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Organocatalytic Enantioselective Synthesis of Pyrazolidines, Pyrazolines and Pyrazolidinones

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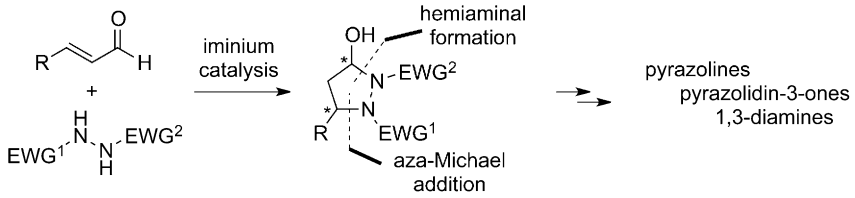
Abstract: Enantiopure pyrazolidines, pyrazolines and pyrazolidinones have been accessed in a direct and efficient manner through an organocatalytic, enantioselective aza-Michael/hemiaminal formation cascade process from enals and *N,N′*-disubstituted hydrazides. The process takes place with high regio- and stereoselectivities and furnishes the target compounds in high overall yields by means of an operationally very simple methodology.

Keywords: asymmetric catalysis; domino reaction; heterocycles; hydrazines; organocatalysis

Pyrazolidines are privileged heterocyclic structures in medicinal chemistry, principally due to their presence, as important subunits, in many natural and synthetic bioactive compounds.[1,2] Pyrazolidines can be easily oxidized to afford pyrazolines, which are also motifs of high relevance because of their presence in a wide range of biologically active molecules.[3] However, despite their interest and potential as promising candidates in drug discovery programs, the number of available synthetic procedures for the stereoselective preparation of pyrazolidines and/or pyrazolines is still very limited. Most of the methodologies reported rely on the use of chiral Lewis acids, involving typically [3+2] cycloaddition chemistry using dipoles such as diazoalkanes,[4] nitrile imines[5] or hydrazones,[6] or by means of metal-catalyzed amination of allenes.[7] Alternatively, one report addressed the access to these heterocycles in a stereocontrolled manner by cyclocondensation of chalcones with a primary hydrazine, also in the presence of chiral transition metal complexes as catalysts, although only moderate levels of enantioselectivity were obtained.[8]

In this context, organocatalysis has emerged as a useful alternative tool for the development of enantioselective versions of certain transformations which do not proceed efficiently with metal catalysis. The enantioselective synthesis of pyrazolines is a representative example of the complementary natures of these two different methodological approaches, with a couple of reports describing the access to these heterocycles under metal-free conditions. On the one hand, List and co-workers developed an enantioselective version of the Fischer reaction that proceeds through a 6π-electrocyclization mechanism in the presence of a chiral Brønsted acid catalyst, generating 5-substituted 3-methylpyrazolines by reacting methyl alkenyl ketones with primary hydrazines.[9] Excellent results were obtained for β-aryl-substituted enones, but the use of β-alkyl-substituted substrates led to an important reduction of both yield and enantioselectivity. Alternatively, cyclocondensation of enones with primary monosubstituted hydrazides has been reported by Brière and co-workers using chiral phase-transfer catalysis.[10] Although very efficient and straightforward, this later methodology was limited to the use of chalcones. It should also be highlighted that these two approaches rely on the use of enones as starting materials, thus generating pyrazolines containing an aryl or a methyl substituent at the 3-position. However, the use of α,β-unsaturated aldehydes in this transformation which would lead to enantioenriched pyrazolines without any substitution at this 3-position still remains elusive.

With these precedents in mind, we envisaged that pyrazolidin-3-ols could be accessible by the reaction between α,β-unsaturated aldehydes and *N,N′*-disubstituted hydrazines, by means of a cascade process consisting of an aza-Michael/hemiaminal formation sequence (Scheme 1). Moreover, this proposal presents a possibility for the development of an enantioselec-



Scheme 1. Direct organocatalytic enantioselective pyrazolidine synthesis through iminium activation.

tive version of the transformation, using organocatalysis as the methodological approach, *via* iminium activation.

These pyrazolidin-3-ols have the potential to be further elaborated in order to obtain an array of chemically related heterocyclic structures of interest, such as 3-unsubstituted pyrazolines. What is more, simple transformations of these adducts can also provide a direct access to chiral pyrazolidin-3-ones and 1,3-diamines, which are also important chiral building blocks in synthesis.

We thought that the design of the proposed reaction could show some selectivity issues due to the similar nucleophilic characters of both the catalyst and the hydrazine. The idea of using monosubstituted hydrazines was discarded from the beginning, since these would probably undergo either a condensation with the enal furnishing a highly stable hydrazone side product or, alternatively, they could undergo uncatalyzed cyclocondensation reactions, affording racemic pyrazoline adducts. In order to avoid these perceived condensation issues, *N,N′*-disubstituted hydrazines were selected for the transformation, although issues regarding selectivity towards 1,4-addition *vs.* undesired 1,2-addition to the enal have still to be considered. Moreover, for the cases in which the two substituents of the hydrazine are different, an additional regioselectivity issue appears. In addition, it is known that aza-Michael transformations are reversible in nature, which in turn results in the conjugate addition products very often being configurationally unstable. However, this reversibility problem was thought to be irrelevant to our case, since the subsequent intramolecular hemiaminal formation step would presumably make the overall process irreversible.

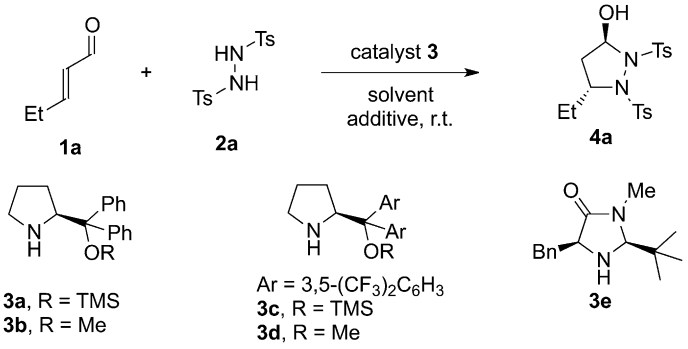
In an initial approach and in order to avoid the aforementioned regioselectivity problem related to the use of hydrazines with two different substituents, *N,N′*-bis(*p*-toluenesulfonyl)hydrazide (**2a**) was selected as model substrate, also considering that the high acidity of the N−H protons would favourably assist the first conjugate addition step (Table 1). The viability of the reaction was initially tested for different catalysts using toluene as solvent and working at room temperature. In this context, diphenylprolinol derivatives **3a** and **3b** delivered the desired product **4a** in high isolated yield and diastereoselectivity, although with low enantiocontrol (entries 1 and 2). In contrast, enantioselectivity was improved when the bulkier catalysts **3c** and **3d** were employed, although the yield was diminished (entries 3 and 4). Imidazolidinone **3e** developed by MacMillan was also tested, providing **4a** in good yield but low enantioselectivity (entry 5). Next, the effect of the solvent was studied in conjunction with optimal catalyst **3c** (entries 6–9), but it was observed that the use of more polar solvents resulted in a less efficient reaction. In an attempt to improve the yield of the transformation, we also surveyed the incorporation of a base as a co-catalyst, which was thought to activate the hydrazide by forming the corresponding anion. However, no reaction was observed when employing DABCO (entry 9) and, although DBU gave an improved yield of the pyrazolidin-3-ol, enantiocontrol was lost (entry 10).

Using the conditions shown in entry 3 of Table 1, we decided to investigate the influence that the substitution pattern of the hydrazide reagent would have on the reaction. In this context, a family of different *N,N′*-disubstituted hydrazides was tested in the reaction (Table 2). Initially, no reaction was observed when the less acidic hydrazide **2b** was used (entry 2), and low yields of the pyrazolidinol adduct were observed when phthalohydrazide **2c** was employed (entry 3). The need for two strongly electron-withdrawing substituents like the tosyl group was confirmed when hydrazides **2d** and **2e** were tested, for which no reaction was observed (entries 4 and 5). In contrast, the reaction between the enal **1a** and the unsymmetrically substituted *N*-Boc-*N′*-(*p*-nitrobenzenesulfonyl) hydrazide **2f** proceeded smoothly, providing the desired pyrazolidin-3-ol **4f** in excellent yield, enantioselectivity and remarkably as a single regioisomer (entry 6). The high reactivity and complete regioselectivity observed may be understood in terms of the higher acidity of the N−H group attached to the nosyl (Ns) substituent, which presumably makes this nitrogen group more nucleophilic for the initial aza-Michael process.

We next proceeded to extend the reaction to the use of α,β-unsaturated aldehydes with different substitution patterns in order to survey the scope of the reaction and its performance for the preparation of differently substituted pyrazolidin-3-ols (Table 3).

From the results summarized in Table 3 we observed that hydrazide **2f** reacted efficiently with α,β-unsaturated aldehydes containing linear alkyl chains

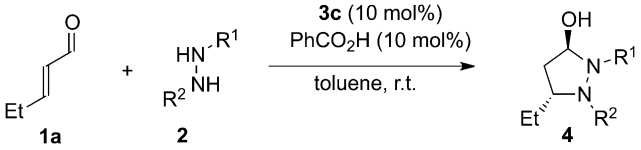
Table 1. Screening for the best reaction conditions.[a]

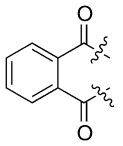


Entry	Solvent	3	Additive[b]	Yield of **4a** [%][c]	*dr*[d]	*ee* [%][e]
1	toluene	**3a**	$PhCO_2H$	83	>10:1	20
2	toluene	**3b**	$PhCO_2H$	80	>10:1	11
3	toluene	**3c**	$PhCO_2H$	54	>10:1	97
4	toluene	**3d**	$PhCO_2H$	30	>10:1	92
5	toluene	**3e**	TFA	67	10:1	45
6	CH_2Cl_2	**3c**	$PhCO_2H$	24	>10:1	38
7	CH_3CN	**3c**	$PhCO_2H$	38	>10:1	36
8	EtOH	**3c**	$PhCO_2H$	32	>10:1	39
9	toluene	**3c**	DABCO	<10	n.d.[f]	n.d.[f]
10	toluene	**3c**	DBU	61	>10:1	0

[a] Reactions performed on a 0.2-mmol scale of **1a** and **2a** using 10 mol% of catalyst **3** in 2.0 mL of the corresponding solvent.
[b] 10 mol% used.
[c] Isolated yield.
[d] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[e] Determined by HPLC on a chiral stationary phase.
[f] n.d.: not determined.

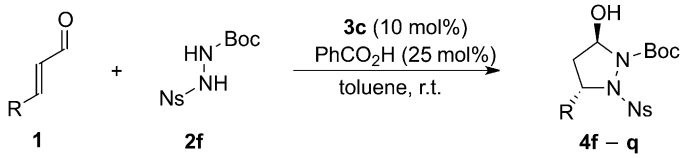
Table 2. Effect of hydrazide substitution.[a]



Entry	2	R^1	R^2	4	Yield [%][b]	*dr*[c]	*ee* [%][e]
1	**2a**	Ts	Ts	**4a**	54	>10:1	97
2	**2b**	Boc	Boc	**4b**	<5%	–	–
3	**2c**			**4c**	23	n.d.[f]	n.d.[f]
4	**2d**	*p*-MeO-C_6H_4	Ts	**4d**	<5%	–	–
5	**2e**	*p*-NO_2-C_6H_4	Ts	**4e**	<5%	–	–
6	**2f**	Boc	Ns	**4f**	87	>10:1	93

[a] Reactions performed on a 0.2-mmol scale of **1a** and **2**.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[e] Determined by HPLC on a chiral stationary phase.
[f] n.d.: not determined.

Table 3. Scope of the reaction.[a]



Entry	**1** (R)	**4**	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**1a** (Et)	**4f**	87	>10:1	93
2[e]	**1b** (Me)	**4g**	93	>10:1	85
3	**1c** (*n*-Pr)	**4h**	99	>20:1	92
4	**1d** (*n*-Bu)	**4i**	91	>20:1	94
5	**1e** (n-C_5H_{11})	**4j**	95	>20:1	93
6	**1f** (n-C_6H_{13})	**4k**	78	>20:1	93
7	**1g** (n-C_7H_{15})	**4l**	78	>20:1	92
8	**1h** (n-C_8H_{17})	**4m**	99	>20:1	94
9	**1i** (Z-EtCH=CHCH$_2$CH$_2$-)	**4n**	68	>20:1	90
10	**1j** (*i*-Pr)	**4o**	50	>20:1	97
11	**1k** (CO_2Et)	**4p**	65	20:1	89
12	**1l** ($CH(OMe)_2$)	**4q**	95	>20:1	>99
13[f]	**1a** (Et)	**4a**	54	>10:1	97
14[f]	**1d** (*n*-Bu)	**4r**	21	>20:1	96

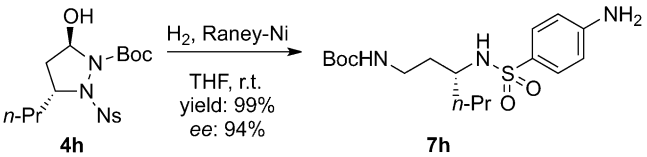
[a] Reactions performed on a 0.2-mmol scale of **1** and **2f** using 10 mol% of catalyst **3c** in 2.0 mL of toluene.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the reaction mixture.
[d] Determined by HPLC on a chiral stationary phase.
[e] Reaction carried out at 4 °C.
[f] Hydrazide **2a** was used.

of different length and size, whilst maintaining both high yield and high levels of stereoselectivity (entries 1–8).[11] Furthermore, branched and unsaturated β-alkyl substituents were tested with success in the reaction (entries 9 and 10). Functionalized α,β-unsaturated aldehydes, such as **1k** or **1l** also performed well, furnishing the final adducts in high yield and stereocontrol (entries 11 and 12). Again, all these cases showed the formation of a single regioisomer, regardless the substitution pattern at the enal reagent. It is interesting to note that when hydrazide **2a** was employed, a very significant dependence of the yield on the length of the β-alkyl substituent was observed, obtaining very poor yields when longer substituents were incorporated, although enantioselectivity remained high (entries 13 and 14). The absolute configuration of products **4** was assigned by analogy after a single-crystal X-ray analysis of a pyrazolidine product obtained from the reduction of the pyrazolidin-3-ol **4a** (see the Supporting Information).[12]

Having established a robust route to the pyrazolidine motif, we proceeded to run a series of simple transformations in order to synthesize other pyrazolidine-related heterocyclic structures of interest (Table 4). Treating compounds **4** with TFA led to sequential deprotection/dehydration, obtaining a series of pyrazolines **5** in excellent yields whilst maintaining the stereochemical integrity of the stereocenter, although these types of heterocycles have been found to be rather configurationally unstable.[13] Additionally, pyrazolidin-3-ones **6** were also obtained in excellent yields and as highly enantiopure materials by oxidation of pyrazolidin-3-ols.

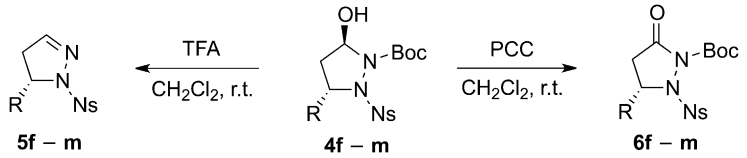
Another potential synthetic application of this type of heterocycle relies on the possibility to cleave the N–N bond, giving access to highly important enantioenriched 1,3-diamines.[6,14] In particular, enantiopure 1,3-diamine **7h** could be obtained after treating pyrazolidin-3-ol **4h** with H_2 in the presence of Raney-Ni, which occurred concomitant with the reduction of the nitro group present at the nosyl substituent (Scheme 2).

In conclusion, we have developed the first asymmetric aminocatalytic direct synthesis of pyrazolidines based on the aza-Michael/hemiaminalization reaction of α,β-unsaturated aldehydes and hydrazides under iminium activation. The reaction was catalyzed by the



Scheme 2. Synthesis of 1,3-diamine **7h** from pyrazolin-3-ol **4h**.

Table 4. Synthesis of pyrazolines **5** and pyrazolidinones **6**.



5f – m **4f – m** **6f – m**

Entry	**4** (R)	Yield of **5** [%][a]	*ee* of **5** [%][b]	Yield of **6** [%][a]	*ee* of **6** [%][b]
1	**4f** (Et)	97	92	95	93
2[c]	**4g** (Me)	85	85	94	84
3	**4h** (*n*-Pr)	99	92	97	92
4	**4i** (*n*-Bu)	99	91	90	90
5	**4j** (*n*-C_5H_{11})	87	91	97	91
6	**4k** (*n*-C_6H_{13})	86	90	93	91
7	**4l** (*n*-C_7H_{15})	99	92	96	91
8	**4m** (*n*-C_8H_{17})	99	90	94	90

[a] Isolated yield.
[b] Determined by HPLC on a chiral stationary phase (see Supporting Information).
[c] Reaction carried out at 4 °C.

commercially available diarylprolinol silyl ether **3c** and took place in very high yields and excellent stereoselectivities, allowing the synthesis of a wide array of nitrogen-containing heterocycles of relevance in medicinal chemistry. Furthermore, a series of simple transformations of adducts has been presented, which easily allows the formation of some pyrazolidine derivatives, increasing the utility of the presented methodology.

Experimental Section

General Methods and Materials

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, $\delta = 7.26$ ppm for ^{1}H NMR, $CDCl_3$, $\delta = 77.0$ ppm for ^{13}C NMR). IR spectra were measured in a Perkin–Elmer 1600 and a Perkin–Elmer Spectrum BX apparatus. Mass spectra (MS) were recorded on an Agilent 7890 A gas chromatograph coupled to an Agilent 5975 mass spectrometer. High-resolution mass spectra (HR-MS) were recorded on a micromass GCT spectrometer using chemical ionization (CI) or Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using the electrospray (ESI) technique. Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or *p*-anisaldehyde dip. Melting points were measured in a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on Perkin–Elmer 241 and Jasco P-2000 polarimeters. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC in a Waters 2695 with a Waters 2998 photodiode array detector (Daicel Chiralpak IA, IC, AS-H and AD-H columns).

Analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230–400 mesh, Merck) was employed.

General Procedure for the Preparation of Pyrazolidinols 4

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **3c** (0.02 mmol, 10 mol%), PhCOOH (0.05 mmol, 25 mol%) and toluene (2 mL). Then, hydrazine **2** (0.20 mmol) and the α,β-unsatured aldehyde **1** (0.20 mmol) were added. The stirring was maintained at room temperature until the reaction was complete (24–72 h) and the crude reaction mixture was concentrated and directly charged onto silica gel and subjected to FC. The racemic standards for HPLC separation conditions were prepared using D,L-proline (0.02 mmol, 10 mol%) instead of catalyst **3c**, without PhCOOH and in CH_2Cl_2 (2 mL) at room temperature.

General Procedure for the Deprotection of Pyrazolidinols 4: Synthesis of Pyrazolines 5

A vial equipped with a magnetic stirring bar was charged with the pyrazolidinol **4** (0.2 mmol) in 2 mL of CH_2Cl_2. Then TFA (2 mmol) was added. The reaction mixture was stirred at rrom temperature until completion of the reaction (5 h). The reaction mixture was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude was charged onto silica gel and subjected to FC.

General Procedure for the Oxidation of Pyrazolidinols 4: Synthesis of Pyrazolidin-3-ones 6

A vial equipped with a magnetic stirring bar was charged with the pyrazolidinol **4** (0.18 mmol) in CH_2Cl_2 (5 mL). Then PCC (0.91 mmol) and molecular sieves (4 Å) were added. The reaction mixture was stirred at room temperature until completion (16 h) and the crude mixture was con-

centrated and directly charged onto silica gel and subjected to FC.

Supporting Information

General methods and materials, experimental procedures, characterization data, and determination of the absolute configuration as well as copies of the NMR spectra and HPLC traces are available in the Supporting Information.

Acknowledgements

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[11] β-Aryl-substituted enals reacted very slowly, providing in all cases yields below 15% yield.

[12] CCDC 844059 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[13] Compounds **5** and **6** were found to slowly racemize upon standing at room temperature as $CHCl_3$ solutions.

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