Catalytic Enantioselective Synthesis of α-Arylaminocyclobutanones

David J. Aitken,^a Pierluigi Caboni,^b Hendrik Eijsberg,^{a,c} Angelo Frongia,^{c,*} Régis Guillot,^a Jean Ollivier,^a Pier Paolo Piras,^c and Francesco Secci^c

 ^a Laboratoire de Synthèse Organique et Méthodologie, Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO - CNRS UMR 8182), Université Paris-Sud, 15 rue Georges Clémenceau, 91405 Orsay, France

^b Dipartimento di Scienze della vita e dell'ambiente, Università degli studi di Cagliari, via Ospedale 72, 09124, Cagliari, Italy

^c Dipartimento di Scienze Chimiche e Geologiche, Università degli studi di Cagliari, Complesso Universitario di Monserrato, S.S. 554, Bivio per Sestu, 09042, Monserrato, Cagliari, Italy Fax: (+39)-070-675-4388; phone: (+39)-070-675-4449; e-mail: afrongia@unica.it

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Abstract: A catalytic enantioselective synthesis of α -arylaminocyclobutanones from racemic α -hydroxycyclobutanone and a selection of *N*-alkylanilines has been established, *via* a tandem condensation/keto-enol tautomerization process reminiscent of the Amadori and Heyns rearrangements.

Keywords: amines; carbocycles; enantioselectivity; organocatalysis; tautomerism

Recently there has been considerable interest in methods for the preparation of chiral α -aminocarbonyl compounds, due to the increasing applications of such compounds in the stereoselective synthesis of a wide range of biologically and pharmaceutically relevant nitrogen-containing structures of both natural and synthetic origins.^[1] Among the numerous methods that have been developed, electrophilic α -amination of carbonyl compounds is the most widely applied enantioselective catalytic technology.^[2]

This approach still has some limitations, however; the substrate scope has so far remained relatively narrow and, in particular, its application for the asymmetric α -amination of ketones has remained modest.^[3]

The α -aminocyclobutanones are an interesting yet arguably under-exploited class of molecules: ring-substituted 2-aminocyclobutanes have been targeted as intermediates for the total synthesis of natural products^[4,5] and have been used as ligands for specific serine proteases,^[6,7] while simpler *N*-substituted derivatives have served as starting materials for the synthesis of antimicrobial natural products.^[8] Like other cyclobutanes, they can be considered as versatile building blocks in organic synthesis owing to their inherent ring strain.^[9]

Despite the above-noted interest, no enantioselective synthesis of α -aminocyclobutanones has been described to date.^[10,11] The standard entry to the α -aminocyclobutanone core employs the condensation of the requisite amine with an α -hydroxycyclobutanone or its bis-trimethylsilylated enol ether derivative.^[12]

In continuation of our studies on synthetic methodologies for the chemo- and stereoselective functionalization of substituted cyclobutanones,^[13] we describe here the development of an enantioselective organocatalyzed version of the condensation reaction between α -hydroxycyclobutanone and substituted anilines, to provide an asymmetric synthesis of α -arylaminocyclobutanones.

We first examined the reaction between racemic α -hydroxycyclobutanone **1** and *N*-methylaniline **2a** at room temperature in toluene to screen a selection of commercially available *Cinchona* alkaloids and derivatives (**I–VIII**) for catalytic activity;^[14] the results are presented in Table 1. No reaction was observed in the absence of an alkaloid (entry 1), and we were pleased to note that the desired α -arylaminocyclobutanone **3a** could be isolated in 69% yield and with moderate enantioselectivity (51% *ee*) when (DHQD)₂PHAL **VIII** (30 mol%) was employed (entry 9).

Inclusion of 4Å molecular sieves in the reaction medium led to a slight improvement in both yield and *ee* (entry 10). Lowering the reaction temperature to 0°C further increased the enantioselectivity to 81% *ee* without compromising the yield (entry 11), while the use of a lower catalyst loading eroded both factors

Table 1. Initial screening studies.^[a]



Entry	Catalyst ^[b]	Temp. [°C]	Solvent	Yield [%] ^[c]	ee [%] ^[d]	Time [h]
1	none	r.t.	toluene	_	_	72
2	I	r.t.	toluene	87	-30	27
3	П	r.t.	toluene	67	38	15
4	Ш	r.t.	toluene	69	28	14
5	IV	r.t.	toluene	67	-16	9
6	V	r.t.	toluene	79	-6	52
7	VI	r.t.	toluene	77	14	50
8	VII	r.t.	toluene	64	-24	30
9	VIII	r.t.	toluene	69	51	42
10 ^[e]	VIII	r.t.	toluene	72	68	18
11 ^[e]	VIII	0	toluene	72	81	68
12 ^[e,f]	VIII	0	toluene	69	74	68
13 ^[e]	VIII	0	CH ₃ CN	29	26	19
14 ^[e]	VIII	0	CH_2Cl_2	46	82	72
15 ^[e]	VIII	0	CHCl ₃	72	80	72
16 ^[e]	VIII	0	THF	7	$n.d.^{[g]}$	72
17 ^[e]	VIII	0	$\rm CH_3OH$	traces	$n.d.^{[g]}$	66

^[a] *Conditions:* 0.669 mmol of **1**, 0.224 mmol of **2a**, 0.0669 mmol of catalyst, 0.5 mL solvent.

- ^[b] I=quinidine, II=quinine, III=(-)-cinchonidine, IV= hydroquinine-4-methyl-2-quinolyl ether, V= $(DHQ)_2PYR$, VI= $(DHQD)_2AQN$, VII= $(DHQ)_2PHAL$, VIII= $(DHQD)_2PHAL$.
- ^[c] Isolated yield after chromatography.
- ^[d] Determined by HPLC analysis using a chiral stationary column. Negative values indicate the preferential formation of the opposite enantiomer.
- ^[e] 4Å MS were included in the reaction mixture.
- ^[f] 20 mol% of catalyst was used.
- ^[g] n.d. = not determined.

slightly (entry 12). Screening of different solvents (entries 13–17) revealed that the initial choice of toluene had been judicious, although chloroform turned out to be equally satisfactory.

With the optimized conditions in hand, the substrate scope of the enantioselective reaction was investigated and the results are summarized in Scheme 1. Moderate to high enantioselectivities were obtained with a series of *N*-methylanilines **2a-k** with various ring-substituent patterns. Similarly to **2a**, *para*-substituted anilines **2b-g** gave rise to the desired α -arylaminocyclobutanone **3b-g** in reasonable-to-high yields (50–88%) and enantioselectivities (71–81%). Anilines **2h-k** having substituents at the *meta*- or *ortho*-position also gave the corresponding products **3h-k** albeit in somewhat lower yields (30–88%) and/



^[4] Conditions: 0.669 mmol of **1**, 0.224 mmol of **2**, 0.0669 mmol of (DHQD)₂PHAL (**VIII**), 0.6 g molecular sieves 4 Å, 0.5 mL toluene, 0 °C. Yields are given for isolated materials after column chromatography.

Scheme 1. Scope of the reaction.^[a]

or enantioselectivities (52–76%). *N*-Alkylanilines **2l–o** bearing more sterically congested alkyl substituents proved to be equally valid substrates for the reaction with **1**; however, the products **3l–o** were obtained with low enantioselectivities (10–32%). In contrast, the cyclic secondary amines **2p** and **2q** gave much better results, providing **3p** (90% yield, 62% *ee*) and

^[b] The reaction was carried out at room temperature.



Scheme 2. Synthesis of tosylate 6 and its X-ray crystallographic structure.

2q (92% yield, 65% *ee*), respectively. A representative primary aniline, *para*-anisidine **2r**, was not tolerated under the reaction conditions and a complex mixture of products was obtained.

The literature provides no precedent for polarimetric measurements, so in order to establish the absolute configuration of the α -arylaminocyclobutanones 3, we sought a crystallographic technique. Frustratingly, all of the enantiomerically enriched products 3 were obtained as oils, with the exception of **3g** which gave no useful crystals. A sample of product 3a (81% ee) was therefore reduced to give a mixture of the diastereomeric β -amino alcohols which were separated by silica gel column chromatography to provide 4 (42%) and 5 (38%). Treatment of the *cis*-isomer 4 with tosyl chloride and Et₃N/DMAP in dichloromethane furnished the crystalline tosylate 6. Single crystal X-ray diffraction analysis of this compound revealed an Sconfiguration at the cyclobutane C-2 center, as depicted in Scheme 2.^[15] All isolated samples 3a-k were dextrorotatory, so we suggest by analogy that the Senantioselectivity is general, at least for reactions involving N-methylanilines.

The reaction and the enantioselectivity can be rationalized in terms of the working model for the mechanism shown in Scheme 3. Since the condensation does not proceed in the absence of the alkaloid derivative (DHQD)₂PHAL, this compound facilitates the generation of 1,2-enaminol **B** by abstraction of water from the initially formed adduct **A**. Water is returned by (DHQD)₂PHAL in an *in situ* enantioselective enol-keto tautomerization depicted in **C**.^[16,17] It is



Scheme 3. Proposed catalytic cycle.

noteworthy that exposure of racemic 3a to $(DHQD)_2PHAL$ (30 mol%) in toluene at 0°C for 40 h did not provide 3a with any significant enantiomeric enrichment, which rules out an alternative mechanism implicating initial formation of racemic 3 followed by deprotonation/enantioselective reprotonation.^[18]

In conclusion, we have developed a metal-free and conceptually novel method for the synthesis of highly functionalized, optically active α -arylaminocyclobutanones using a tandem condensation–intramolecular rearrangement–proton transfer reaction from the readily available α -hydroxycyclobutanone and an *N*-alkylaniline, catalyzed by *Cinchona* alkaloids, for the first time. Overall, the process has some resemblance with the Amadori/Heyns rearrangements, better known in carbohydrate and food chemistry.^[19]

These encouraging results suggest that further work is warranted, with a view to broadening the applicability of the method, by diversifying the nature of the nitrogen substituents to include cleavable functions. Such developments are currently under consideration.

Experimental Section

General Procedure for α-Arylamination of α-Hydroxycyclobutanones

To a solution of freshly distilled α -hydroxycyclobutanone **1** (0.669 mmol, 0.058 g), (DHQD)₂PHAL (0.0669 mmol, 0.0521 g) and oven-activated 4Å molecular sieves (0.6 g, beads, diameter 2.4–4.8 mm) in dry toluene (0.5 mL) at 0°C was added the *N*-alkylaniline **2** (0.224 mmol), and the mixture was stirred for 38–71 h. The crude reaction mixture was directly loaded on a silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of hexane/ether, 5:1 \rightarrow

1:1). The racemates were synthesized using DMAP as catalyst at room temperature. Spectra and analytical data are provided in the Supporting Information.

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