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STEREOCHEMICAL EFFECTS OF TRIMETHYLSILYL CHLORIDE (TMSCl) ON THE CONJUGATE ADDITION OF ORGANOCOPPER REAGENTS

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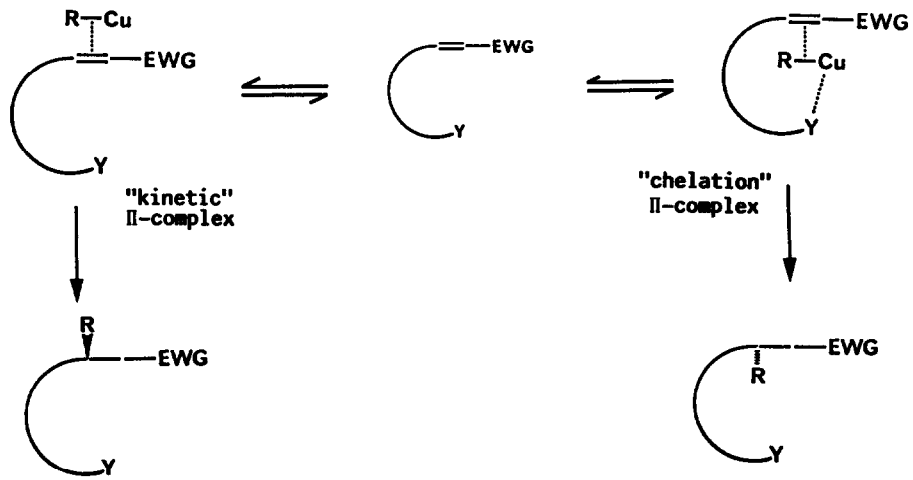
Abstract : The stereochemical course of the conjugate addition of organocopper reagents, in the presence of TMSCl, is not affected by remote chelation effects, whereas in its absence, the latter may predominate. By this way, it is possible to distinguish the relative effets of the chelation and of the steric hindrance.

We reported, recently, the highly diastereoselective conjugate addition of organocuprate reagents to cinnamates bearing, in ortho position, a chiral imidazolidine or oxazolidine ring[1]. This diastereoselectivity was ascribed to either steric or chelation factors. Such a hypothesis on a chelation by a remote functionnality finds, now, a stronger support by the results described in this letter.

The primary step in the conjugate addition of an organocopper reagent is the formation of reversible d-Π^*complex[2,3]. This step is followed by a two (simultaneous or not[3]) electron transfer to afford a Cu(III) intermediate[2,3], a step which seems to be still reversible[4]. Reductive elimination, then leads irreversibly to the final adduct. The stereofacial selectivity of this first "kinetic" Π -complex obeys, usually, to steric (bulky adjacent group) or stereoselectronic (preferential axial attack on cyclic substrates) factors[5]. This primary Π-complex equilibrates more or less rapidly with many other new Π-complexes[2], among which a remote additional chelation may play a role.



When the diastereoselectivity of the final conjugate adduct is due to such chelation effect, two possibilities may account for it. One possibility is an acceleration of the next steps of the conjugate addition process[6], even if this Π-complex is among the least stable (Curtin-Hammett principle). On the other hand it is also possible that the new Π-complex becomes, largely, stabilized by this additionnal chelation ; provided that the kinetics of the next steps are similar, the final diastereoisomer will reflect the statistical abundance of this stable Π-complex.

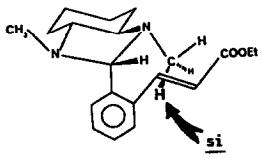
Whatever the exact process, this chelation effect may alter the expected diastereoselectivity if it overcomes the steric requirements, or happily, it may boost it to very high values if both effects favor the same diastereoisomer.
A way to avoid such chelation effects would be to trap, rapidly enough, the "kinetic" Π-complex, through the irreversible formation of the conjugate adduct. We[7], and others[8], have described recently the accelerating effect of trimethylsilyl chloride (TMSCl) on the conjugate addition of organocopper reagents to α-ß unsaturated carbonyl derivatives. If the addition of TMSCl enhances the rate of the conjugate addition to such an extent as to overcome the kinetics of the equilibration between the "kinetic" and the "chelation" Π-complexes, then the stereochemistry of the final adduct will be representative of only the steric and/or the stereoelectronic effects[9].

This hypothesis was tested on our previously reported cinnamates bearing a chiral imidazolidine or oxazolidine ring[1]. Our result with R,R imidazolidine **A** was explained by steric factors (see scheme) where the re face was blocked by one of the two N-Me groups. Thus, the final adduct, was of S configuration. On the other hand, R,R imidazolidine **B**, having the same absolute configuration as **A**, gave the opposite enantiomer, R ! In this case, the result was ascribed to a chelation between the cuprate reagent and one of the two nitrogen atoms of the imidazolidine ring. This chelation was able to overcome the steric requirements which should have led to the S enantiomer[10].

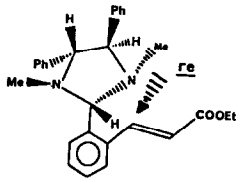
Based on the above mentioned hypothesis, we expected to restore the normal outcome of the latter reaction, just by running the experiment in the presence of TMSCl. It was also expected that the stereochemical outcome of the reaction with **A** would not be affected by TMSCl. The experimental result, completely fulfilled our expectetations (see table). In the case of imidazolidine **A**, the absolute configuration of the conjugate adduct remains the same. On the other hand, in the case of imidazolidine **B**, the absolute configuration of the final adduct is completely reversed, giving, now, the S enantiomer, the same as with imidazolidine **A**.

Analogous results were also observed with oxazolidines **C** and **D**. Oxazolidine **C**, from (-) ephedrine, gave, upon conjugate addition, the adduct of R configuration. Model calculations showed that in the most stable conformer the phenyl group completely hinders the si face of the cinnamate, thus preventing any chelation between the oxygen atom[11] of the ring and the organometallic reagent. As predicted the reaction in the presence of

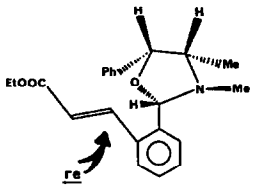
TMSCl does not affect the stereochemical outcome of the reaction (see table). On the other hand oxazolidine **D**, from (+) pseudoephedrine, differs from oxazolidine **C**, only by the stereochemistry of the phenyl group. This phenyl group, now, does not hinder anymore the chelation between the oxygen of the oxazolidine ring and the cuprate reagent. The R stereochemistry of the final adduct reflects the stereochemistry of the "chelation" Π-complex. When the same reaction is run with TMSCl (see table), the opposite enantiomer R is obtained, the same as with oxazolidine **C**. Thus, in both cases, the R enantiomer reflects the steric requirements of the initial cinnamate.



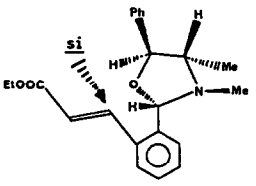
A



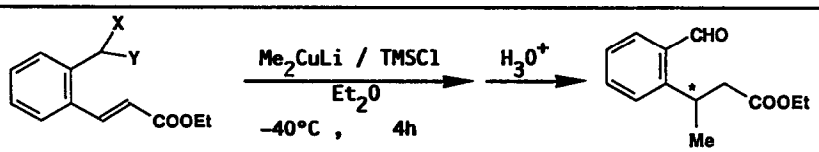
B

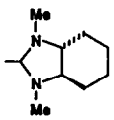
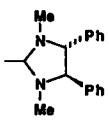
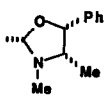
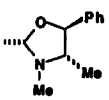


C



D



Starting cinnamate		Chemical yield % with TMSCl (without TMSCl)[1]	Enantiomeric excess with TMSCl (without TMSCl)[1]	Absolute configuration with TMSCl (without TMSCl)[1]
	**A**	62% (55%)	78% (94%)	S (S)
	**B**	68% (57%)	53% (78%)	S (R)
	**C**	55% (51%)	60% (55%)	R (R)
	**D**	61% (43%)	38% (93%)	R (S)

These results have far more implications than the examples shown above[12]. One should be very careful in running conjugate additions in the presence of TMSCl. The benefit of its accelerating effect may be altered by the stereochemical result which may differ from the one obtained without it. On the other hand, one may take advantage of this fact to distinguish the steric from the chelation factors which may affect the stereochemical outcome of a given conjugate addition.

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5. Several examples are listed in reviews :
   a/ Posner, G.H. : Organic reactions (1972) 19 1 and (1975) 22 253
   b/ Jukes, A.E. in "Advances in Organometallic Chemistry" Vol. 12, Stone F.G.A. ; West, R. : Academic Press, New York, 1974
   c/ Erdik, F. : Tetrahedron (1984) 40 641
   d/ Lipshutz, E.H. ; Wilhelm, R.S. ; Kozlowski, J.A. : Tetrahedron (1984) 40 5005
   e/ Taylor, R.J.K. : Synthesis (1985) 364
   f/ Yamamoto, Y. : Ang. Chem. Int. Ed. (1986) 25 947
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   b/ Nakamura, E. ; Matsuzawa, S. ; Horiguchi, Y. ; Kuwajima, I. : Tetrahedron Lett. : (1986) 27 4029
   c/ Johnson, C.R. ; Marren, T.J. : Tetrahedron Lett. (1987) 28 27
   d/ Bergdahl, M. ; Lindstedt, E.L. ; Nilsson, M. ; Olsson, T. : Tetrahedron (1988) 44 2055.
9. We assume that TMSCl enhances in an equal manner the transformation of any Π-complex into the conjugate adduct. However it does not affect the rate of equilibration of a given Π-complex into an other one, since it does not act as a Lewis acid. BF_3 accelerated conjugate additions, on the other hand, should affect this rate because they interact with enones before the formation of any Π-complex.
10. Close results on cinnamates were also obtained by prof. Ullenius : See ref. 2.a/ and Christenson, B. : Licentiate Thesis, Chalmers University of Technology, Göteborg, Sweden, 1989. See also : Hutchinson, D.K. ; Hardinger, S.A. ; Fuchs, P.L. : Tetrahedron Lett. (1986) 27 1425
11. It is usually admitted, that, in oxazolidine rings, it is the oxygen atom which is the most electron donating. See Ficini, J. ; Normant, H. : Bull. Soc. Chim. France (1957) 1454
12. Other examples of stereochemical differences in conjugate additions of R_2CuLi with or without TMSCl are known :
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   b/ Smith III, A.B. ; Dunlap, N.K. ; Sulikowski, G.A. : Tetrahedron Lett. (1988) 29 439.
   c/ Ullenius, C. ; Christenson, B. : private communication.
   d/ Normant, J.F. ; Courtemanche, G. ; Alexakis, A. : unpublished results.

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