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Asymmetric 1, 3-Dipolar Cycloadditions of a Chiral Non-Racemic Azomethine Imine.

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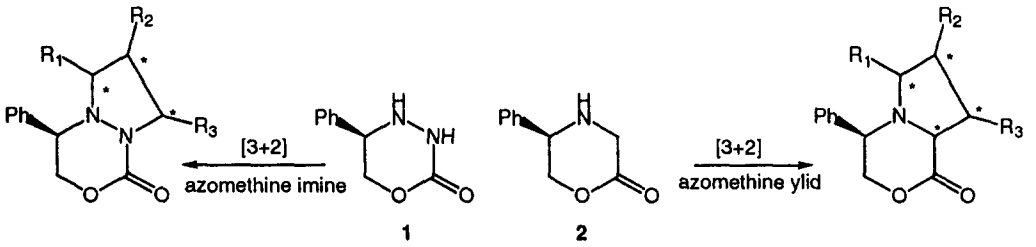
Abstract: : Chiral non racemic carbazate **1**, derived from (*R*)-(-)-phenylglycinol, reacts regioselectively with benzaldehyde or its dimethylacetal to give an azomethine imine. The facial, *endo/exo* and regio selectivities of 1,3-dipolar cycloadditions of this reactive species with various dipolarophiles have been studied and are described in this paper. In the best cases, up to three contiguous asymmetric centers could be generated simultaneously, in a complete enantio- and diastereoselective fashion.

Diels-Alder reactions and 1,3-dipolar cycloadditions have become powerful methods for the straightforward elaboration of complex structures[1]. The good control of the relative configuration of neighbouring asymmetric centers contributes to their high synthetic value. In the course of our work on the diastereoselective functionalization of chiral non-racemic hydrazinolactams, we were able to prepare compound **1** in four steps from N-benzyl (*R*)-(-)-phenylglycinol on a multigram scale[2]. This stable, crystalline building block is an aza-analog of morpholinone **2**, which has been extensively used as an azomethine ylid precursor in 1,3-dipolar cycloadditions (Scheme 1)[3].



Scheme 1

Although less popular than azomethine ylids, azomethine imines are known to react with several dipolarophiles, leading to polysubtituted pyrrazolidines[4]. The efficiency of the intramolecular version of this reaction was highlighted by the Jacobi synthesis of saxitoxin[5]. Several examples of intermolecular 1,3-dipolar additions with these reactive species were also reported, but generally in racemic series[6].

All these results prompted us to study the formation and reactivity of chiral non-racemic azomethine imines from compound **1**. If regio- and diastereoselective, these cycloadditions would permit the preparation of enantiopure polysubstituted 1,3-diamines in a versatile and straightforward manner, after removal of the chiral template and reductive cleavage of the hydrazine bond. In this communication we report our preliminary results in this field.

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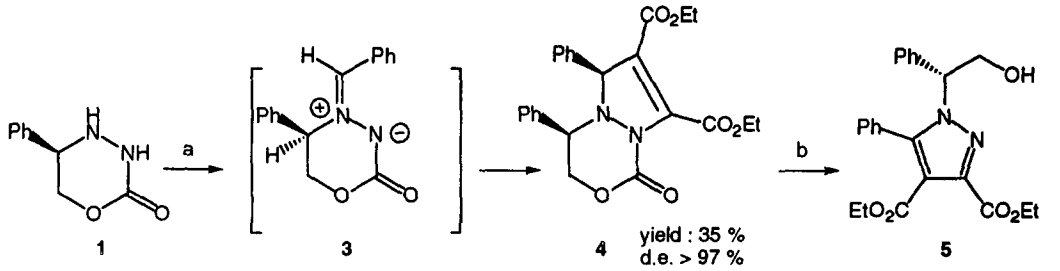
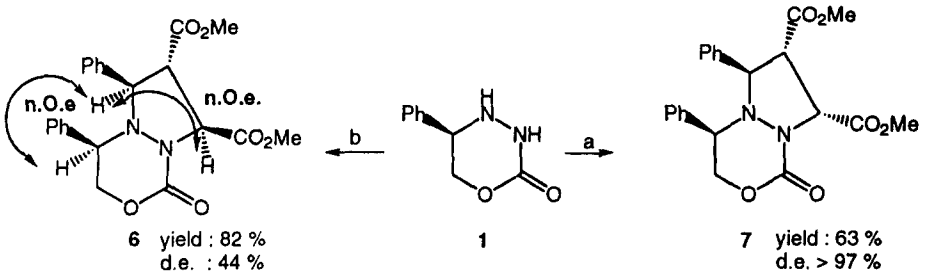
In order to evaluate the facial stereoselectivity of the cycloaddition, carbazate **1** was condensed with benzaldehyde dimethyl acetal and the resulting azomethine imine intermediate **3** was directly reacted with the dipolarophile diethyl acetylenedicarboxylate. Compound **4** was obtained as a single diastereomer in 35 % yield. The modest yield of the reaction was due to the formation of 1,4-addition by-products and to the low stability of **4** which could be stored for weeks after crystallization but which was rapidly oxidized to **5** in the presence of air when kept as an oil (Scheme 2).



Scheme 2. *Reagents and conditions* : a) i $PhCH(OMe)_2$, PTSA, toluene, 70 °C, M.Sieves; ii $EtO_2C\text{-}C{\equiv}C\text{-}CO_2Et$ b) air.

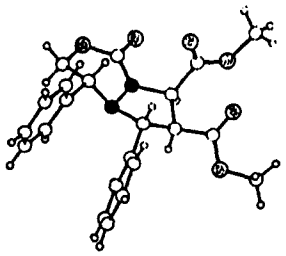
The absolute configuration of **4** was determined by its crystal structure X-ray analysis. The stereoselectivity is in agreement with an approach of the dipolarophile from the less sterically hindered face of a S-shape ylid **3**, as already proposed by Harwood and coll. in the related azomethine series[3f].

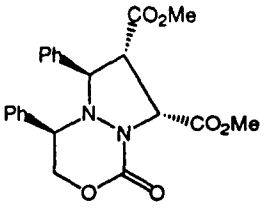
We then investigated the *endo/exo* selectivity of the reaction with symmetrical dipolarophiles (Scheme 3)[7].



Scheme 3. *Reagents and conditions* : a) PhCHO (5 eq.), dimethyl maleate (5 eq.), H_2O (1 eq.), $CHCl_3$, Δ, 48 h. b) PhCHO (5 eq.), dimethyl fumarate (4eq.), H_2O (1 eq.), $CHCl_3$, Δ, 48 h.

Once again, the facial selectivity was excellent. The relative configuration of the major adduct **6** was established by NMR n.O.e. experiments. The approach of dimethyl maleate proved to be exclusively *endo*, as depicted by a crystal structure X-ray analysis of compound **7** (Figure)[8,9].



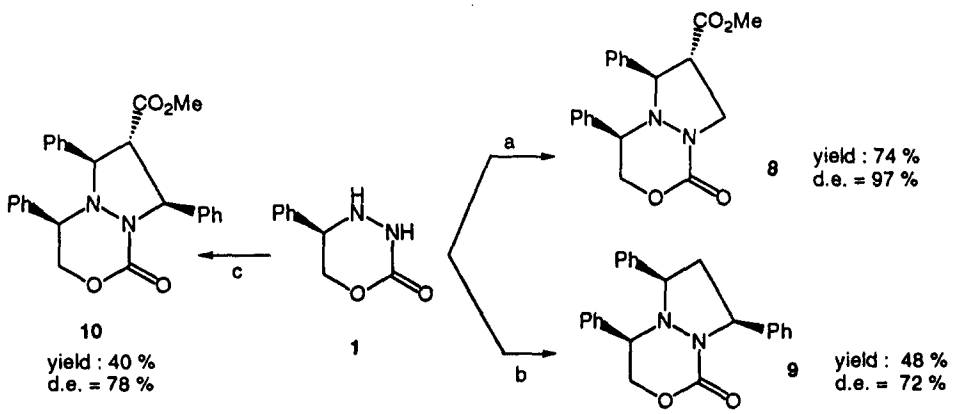


7

X-ray crystal structure of compound **7**

Figure

Finally, the regioselectivity of the cycloaddition was tested (Scheme 4). The opposite regioselectivity was observed between dipolarophiles bearing electron-withdrawing groups and conjugated olefins. The *endo* selectivity was again excellent with methyl acrylate.



Scheme 4. *Reagents and conditions* : a) PhCHO (5 eq.), methyl acrylate (5 eq.), H_2O (1 eq.), $CHCl_3$, Δ, 48 h. b) PhCHO (5 eq.), styrene (5 eq.), DCE, Δ, 24 h. c) PhCHO (5 eq.), methyl cinnamate (5 eq.), DCE, Δ, 48 h.

Preliminary FMO calculations suggest that the cycloaddition is HOMO controlled with methyl acrylate and cinnamate, and LUMO controlled when using styrene as the dipolarophile, leading to a reversal of regioselectivity and *endo/exo* control. Additional examples are needed to confirm this hypothesis.

In conclusion, **1** proved to be a good chiral template for asymmetric 1,3-dipolar cycloadditions. The azomethine imine is formed regioselectively, and reacts with various dipolarophiles in good yield and selectivity. In the best cases, three contiguous asymmetric centers could be created in a single step with complete control of relative and absolute configurations. Scopes and limitations of this new method are under investigation, and the extension to the synthesis of optically pure polysubstituted 1,3-diamines is in progress.

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References and Notes

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[7]. Typical procedure : To a solution of Carbazate **1** (100 mg, 0.56 mmol) in $CHCl_3$ (5 mL) were added benzaldehyde (285 µL, 2.81 mmol), dimethylmaleate (350 µL, 2.81 mmole) and water (10 µL). The solution was stirred at reflux temperature for 48 h, and concentrated. The crude product was dissolved in Et_2O and kept in the fridge for 24 h. The precipitate was filtered and washed with water to give a white solid (129 mg). Further purification was performed by flash chromatography on silica gel (EtOAc:Cyclohexane 1:9) to give **7** as colourless crystals (92 mg, 63 %, d.e. > 97%). $[\alpha]_D^{25}$ = - 142 (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, C_6D_6) (δ, ppm; J, Hz) : 3.05 (s, 3H), 3.44 (s, 3H), 3.47 (dd, 1H, J = 11.3, 8.8), 3.74 (dd, 1H, J = 10, 2.4), 4.13 (t, 1H, J = 10.2), 4.20 (dd, 1H, J = 10.3, 2.4), 4.59 (d, 1H, J = 11.3), 5.08 (d, 1H, J = 8.8), 7.0 (m, 10H). ^{13}C NMR (75.43 MHz, $CDCl_3$; δ, ppm) : 52.4, 52.9, 53.1, 60.5, 66.1, 70.5, 72.6, 128.3, 131.7, 136.2, 149.7, 167.8, 169.1. IR : 1748, 1694 cm^{-1}. MS (CI) : 411 (MH^+).

[8]. Surprisingly, an exo selectivity, based on NMR considerations, has been recently described for very similar adducts in racemic series : see ref. 6a.

[9]. Compound (-) **7**. Small colourless crystal (0.26 x 0.33 x 0.36 mm) recrystallized from a mixture of cyclohexane/ethyl acetate. $C_{22}\ H_{22}\ N_2\ O_6$, M_w = 410.42, Mp = 178-180 °C. Orthorhombic system, space group $P\ 2_12_12_1$, Z = 4, a = 5.882 (2), b = 16.606 (5), c = 20.475 (8) Å, V = 1999,9 $Å^3$, d_c = 1.363 g cm^{-3}, F(000) = 864, λ (Cu Kα) = 1.5418 Å, μ = 0.83 mm^{-1} ; 4238 data measured (Nonius CAD-4 diffractometer), 3632 unique (Rint = 0.0125) of which 3412 considered as observed with $I \geq 2.0\ \sigma(I)$; absorption ignored. The structure was solved by *SHELXS86* and refined by *SHELXL93* . Refinement converged to $R_1(F) = 0.0363$ (for the 3412 observed Fo) and $wR_2(F^2) = 0.1169$ (for all the 3632 data with goodness-of-fit S = 1.172). In the final difference map, the residual electron density was found between -0.20 and 0.18 $eÅ^{-3}$. In the packing of the molecules, only normal van der Waals contacts are observed. Lists of the fractional atomic coordinates, thermal parameters, distances, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material (CIF file).