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Intramolecular Michael Addition of Chiral Imines to Enoates : a New Asymmetric Carbocyclization Reaction

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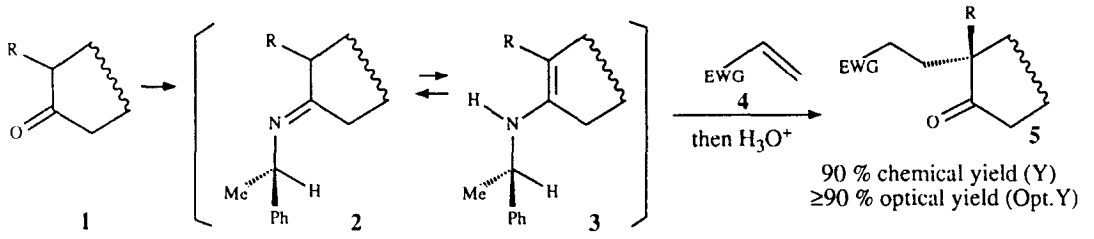
Abstract : Imines **6-8** have been cyclized into ketones **9-11** by using three methods of activation : heating, high pressure and Lewis acid ($MgBr_2$). Low to excellent stereoselectivities were observed.

We have previously reported that chiral imines **2**, derived from *racemic* α-substituted cyclanones **1** and optically active 1-phenylethylamine, add to electrophilic alkenes **4** (the reactive nucleophilic species being the tautomeric secondary enamines **3**) to lead, after hydrolytic work-up, to α-disubstituted cyclanones **5**, with a high degree of regio- and stereoselectivity[1].



In this communication we show that *acyclic* imines **6**, **7**, **8**, in which the imine function is separated from an enoate moiety by a 3, 4 or 5 carbon atom chain, undergo a facile *intramolecular cyclization reaction*[1,2] giving, after hydrolytic work-up, the 5 or 6 membered carbocyclic derivatives **9**, **10**, **11**, respectively. Low to excellent stereoselectivities are observed in these Michael additions, depending on the length of the carbon atom chain in the starting imine and on the method of cyclization.

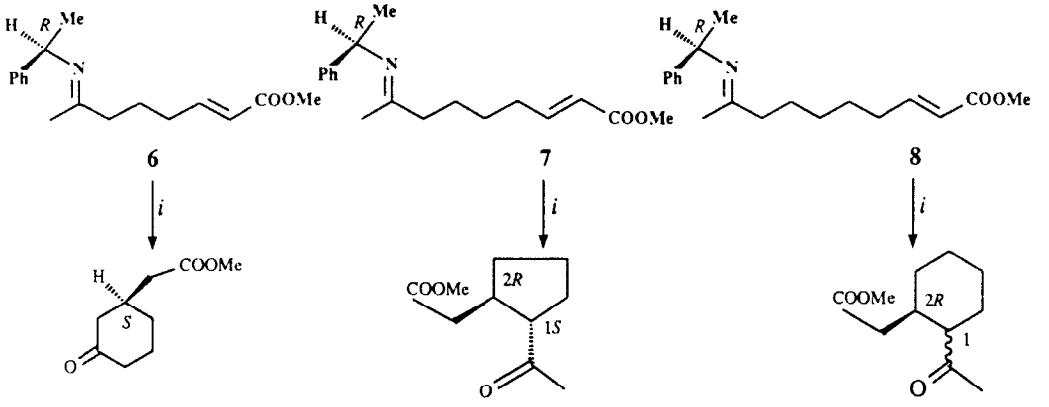
Results

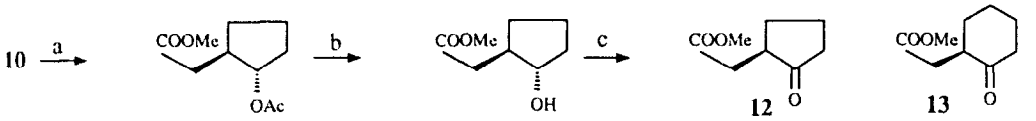
Chiral imines **6-8**[3] were cyclized by using three methods of activation : heating, high pressure and Lewis acid ($MgBr_2$). The resulting crude cyclic imines were directly hydrolyzed ($AcONa/AcOH/H_2O$) into the corresponding ketones **9-11** which were purified and analyzed. The de (compounds **10**, **11**) were determined by capillary VPC and ^1H NMR, using Resolve-Al EuFOD as shift reagent. The ee were established in all cases by ^1H NMR, using $Eu(hfc)_3$ as chiral shift reagent.

The *S* configuration found in known ketone **9**[4] has been determined by comparison of its optical rotation with the data of the literature. The *R* configuration at C-2 center in ketone **10**[5] has been assigned by correlation with known (*R*) keto-ester **12**[6]. Similarly, compound **11** was converted into (*R*) keto-ester **13**[7].

Discussion

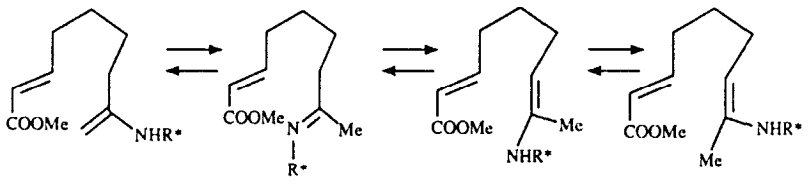
When, for a given carbocyclization reaction, similar stereochemical results are obtained by using thermal or high pressure-induced conditions of cyclization, the use of $MgBr_2$ as Lewis acid strongly modifies the selectivity. However, it is worthy of note that *the same enantiomer always predominates, regardless of the method of activation.*





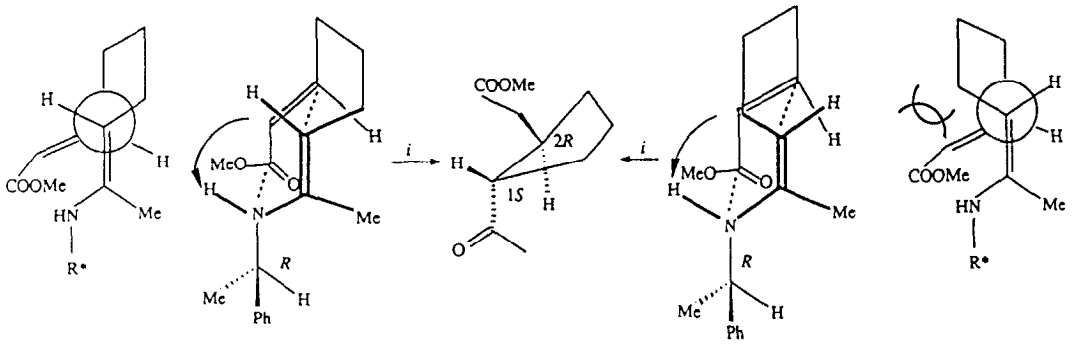
a : MCPBA , refluxing CH_2Cl_2, 48 h, b : *i* LiOH *ii* careful acidification *iii* CH_2N_2, c : Jones reagent

Carbocyclizations [7 → 10] and [8 → 11], exemplified by [7 → 10]. By analogy with the aforementioned related intermolecular process [**1** → **5**], we have first to take into account the equilibrium between the starting imine **7** and tautomeric secondary enamines **14**, **15*E***, **15*Z***, the potential nucleophilic species in the present Michael addition. The intramolecular cyclization of "external" enamine **14** should give a *seven-membered* carbocycle (not observed), while both "internal" stereoisomeric enamines **15*E*** and **15*Z*** can lead to the observed *five-membered* keto-ester **10**.



The present stereochemical outcome may be easily rationalized, making the assumption that this intramolecular Michael addition proceeds through the *cyclic, chair-like* transition states[1,8] **16***E* and/or **16***Z*, stabilized by an attractive HOMO-LUMO N...CO interaction [9]. These structures involve the *syn* approach of the enamine and enoate parts in relevant species **15***E*, **15***Z*, as shown in the corresponding Newman projections **17***E*, **17***Z* (in this respect, it should be noted that, compared to approach **17E**, an additional *gauche* interaction destabilizes approach **17Z**). In both transition states the transfer of the proton borne by the enamine nitrogen atom to the α-vinylic carbon center of the enoate part is allowed (arrow), *concertedly* with the creation of the C-C bond (*"aza-ene-synthesis like "transition state*)[1]. Assuming that the addition takes place mainly on the π-face of the enamine *opposite* the phenyl ring of the chiral amine appendage (when this depicted in its energetically preferred conformation)[10], the predominant *R* configuration at C-2 center in keto-ester **10** is expected, *regardless of the enamine geometry*. The *S* configuration found at the highly epimerizable C-1 center reflects the thermodynamic diastereoselection (pure *trans* relationship between the adjacent acetate and acetyl side-chains).

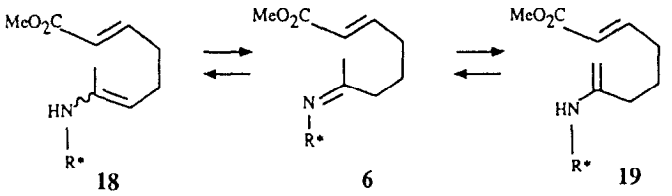
A similar mechanism may be evoked for the related carbocyclization [**8** → **11**], except that the epimerization of the final molecule **11** led to a 4:1 (*trans/cis*) mixture of diastereoisomers.



i : after hydrolytic work-up

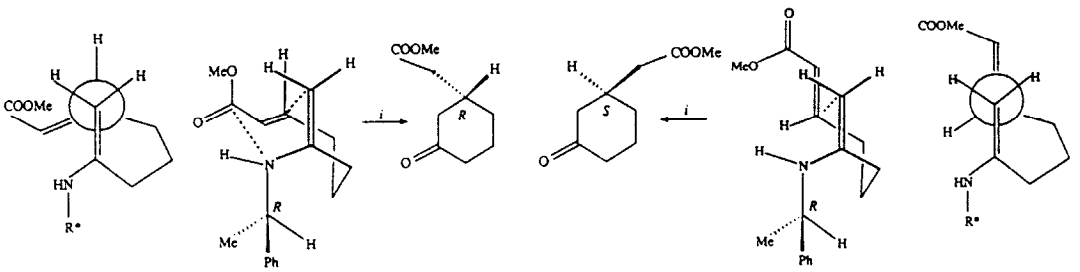
Carbocyclization [6 → 9]. Compared to the foregoing two reactions, the rate of the present thermally-induced cyclization is substantially lower, with a dramatic decrease of the Opt.Y. On the other hand, the rate of the $MgBr_2$-promoted addition is amazingly rapid, with a notable recovery of the selectivity : *a change in the mechanism of this carbocyclization must be therefore considered.*

Starting imine **6** is in potential tautomeric equilibrium with secondary enamines **18** and **19**. By intramolecular addition, "internal" enamine **18** should lead to a *four-membered* carbocycle (not observed), while the "external" regioisomeric congener **19** is the precursor of the observed *six-membered* keto-ester **9**.



Let us first consider that the reaction proceeds, as before, through a *cyclic* transition state, namely the energetically disfavored *boat-like* structure **20**[11]. This pathway involves the *syn* approach of the enamine and enoate moieties in species **19** (Newman projection **21**). Assuming that the addition occurs, as usually[1], on the π-face of the enamine *opposite* the phenyl ring of the auxiliary chiral amine, the predominant *R* configuration in final keto-ester is predicted (*ent*-**9**).

If we now consider the alternative *acyclic* transition state **22** (*anti* approach **23**), the addition on the π-face of the enamine *opposite* the phenyl ring of the chiral amine appendage leads to the observed *S* configuration in keto-ester **9**.



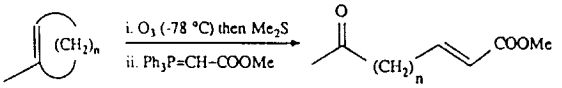
21 **20** *ent*-**9** **9** **22** **23**

i : after hydrolytic work-up

References and Notes

1. J. d'Angelo, C. Ferroud, C. Riche, A. Chiaroni, *Tetrahedron Lett.*, **30**, 6511 (1989) and references cited therein.
2. Other examples of asymmetric intramolecular Michael addition : T. Wakabayashi, K. Watanabe, Y. Kato, M. Saito, *Chemistry Letters* , 223 (1977). B.M. Trost, C.D. Shuey, F. DiNinno, Jr., S.S. Mc Elvain, *J. Am. Chem. Soc.*, **101**, 1284 (1979). G. Stork, N.A. Saccomano, *Nouv. J. Chim.*, **10**, 677 (1986). Y. Hirai, T. Terada, T. Yamazaki, *J. Am. Chem. Soc.*, **110**, 958 (1988). M. Ihara, Y. Takino, K. Fukumoto, T. Kametani, *Tetrahedron Lett.*, **29**, 4135 (1988). R.K. Hill, L.A. Renbaum, *Tetrahedron*, **38**, 1959 (1989). D.A. Oare, C.H. Heathcock in Topics in Stereochemistry, vol. 19, p. 227, John Wiley & Sons (1989).

3a. Imines **6-8** have been prepared quantitatively from the corresponding (*E*) keto-esters **24** and (*R*) 1-phenylethylamine (1 h at 40 °C in cyclohexane in the presence of powdered molecular sieves). The requisite keto-esters were obtained (75-80 % overall yield) in two steps from 1-methylcycloalkenes :



24

b. Keto-esters **24** (n = 4,5) have been cyclized under thermal condition : C. Moreau, J.M. Conia, F. Rouessac, *Bull. Soc. Chim. Fr.*, 545 (1970).
4. G.H. Posner, M. Weitzberg, T.G. Hamill, E. Asirvatham, He Cun-Heng, J. Clardy, *Tetrahedron*, **42**, 2919 (1986).
5. **10** (ee = 61 %) : $[\alpha]^{20}_D$ + 16.6° (c = 3.8, MeOH).
6. J.J. Partrige, N.K. Chadha, M.R. Uskoković, *J. Am. Chem. Soc.*, **95**, 7171 (1973).
7. Compound **13** exhibits very similar CD spectrum to the one reported for (*R*) ethyl ester analog : K. Hiroi, K. Achiwa, S. Yamada, *Chem. Pharm. Bull.*, **20**, 246 (1972).
8. J. d'Angelo, A. Guingant, C. Riche, A. Chiaroni, *Tetrahedron Lett.*, **29**, 2667 (1988).
9. A. Sevin, J. Tortajada, M. Pfau, *J. Org. Chem.*, **51**, 2671 (1986).
10. J. d'Angelo, G. Revial, A. Guingant, C. Riche, A. Chiaroni, *Tetrahedron Lett.*, **30**, 2645 (1989).
11. In this series it has been actually established that a *boat-like* transition state is about 4.4 kcal mol^{-1} less stable than the corresponding *chair-like* structure [9].