Control of Absolute Stereochemistry during Ene-type Coupling between Diene–$Fe(CO)_3$ Groups and Alkenes

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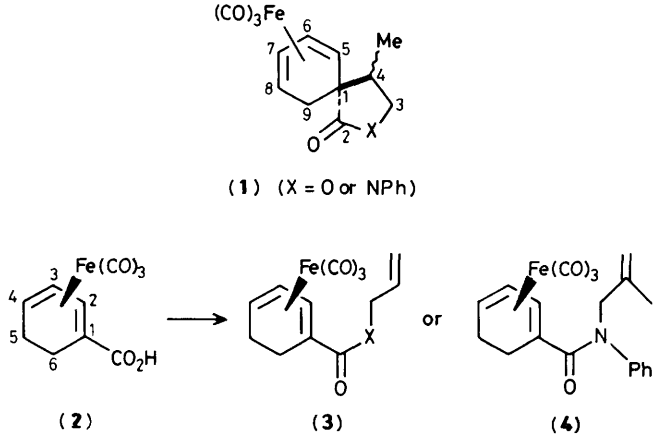
Excellent stereocontrol during the ene-type coupling between diene–$Fe(CO)_3$ groups and alkenes can be achieved by appropriate substitution at C(5) of the diene ring, allowing the preparation of spirolactams and spirolactones in enantiomerically pure form, thus showing the cyclization reaction to be a valuable tool in the asymmetric construction of quaternary and spiro carbon centres.

The stereocontrolled construction of quaternary[1] and spiro carbon[2] centres remains a challenging problem in organic synthesis. Recently, we described a unique iron-mediated intramolecular ene-type reaction, resulting in the high-yielding formation of spirolactones and spirolactams of type (**1**)[3] but this earlier work indicated that the process was non-stereoselective. We now report on a method for controlling this reaction, leading to an asymmetric, diastereospecific construction of quaternary carbon centres.

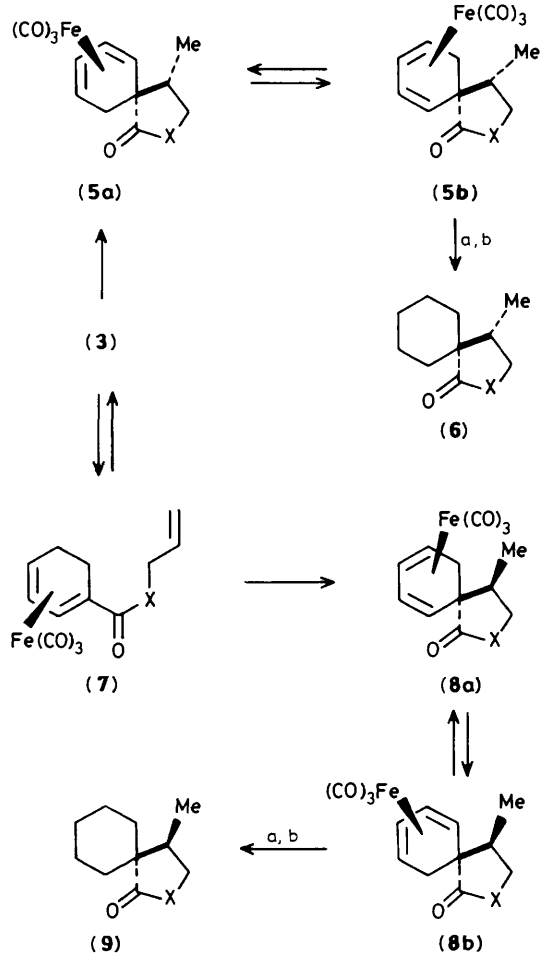
The enantiomerically pure acid (**2**), prepared by the method of Birch *et al.*,[4] was used to generate the optically pure allyl ester (**3**; X = O), *N*-allyl-*N*-phenylamide (**3**; X = NPh), and *N*-methallyl-*N*-phenylamide (**4**) complexes *via* standard methods (Scheme 1). The products obtained from thermally induced spirocyclization (Bu^n_2O, reflux, 5—6 h, under CO atmosphere) of these complexes are shown in Schemes 2 and 3. Although an epimeric mixture of lactones (or lactams) is apparently produced from (**3**; X = O or NPh), each individual epimer showed optical activity which indicated that the C(4) stereocentre may be fixed, as indicated in structures (**5a**) and (**5b**). To confirm this, demetallation of the mixture followed by hydrogenation of the resulting dienes gave spirolactone (spirolactam) in 40% enantiomeric excess [Scheme 2, structures (**6**) and (**9**)]. These results indicate that the actual cyclization is stereospecific, but the product undergoes rapid rearrangement of the diene–$Fe(CO)_3$ unit, and that racemization of the starting complex is a (slower) competing reaction, which accounts for some loss of optical purity (Scheme 2). In accordance with this, cyclization of optically pure *N*-methallyl-*N*-phenylamide complex (**4**) (Scheme 3) afforded racemic spirolactam (**10**).

Deuterium labelling studies supported these observations. Compound (**11**; X = O) (>95% deuterium) underwent cyclization to give lactones (**12a**) and (**12b**), each containing deuterium in a distinct location on the diene ring as indicated. Identical results were obtained from (**11**; X = NPh) and, as expected, the methallyl amide derivative (**13**) yielded a single compound (**14**) with deuterium equally distributed as shown in Scheme 4.

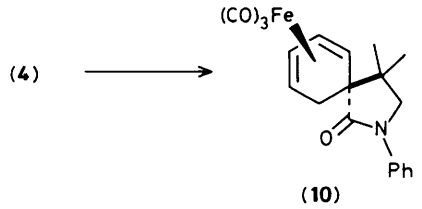
Clearly, if the cyclization is stereospecific, suppression of starting material racemization and postcyclization rearrangement should allow the generation of these spirocyclic systems in optically pure, diastereoisomerically pure form, and we argued that the presence of an appropriate substituent would effect such control. Preliminary experiments demonstrated that the optically pure methyl ester complex (**19**) ($[\alpha]_D^{25}$



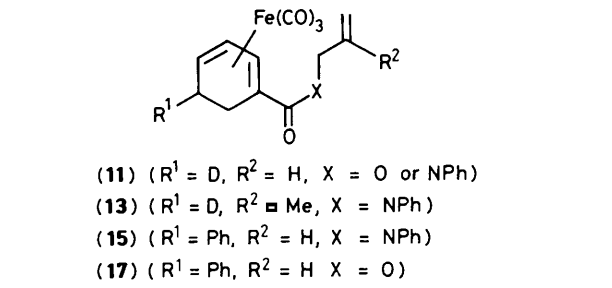
Scheme 1



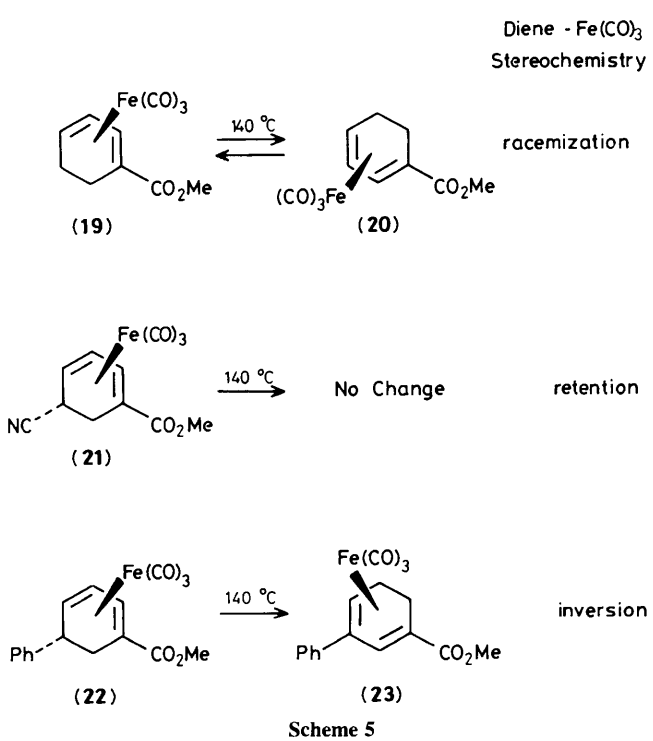
Scheme 2. *Reagents:* a, Me_3NO, C_6H_6, 40 °C, 1 h; b, H_2, Pd–C, C_6H_6–MeOH (1 : 1), room temp., 28 h.



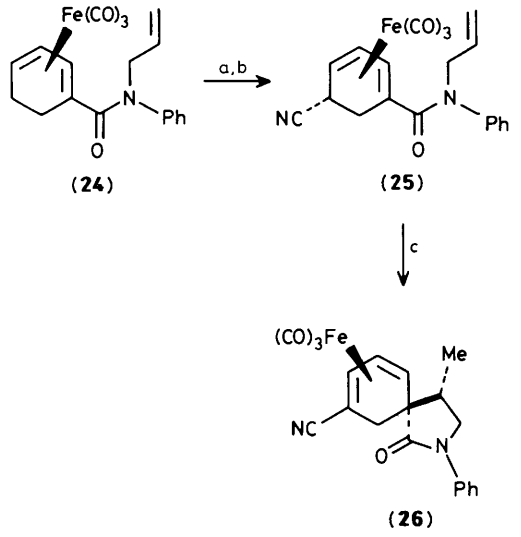
Scheme 3



Scheme 4



Scheme 5



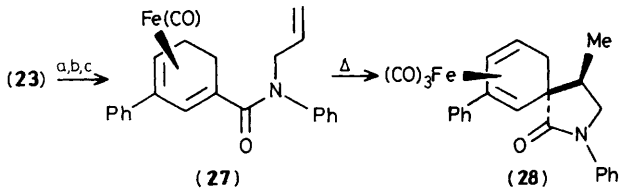
Scheme 6. *Reagents:* a, $Ph_3C^+PF_6^-$, CH_2Cl_2, room temp., 3 h; b, NaCN, MeCN, room temp., 16 h; c, Bu_2O, CO atm., reflux, 6 h.

$-18.5°$, acetone, *c* 3) is (unexpectedly) completely racemized† under the thermal conditions used for cyclization, but the nitrile substituted complex (**21**) ($[\alpha]_D^{25}$ $-78°$, acetone, *c* 1.5) remains unaffected (Scheme 5). On the other hand, the phenyl substituted complex (**22**) ($[\alpha]_D^{25}$ $-117°$, acetone, *c* 3) is completely rearranged to give (**23**) ($[\alpha]_D^{25}$ $-18.5°$, acetone, *c* 1.5). Hydride abstraction from the *N*-allyl-*N*-phenylamide derivative (**24**) ($[\alpha]_D^{25}$ $+136°$, acetone, *c* 3) followed by addition of cyanide gave the optically pure nitrile (**25**) ($[\alpha]_D^{25}$ $+9.4°$, acetone, *c* 3), which yielded enantiomerically pure spirolactam (**26**) ($[\alpha]_D^{25}$ $+96.7°$, acetone, *c* 1.5) in 87% yield under thermal conditions (Scheme 6).‡

Complementary to this, treatment of the racemic hexafluorophosphate salt, derived from (**24**), with Ph_2CuLi afforded (**15**) which gave a 10:1 mixture of spirolactams (**16b**) and (**16a**) when subjected to thermal cyclization conditions. A similar mixture of spirolactones (**18b**) and (**18a**), favouring the product formed *via* dienyl migration, was observed for the cyclization of the corresponding allylester derivative (**17**).

† This result is somewhat unexpected because we did not find products corresponding to structural rearrangement, *i.e.*, 2-CO_2Me or 5-CO_2Me substituted diene complexes, which might have been expected to accompany racemization. This will be investigated further.

‡ All new compounds were fully characterized by i.r., n.m.r., and high resolution mass spectrometry or combustion analysis. Stereochemical assignments are based on *X*-ray structural and n.m.r. data as reported in ref. 3. Spectral data for representative compounds: (**26**): i.r. (CCl_4) $\nu_{max.}$ 2205, 2025, 1995, 1700, 1595, 1495, 1390, 1375, 1300, and 1250 cm^{-1}; n.m.r. ($CDCl_3$) δ 7.6—7.1 (5H, m, Ph), 5.9 (1H, d, *J* 3.8 Hz, 'inner' diene), 5.6 (1H, dd, *J* 6.8, 4.35 Hz, 'inner' diene), 3.9 (1H, dd, *J* 9.9, 6.5 Hz, lactam CH_2), 3.4 (1H, dd, *J* 9.8, 4.4 Hz, lactam CH_2), 3.0 (1H, dd, *J* 6.6, 1.0 Hz, 'outer' diene), 2.3 (1H, m, C*H*Me), 2.0 (1H, d, *J* 14.5 Hz, diene ring CH_2), 1.9 (1H, d, *J* 14.5 Hz, diene ring CH_2), and 1.3 (3H, d, *J* 7.0 Hz, Me). (**28**): i.r. (CCl_4) $\nu_{max.}$ 2040, 1970, 1700, 1595, 1500, 1385, and 910 cm^{-1}; n.m.r. ($CDCl_3$) δ 7.6—7.2 (10H, m, Ph), 5.8 (1H, d, *J* 6.4 Hz, 'inner' diene), 3.8 (1H, dd, *J* 9.8, 6.6 Hz, lactam CH_2), 3.5 (1H, dd, *J* 9.8, 4.6 Hz, lactam CH_2), 3.2 (2H, d + m; d: 1H, 1.6 Hz, 'outer' diene, m: 1H, 'outer' diene), 2.3 (1H, m, lactam C*H*Me), 2.1 (1H, dd, *J* 15, 1.7 Hz, diene ring CH_2), 1.9 (1H, dd, *J* 15, 3.0 Hz, diene CH_2), and 1.3 (3H, d, *J* 7.0 Hz, Me).



Scheme 7. *Reagents:* a, KOH, MeOH, room temp., 12 h; b, $(COCl)_2$ CH_2Cl_2, room temp., 3 h; c, pyridine, *N*-allylaniline, C_6H_6, 16 h.

These mixtures can be avoided by allowing rearrangement of the diene prior to cyclization. Thus, conversion of (**23**) into (**27**), followed by cyclization gave the single spiro complex (**28**) in 84% yield (Scheme 7).‡

In summary, the intramolecular coupling between alkenic moieties and an appropriately C(5)-substituted diene–$Fe(CO)_3$ complex proceeds with extremely high stereoselectivity. The diastereomer (enantiomer) which is produced can be pre-determined by using either an electron-withdrawing (CN) or electron-donating (Ph) substituent at C(5). This methodology promises to be useful for the asymmetric synthesis of spirocyclic natural products.

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References

1 S. F. Martin, *Tetrahedron*, 1980, **36**, 419, and references cited therein.
2 M. Vandewalle and P. DeClercq, *Tetrahedron*, 1985, **41**, 1767, and references cited therein; 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, 1983, vol. 5; A. P. Krapcho, *Synthesis*, 1976, 425; 1974, 383; J. A. Marshall, S. F. Brady, and N. H. Anderson, *Fortschr. Chem. Org. Naturst.*, 1974, **31**, 283.
3 A. J. Pearson, M. Zettler, and A. A. Pinkerton, *J. Chem. Soc., Chem. Commun.*, 1987, 264.
4 A. J. Birch and B. M. R. Bandara, *Tetrahedron Lett.*, 1980, **21**, 2981.