeric excess was observed (entry 5).

Despite the formation of three stereocenters only two diastereomers were detected, albeit in a moderate or low dr. HPLC separation of the mixtures of diastereomers was easily achieved on chiral stationary phase, except for the *p*-NO_2 derivative **2b**. In this case, after a chromatographic purification, we were able to determine the ee only of the separated major diastereomer (Entry 2, Table 2).

Attempts at crystallization of the enantioenriched compounds, which appear as wax-like solid, failed. On the other hand, also the crystallization of racemates proved to be critical: only the major diastereomer of *rac*-**2f** was able to crystallize but all the crystals were very weakly diffracting. In any case, the collected crystallography data were consistent to solve and refine the structure of *rac*-**2f** (Fig. 2), showing the information on the relative configuration. This was sufficiently clear to highlight a 1,3-*cis*-1,4-*trans* relationship between the contiguous tertiary and quaternary stereocenters (see also Scheme 3).

Further efforts were directed to get information on the geometry of the minor diastereomer. To that purpose we exploit previous findings on the oxidation of the hemi-aminal group of benzoindolizidines.[10,13] The removing of the stereocenter at the hemi-aminal functionality by PCC oxidation on *rac*-**2f** (mixture of diastereomers), led to the interesting imide derivative **10** with an unchanged dr with respect to *rac*-**2f** (Scheme 3). This outcome



Scheme 4. Proposed mechanism.

highlights that **2f** and consequently **10** are mixtures of diastereomers which differ for the relative configurations at the contiguous quaternary and tertiary stereocenters. In addition, Spartan calculations performed on the minor diastereomer *cis*-**2f** point out a higher stability of about 3.5 Kcal/mol for the isomer in which the OH group in *cis* with the COOEt (Scheme 3).

Comparing the ^{1}H NMR spectra of **2f**, this relative configuration can be confidently extended to the other tricyclic derivatives.

On the basis of the mechanism established in the literature,[24] one can assume that the nucleophilic attack of **a** should occur at the less hindered *si* face of **b** to give **c**, providing information on the absolute configuration of the newly formed stereocenters (Scheme 4). The catalyst is, then, regenerated for the next catalytic cycle through hydrolysis of the intermediate **c** and the resulting acyclic adduct **d** undergoes diastereoselective cyclization to give **2**.

Conclusions

We have developed the first asymmetric synthesis of highly substituted benzopyrrolizidines via an efficient organocatalyzed cascade Michael/hemi-aminalization reaction employing the 3-carboxylate substituted isoindolinone **4** as the nucleophile. High yields and very good enantioselectivity were usually observed. Despite the formation of three stereocenters, only two diastereomers were obtained, but with moderate or low dr. In addition, preliminary investigation on the second reactivity of the obtained tricyclic compounds, structure elucidation, and a plausible mechanistic pathway have also been discussed.

Synthetic applications and the discovery of new asymmetric reactions based on this concept and on the use of **4** are ongoing in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (procedures, spectra and HPLC traces of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.028.

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