Stereochemistry of Allylic Alkylation of the Tetracarbonyliron Complexes of (*R*)-1-Acetyl-5-isopropoxy-3-pyrrolin-2-one

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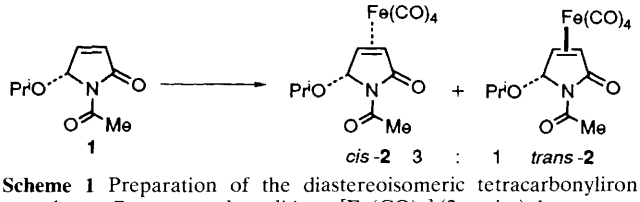
The two diastereoisomeric title complexes react with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ to give nucleophilic substitution at C-5 to the corresponding 5-allyl derivatives; the reaction of the *cis*-complex proceeds slowly and with predominant inversion, whereas the *trans*-complex reacts quickly and with complete retention of configuration at C-5.

The selective introduction of carbon nucleophiles at the allylic position is a challenging synthetic problem. Transition metal mediated procedures appear to be most suitable to achieve this transformation with high chemo-, regio- and stereoselectivity.[1] Thus, palladium-catalysed alkylation of allylic acetates with soft nucleophiles has been shown to usually occur with net retention of configuration.[2] Several other metals are also used for this purpose,[3] but the stereochemical details of these processes are not always clear.[4] In this communication we present detailed stereochemical information on an iron-mediated allylic alkylation process[5] by using the enantiopure cyclic allylic ether **1** as substrate.

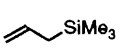
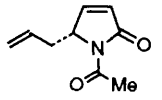
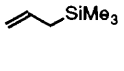
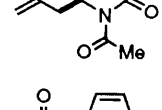
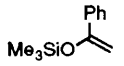
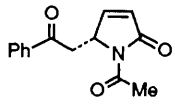
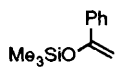
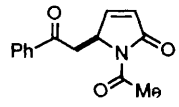
We recently reported the synthesis of the multifunctional building block **1** from (*S*)-malic acid.[6] The utility of **1** lies in its electron-poor double bond, which shows good reactivity and diastereoselectivity in Diels–Alder[6] and conjugate addition reactions.[7] Subsequently, C-5 can be functionalized by using *N*-acyliminium chemistry.[8] However, for a particular application in alkaloid total synthesis we then wished to perform stereoselective substitution at C-5 while leaving the double bond unchanged. To realize this goal our attention was caught by a recent article, which describes nucleophilic substitution at the γ-position of an acyclic α,β-unsaturated ester by using tetracarbonyliron intermediates.[9] Herein, we report (*i*) the isolation and characterization of the two diastereoisomeric tetracarbonyliron complexes of **1** and (*ii*) the Lewis acid-mediated reactions of the separate isomers with allyltrimethylsilane and α-(trimethylsiloxy)styrene.

When pyrrolinone **1** was stirred with $[Fe_2(CO)_9]$ (2 equiv.) in benzene or diethyl ether under nitrogen in the dark at room temp. for 24 h, a 3 : 1 mixture of the *cis* and *trans* complexes



Scheme 1 Preparation of the diastereoisomeric tetracarbonyliron complexes. *Reagents and conditions*: $[Fe(CO)_9]$ (2 equiv.), benzene or diethyl ether, 18 h

Table 1 Results of the $BF_3{\cdot}Et_2O$-mediated alkylation of the iron complexes and subsequent removal of iron with Me_3NO

Entry	Iron complex	Nucleophile	Reaction time/h	Major product	(yield,[a] e.e.,[b] rotation)
1	*trans*-**2**		3		(*R*)-**3** (51%, e.e. >95%, $[\alpha]_D^{20}$ −282, *c* 0.76, $CHCl_3$)
2	*cis*-**2**		18		(*S*)-**3** (53%,[a] e.e. 55%, [α] not determined)
3	*trans*-**2**		3		(*R*)-**4** (48%, e.e. >95%, $[\alpha]_D^{20}$ −345, *c* 0.35, $CHCl_3$)
4	*cis*-**2**		18		(*S*)-**4** (18%, e.e. 33%, $[\alpha]_D^{20}$ + 130, *c* 0.34, $CHCl_3$)

[a] Yields refer to isolated yields, except for entry 2, which lists the ^1H NMR yield in an inseparable mixture with 27% of **1**. [b] The e.e. values in entries 1 and 2 refer to optical yields determined for pyrrolidinone **5** (see text); the e.e. values in entries 3 and 4 were determined using ^1H NMR with [Eu(hfc)$_3$] = tris[heptafluoropropylhydroxymethylene-(+)-camphorato]europium(III).

cis-**2** and *trans*-**2**, respectively, was obtained in 50–70% yield after flash chromatography under nitrogen (Scheme 1). Remarkably, the *cis*-isomer was the sole isomer present in *ca.* 30% yield (NMR) after 3 h, so that the eventual 3 : 1 ratio must be a result of slow thermodynamic equilibration. The literature contains precedent for the preferred (heteroatom directed) *cis*-complexation of tetracarbonyliron.[10] The isomers were separated by flash chromatography using degassed silica under nitrogen pressure. These iron complexes were only moderately air-stable, but could be stored under nitrogen at −20 °C. Both isomers *cis*-**2** [needles from pentane, m.p. (decomp.) 67.5–70 °C]† and *trans*-**2** (oil)† showed the well-known upfield shift of the olefinic hydrogens and carbons in the NMR spectra, but definitive proof of their structures had to await X-ray crystallography. As the crystals of *cis*-**2** made from (*R*)-**1** appeared unsuitable, we eventually found crystals of racemic *trans*-**2** [m.p. (decomp.) 63–68 °C, prepared from racemic **1**] amenable to an X-ray crystal structure determination (Fig. 1).‡ When comparing the bond lengths in the organic ligand of *trans*-**2** with those in **1**, the lengthening of the C(3)–C(4) bond in the complex with 0.10 Å is the most obvious feature.

With the diastereoisomerically pure complexes *cis*-**2** and *trans*-**2** in hand we investigated the reactivity towards π-nucleophiles in the presence of Lewis acid. First, in a comparison experiment, the uncomplexed **1** appeared completely unreactive when treated at room temp. with allyltrimethylsilane (3 equiv.) and $BF_3{\cdot}Et_2O$ (3 equiv.) in dichloromethane. This observation confirmed the notion that iminium ion intermediates are not readily formed from imides. However, when the iron complex *trans*-**2** was subjected to the same reaction conditions a fast reaction took place as shown by TLC. After 3 h trimethylamine *N*-oxide (4 equiv.) was added to remove the iron. Work-up and chromatographic purification provided enantiopure 5-allylpyrrolinone (*R*)-**3** as a colourless oil in 51% yield (Table 1, entry 1).§ Treatment of *cis*-**2** with allyltrimethylsilane under the same conditions gave rise to a much slower and less selective reaction. After 18 h an inseparable 2 : 1 mixture of (*S*)-**3** [≤55% enantiomeric excess (e.e.)] and **1** was obtained in 79% yield (Table 1, entry 2) after flash chromatography. Likewise, $BF_3{\cdot}Et_2O$ mediated reaction of iron complex *trans*-**2** with α-(trimethylsiloxy)styrene proceeded fast and with excellent selectivity to give enantiopure (*R*)-**4** [m.p. (decomp.) 130.5–132.5 °C],§ whereas *cis*-**2** reacted slowly to give (*S*)-**4** in only 33% e.e. and low yield (Table 1, entries 3 and 4).

To establish the stereochemical course of the above reactions, the allylation products from both *trans*-**2** and *cis*-**2** were treated with *tert*-butylcuprate in the presence of Me_3SiCl, followed by removal of the *N*-acetyl function (shown in Scheme 2 for the product from *trans*-**2**). Conjugate addition occurred solely *trans* with respect to C-5 to give the *trans*-4,5-disubstituted pyrrolidinone **5**. After chromatographic purifi-

† *Spectroscopic data*: Complex *trans*-**2**: $[\alpha]_{578}^{20}$ +368 (*c*, 0.10, pentane); IR (pentane) ν/cm^{-1} 2098, 2033, 2020, 2003, 1742, 1708, 1295, 1055; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 and 1.32 (2 × d, 6 H, *J* 6.1 Hz, Pr^i), 2.42 (s, 3 H, Ac), 3.70 (d, 1 H, *J* 5.3 Hz, 3-H), 3.81 (d, 1 H, *J* 5.3 Hz, 4-H), 4.22 (sept, 1 H, *J* 6.1 Hz, Pr^i), 5.67 (s, 1 H, 5-H); ^{13}C NMR (50 MHz, C_6D_6) δ 207.7 (FeCO), 176.7 and 171.5 (Ac, C-2), 89.9 (C-5), 73.4 (Pr^i), 57.2 (C-4), 46.6 (C-3), 25.6 (Ac), 23.9 and 23.8 (Pr^i). Complex *cis*-**2**: $[\alpha]_{578}^{20}$ −416 (*c* 0.14, pentane); IR (pentane) ν/cm^{-1} 2100, 2038, 2020, 2003, 1740, 1710, 1300, 1088; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 and 1.30 (2 × d, 6 H, *J* 6.1 Hz, Pr^i), 2.40 (s, 3 H, Ac), 3.78 (d, 1 H, *J* 5.5 Hz, 3-H), 4.12 (dd, 1 H, *J* 4.6, 5.3 Hz, 4-H), 4.38 (sept, 1 H, *J* 6.1 Hz, Pr^i), 5.75 (d, 1 H, *J* 4.6 Hz, 5-H); ^{13}C NMR (63 MHz, C_6D_6) δ 208.3 (FeCO), 176.1 and 171.1 (Ac, C-2), 86.7 (C-5), 74.3 (Pr^i), 60.3 (C-4), 47.5 (C-3), 25.9 (Ac), 23.8 and 23.3 (Pr^i).

‡ Details of the X-ray crystal structure determinations of (*R*)-**1** and racemic *trans*-**2** will be reported elsewhere.

§ *Spectroscopic data*: (*R*)-**3**: $[\alpha]_D^{20}$ −282 (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 1725, 1685; ^1H NMR (200 MHz, $CDCl_3$) δ 2.52 (s and m, 4 H, Ac, allyl), 2.81 (m, 1 H, allyl), 4.79 (m, 1 H, 5-H), 5.05 (d, 1 H, *J* 7.5 Hz, allyl), 5.12 (s, 1 H, allyl), 5.59 (m, 1 H, allyl), 6.11 (dd, 1 H, *J* 1.5, 6.0 Hz, 3-H), 7.24 (dd, 1 H, *J* 2.0, 6.0 Hz, 4-H). (*R*)-**4**: $[\alpha]_D^{20}$ −345 (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 1730, 1680, 1590; ^1H NMR (250 MHz, $CDCl_3$) δ 2.56 (s, 3 H, Ac), 2.87 (dd, 1 H, *J* 10.4, 17.2 Hz, *H*CH–CO), 4.20 (dd, 1 H, *J* 3.6, 17.2 Hz, HC*H*–CO), 5.22 (dm, 1 H, *J* 10.4 Hz, 5-H), 6.13 (dd, 1 H, *J* 1.5, 6.1 Hz, 3-H), 7.45 (m, 2 H, *m*-Ph), 7.56 (m, 2 H, *p*-Ph and 4-H), 7.92 (m, 2 H, *o*-Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.9, 170.3, 169.8, 152.4, 136.2, 133.7, 128.8 (2 × C), 128.0 (2 × C), 126.2, 58.4, 40.5, 25.0; satisfactory C, H and N analyses were obtained.

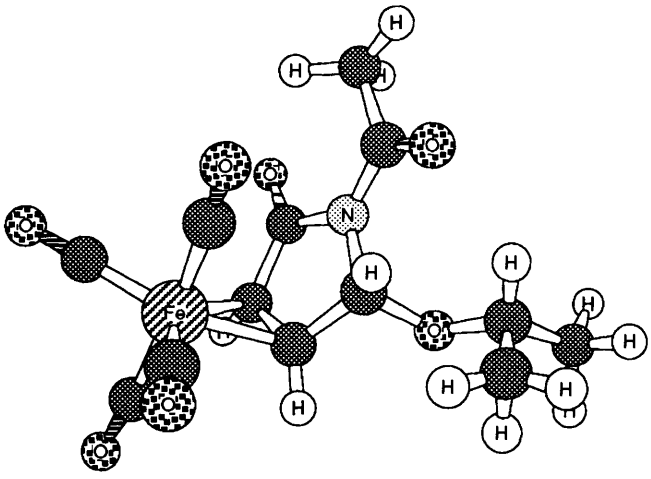
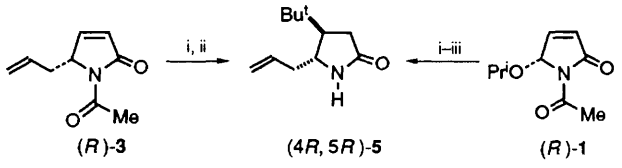


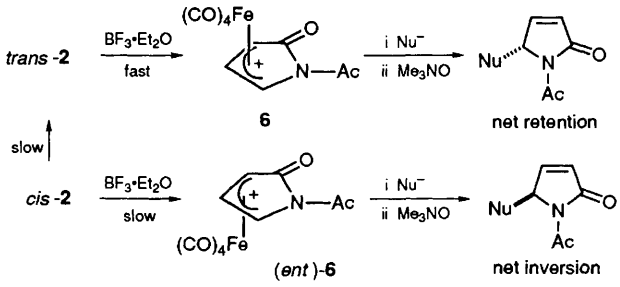
Fig. 1 Chem3D perspective view of the crystal structure of racemic *trans*-**2**



Scheme 2 *Reagents and conditions*: i, CuI (3 equiv.), Bu^{t}Li (4 equiv.), Me_3SiCl (10 equiv.), tetrahydrofuran (THF), −78 °C to room temp. ii, Me_2NH (10 equiv.) dimethylformamide (DMF), room temp.; iii, allyltrimethylsilane (3 equiv.), $BF_3{\cdot}Et_2O$ (3 equiv.), CH_2Cl_2, room temp.

cation we obtained from *trans*-**2** crystalline (+)-**5** ($[\alpha]_D^{20}$ + 29, *c* 0.13, $CHCl_3$), while *cis*-**2** led to (−)-**5** isolated as a colourless oil ($[\alpha]_D^{20}$ −16; *c* 0.76, $CHCl_3$). The absolute configuration of (+)-**5** was established as (4*R*,5*R*) by means of its preparation from (*R*)-**1** (see Scheme 2).[7] Both the conjugate addition of *tert*-butylcuprate to **1** and the *N*-acyliminium allylation of the product (after removal of the acetyl substituent) proceeded with complete *trans* stereoselectivity. This reaction sequence led to (+)-**5** (m.p. 58.5–60.5 °C; $[\alpha]_D^{20}$ + 29; *c* 0.49, $CHCl_3$) in 55% overall yield from **1**. In this manner the absolute configuration of **3** was ascertained. By analogy we assigned the (*R*)-stereochemistry to (−)-**4** (Table 1, entry 3).

Our results show that the *trans*-**2** gives Lewis acid-mediated substitution at C-5 in a fast process with retention of configuration. A logical intermediate in this reaction is the cationic π-allyliron complex **6** (Scheme 3). Nucleophiles then react with the allylic system *anti* to the tetracarbonyliron moiety. The high regioselectivity of this process is caused by the C-2 carbonyl moiety which puts most positive charge in the allylic cation at C-5.[9] Our results further indicate that the *cis*-**2** gives rise to two stereochemically divergent processes, one leading to net retention and one to net inversion. The retention pathway can best be explained by invoking a slow isomerization of *cis*-**2** to *trans*-**2** (the same process is presumed in their preparation from **1**, *vide supra*) followed by a fast reaction with the nuclophile. The inversion route must proceed *via* slow formation of the enantiomeric π-allyliron complex (*ent*)-**6** (Scheme 3), possibly preceded by epimerisation at C-5. The latter notion was suggested by the recovery of partly racemised starting material **1** in one alkylation experiment.



Scheme 3 Mechanistic proposal of the iron-mediated allylic alkylation

In conclusion, we have shown that pyrrolinone **1** can be cleanly alkylated at C-5 *via trans*-**2** with retention of configuration. The more readily available *cis*-**2** complex of **1** can also be alkylated at C-5 but in a much slower process and with loss of stereochemical integrity. To the best of our knowledge this is the first report on the detailed stereochemical course of formation and reactions of enantiopure π-allyl tetracarbonyliron complexes. From the synthetic point of view, the present methodology complements recent work on the anionic reactivity of the pyrrolinone skeleton.[11] Our further work will be directed at improving yields and selectivity of the processes and applying other nucleophiles.[12]

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