Pergamon

*Tetrahedron Letters*, Vol. 35, No. 52, pp. 9705-9708, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02137-6

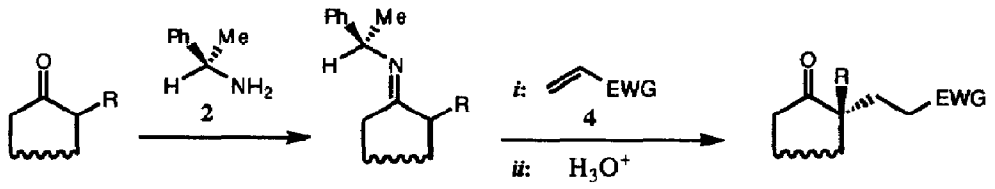
# The Asymmetric Michael Reaction Using Chiral Imines under Neutral Conditions: Stereochemical Evidences in Support of a Cyclic Transition State

**Lydia Ambroise, Didier Desmaële, Jacqueline Mahuteau, Jean d'Angelo***

Unité de Chimie Organique Associée au CNRS, Centre d'Etudes Pharmaceutiques,
Université Paris-Sud, 5, rue J.- B. Clément, 92296 Châtenay-Malabry (France).

***Abstract***: Stereochemical outcome observed in addition [**6** + **7**], [*ent*-**6** + **15**] and [**18** + methyl acrylate] have been rationalized by evoking the participation of the corresponding compact approaches **14**, **21** and **22**.

We have disclosed that chiral imines **3**, prepared from *racemic* α-substituted cyclanones **1** and optically active 1-phenylethylamine **2**, add to electron-deficient olefins **4** leading, after hydrolytic work-up, to α-disubstituted adducts **5** in high yield and with excellent regio- and stereoselectivity.[1]

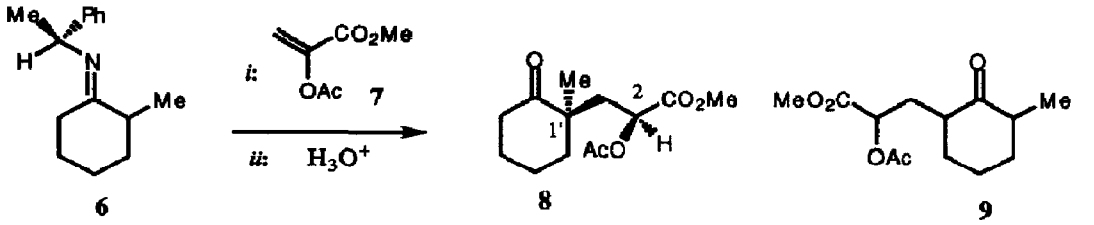



ee: 90-95 %

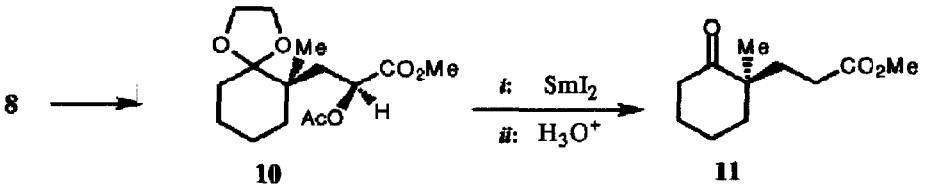
This asymmetric reaction, which is one of the most efficient methodologies for the enantioselective elaboration of quaternary carbon centers, has been widely applied to the synthesis of various compounds of natural origin, including terpenes, steroids, and alkaloids.[1b] The mechanistic aspects of this addition, and in particular, the factors that lead to the unusually high degree of regio- and stereoselectivity observed, have been tentatively explained through both chemical experiments and theoretical calculations.[1b] It has thus been proposed that this reaction involves a secondary enamine in tautomeric equilibrium with imine **3** and is concerted, proceeding through a cyclic transition state.

In the present paper we report three novel experiments [**6** + **7** → **8**, *ent*-**6** + **15** → **16** and **18** + methyl acrylate → **19**] in which the stereochemical course strongly supports this mechanism. To probe the mechanism of this addition, we first chose to use as the electrophile a *gem*-disubstituted electron-deficient alkene, namely methyl 2-acetoxy-acrylate **7**[2], considering that the potential simultaneous control of a second, tertiary stereogenic center in the β to the quaternary one would be of particular value. Thus, addition of imine **6**,[1a]

obtained by condensation of 2-methylcyclohexanone and optically pure (*S*)-1-phenylethylamine, to 7[2] proceeded smoothly (neat, 1.5 h, 20 °C, then 20 % aqueous AcOH, 1 h, 20 °C), leading to adduct (2*S*, 1'*R*)-**8**,[3] (60 % yield), accompanied by *ca.* 10 % of regioisomer **9** (isolated as a mixture of stereomers).

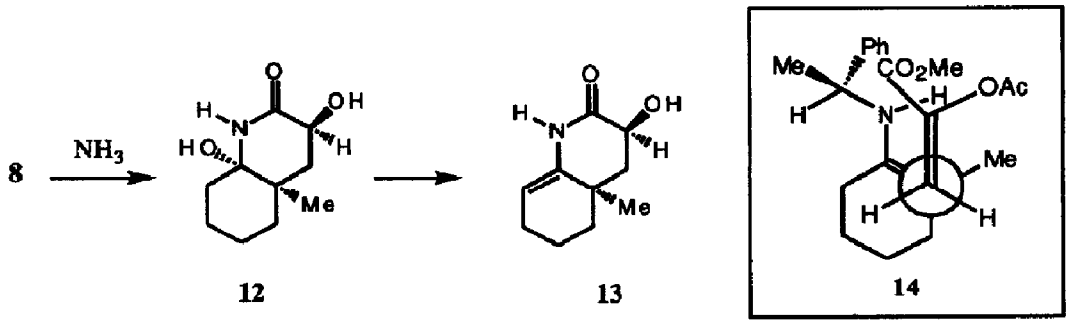



Analysis of adduct **8** by GC, $^1H$ and $^{13}C$ NMR spectroscopy revealed the presence of a ***single*** diastereomer. The *R* configuration at the quaternary carbon center was determined as follows. Ketoester **8** was first protected as ketal **10**.[4] The acetoxy group of this ketal was then cleaved by reduction ($SmI_2$ in HMPA / THF/ MeOH)[5] leading, after acidic hydrolysis, to the known, enantiopure ketoester (*R*)-**11**[1a] (88 % overall yield).

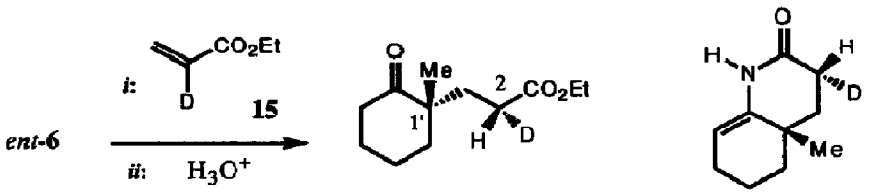



The 2*S* configuration in adduct **8** was established by converting this compound by addition of ammonia ($NH_3$ in MeOH, 4 days at 20 °C, 72 % yield) into bicyclic lactam **12** (concomitant cleavage of the acetoxy group by ammonia took place during this reaction). Subsequent dehydration of **12** afforded **13**[6] (*p*-TsOH, 2 h in refluxing benzene, 90 % yield). Careful analysis of the $^1H$ NMR spectrum of **13**, including 1-D NOE difference experiments, revealed that the angular methyl group and the OH substituent are *anti*, thereby establishing the stereochemistry at C-2 in the parent adduct **8**.

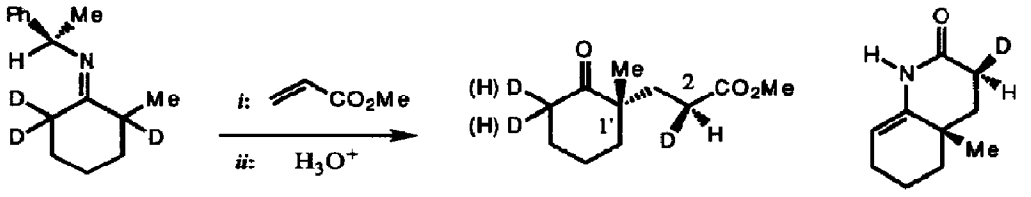
The remarkable complete stereocontrol of the two stereogenic centers in adduct **8** is best interpreted by evoking (as proposed earlier[1b]) for the addition the compact approach **14** that involves a *synclinal* arrangement of the two partners: electrophile **7** and as nucleophilic species, the more substituted secondary enamine, which is in tautomeric equilibrium with imine **6**. According to such a model, the alkylation takes place *anti* to the phenyl ring of the chiral amine moiety in its energetically preferred conformation (C-H eclipsing the cyclohexane ring), thereby generating the *R* configuration at the quaternary carbon center. The total stereocontrol observed at the tertiary center requires that the transfer of the N-H proton of the enamine to the C-2 carbon atom of the electrophilic alkene **7** be *concerted* to the creation of the C-C bond. It is worthy of note that in order to account for the observed 2*S* configuration, the electrophilic partner **7** needs to be arranged as depicted, namely with the carbomethoxy group "*endo*" to the enamine part.




The behavior of ethyl 2-deuteroacrylate **15**[7] as the electrophile was next examined, because a deuterium atom offers the advantage over other substituents of not introducing any significant steric and/or electronic effects. Addition of imine *ent*-**6** to **15** (neat, 48 h, 20 °C then 20 % aqueous AcOH, 2 h, 20 °C) led in 75 % yield to ketoester (2*R*, 1'*S*)-**16**. The relative configuration of the two stereogenic centers in adduct **16** was proved by $^1$H NMR analysis of the corresponding bicyclic lactam **17**,[8] prepared by a procedure in all aspects identical with the conversion [**8** → **13**], NOE difference experiments establishing unambiguously the *anti* relationship of the angular methyl group and the deuterium atom.

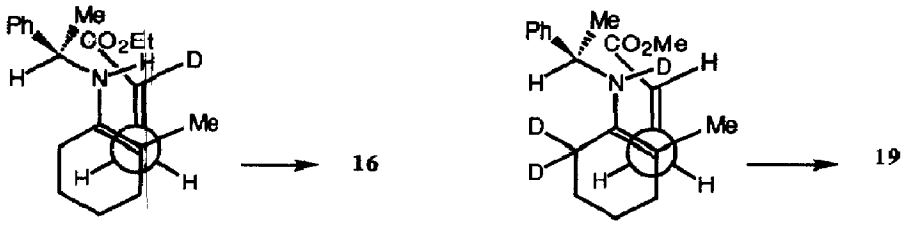



In light of the preceding observation, it was predicted that the reaction of deuterated imine **18** with methyl acrylate would afford the *opposite* stereochemistry at C-2 in the Michael adduct. This prediction proved correct: the addition of imine **18** (prepared by stirring *ent*-**6** overnight at 20 °C with MeOD)[9] to methyl acrylate led cleanly to adduct (2*S*, 1'*S*)-**19** (partial, but irrelevant D/H exchange took place in the position α to the keto group during the aqueous work-up of this reaction). This stereochemistry was again assigned by $^1$H NMR analysis of the corresponding bicyclic lactam **20**.[10]




The stereochemical outcome observed in the two previous experiments may be rationalized by evoking the compact approaches **21** and **22**, respectively, for these reactions. As for addition [**6** + **7**], the high stereocontrol exhibited at C-2 in adducts **16** and **19** clearly shows that the hydrogen (or deuterium) borne by the nitrogen atom of the secondary enamines, in tautomeric equilibrium[11] with imines *ent*-**6** and **18**, is transferred to the

C-2 center of the acrylate partner in a manner concerted (but not necessarily synchronous) with the creation of the C-C bond. Futhermore, in order to account for the configuration at C-2, the ester group of the acrylates is orientated in both cases *endo* relative to the enamine part, as proposed for the addition [**6** + **7**].




The *endo* spatial arrangement of the electrophilic partner in approaches **14**, **21** and **22** does not appears to be general. Indeed additions of methyl 2-phenylthioacrylate to imine **6**[12] and methyl methacrylate to a related chiral enaminoester [13] both take place through an *exo*-arrangement. Factors responsible for the *endo*/*exo* orientation of the electrophile are currently under investigation.

## References and Notes


1. a) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.*, **1985**, *107*, 273-274. b) For a review : d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron : Asymmetry*, **1992**, *3*, 459-505.
2. Wolinsky, J.; Novak, R.; Vasileff, R. *J. Org. Chem.*, **1964**, *29*, 3596-3598.
3. **8**: $[\alpha]_D^{20}$ = -11.0 (EtOH, c = 7.5); IR (neat, $cm^{-1}$) 1748, 1708, 1440; $^1H$ NMR (200 MHz, $CDCl_3$) δ 4.97 (dd, *J* = 9.0, 3.2 Hz, 1H), 3.69 (s, 3H), 2.50-2.30 (m, 2H), 2.20 (dd, *J* = 15.0, 3.2 Hz, 1H), 2.07 (s, 3H), 1.92 (dd, *J* = 15.0, 9.0 Hz, 1H), 1.90-1.60 (m, 6H), 1,13 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ 213.9(C), 170.7(C), 169.9(C), 69.6 (CH), 52.2($CH_3$), 47.4(C), 39.1($CH_2$), 38.2($CH_2$), 37.9($CH_2$), 27.0($CH_2$), 22.2($CH_3$), 20.7($CH_2$), 20.4($CH_3$); MS (70 eV) m/z: 256($M^{+\cdot}$, 0.5), 214(8), 183(7), 155(14), 125(17), 112(100).
4. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.*, **1980**, *21*, 1357-1358.
5. Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.*, **1989**, *30*, 2945-2948.
6. **13**: IR (neat, $cm^{-1}$) 3380, 3200, 1680, 1660; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40 (m, 1H), 4.80 (t, *J* = 3.7 Hz, 1H), 4.35 (dd, *J* = 12.1, 6.3 Hz, 1H), 3.40 (s, 1H), 2.20-2.00 (m, 2H), 1.80-1.20 (m, 6H), 1.21 (s, 3H); a strong NOE was observed between the angular methyl group and the proton in the α-position to the carbonyl; $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ 172.3(C), 138.7(C), 105.2(CH), 65.3(CH), 41.9($CH_2$), 36.7 ($CH_2$), 32.3 (C), 23.7($CH_3$), 23.2($CH_2$), 17.2($CH_2$).
7. Mathias, L. J.; Colletti, R. F. *Macromolecules*, **1988**, *21*, 857-858.
8. **17**: $^1H$ NMR (400 MHz, $C_6D_6$) δ 9.10 (m, 1H), 4.83 (t, *J* = 3.8 Hz, 1H), 2.27 (m, 1H), 1.80 (m, 2H), 1.46-1.36 (m, 1H), 1.35-1.30 (m, 1H), 1.18 (dt, *J* = 13.0, 3.3, 3.3 Hz, 1H), 1.09 (t, *J* = 13.2 Hz, 1H), 1.04 (td, *J* = 13.0, 13.0, 3.3 Hz, 1H), 0.99 (dd, *J* = 13.2, 6.8 Hz, 1H), 0.79 (s, 3H); a NOE (*ca.* 10 %) was observed between the methyl group and the proton in the α-position to the carbonyl; $^{13}C$ NMR ($CDCl_3$, 50 MHz), δ 170.3(C), 139.2(C), 104.0(CH), 36.8($CH_2$), 33.9($CH_2$), 31.0(C), 28.2(t, *J* = 18 Hz, CD), 23.4 ($CH_2$), 22.6($CH_3$), 18.1($CH_2$); MS (70 eV) m/z: 166($M^{+\cdot}$,100), 151(68), 138(49), 123(37), 110(46), 95(27).
9. Pfau, M.; Ribière, C. *J. Chem. Soc., Chem. Comm.*, **1970**, 66-67. Boyd, D., R.; Jennings, W. B.; Waring, L. C. *J. Org. Chem.*, **1986**, *51*, 992-995.
10. **20**: $^1H$ NMR (400 MHz, $C_6D_6$) δ 9.57 (m, 1H), 4.94 (t, *J* = 3.5 Hz, 1H), 2.28 (m, 1H) , 1.82 (m, 2H), 1.50-1.37 (m, 1H), 1.36-1.30 (m, 1H), 1.19 (dt, *J* = 13.0, 3.3, 3.3 Hz, 1H), 1.12-1.08 (m, 1H), 1,05 (td *J* = 13.0, 13.0, 3.3 Hz, 1H), 1.00 (broad d, *J* = 13.4 Hz, 1H), 0.79 (s, 3H); no significant NOE was observed between the angular methyl group and the proton in the α-position to the carbonyl; $^{13}C$ NMR ($C_6D_6$, 50 MHz), δ 170.3(C), 139.9(C), 103.5(CH), 37.1($CH_2$), 34.2($CH_2$), 31.0(C), 28.6(t, *J* = 18.5 Hz, CD), 23.8 ($CH_2$), 22.5($CH_3$), 18.5($CH_2$); MS (70 eV) m/z: 166($M^{+\cdot}$,100), 151(60), 138(52), 123(43), 110(54), 95(35).
11. De Jeso, B.; Pommier, J. C. *J. Chem. Soc., Chem. Comm.*, **1977**, 565-566. De Jeso, B.; Pommier, J.- C. *J. Organomet. Chem.*, **1977**, *137*, 23-29. Capon, B.; Wu, Z.-P. *J. Org. Chem.*,**1990**, *55*, 2317-2324.
12. d'Angelo, J.; Guingant, A.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.*,**1988**, *29*, 2667-2670.
13. Cavé, C.; Daley, V.; d'Angelo, J.; Guingant, A., *Tetrahedron : Asymmetry*, in press.


(*Received in France* 26 *September* 1994; *accepted* 27 *October* 1994)