

First [4 + 2] Cycloaddition Reaction between Vinyl Fischer Type Carbene Complexes and Chiral 2-Amino-1,3-dienes

José Barluenga,^a Fernando Aznar,^a Alfredo Martín,^a Sofia Barluenga,^a Santiago García-Granda^b and Armando A. Paneque-Quevedo^b

^a Instituto Universitario de Química Organometálica 'Enrique Moles' and ^b Departamento de Química Física y Analítica (X-Ray Analysis), Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain

The reaction between 2-aminobuta-1,3-dienes derived from (*S*)-2-methoxymethylpyrrolidine and vinyl Fischer type tungsten carbene complexes leads to cyclohexenyl carbene complex derivatives with acceptable yields and good enantiomeric excess.

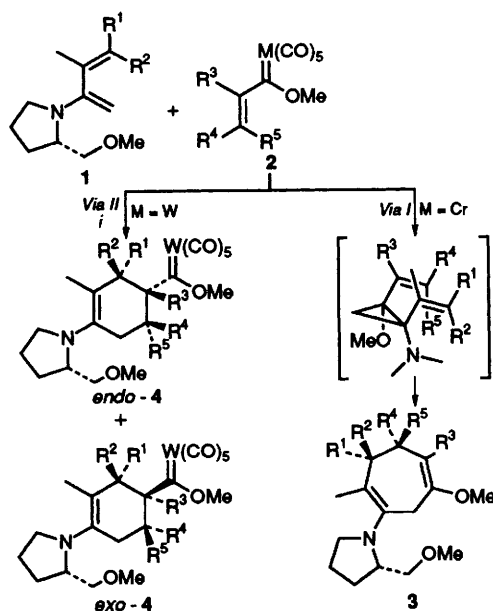
Fischer carbene complexes are proving increasingly attractive reagents for the synthesis of novel compounds.¹ The [4 + 2] cycloaddition of chromium and tungsten vinyloxycarbene complexes is a characteristic reaction of this type of compounds since its initial report by Wulff in 1983.² Thus, these

vinyl complexes show a behaviour comparable to that in the Lewis acid-catalysed reactions of the corresponding α,β -unsaturated alkyl carboxylates, which allows their use as synthons.³ Nevertheless, as far as we know, [4 + 2] cycloadditions using chiral 1,3-dienes and a vinyl Fischer type carbene have not hitherto been described. On the other hand, the readily available chiral aminocarbene complexes⁴ are significantly less reactive than their alkoxy analogues, and they have not so far proved to be suitable for cycloaddition reactions.³

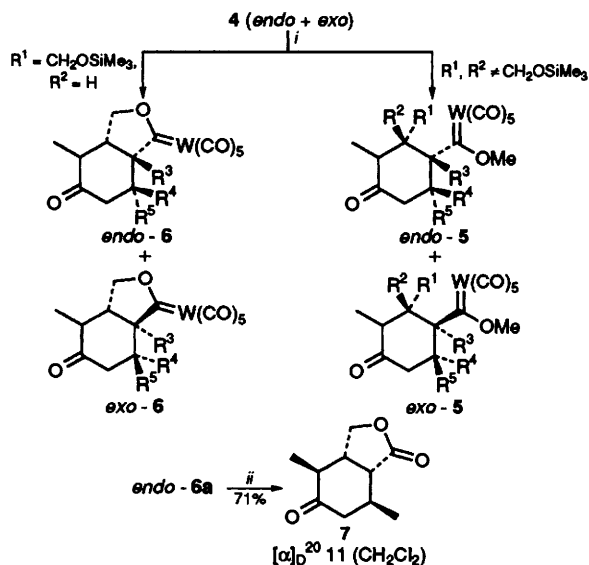
We have been studying the behaviour and synthetic applications of chiral 2-aminobuta-1,3-diene derivatives, and have recently demonstrated that a 2-(*S*)-2-methoxymethylpyrrolidyl substituent on the diene induces high enantioselectivity in some [4 + 2] cycloadditions as well as in cyclopropanation processes towards vinyl chromium Fischer type carbenes.⁵ Thus, 2-aminodienes **1** react with vinylchromium carbene complexes to give aminocycloheptadienes **3** via tandem cyclopropanation–Cope rearrangement processes with quite good yields and high enantioselectivities (Scheme 1, via I).

We report here our preliminary results on the first asymmetric [4 + 2] cycloaddition of α,β -unsaturated Fischer type tungsten carbene complexes with chiral 2-amino-1,3-dienes **1** derived from commercially available (*S*)-2-methoxymethylpyrrolidine. Thus, when the 2-aminodiene **1** reacts with the tungsten vinyl carbene **2** (molar ratio 1 : 1; from -78 to 25°C , THF, 24 h),[†] the new cyclohexenyl tungsten carbene **4** is obtained as a mixture of two diastereoisomers, corresponding to a formal *endo*/*exo* topology of the diene and dienophile (Scheme 1, via II).

The *endo*/*exo* ratios for **4** (Scheme 1) were deduced from the ¹H and ¹³C NMR spectral the crude mixture;[‡] attempted



Scheme 1 Conditions: i, THF, -78 to 25°C , 24 h



Scheme 2 Conditions: i, THF, 3 mol dm⁻³ HCl (aq), room temp., 3 h; ii, 0.5 mol dm⁻³ Ce(NH₄)₂(NO₃)₆ in THF, 2% HNO₃ (aq), room temp., 10 min

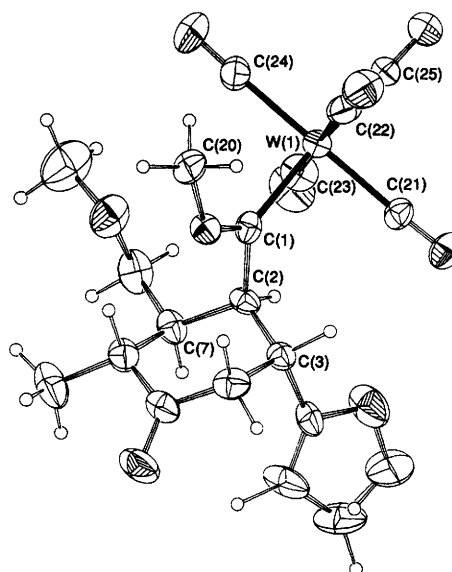


Fig. 1 Perspective view of compound *exo*-**5b**

Table 1 Compounds 5 and 6 prepared from 1

Entry	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)	Molar ratio E.e. (%)		
							<i>endo</i> : <i>exo</i>	<i>endo</i>	<i>exo</i>
5a	CH ₂ OMe	H	H	2-Fu ^b	H	40	2.0:1.0	50	99
5b	H	CH ₂ OMe	H	2-Fu	H	45	2.3:1.0	20	94
5c	CH ₂ OMe	H	H	Me	H	57	4.3:1.0	18	82
6a	CH ₂ OSiMe ₃	H	H	Me	H	53	15.0:1.0	81	^a
6b	CH ₂ OSiMe ₃	H	H	Me	Me	43	5.4:1.0	72	^a
6c	CH ₂ OSiMe ₃	H	Me	H	H	51	4.3:1.0	90	^a

^a Product could not be properly isolated. ^b Fu = furyl.

purification by column chromatography led to a mixture of products arising from partial hydrolysis of the enamine group. The stereochemical assignment was therefore established from the NMR data of their hydrolysis products 5 and 6. Compounds 6 are obtained when R¹ is CH₂OSiMe₃ and are formed by displacement of this group under the hydrolysis conditions followed by an intramolecular cyclization process (Scheme 2). Moreover, the structure of 5b as the *exo*-isomer was confirmed by an X-ray crystal structure determination (Fig. 1). Compounds 5 and 6 can be obtained in diastereoisomerically pure form by treatment of 4 with 3 mol dm⁻³ HCl in THF§ followed by column chromatography (silica gel; hexane–diethyl ether–dichloromethane)¶ (Scheme 2 Table 1).

We have found that the stereoselectivity of the reaction is dependent not only on the nature of the substituents at the carbon–carbon double bond in the carbene complex but also on the size of the substituent at the C-4 position of the diene. Thus, the *endo*:*exo* ratio of 4.3:1 found when R⁴ = Me (5c) decreases to 2:1 for R⁴ = furyl (5a). On the other hand, the ratio is 15:1 when R¹ is CH₂OSiMe₃ (6a) dropping to 4.3:1 when R¹ is CH₂OMe (5c) (Table 1).

The enantiomeric excesses (e.e.) of 5 and 6 were determined by chiral HPLC (Chiracel OD-H, UV–VIS photodiode array detector; THF–hexane or ethyl acetate–hexane as eluent; flow rates between 0.8 and 1.0 ml min⁻¹) and their absolute configuration was based on that of 5b, which was determined by an X-ray crystallographic analysis (Fig. 1).||

In order to use products 5 and 6 in organic synthesis it is necessary to remove the metal from the complexes in a clean and productive manner. Treatment of the complexes with conventional oxidants for Fischer carbenes proved to be successful affording cyclohexanecarboxylic acid derivatives and γ -lactones. Thus, *endo*-6a furnished 7 in good yield on treatment with cerium(IV) ammonium nitrate as oxidant (Scheme 2).

An unusual aspect of this reaction is the fact that both diastereoisomers of the diene, *Z* and *E*, can be prepared, so both isomers of 5 and 6 can be obtained in very high e.e. by selecting the appropriate diene (see 5a and 5b, Table 1).

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Footnotes

† The dramatic effect of the nature of the metal in product distribution has been previously reported.⁷

‡ When R⁴ in the carbene complex 2 is furyl small amounts of 3 were observed as side products.

§ Because of the epimeric character of the stereogenic centre α to the carbonyl group, variable amount of epimers can be obtained in some cases depending on the hydrolysis conditions.

¶ Spectroscopic data: e.g. *exo*-5a: mp 107–108°C (from hexane); δ_{H} (300 MHz; CDCl₃; Me₄Si; *J* in Hz): 1.10 (3H, d, *J* 7.0, CH₃), 2.13 (1H,

dq, *J* 7.3, 5.9, CHCH₂O), 2.38 (1H, dd, *J* 16.3, 3.9, CH₂CO), 2.64 (1H, qd, *J* 7.0, 5.7, CHCH₃), 2.85 (1H, dd, *J* 16.3, 9.2, CH₂CO), 3.17 (3H, s, OCH₃), 3.38–3.47 (3H, m, CH₂O + CHFu), 4.50 (1H, dd, *J* 10.7, 7.0, CHCW), 4.64 (3H, s, CH₃OCW), 5.89 (1H, d, *J* 3.4, Ar), 6.19 (1H, dd, *J* 3.4, 1.9, Ar) and 7.21 (1H, d, *J* 1.9, Ar); δ_{C} (75 MHz, CDCl₃) 11.4 (CH₃), 37.9 (CH), 40.8 (CH₂), 43.0 (CH), 43.5 (CH), 58.8 (CH₃), 70.3 (CH), 72.0 (CH₂), 72.8 (CH₃), 106.0 (CH), 110.2 (CH), 141.6 (CH), 154.0 (C), 196.8 (C), 202.8 (C), 210.8 (C) and 340.7 (C); *m/z* 588 (M⁺, 3%), 532 (10), 474 (15), 431 (20), 401 (37), 313 (38), 262 (77), 169 (71), 155 (100) and 45 (98); $[\alpha]_{\text{D}}^{20} +34$ (c 1.15 $\times 10^{-3}$ in CH₂Cl₂); e.e. 99%.

exo-6c: mp. 130–131°C (from hexane); δ_{H} (300 MHz, CDCl₃, Me₄Si) 0.99 (d, *J* 6.4 Hz, 3H, CH₃CH), 1.20 (3H, s, CH₃C), 1.90 (1H, ddd, *J* 11.8, 5.5, 2.5, CHCH₂CO), 2.02 (1H, dq, *J* 11.8, 6.4, CHCH₃), 2.24 (1H, ddd, *J* 13.0, 11.4, 6.0, CH₂CH₂), 2.41 (2H, m, CH₂CH₂), 2.55 (1H, ddd, *J* 13.0, 7.9, 5.4, CH₂CH₂), 4.83 (1H, dd, *J* 10.8, 2.5, CH₂O) and 4.91 (1H, dd, *J* 10.8, 5.5, CH₂O); δ_{C} (75 MHz, CDCl₃) 12.8 (CH₃), 23.5 (CH₃), 32.7 (CH₂), 36.4 (CH₂), 43.6 (CH), 48.1 (CH), 70.6 (C), 88.3 (CH₂), 196.7 (C), 202.5 (C), 210.1 (C) and 325.9 (C); $[\alpha]_{\text{D}}^{20} +47$ (c 6.70 $\times 10^{-3}$ in CH₂Cl₂), e.e. 90%.

7: mp 49–51°C (from hexane–CH₂Cl₂); $[\alpha]_{\text{D}}^{20} +11$ (c 2.10 $\times 10^{-3}$ in CH₂Cl₂), e.e. 81%.

|| Crystal data for 1. C₂₀H₂₀O₉W, *M_r* = 588.22, orthorhombic, *P*2₁2₁, *a* = 8.537(9), *b* = 9.932(3), *c* = 26.18(3) Å, *V* = 2220(4) Å³, *Z* = 4, *D_x* = 1.76 g cm⁻³, μ (Mo-K α) = 53.6 cm⁻¹, *T* = 293 K, colourless crystal, 0.10 \times 0.10 \times 0.06 mm size, Mo-K α radiation (λ = 0.71073 Å), graphite monochromator. 4551 reflections measured on an Enraf-Nonius CAD4 (ω -2 θ scan technique), range 0 < θ < 25°; 3892 unique reflections (*R*_{int} = 0.044, averaging some doubly measured reflections) and 2372 observed [*I* > 3 σ (*I*)]. Final *R* = 0.027 [*R_w* = 0.025, *w* = 1/(σ^2 (*F_o*) + 0.000095*F_o*²)]. The absolute configuration was tested using the program BIJVOET, giving *B* = 1.0000(1) for the 110 strongest Friedel pairs. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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