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The first chiral racemic Fischer-type aminocarbene complex bearing a C_2 symmetry amine: stereochemical characteristics and application to Michael addition reactions

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Abstract

The synthesis of [*trans*-methyl(2,6-dimethyl)morpholinocarbene]pentacarbonylchromium(0) complex (**3**) is reported, together with the stereoselective Michael addition of the conjugate base of complex **3** to enones.

Keywords: Chromium; Carbene complex; Michael addition; Stereochemistry

The use of aminocarbene complexes of the Fischer-type in the synthesis of a variety of interesting organic compounds is currently a topic of great interest, and important contributions in this field have appeared [1]. One of the reasons for this interest is undoubtedly the fact that chiral aminocarbene complexes can be easily obtained if the aminolysis of the alkoxy alkyl carbene complexes is performed using a chiral amine [2], and the use of optically pure Fischer-type amino carbene complexes has proven to be useful in achieving the stereoselective formation of new carbon–carbon bonds [2,3].

As a development of our work on amino carbene complexes, [4,5] we turned our attention towards chiral derivatives and we considered the possibility of synthesizing new aminocarbene complexes bearing a C_2 symmetry amine as a stereogenic unit. The peculiarity that has facilitated the use of chiral auxiliaries with a C_2 symmetry axis in asymmetric synthesis over the last few years is that the number of possible diastereomeric transition states is reduced [6]. In the case of aminocarbene complexes, the presence of a C_2 symmetry amine as a substituent on the carbene carbon atom could be particularly interesting. The rotational barrier about the C_{carb}–N bond is quite high and at room temperature allows the existence of two configurationally stable rotamers in compounds bearing an unsymmetrically substituted amine [7]. The use of a chiral C_2 symmetry amine would generate aminocarbene complexes in which the two rotamers are identical. The importance of this is evident when chiral amino carbene complexes are used in stereoselective synthesis. Also, the determination of stereoselectivity in reactions involving such complexes could be simplified by the absence of the two rotational isomers.

As a first approach, we chose the racemic *trans*-2,5-dimethylpyrrolidine obtained through the separation of a mixture of *cis* and *trans* isomers [8], but the results with this amine were very disappointing. In fact, from the reaction of the (methoxy or acyloxymethylcarbene)pentacarbonylchromium(0) (**1**) with the *trans*-2,5-dimethylpyrrolidine under a variety of conditions, the expected aminocarbene complex was not detected and only a rapid decomposition of the starting complex **1** was observed. *cis*-2,5-Dimethylpyrrolidine easily gave the aminolysis of complex **1**, producing the corresponding aminocarbene complex (which, however, has no practical use in stereoselective synthesis). These results can be interpreted by considering that hindered secondary amines are poorly reactive in the aminolysis

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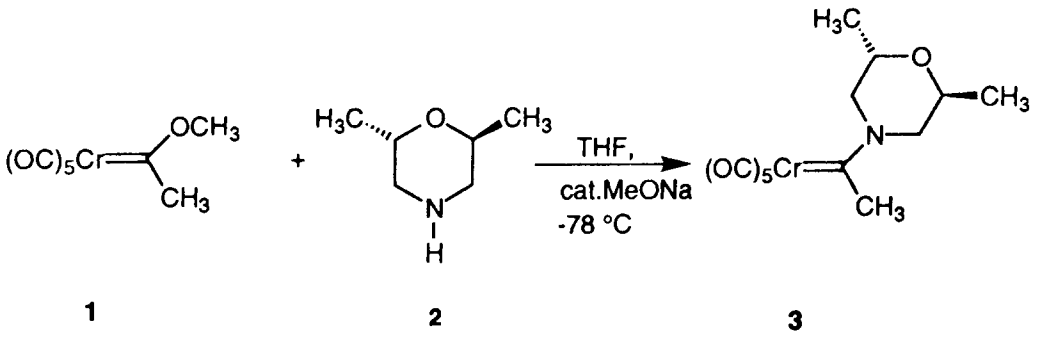


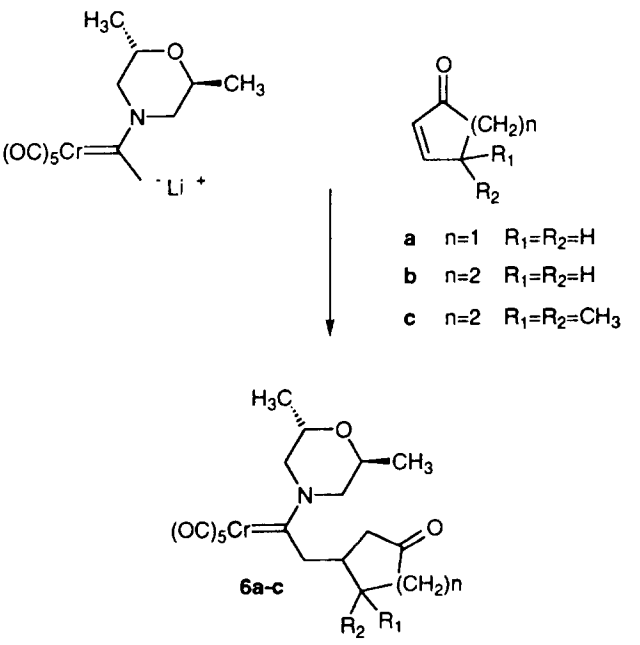
1 2 3

Scheme 1.

reactions of alkoxyalkylcarbene complexes [7]. In the present case, the reactivity is even lower since the *trans*-2,5-dimethylpyrrolidine has both faces of the ring shielded by the presence of a methyl group, thus making the aminolysis process impossible. We therefore turned our attention towards *trans*-2,6-dimethylmorpholine **2**, a less crowded chiral secondary amine. In addition to being a C_2 symmetry amine, this heterocyclic compound is a fundamental constituent of biologically active molecules (as is shown by the large number of patents reported in the literature) and can be easily obtained from a commercial mixture of the *cis* and *trans* isomers [11].

As far as we know, this C_2 symmetry amine has never been used as a chiral auxiliary in asymmetric synthesis. We reasoned that the shift of methyl substituents from the α to the β-position could make aminolysis of the alkoxycarbene complex **1** easier. In addition, the shift of the stereogenic centres from the α to β-position could not be considered "a priori" a determinant drawback affecting the stereoselectivity of the reactions on the α-carbon atom of the resulting chiral carbene complex **3**.

The aminolysis reaction of complex **1** with (±)-**2** was performed in a tetrahydrofuran solution at −78 °C for 6 h in the presence of a catalytic amount of sodium methoxide, and gave pentacarbonyl[(±)-methyl(2,6-dimethyl)morpholinocarbene]chromium(0) **3** in 86% yield (Scheme 1) [15]. Complex **3** represents the first example of a chiral Fischer-type carbene complex bearing a C_2 symmetry amine. This complex was then used as a new substrate in stereoselective Michael addition reactions (Scheme 2). The typical procedure was as follows. To a tetrahydrofuran solution of the conjugate base of the complex **3** (generated by adding 1.1 mmol of a 1.6 M $LiBu^n$ solution in hexane to 1 mmol of **3** in THF (5 ml) at −78°C and keeping the mixture at −78°C for 20 min) an excess of enones **5a,c** (2.1 mmol) was added using a syringe at −78°C under argon. The mixture was allowed to react at −78°C for 20 min. The reaction was quenched with 5 ml of NH_4Cl saturated aqueous solution, diluted with water (30 ml), and extracted with diethyl ether (2 × 50 ml). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The unreacted starting complex **3** was quickly removed by filtering over a silica gel pad (eluent heptane/diethyl ether 1:1), and the diastereoisomeric mixture of the complex **6a,c** was recovered completely using ethyl acetate. The pure diastereoisomers of complex **6a** were obtained by flash chromatography (eluent CH_2Cl_2/ethyl acetate 4:1). The pure major diastereoisomer of complex **6c** was obtained by crystallization of the diastereoisomeric mixture from CH_2Cl_2/heptane [16].



	yield(%)	d.e.(%)
6a:	76	56
6b:	75	59
6c:	66	> 92

Scheme 2.

We wish to emphasize that the use of the particular chiral aminocarbene **3** made very easy the determination of the stereoselections by direct analysis of the NMR spectra of the crude reaction mixtures.

We are now studying the separation of (±)-**2** into enantiomers, and the limits within which this new amine can be effective as chiral auxiliary or catalyst in both carbene complex chemistry and enantioselective synthesis.

In conclusion, *trans*-2,6-dimethylmorpholine **2** shows some peculiar and interesting features.

It easily gives the aminolysis with carbene complex **1** to the corresponding chiral complex **3** as a single isomer and therefore it constitutes a valid alternative for α,α'-disubstituted C_2 symmetry amines such as *trans*-2,5-dimethylpyrrolidine which does not give the aminolysis reaction with alkoxycarbene complexes. It avoids the problems associated with the presence of rotamers so that the determination of the stereoselection is performed directly on the crude reaction mixture, without decomplexation of the product; this aspect is particularly useful if the complex has to be used for further reactions. Its complex derivative **3** gives good diastereoselection in the Michael addition reactions regardless of the fact that the stereogenic centres on the morpholine ring are far from the reacting site. We wish to underline that it has been reported [17] that a very low diastereoselection was obtained when the (3*S*,4*S*)dimethoxypyrrolidine was used as chiral auxiliary in the place of (2*S*,5*S*)-dimethylpyrrolidine and the reason was attributed to the distance of the stereogenic centres from the reaction site.

We think that the characteristics of amine **2** open the possibility of using C_2 symmetry amines as stereogenic units in the Fischer-type aminocarbene complex chemistry.

Acknowledgements

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[15] Data for **3**: m.p. 98–99°C (yellow crystals CH_2Cl_2); IR(nujol): 2054(*ν* CO *trans*), 1980–1850(*ν* CO *cis*) cm^{-1}; ^{1}H-NMR(300 MHz, $CDCl_3$) *δ* ppm: 4.73 (1H, dt, $J_{gem} = 12.9$ Hz, $J_{ax\text{-}eq} = J_{1,5} = 2.3$ Hz, N_Z-CH_{eq}-); 4.25–4.10 (2H, m, CH_3CH-O); 3.91 (1H, ddd, $J_{gem} = 12.9$ Hz, $J_{ax\text{-}eq} = 4.1$ Hz, $J_{1,5} = 1.7$ Hz, N_E-CH_{eq}-); 3.73 (1H, dd, $J_{gem} = 12.9$ Hz, $J_{ax\text{-}ax} = 9.0$ Hz, N_Z-CH_{ax}-); 3.67 (1H, dd, $J_{gem} = 13.2$ Hz, $J_{ax\text{-}eq} = 3.6$ Hz, N_E-CH_{ax}-); 2.70 (3H, s, CH_3-C=Cr); 1.28 (3H, d, $J_{vic} = 6.3$ Hz, O_Z-CH-CH_3); 1.21 (3H, d, $J_{vic} = 6.6$ Hz, O_E-CH-CH_3); ^{13}C-NMR (200 MHz, $CDCl_3$) *δ* ppm: 274.5 (C=Cr); 224.0 (CO_{trans}); 218.4 (CO_{cis}); 68.2 (d, O_Z-CH-CH_3); 67.9 (d, O_E-CH-CH_3); 66.8 (t, N_Z-CH_2-); 56.0 (t, N_E-CH_2-); 40.0 (q, Cr=C-CH_3); 18.5 (q, O_Z-CH-CH_3); 17.2 (q, O_E-CH-CH_3). Elemental analysis: found, C 45.71; H 4.32; N 4.04; calcd. for $C_{13}H_{15}CrNO_6$, C 46.84; H 4.50; N 4.20%; MS (EI), $m/z = 333(M^+)$; 305(M^+-CO); 277(M^+-2CO); 249(M^+-3CO); 221(M^+-4CO); 193 (M^+-5CO); 140[M^+-Cr(CO)$_5$].

[16] All of the compounds **6a–c** gave spectra and analytical data consistent with the assigned structures. The diastereoisomeric ratio was evaluated by ^{1}H-NMR spectroscopy on the diastereoisomeric mixture of the complexes **6a–c** purified from the unreacted complex **3**. The results are comparable with those reported using the optically pure pentacarbonyl [methyl(methoxymethyl)pyrrolidinocarbene]chromium(0) [3].

Selected data for the major diastereoisomer of complex **6c**: m.p. 138–139°C (yellow crystal CH_2Cl_2/heptane); IR (nujol): 2053, 1975, 1932, 1918, 1905, 1705 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) *δ* ppm: 4.77 (1H, dt, $J_{gem} = 13$ Hz, $J_{1,2} = J_{1,5} = 2$ Hz, N_Z-CH(H)-); 4.25–4.17 (2H, m, CH_3CH-O); 3.94 (1H, ddd, $J_{gem} = 13$ Hz, $J_{1,2} = 3.7$ Hz, $J_{1,5} = 2$ Hz, N_E-C(H)*H*-); 3.79 (1H, dd, $J_{gem} = 13$ Hz, $J_{1,2} = 9.3$, N_Z-C(H)*H*-); 3.66 (1H, dd, $J_{gem} = 13.2$ Hz, $J_{1,2} = 3.5$ Hz, N_E-C*H*(H)-); 3.31 (1H, t, $J_{gem} = 12.1$ Hz, $J_{1,2} = 4.3$ Hz, -C(H)*H*-C=Cr); 2.99 (1H, t, $J_{1,2} = J_{gem} = 12.1$ Hz,

-C*H*(H)-C=Cr); 2.55–2.43 (1H, m, C*H*-CH_2-C=Cr); 2.40–2.35 (2H, m, -CH_2-C=O); 2.15–1.95 (2H, m, -CH_2-C=O); 1.80–1.65 (2H, m, -CH_2-CH_2-C=O); 1.29 (3H, d, J_{vic} = 6.2 Hz, O_Z-CH-CH_3); 1.22 (3H, d, J_{vic} = 6.6 Hz, O_E-CH-CH_3); 1.21 [3H, s, C(CH_3)CH_3]; 1.13 [3H, s, CCH_3(CH_3)]; ^{13}C-NMR (200 MHz, $CDCl_3$) δ ppm: 280.5 (C=Cr); 223.2 (CO_{trans}); 218.7 (CO_{cis}); 210.2 (C=O); 68.6 (O_Z-*C*H-CH_3); 68.4 (N_Z-CH_2); 67.7 (O_E-*C*H-CH_3); 58.0 (N_E-CH_2-); 50.9 (CH_2-C=Cr); 45.7 (*C*H-CH_2-C=Cr); 42,7 (CH-*C*H_2-C=O); 40.3 (*C*H_2C=O); 38.6 (*C*H_2-CH_2-C=O); 34.3[*C*(CH_3)$_2$]; 28.9 [C(CH_3)*C*H_3]; 21.5 [C*C*H_3(CH_3)]; 18.6 (O_Z-CH-*C*H_3); 17.4 (O_E-CH-*C*H_3). Elemental analysis: found, C 54.77; H 6.28; N 2.95; calcd. for $C_{21}H_{27}CrNO_7$, C 55.02; H 6.16; N 3.05%; MS (EI), m/z = 457(M^+), 429(M^+-CO), 373(M^+-3CO), 345(M^+-4CO), 317(M^+-5CO).

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