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Enantioselective Michael-type Reaction of Chiral Linear α,α-Disubstituted Secondary Enamines

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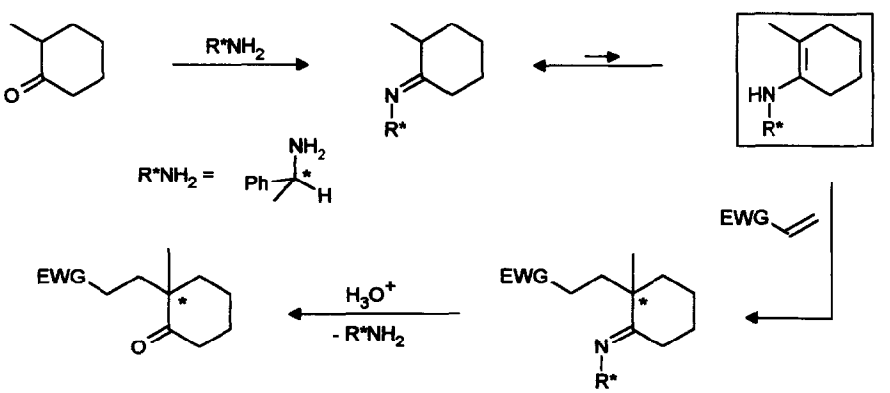
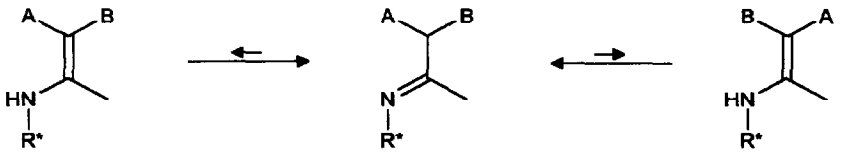
Abstract: The enantioselective Michael-type reaction of chiral 2-substituted *cyclic* imines, reacting as their secondary enamine tautomers, has been extended to a *linear* ketimine possessing an oxo group on one of the substituents. A single secondary enamine tautomer is observed, due to H-bonding of the NH group, thus allowing the reaction to proceed with a high degree of stereoselectivity.

A general method of "deracemizing alkylation" which involves imines arising from a chiral non racemic amine and 2-substituted *cyclic* ketones has been described previously. These imines react as their secondary enamine tautomers with electrophilic olefins and functionalized 2,2-disubstituted cyclanones are obtained after hydrolysis, in excellent yield and enantioselectivity[1] (Scheme 1).



Scheme 1

An *a priori* limitation of the method is the fact that if a ***linear*** carbonyl compound is considered, the problem of the formation of both *E* and *Z* secondary enamine tautomers (Scheme 2) must be taken into account since it influences the relative proportions of the diastereoisomers formed by the reactions of the enamines with the electrophilic olefin, therefore on the *ee* of the carbonyl compound obtained after hydrolysis.



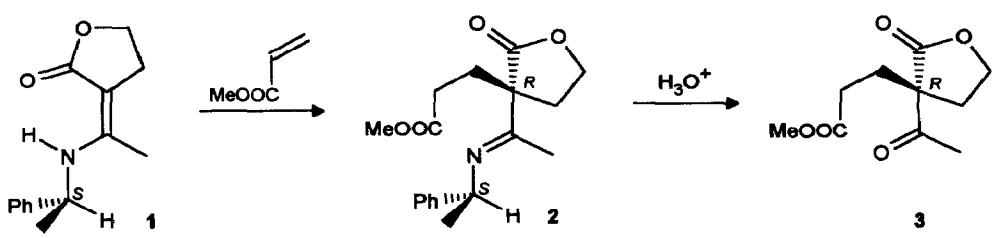
Scheme 2

An initial approach to this problem is to choose an imine with A and B substituents of very different sizes in order to minimize by steric hindrance the formation of one of the secondary enamine tautomers.[2]

Another way would be to create a hydrogen bond for one of the secondary enamine by introducing the appropriate substituent in the imine, thus preventing the occurrence of the other tautomer. This Communication presents our results dealing with this approach.

Commercially available 2-acetylbutyrolactone was reacted with *(S)*-2-methylbenzylamine (1 equiv., r.t., 4h) and the solid obtained was flash chromatographed (40% EtOAc/hexanes) to afford pure secondary enamino-lactone **1**, mp 73-74 °C (30% EtOAc/hexanes), $[\alpha]_D^{20}$ + 507 (*c* 2.25, EtOH), in 92% yield[3] (Scheme 3). GC-MS, ^1H and ^{13}C NMR of enamine **1** showed the presence of a ***single compound*** in accordance with the structure displayed (in particular a low-field chemical shift at 8.61 ppm in the ^1H NMR spectrum is observed, which is characteristic for a hydrogen bonded N-H group) thus fulfilling our initial expectation of dealing with only one secondary enamine tautomer.

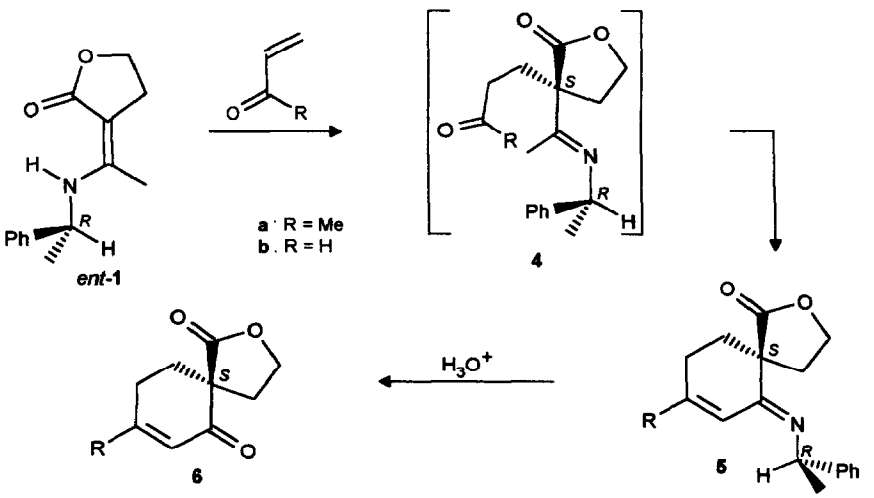
Alkylation of compound **1** was performed with 1.2 equivalent of methyl acrylate (Scheme 3) by heating the mixture without solvent at 80 °C for 12 h. Excess methyl acrylate was evaporated and GC-MS analysis of the residual oil showed a 89:11 diastereoselectivity for compound **2** (> 98% yield) which was then hydrolyzed without further purification (AcOH 10%, 1.2 equiv., THF, 40 °C, 24 h). Ether extraction followed by flash chromatography (40% EtOAc/hexanes) afforded trifunctional compound **3**, *ee* = 78%, $[\alpha]_D^{20}$ + 38 (*c* 3.4, EtOH) in 90% overall yield from enamino-lactone **1**.[4]



Scheme 3

Alkylation of *ent*-**1** in this case was then carried out with 1.1 equivalent of methyl vinyl ketone (THF, 65 °C, 16 h, 100% conversion) (Scheme 4). In this instance, the initial adduct **4a** was spontaneously cyclized by virtue of the imine-enamine tautomerism allowing an aldolization-crotonization process to take place.[6] Flash chromatography of the mixture (40% EtOAc/hexanes) thus afforded crude compound **5a** in 83% yield with a 93:7 diastereoselectivity (^1H NMR). Recrystallization yielded pure enimino-lactone **5a**, mp 138 °C (30% EtOAc/hexanes), $[\alpha]_D^{20}$ + 208 (*c* 1.07, EtOH). The relative and absolute configurations of compound **5a** are given in analogy with that of compound **5b** [*vide infra* and Note (4)].

Hydrolysis of compound **5a** (AcOH 10%, 2 equiv., THF, r.t., 24 h) followed by CH_2Cl_2 extraction and flash chromatography (50% EtOAc/hexanes) afforded crude compound **6a** in 81% yield. By recrystallization, pure spiranic enone-lactone **6a**, mp 90-91 °C (EtOAc), $[\alpha]_D^{20}$ + 149 (*c* 1.36, EtOH), was obtained.



Scheme 4

Alkylation of *ent*-**1** was also tried with acrolein (1.2 equiv., THF, r.t., 36 h, 100% conversion) (Scheme 4). Compound **5b** was obtained with a 96:4 diastereoselectivity (GC-MS) and flash chromatography (40% EtOAc/hexanes) afforded crude compound **5b** in 52% yield. Recrystallization yielded pure enimino-lactone **5b**, mp 116-117 °C (10% EtOAC/hexanes), $[\alpha]_D^{20}$ + 148 (*c* 1.26, EtOH). A single crystal X-ray analysis of compound **5b**[8] allowed the determination of the absolute configuration of the quaternary carbon center (Fig. 1) which is the one anticipated by the general rule[5] (Fig. 2. See also Note 4).

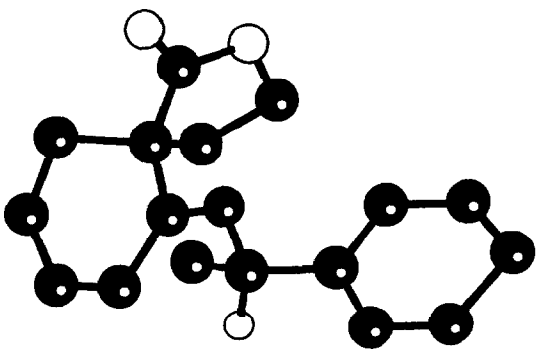


Fig. 1. X-ray determination of the absolute configuration of compound **5b**

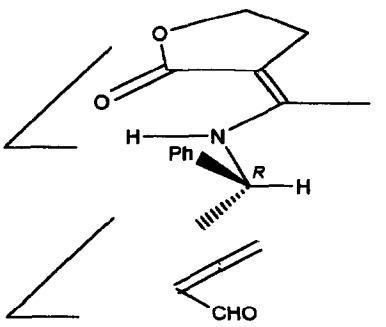


Fig. 2. Chair complex approach of reactants *ent*-**1** and acrolein

Hydrolysis of imine **5b** in the same conditions as those used for imine **5a** gave crude compound **6b** in 62% yield. Through molecular distillation, pure enone-lactone **6b**, bp 90-95 °C (0.05 torr), $[\alpha]_D^{20}$ + 72 (*c* 2.76, EtOH), was obtained.

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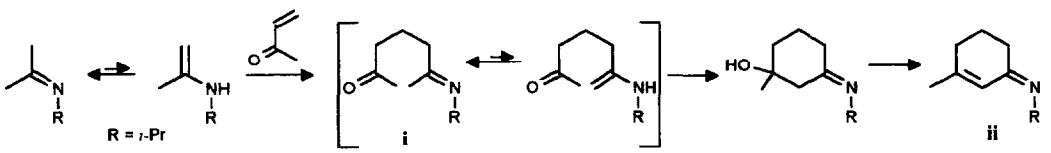
2. Preliminary results with a chiral imine of 2-phenylpropionaldehyde show that reactions with methyl acrylate and methyl vinyl ketone are highly diastereoselective (Revial, G., unpublished results).
3. All new compounds described in this Communication gave MS, IR, ^1H and ^{13}C NMR spectra in accordance with their displayed structures
4. When the alkylation was carried out at room temperature for 42 days (77% conversion), the diastereoselectivity rose to 94:6 for imine **2**, *i.e.* compound **3** was obtained with *ee* = 88%. The absolute configuration of compound **3** is given in analogy with that of compound **6b** *(vide infra)*. This assignment is also in accordance with that which can be anticipated by the rule elaborated previously[5] and with all past examples observed with chiral imines in Michael reactions.[1]
5. Sevin, A.; Tortajada, J.; Pfau, M. *J .Org. Chem.*, **1986**, *51*, 2671-2675; Sevin, A.; Masure, D ; Giessner-Prettre, C.; Pfau, M. *Helv. Chim. Acta* **1990**, *73*, 552-573.
6. The same behaviour has been already encountered with transient imino-ketone **i** (the presence of which was demonstrated) leading to α,β-ethylenic ketimine **ii**.[7]



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8. X-ray structure determination of compound **5b** ($C_{17}H_{19}O_2N$, M = 269.35). A suitable crystal of size 0.32 mm ×0.15 mm×0.12 mm was investigated on a Synthex $P2_1$ diffractometer (MoKα radiation λ = 0.71069 Å, graphite monochromator). Cell dimensions were determined by a least-squares fit to the setting angles of 30 reflections with 5.41° < 2θ < 20.35°; monoclinic, space group $P2_1$, Z = 2, a = 8.521(3), b = 11.015(3), c = 8.921(3), β = 117.97(3)°, V = 739.5(5) Å^3, d_x = 1.21 g·cm^{-3}, μ = 0.045 mm^{-1}. 1530 reflections were measured up to 2θ = 55° of which 904 with I≥4σ(I) were kept in refinement calculations. The structure was solved by direct methods using SHELXS86[9] and refined by full matrix least-squares with SHELX76,[10] minimizing the quantity $\Sigma w(F_O-F_C)^2$. Non hydrogen atoms were refined with anisotropic temperature factors; hydrogen atoms were located in difference Fourier map at observed positions. Convergence was reached at R = 0.053. The residual electron density in the final difference Fourier map does not show any features up to 0.20 e·Å^{-3} and down to –0.17 e·Å^{-3}. Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.
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10. Sheldrick, G. M. (1986). SHELXS86. Program for crystal structure determination. University of Göttingen, Germany.

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