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ASYMMETRIC AZA-DIELS-ALDER REACTION USING THE CHIRAL 1-PHENYL-ETHYL IMINE OF METHYL GLYOXYLATE [1]

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Abstract: The Diels-Alder reaction between cyclopentadiene and the chiral 1-phenyl-ethyl imine of methyl glyoxylate takes place very easily by activation with trifluoroacetic acid and boron trifluoride etherate to provide diastereoselectively (total *face* selectivity and up to 98% *exo* selectivity) a near quantitative yield of 3-*exo*-carbomethoxy -N-α-methylbenzyl-2-aza-5-norbornene adduct **4** resulting from *unlike* topicity.

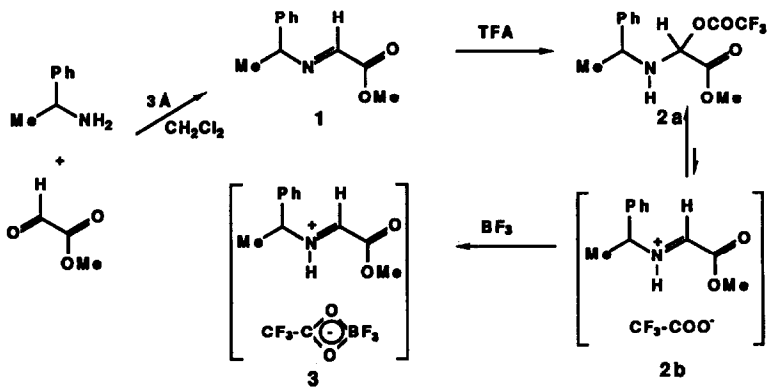
The Diels-Alder reaction is clearly one of the most useful synthetic tools because of the high regio- and stereo-control of chemistry it provides, and a spate of reports have appeared in recent years underlining its importance in the field of asymmetric synthesis. [2] Despite the fact that hetero-Diels-Alder cycloadditions using various imines as dienophiles have been known for almost 40 years, [3] relatively few synthetic applications of this type of methodology have been described, and mechanistic studies in this area are virtually non existent. [4] Particularly, the synthesis of cyclic α-amino acid derivatives by imino-Diels-Alder was surprisingly unexplored [5] prior to the very recent paper of Bailey, Wilson and Brown. [6] This prompts us to disclose now our first finding concerning the very high diastereoselective aza-Diels-Alder cycloaddition [7] performed with the chiral α-methylbenzyl imine of methyl glyoxylate. This result is particularly important for the synthesis of the optically active α-amino acid. [8]

The 1-phenyl-ethyl imine of methyl glyoxylate **1** is readily prepared [9] *in situ* from polymeric glyoxylate , 1-phenyl-ethylamine and 3Å molecular sieves in dichloromethane. In this solvent, contrary to more widely used aqueous conditions, [10] the use of either Lewis acid catalysts and low temperatures is allowed and this is generally essential to reach good yields and high diastereoselectivity.

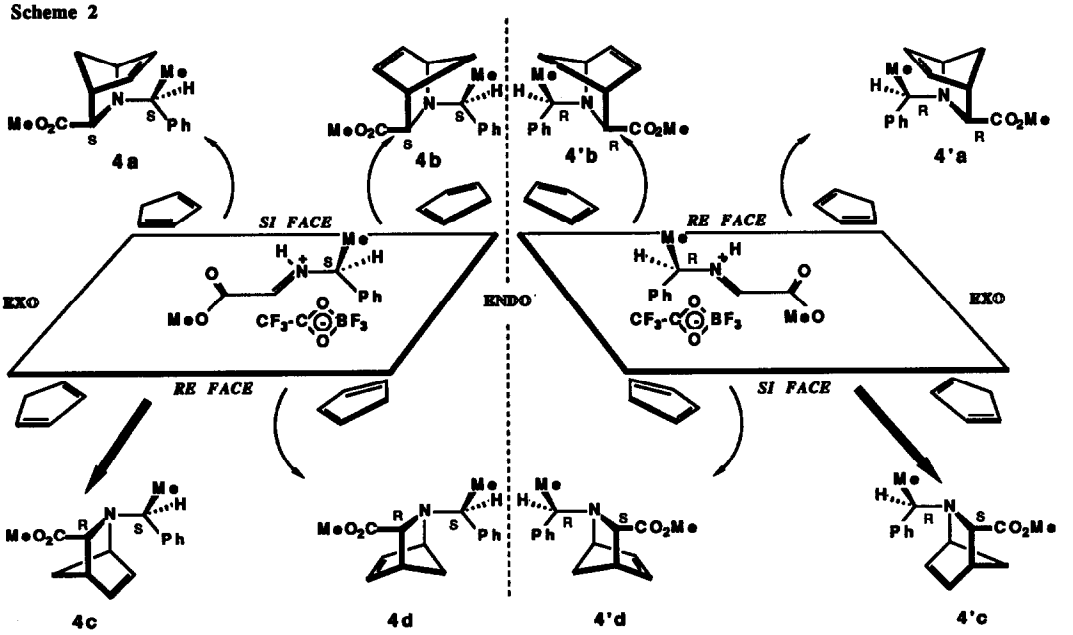
Treated with trifluoroacetic acid, the imine **1** gives formally the iminium trifluoroacetate **2** [11] (scheme 1) which in fact, did not undergo a clean cycloaddition reaction with conjugated dienes such as isoprene, 1,3-cyclohexadiene or cyclopentadiene. Very likely, owing to the particularly high electrophilic character of the captodative carbenium ion [12] in compound **2b**, the covalent form **2a** is preferred to the ionic one **2b**, exactly as it is for amide chlorides bearing electron-

withdrawing substituents. [13] However, subsequent addition of a complexing agent such as boron trifluoride etherate [11] results in the production of the reactive ionic species **3**, a dissociated iminium salt in which the anion is non nucleophilic. This more reactive heterodienophilic species reacts very readily with cyclopentadiene (1 equiv.) at 0°C and even at -80°C to give exclusively *unlike* [14] products **4c+4d**. While the diastereoface selectivity is completely controlled at 0°C (*like* products **4a** and **4b** were not obtained, see scheme 2), the *exo/endo* selectivity increases as the temperature decreases (*87/13* at 0°C and *98/2* at -80°C). [15,16] The single diastereoisomer is isolated in crystalline form as a pure racemic compound **4c+4'c** and its structure is determined by X-ray crystallography [17] as shown in the Figure. The optically pure enantiomers **4c** and **4'c**, prepared in the same way from both the optical antipodes of the chiral imine could not be obtained in crystalline form.

Scheme 1



Scheme 2



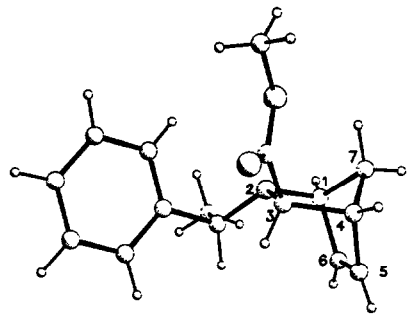


Figure : X-ray structure of **4c-4'c** showing the numbering of the atoms

Interestingly, we found that adducts **4** underwent retro-Diels-Alder reactions at ~ 100°C. The usefulness of this cycloreversion [18] is presently under active investigation. We are now exploring the modeling, scope and generality of the cycloaddition process. Our preliminary results show that other dienes, *e.g.* butadiene, isoprene, 2,3-dimethyl-butadiene, 1,3-cyclohexadiene and some more nucleophilic dienes work well with this imino-dienophile. We will report on these studies in due course.

Typical Diels-Alder reaction : (±)-1-Phenyl-ethylamine (0,380 mL, 3 mmol) was added to a solution of methyl glyoxylate [19] (0,264 g, 3 mmol) in 10 mL methylene chloride containing 3 Å molecular sieves (~1 g) cooled to 0°C. The clear solution was stirred under argon at 0°C for 30 min. It was then cooled to -78°C and treated with trifluoroacetic acid (0,230 mL, 3 mmol), then with boron trifluoride etherate (0,370 mL, 3 mmol) and finally with freshly cracked cyclopentadiene (0,246 mL, 3 mmol, precooled to -10°C). The clear reaction mixture was held at -78°C for 5h and quenched with saturated sodium bicarbonate solution, extracted with methylene chloride, and concentrated in a rotary evaporator. The viscous oil was loaded onto a chromatography column packed with silica gel (70-230 mesh) and eluted with 80% toluene/ethyl acetate to provide the mixture of adducts **4c+4d** $(98+2)^{15,16}$ in 94% yield. The mixture solidified to a white solid which was recristallized from petroleum ether to the pure racemic compound (m.p. 60°C). [20]

Conclusion : The activated chiral imine of methyl glyoxylate **1** is an useful diastereoselective azadienophile. Its advantages include exceptionnal reactivity and complete diastereofacial differentiation. The inexpensive commercial availability of both optical antipodes of the 1-phenyl-ethylamine and of simple alkyl glyoxylates make this imino dienophile attractive for asymmetric synthesis of cyclic α-amino-acids.

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References and Notes

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14. We use the Seebach-Prelog convention (Seebach, D. ; Prelog, V. , *Angew. Chem.; Int. Ed. Engl.* **1982**,*21*, 654) to describe the relative topicities of the approach ; see : Tripathy, R. ; Franck, R. W. ; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257 ; *i.e.* addition to the *si* face of the double bond of the imino dienophile with an adjacent *R* allylic center is *unlike*.
15. The diastereoisomeric ratios were determined by **VPC** (50mx0.28mm WCOT SE-30 column, 0.1μm, 0.8bar H_2, 160°C) [**4c** : R_f =593s, **4d** : R_f = 614s], confirmed by **^{1}H NMR** integration of CO_2CH_3 (∂ 3.35 for **4c**, ∂ 3.78 for **4d**) and by **^{13}C NMR** integration of Ph-CH-CH_3 (∂ 22.55$_4$ for **4c**, ∂ 23.95$_5$ for **4d**).
16. **^{1}H NMR** ($CDCl_3$, 200 MHz) : **4c** ∂ 7.35$_7$-7.16$_1$ (5H, m, aromatics), 6.34$_4$-6.30$_3$ (1H, m, H-6), 6.28$_9$-6.25$_2$ (1H, dd, H-5, J 5.59 Hz, J' 1.70 Hz), 4.31$_3$ (1H, s, H-1), 3.34$_9$ (3H, s, OCH_3), 3.03$_6$ (1H, q, Ph-CH-Me, J 6.5 Hz), 2.91$_2$ (1H, s, H-4), 2.22$_0$ (1H, s, H-3), 2.10$_5$ (1H, d, H-7_{ANTI}, J 8.4 Hz), 1.41$_7$ (3H, d, Ph-CH-CH_3, J 6.5 Hz), 1.42$_0$ (1H, d, H-7_{SYN}, J 8.4 Hz). **4d** ∂ 6.06 (1H, dd, H_5, J 5.6 Hz, J' 1.7 Hz), 3.78$_0$ (3H, s, OCH_3), 1.22 (3H, d, Ph-CH-CH_3). **^{13}C NMR** ($CDCl_3$, 50,3 MHz) : **4c**-{**4d**} ∂ 174.5-{174.5} (CO), 144.84 (C-ipso), 136.42-{135.93}(C-6 or C-5), 132.94-{133.98}(C-5 or C-6) , 127.99-127.85 (C-ortho-meta) , 127.05 (C-para), 64.92{64.92}(C-3), 63.90{64.72}(Me-CH-Ph), 62.57{63.72}(C-1), 51.49{52.36}(C-4), 49.02{49.58}(OCH_3), 45.47{45.96}(C-7), 22.55{23.95}(CH-CH_3). **IR** (neat): **4c** 3027, 3000, 2984, 2894, 2834, 1718, 1431, 1330, 1317, 1290, 1275, 1219, 1207, 1104, 1056, 1025, 764, 746, 706, 537. **MS** [EI, *m/e* (relative intensity)] : **4c** 257(M^+, 5), 242(10), 198(24), 106(22), 105(100), 94(48), 79(15), 77(17), 66(12) ; **4d** 257(M^+,0.8), 198(56), 136(5), 121(6), 120(5), 106(27), 105(50), 94(100), 79(19), 77(25), 51(6).
17. Mr=257.33, monoclinic, $P2_1/c$, a=14.931(5), b=8.055(4), c=11.764(2)Å, β=92.38(2)°, V=1413.6(10)Å^3, Z=4, Dx=1.21g.cm^{-3}, CuKα, λ=1.5418Å, μ =6.42cm^{-1}, F(000)=552, T=291K, R=0.053 for 2288 observed reflections. The atomic coordinates and molecular dimensions have been deposited with the Cambridge Data Centre.
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20. Same procedure could be applied with (+)-R- and (-)-S-1-phenylethylamine.

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