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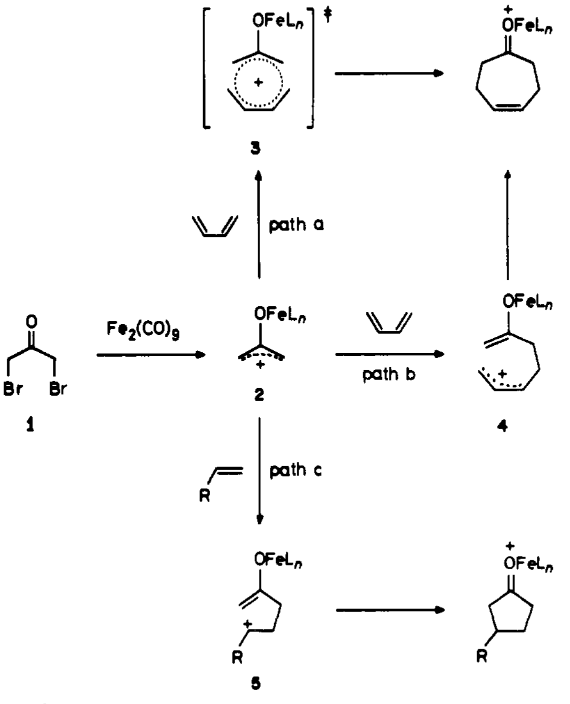
Regioselectivity of the Iron Carbonyl Promoted Cyclocoupling Reaction of α,α′-Dibromo Ketones with Olefins and Dienes[1]

Sir:

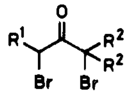
Reaction of α,α′-dibromo ketone **1** and $Fe_2(CO)_9$ generates the reactive 2-oxyallyl–Fe(II) species **2**[2] which can cycloadd across 1,3-dienes in a [3 + 4 → 7] fashion to give the corresponding 4-cycloheptenones.[3,4] In addition, the reactive intermediate **2** can be trapped by certain olefins in a [3 + 2 → 5] manner, producing cyclopentanone derivatives.[5] Discovery of such cationic cycloadditions has led to two fundamental questions, *viz.*, the concertedness of such reactions and the origin of the regioselectivity in the reaction of unsymmetrically substituted reactants.

The [3 + 4] reaction of **2** and dienes is classified as a [$_\pi 2$ + $_\pi 4$] process. If this cationic cycloaddition of symmetry-allowed type proceeds indeed in a concerted manner through the transition state **3** (path a in Scheme I), the regioselectivity would be controlled by frontier MOs of the cycloaddends.[6] On the other hand, if the cycloaddition went in a stepwise manner via path b, the orientation would be determined by the relative stabilities of the regioisomeric zwitterions of type **4**.

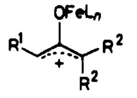
Scheme I



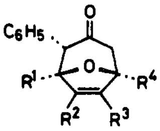
L = Br, CO, solvent, etc.



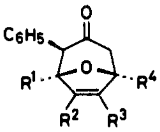
6, $R^1 = C_6H_5$; $R^2 = H$
7, $R^1 = C_6H_5$; $R^2 = CH_3$
8, $R^1 = R^2 = CH_3$



9, $R^1 = C_6H_5$; $R^2 = H$
10, $R^1 = C_6H_5$; $R^2 = CH_3$
11, $R^1 = R^2 = CH_3$



12, $R^1 = R^3 = R^4 = H$; $R^2 = CH_3$
13, $R^1 = R^2 = R^4 = H$; $R^3 = CH_3$
16, $R^1 = R^3 = R^4 = H$; $R^2 = Br$
17, $R^1 = R^2 = R^4 = H$; $R^3 = Br$
20, $R^1 = R^3 = R^4 = H$; $R^2 = COOC_2H_5$
21, $R^1 = R^2 = R^4 = H$; $R^3 = COOC_2H_5$
22, $R^1 = COOC_2H_5$; $R^2 = R^3 = R^4 = H$
23, $R^1 = R^2 = R^3 = H$; $R^4 = COOC_2H_5$
24, $R^1 = COOCH_3$; $R^2 = CH_3$; $R^3 = R^4 = H$
25, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COOCH_3$
26, $R^1 = COOCH_3$; $R^2 = R^3 = H$; $R^4 = CH_3$
27, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = COOCH_3$
28, $R^1 = COOCH_3$; $R^4 = H$; $R^3 = CH_3$
29, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = COOCH_3$



14, $R^1 = R^3 = R^4 = H$; $R^2 = CH_3$
15, $R^1 = R^2 = R^4 = H$; $R^3 = CH_3$
18, $R^1 = R^3 = R^4 = H$; $R^2 = Br$
19, $R^1 = R^2 = R^4 = H$; $R^3 = Br$

Thus the dibromo ketone **6** was treated with $Fe_2(CO)_9$ and the resulting oxyallyl species **9** was trapped with various furan derivatives, leading to the bicyclic adducts **12–29**. The results are summarized in Table I. Apparently, the experimental findings are not consistent with the stepwise mechanism but agree with the concerted process where the regioselectivity is under frontier MO control. Unless other special factors are operating, the more stable regioisomeric transition state arises through interaction of the *reaction sites* having the larger MO coefficient and of those with the smaller coefficient (primary MO interaction). The validity has been demonstrated by the reaction of furans bearing three different kinds of substituents (methyl, halogen, and ester) at C-3 position (runs 1–3); these furans have similar MO shapes with respect to the C-2 and C-5 positions (Figure 1)[7] and therefore the reaction exhibits the same regioselectivity. The results obtained with certain 2-furoates, except for one case, do fit in with the prediction, but the bias toward the prediction of the major isomer, we feel, is far greater than that expected from the degree of MO inclination (particularly run 4). This is presumably due to the operation of the secondary MO interactions between the *substituents* where frontier MOs develop to a considerable extent. In view of the relative magnitude of the C-2 and C-5 coefficients of 4-methyl-2-furoate, its reaction might have been conceived to give **29** as the major product. In fact, however, the regioisomer **28** formed predominantly (run 7), because there exists strong MO interaction between ortho carbon in phenyl ring of **9** and carbonyl oxygen of the furoate.

The [3 + 2 → 5] cycloaddition exhibits a different feature

Table I. Regioselectivity in the Reaction of Dibromo Ketone **6** and Substituted Furans[a]

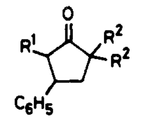
Run	Furan	Product[b] (% yield)	Ratio[c,d]	Fitness of prediction based on Frontier MOs[e]	Fitness of prediction based on Intermediate stability
1	3-Methylfuran	**12** + **13** (29)	56:44	+	−
		14 + **15** (19)	56:44	+	−
2	3-Bromofuran	**16** + **17** (44)	65:35	+	−
		18 + **19** (29)	66:34	+	−
3	Ethyl 3-furoate	**20** + **21** (52)	55:45	+	+
4	Ethyl 2-furoate	**22** + **23** (56)	90:10	+	−
5	Methyl 3-methyl-2-furoate	**24** + **25** (63)	92:8	+	−
6	Methyl 5-methyl-2-furoate	**26** + **27** (65)	65:35	+	−
7	Methyl 4-methyl-2-furoate	**28** + **29** (68)	76:24	−	?

[a] The reaction was performed with **6**, $Fe_2(CO)_9$, and a furan derivative (1:1.2:4 mol ratio) in benzene at 30 °C under nitrogen. [b] Products having phenyl group of α and β stereochemistry are treated separately, because these are considered to arise from different types of transition states, compact and extended transition state, respectively.[4] [c] The ratio was determined by NMR and/or GLC analysis of the isomeric mixture. [d] Use of Zn/Cu couple (4-6 equiv, dimethoxyethane, −10 °C) in place of $Fe_2(CO)_9$ gave similar results. [e] Only the primary MO interaction is considered.

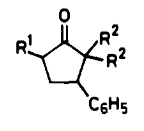
Table II. Regioselectivity in the [3 + 2] Reaction between Dibromo Ketones and Olefins[a]

Run	Dibromide	Olefin	Product[b] (% yield)	Ratio[c]	Fitness of prediction based on Intermediate stability	Fitness of prediction based on Frontier MOs
1	**6**	Styrene	**30** + **31** (44)	100:0	+	−
2	**7**	Styrene	**32** + **33** (49)	100:0	+	−
3	**8**	Styrene	**34** + **35** (31)	6:94	+	−
4	**6**	1-Morpholinocyclohexene	**36**[d] + **37** (22)	76:24	+	−
5	**7**	1-Morpholinocyclohexene	**38**[d] + **39** (61)	75:25	+	−
6	**8**	1-Morpholinocyclohexene	**40**[d] + **41** (86)	41:59	+	−

[a] The reaction was carried out with dibromo ketone, $Fe_2(CO)_9$, and the olefin in a 1:1.2-1.5:3-4 mol ratio in benzene at 55 °C (styrene) or 30 °C (enamine). [b] The cyclopentanone derivatives were readily epimerizable and were obtained as a mixture of epimers or a single, trans isomer. [c] The product ratio was determined by NMR, GLC, or HPLC analysis of the appropriate crude reaction mixture. [d] The labile β-morpholinocyclopentanones were isolated after quantitative conversion to the stable cyclopentenone products by treatment with 3% ethanolic NaOH or silica gel.

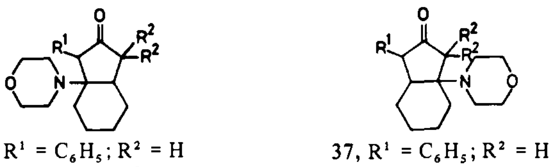


30, $R^1 = C_6H_5$; $R^2 = H$
32, $R^1 = C_6H_5$; $R^2 = CH_3$
34, $R^1 = R^2 = CH_3$



31, $R^1 = C_6H_5$; $R^2 = H$
33, $R^1 = C_6H_5$; $R^2 = CH_3$
35, $R^1 = R^2 = CH_3$

in its regioselectivity. The oxyallyl species **9–11** were generated from the corresponding dibromo ketones **6–8** and reacted with styrene and 1-morpholinocyclohexene. The results are given in Table II. The [3 + 2] cycloaddition of 2-oxyallyl and an olefinic substrate is categorized as a $[_\pi 2 + _\pi 2]$ process and must proceed in a stepwise manner as outlined by path c in Scheme I.[1,5] The observed regioselectivity is best interpreted in terms of stability of the zwitterionic intermediate of type **5** (or a late transition state, leading to it, whose structure is approximated by that of the zwitterion).[8] Since the cationic part of **5** is emphatically stabilized by the aromatic or amino group, the prime importance in controlling this matter, we postulate, is the relative stabilities of the enolate moieties.[9] The following stability sequence is fully compatible with the observation (R = C_6H_5 or $N(CH_2CH_2)_2O$):



36, $R^1 = C_6H_5$; $R^2 = H$
38, $R^1 = C_6H_5$; $R^2 = CH_3$
40, $R^1 = R^2 = CH_3$

37, $R^1 = C_6H_5$; $R^2 = H$
39, $R^1 = C_6H_5$; $R^2 = CH_3$
41, $R^1 = R^2 = CH_3$

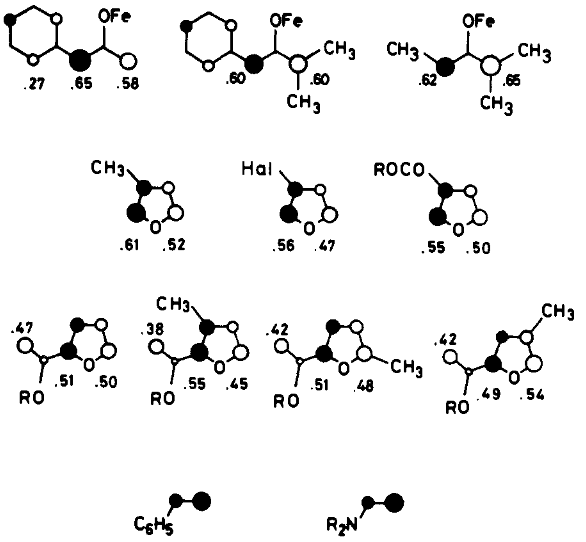
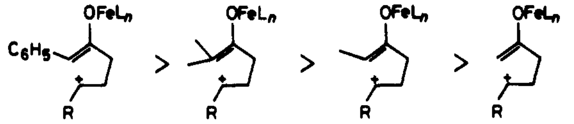


Figure 1. LUMOs of 2-oxyallyls and HOMOs of furans, styrene, and enamines.



Notably, the observed directing effect of the substituents is not in accord with the prediction based on the frontier MO consideration that has been successfully applied to the analysis of polar stepwise [2 + 2] cycloaddition of olefins.[10] As can be seen from Figure 1, initial bond making at the sp^2 termini with the greater MO coefficient through dominant interaction between the low-lying LUMO of oxyallyl and high-lying HOMO of an olefin has to produce the product-determining zwitterion **5** leading to the regioisomer which was actually obtained as only a minor component, or even did not form. In addition, judging from the MO coefficients of the oxyallyl **10**, the reaction had been expected to exhibit only poor selectivity. This was not the case, however.

Thus the [3 + 4] cycloaddition involving 2-oxyallyls is occurring in a concerted manner, and both the primary and secondary frontier MO interactions are equally important in determining the regioselectivity. On the other hand, the preferred orientation of the [3 + 2] cycloaddition is the one that affords the maximal stabilization of the zwitterionic intermediate.

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Electron Nuclear Double Resonance Study of Some Nitroxide Radicals Produced in Spin Trapping

Sir:

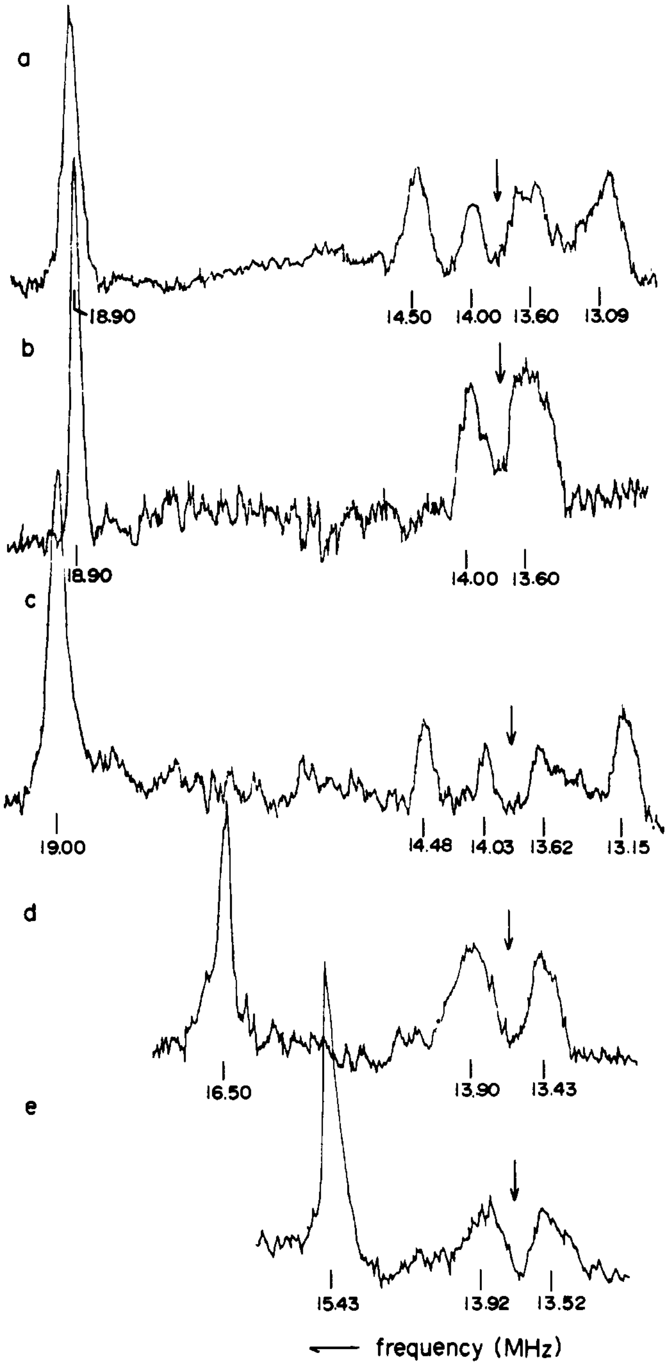
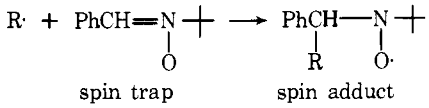


Figure 1. ENDOR spectra of spin adducts: (a) methyl adduct in toluene; (b) trideuteriomethyl adduct in toluene; (c) *n*-butyl adduct in 2-propanol; (d) phenyl adduct in toluene; (e) benzoyloxy adduct in toluene. Vertical arrow shows the free proton frequency. Note the disappearance of the signals at 14.50 and 13.09 MHz in b.

A variety of chemicals which are capable of producing stable nitroxide radicals upon reaction with short-lived free radicals have been used as "spin traps" in the spin trapping technique.[1] Among them nitroso and nitrone compounds have been frequently used because both the spin traps and the resulting nitroxide radicals (spin adducts) are quite stable. As discussed in detail by Janzen,[1] the essential difference is that of the ESR pattern of their adducts. When one uses the nitroso compound, the adding radical is bonded directly to the nitroxide function of the spin adduct and its ESR spectrum shows hyperfine structure (hfs) from the adding group. In the nitrone case the adding radical is at the β position from the nitroxide function and shows no substantial hfs in the ESR spectrum. Phenyl-*N*-*tert*-butyl nitrone (PBN) is a typical nitrone spin trap and it produces stable spin adducts according to reaction 1.



$$\mathrm{R}\cdot + \mathrm{PhCH}{=}\underset{\mathrm{O}}{\mathrm{N}}{-}\!+ \longrightarrow \underset{\mathrm{R}}{\mathrm{PhCH}}{-}\underset{\mathrm{O}\cdot}{\mathrm{N}}{-}\!+ \qquad (1)$$

spin trap   spin adduct

The spin adduct gives a characteristic ESR spectrum which consists of six lines due to one nitrogen and one β-hydrogen nucleus. Though the magnitude of the β-hydrogen hfs is the key index[2] of identifying trapped radical, the identification has not been always conclusive because the hfs of the adding group is missing. However the stability of both the spin trap and the spin adduct sometimes makes the use of a nitrone more feasible than the use of a nitroso spin trap for the investigation of reaction intermediates. In the present study the detailed obser-