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Organocatalytic Approach to Benzofused Nitrogen-Containing Heterocycles: Enantioselective Total Synthesis of (+)-Angustureine

Santos Fustero,*[a, b] Javier Moscardó,[a] Diego Jiménez,[a] María Dolores Pérez-Carrión,[b] María Sánchez-Roselló,[a] and Carlos del Pozo[a]

Pyrrolidine and piperidine benzofused heterocyclic ring systems have become attractive targets in organic and medicinal chemistry. These families of compounds are extremely valuable scaffolds due to their widespread occurrence in Nature, diverse biological activity, and interesting chemical properties.[1] Therefore, the development of new strategies for the generation of these heterocyclic frameworks, especially in a chiral nonracemic form, is of great interest in organic synthesis.

Regarding the piperidine family, strategies for the catalytic enantioselective preparation of tetrahydroquinolines are mainly based either on the asymmetric hydrogenation of the corresponding aromatic quinoline derivatives by using chiral metal catalysts[2] or, more recently, chiral Brønsted acids;[3] or alternatively an enantioselective aza-Diels–Alder reaction.[4] In the same way, one of the common strategies used to access enantiomerically enriched tetrahydroisoquinolines is based on the asymmetric transfer hydrogenation of isoquinoline and dihydroisoquinoline skeletons.[5] However, probably the most popular method used to access these derivatives relies on the addition of nucleophilic carbon species to the C=N bond of dihydroisoquinolines.[6] In the pyrrolidine benzofused family, the indoline core is the most important substructure, and their synthesis is nowadays the subject of intensive research. In recent years, several reports for the enantioselective formation of indolines have appeared in the literature.[7] However, the construction of the isoindoline core is clearly underdeveloped and only one method for its catalytic enantioselective preparation has been reported very recently.[8]

The addition of nitrogen-centered nucleophiles to α,β-unsaturated systems, that is, the so-called aza-Michael reaction, is one of the simplest and most direct ways to create C–N bonds. The intramolecular version is particularly relevant because it allows the direct generation of nitrogen-containing heterocycles. Despite its synthetic potential, examples of the enantioselective version of this intramolecular reaction[9] are very scarce and all rely on the use of organocatalysts. One of these examples described the organocatalytic synthesis of tetrahydroisoquinolines by using amides as nitrogen nucleophiles, although with poor enantiocontrol.[10] Very recently, the synthesis of pyrazolo–indole compounds was performed by using the indole nitrogen as a nucleophile in the presence of a cinchonidine-derived catalyst.[11] The third example of an organocatalytic intramolecular aza-Michael reaction (IMAMR) reported to date was developed by our research group,[12] and allowed for the generation of several five- and six-membered heterocycles with excellent enantioselectivities by using carbamates as nitrogen nucleophiles.[13] We envisioned the possibility of performing this organocatalytic IMAMR on *ortho*-substituted anilines and benzylamines that have a pendant α,β-unsaturated moiety. Herein we report the easy and enantioselective preparation of tetrahydroquinolines, tetrahydroisoquinolines, indolines, and isoindolines by following the aforementioned transformation. The common synthetic strategy for the synthesis of these four valuable heterocyclic derivatives is depicted in Scheme 1. Our approach started with a cross metathesis (CM) reaction of the terminal alkenylic chain of *ortho*-substituted *N*-protected anilines and benzylamines with acrolein to afford the corresponding α,β-unsaturated derivatives that, in turn, were subjected to an organocatalytic IMAMR and subsequent aldehyde reduction. The starting *N*-protected amines **1**–**4** (Table 1) were prepared according to procedures

[a] Prof. Dr. S. Fustero, J. Moscardó, Dr. D. Jiménez, Dr. M. Sánchez-Roselló, Dr. C. del Pozo
Departamento de Química Orgánica
Universidad de Valencia
46100-Burjassot, Valencia (Spain)
Fax: (+34) 963-544-939
E-mail: santos.fustero@uv.es

[b] Prof. Dr. S. Fustero, M. D. Pérez-Carrión
Laboratorio de Moléculas Orgánicas
Centro de Investigación Príncipe Felipe
46013-Valencia (Spain)
E-mail: sfustero@cipf.es

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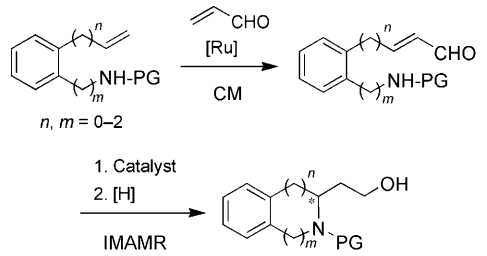
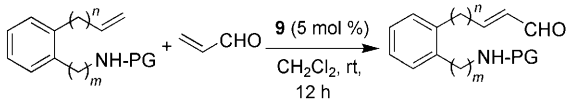


Scheme 1. The synthetic strategy. PG = Protecting group.

Table 1. Preparation of starting *N*-protected amines **5**–**8**.



Entry	Substrate	*n*	*m*	PG[a]	Product	Yield[b] [%]
1	**1a**	0	1	Cbz	**5a**	60
2	**1b**	0	1	Boc	**5b**	70
3	**1c**	0	1	Ts	**5c**	65
4	**1d**	0	1	Ac	**5d**	35
5	**2**	1	0	Cbz	**6**	50
6	**3**	1	1	Cbz	**7**	60
7	**4**	2	0	Cbz	**8**	73

[a] PG abbreviations: Cbz = benzyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, Ts = tosyl, Ac = acetyl. [b] Isolated yields.

previously described in the literature (see the Supporting Information).

Michael acceptors (**5**–**8**) for the organocatalytic conjugate addition were assembled by a CM reaction between compounds **1**–**4** and acrolein, catalyzed by second-generation Hoveyda–Grubbs catalyst **9** Cl_2(IMes)Ru=CH(*o*-*i*PrOC_6H_4). The reaction proceeded at room temperature in dichloromethane, giving rise to the desired aminoaldehydes **5**–**8** as stable products in all cases and in moderate to good yields (Table 1).

With α,β-unsaturated aldehydes **5**–**8** in hand, the first step of our study was the optimization of the cyclization process in terms of the reaction conditions and catalyst employed. We decided to examine the process on *N*-Cbz benzylamine **5a** as a model substrate. Diarylprolinols **I** and **II** and imidazolidinone **III** were chosen as catalysts for the organocatalytic process.[14] The screening process to identify the optimum conditions is summarized in Table 2.

The first attempt was performed at 0 °C with catalyst **I** (20 mol %) in $CHCl_3$, in the presence of benzoic acid

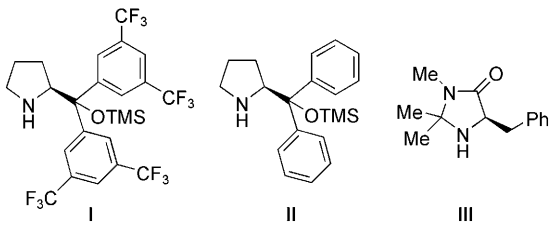
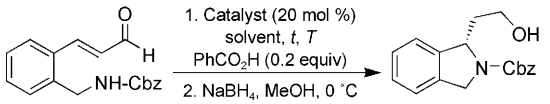


Table 2. Optimization of the reaction conditions.



Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	**10a**[a] [%]	*ee*[b] [%]
1	**I**	$CHCl_3$	0	1	78	82
2	**I**	$CHCl_3$	−20	12	70	92
3	**I**	$CHCl_3$	−30	12	72	98
4	**I**	$CHCl_3$	−40	12	56	>99
5	**I**	toluene	0	48	45	78
6	**I**	THF	−40 to RT	24	trace	–
7	**II**	$CHCl_3$	−30	16	68	>99
8	**III**	$CHCl_3$	−30	12	72	54

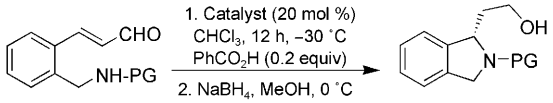
[a] Isolated yields. [b] Determined by chiral HPLC (see the Supporting Information).

(0.2 equiv) as the cocatalyst. The reaction took 1 h to run to completion, affording the desired isoindoline **10a** in 78 % yield and 82 % enantiomeric excess (*ee*) after aldehyde reduction (Table 2, entry 1). With this encouraging result, the next reaction was carried out at −20 °C to give **10a** in 70 % yield and 92 % *ee* after 12 h (Table 2, entry 2). To our delight, when the temperature was lowered to −30 °C, the product was obtained in 72 % yield with an excellent 98 % *ee* (Table 2, entry 3). Lower temperatures (−40 °C) led to complete selectivity (>99 % *ee*) although the yield was slightly inferior. Other solvents, such as toluene, made the process less efficient because **10a** was obtained after 48 h in 45 % yield and the *ee* dropped to 78 %. In THF the process did not take place even after the reaction mixture was warmed up to room temperature (Table 2, entries 5 and 6). It is worth noting that catalyst **II** also afforded the final product with an excellent 99 % *ee* at −30 °C (Table 2, entry 7). However, under the same reaction conditions catalyst **III** afforded isoindoline **10a** in a modest 54 % *ee* (Table 2, entry 8). Therefore, optimized conditions were found to involve exposure of substrate **5a** to either catalyst **I** or **II** in the presence of benzoic acid in $CHCl_3$ at −30 °C, which made the preparation of isoindoline (+)-**10a** in good yield and excellent *ee* possible (Table 2, entries 3 and 7).

To explore the effects of nitrogen substitution on enantioselectivity, substrates **5a**–**d**, which have carbamates, sulfonamides, or acetamides as nitrogen-protecting groups, were synthesized. When the Boc protecting group was used (i.e., **5b**), the process took place with a similar yield but with a slight decrease in the *ee* compared to **5a** (Table 3, entries 1,2 vs. 3,4). The use of tosylamide **5c** as the starting material followed the same trend, giving rise to isoindoline **10c** in good yield and *ee* with catalysts **I** and **II** (Table 3, entries 5 and 6). Finally, the use of acetamide **5d** as the nitrogen nucleophile in the IMAMR produced a dramatic decrease of the yield and rendered **10d** with modest *ee* (Table 3, entries 7 and 8).

With these results in hand, it became apparent that the decrease of the nucleophilicity of the nitrogen source in the IMAMR resulted in lower yields and *ee* values of the final

Table 3. Influence of the nitrogen-protecting group in the IMAMR.



5 (+)-10

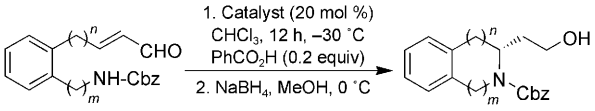
Entry	5	PG	Catalyst	10	Yield [%]	*ee*[a] [%]
1	**5a**	Cbz	**I**	**10a**	72	98
2	**5a**	Cbz	**II**	**10a**	68	99
3	**5b**	Boc	**I**	**10b**	72	94
4	**5b**	Boc	**II**	**10b**	68	91
5	**5c**	Ts	**I**	**10c**	61	94
6	**5c**	Ts	**II**	**10c**	63	91
7	**5d**	Ac	**I**	**10d**	36	64
8	**5d**	Ac	**II**	**10d**	28	58

[a] Determined by chiral HPLC (see the Supporting Information).

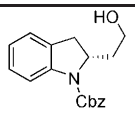
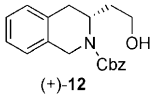
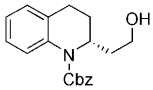
products. Thus, conjugate addition with acetyl amides is much slower (if compared with carbamates and tosyl amides), and alternative reaction pathways promoted by protons liberated during the process (Brønsted acid catalysis) apparently became more important. This is a nonselective process that competes with the iminium activation by the organocatalyst, which translates into the decrease of the selectivity in the overall process.

The extension of this protocol to the synthesis of several enantiomerically enriched benzofused heterocycles was examined next. Thus, when aniline derivative **6** was subjected to the optimized conditions, indoline (+)-**11** was obtained in good yield and excellent *ee* (93% and 92% with catalysts **I** and **II**, respectively; Table 4, entries 1 and 2). When benzylamine derivative **7** was employed, the process gave tetrahydroisoquinoline (+)-**12** in a complete enantioselective fashion (99% *ee*; Table 4, entries 3 and 4). Finally, when the organocatalytic protocol was performed on aniline derivative **8**, tetrahydroquinoline (+)-**13** was formed in up to 92% *ee* (Table 4, entries 5 and 6).

Table 4. Enantioselective synthesis of indolines, tetrahydroisoquinolines, and tetrahydroquinolines.



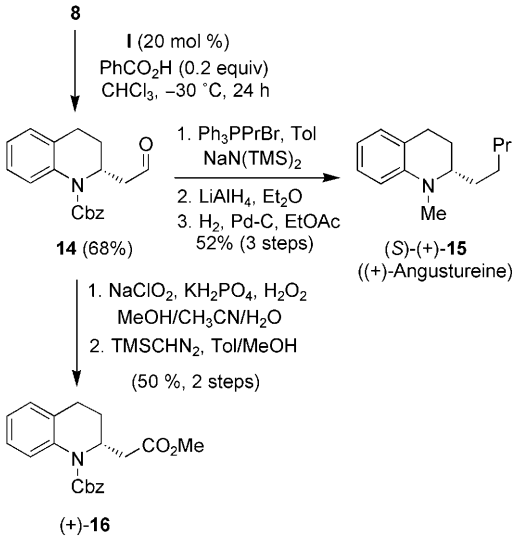
6–8 11–13

Entry	*n*	*m*	Substrate	Catalyst	Alcohol	Yield [%]	*ee*[a] [%]
1	1	0	**6**	**I**	 (+)-**11**	70	93
2	1	0	**6**	**II**		67	92
3	1	1	**7**	**I**	 (+)-**12**	67	99
4	1	1	**7**	**II**		63	99
5	2	0	**8**	**I**	 (+)-**13**	70[b]	92
6	2	0	**8**	**II**		60[b]	91

[a] Determined by chiral HPLC (see the Supporting Information). [b] The formation of tetrahydroquinoline (+)-**13** was slower than the rest, and it was necessary to extend the reaction time to 24 h to obtain the yields shown in the table.

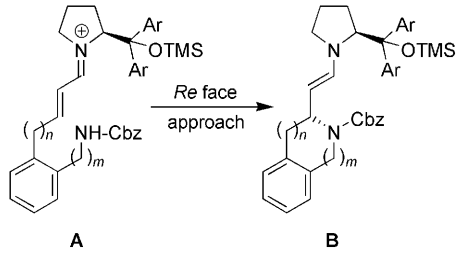
It is worth noting that the IMAMR with benzylamines **5** and **7** led to slightly better *ee* values than aniline derivatives **6** and **8**. This difference between both types of substrates would be rationalized again in terms of nitrogen nucleophilicity because benzylamines possess a more nucleophilic carbamate and afford the corresponding bicyclic derivatives with nearly complete selectivity.

The application of the present method to the enantioselective synthesis of biologically active tetrahydroquinoline alkaloid Angustureine[15] proved its utility.[16] Therefore, after the organocatalytic aza-Michael reaction on compound **8**, under the aforementioned conditions, aldehyde **14** was obtained in 68% yield. Wittig reaction with propyltriphenylphosphonium bromide, followed by carbamate reduction with $LiAlH_4$ and palladium-catalyzed hydrogenation, afforded the desired natural product (*S*)-(+)-**15** in a very simple manner (Scheme 2). Additionally, oxidation of aldehyde **14** and further esterification with trimethylsilyldiazomethane gave rise to tetrahydroquinoline β-amino acid derivative (+)-**16** (Scheme 2).



Scheme 2. Enantioselective synthesis of (+)-Angustureine **15**.

The synthesis of (*S*)-(+)-Angustureine allowed us to indirectly determine the absolute configuration of tetrahydroquinoline **13**. The newly created stereocenter was thus determined to be *R*, which is in agreement with the commonly accepted mechanism to rationalize organocatalytic processes through iminium activation. Once the iminium ion is formed in its preferred *E* conformation (Scheme 3, intermediate **A**), the attack on the nitrogen source that gives rise to enamine intermediate **B** (Scheme 3) takes place from the bottom side (*Re* face) of the diene moiety because the upper side is shielded by the pyrrolidine substituent.[17]



Scheme 3. The stereochemical outcome of the IMAMR on substrates **5**–**8**.

In conclusion, we have developed an efficient and simple method for the enantioselective synthesis of indolines, isoindolines, tetrahydroquinolines, and tetrahydroisoquinolines by means of an organocatalytic IMAMR of the corresponding aniline and benzylamine derivatives. The process took place with good yields and excellent *ee* values if diarylprolinols **I** and **II** were used as catalysts. The application of this method to the synthesis of the alkaloid (+)-Angustureine has also been presented. An investigation into further applications of this methodology is currently underway.

Experimental Section

Synthesis of adducts 10–13: In a flame-dried, 10 mL, round-bottomed flask, unsaturated aldehydes **5**–**8** (1 equiv) were dissolved in dry chloroform (0.1 M) and the solution was cooled to −30 °C. A mixture of catalyst **I** or **II** (20 mol %) and benzoic acid (0.2 equiv) in chloroform was added to this solution, and the resulting solution was stirred at this temperature for 12 h (except for substrate **8**, which was maintained for 24 h). The mixture was then diluted with methanol and $NaBH_4$ (3 equiv) was added portionwise. The mixture was allowed to reach 0 °C and, after 30 min at this temperature, the reaction was quenched with saturated NH_4Cl and extracted with dichloromethane (3 × 10 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness under vacuum. After flash chromatography over silica gel with mixtures of hexane/ethyl acetate as the eluent, the corresponding alcohols **10**–**13** were obtained as colorless oils. The enantiomeric ratios were determined by using HPLC analysis with a Chiracel IC column (25 × 0.46 cm).

Representative example: (1*S*)-*N*-Benzyloxycarbonyl-1-(2-hydroxyethyl)-isoindoline (+)-**10a** was isolated by following the aforementioned procedure and using flash chromatography with hexanes/ethyl acetate 3:1 as the eluent to give a colorless oil (72 % yield, 98 % *ee* with catalyst **I**; 68 % yield, 99 % *ee* with catalyst **II**). The *ee* was determined by using HPLC analysis with a Chiralpack IC column (eluent: hexane/isopropanol 87:13); flow rate = 1.1 mL min^{-1}, t_{major} = 36.9 min, t_{minor} = 39.2 min. $[\alpha]_D^{25}$ = +21.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz): δ = 1.60–1.69 (m, 1H), 2.16–2.27 (m, 1H), 3.70 (brs, 2H), 3.96 (brs, 1H), 4.63 (d, J = 14.9 Hz, 1H), 4.91 (d, J = 14.9 Hz, 1H), 5.22 (s, 2H), 5.38 (d, J = 10.0 Hz, 1H), 7.21–7.40 ppm (m, 9H); ^{13}C NMR (75 MHz): δ = 40.4 (CH_2), 51.8 (CH_2), 59.0 (CH_2), 60.6 (CH), 67.5 (CH_2), 122.4 (CH), 127.6 (2 CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 135.8 (C), 136.3 (C), 141.3 (C), 156.6 ppm (C); HMRS (EI+): m/z calcd for $C_{18}H_{19}NO_3$ [M$^+$]: 297.1365; found: 297.1360.

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Keywords: aza-Michael reaction · cyclization · enantioselectivity · heterocycles · homogeneous catalysis

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