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Stereochemical and Regiochemical Studies on the Alkylation of Pentane-2,4-dione through its Co(II) Complex

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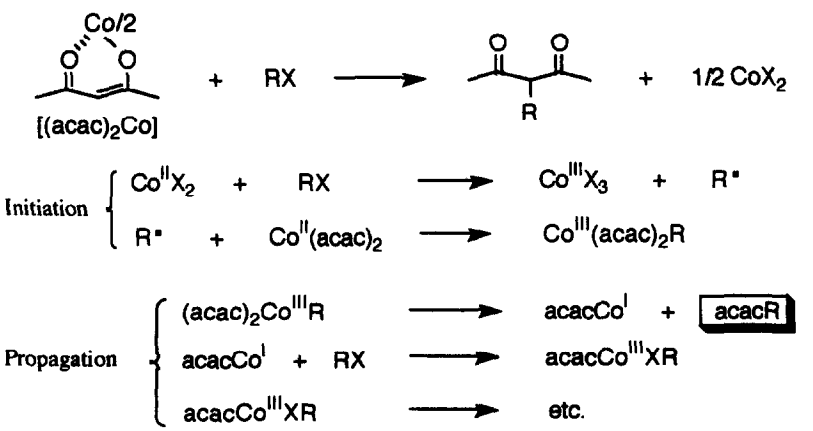
Abstract: Stereochemical and regiochemical results on the alkylation of pentane-2,4-dione with benzyl and allyl halides, through its Co(II) complex in concentrated chloroform solution are interpreted in terms of the mechanistic scheme proposed in the preceding paper,[1] and they suggest a fast starting material isomerization in the presence of cobalt species. Therefore, the reaction occurs under Curtin-Hammett preequilibrium conditions.

INTRODUCTION

The preceding paper in this journal[1] describes a mechanistic study on the reaction of cobalt(II) pentano-2,4-dionate [$(acac)_2Co$] with certain alkyl halides at high concentration conditions (scheme 1). Through the use of cobalt(II) complexes of β-dicarbonyl compounds, some of the limitations of the conventional alkylations of those compounds can be overcome. Thus, the reactions are carried out in neutral media, they lead only to C-alkylated products, and alkyl halides that are not useful in the conventional reactions give good yields of the alkylation products.



Scheme 1

The proposed mechanism[1] for these reactions includes a redox cycle of oxidative additions to Co(I) species, and reductive eliminations from Co(III) species. A great deal of indirect evidence suggests in many cases that the formation of C-C bonds by reductive elimination always proceeds with retention of configuration at carbon.[2] There are many studies in the literature dealing with the stereochemistry of oxidative addition reactions . From them, it is clear that the final reaction outcome depends on the actual case. Thus, when alkyl species add to metal anions, inversion of configuration at carbon is the more commonly observed process. This is the case for some iron,[3] manganese,[4] copper,[5] and cobalt[6] anionic complexes. However, although the bulk of examples proceed with inversion of configuration at carbon, there are clearly other mechanistic possibilities that lie very close in energy. For example the cobaltate anion $[Co(dmgH)_2(py)]^-$ reacts[7] with stericaly hindered alkyl halides with retention of configuration at carbon. Examples of racemization are also known.[8] A radical mechanism has been proposed for those cases. However, formation of racemic products from optically active alkyl halides is not necessarily evidence for a radical mechanism in oxidative addition reactions. In the case of metallate anion nucleophiles, as well as in some neutral complexes, a metal-metal exchange reaction can exist. The racemization of $MeCH(CO_2Et)Mn(CO)_5$ in the presence of excess $[Mn(CO)_5]^-$ has been attributed to such a process.[4]

When alkyl species react with neutral complexes, the situation is less defined. Thus, in one of the most thoroughly examined examples, the oxidative addition of alkyl halides to an Ir(I) system, the Vaska's complexes, the mechanism of the reaction depends on the alkylating agent.[9] The same occurs in the oxidative additions to some Pd and Pt complexes.[10] In many cases S_N2 mechanisms[11] have been proposed but generally, the stereochemical studies have been plagued by the rapid metal-metal interchange process.

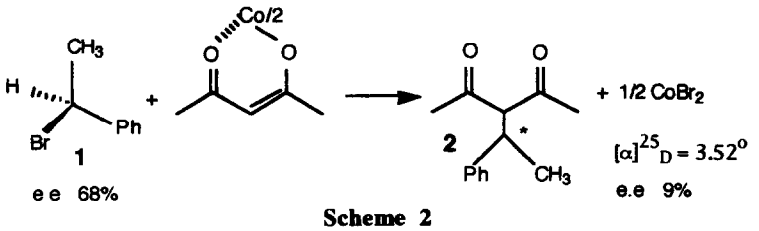
Another interesting aspect of oxidative addition reactions is their regiochemistry. Allylic halides have been observed[12] to undergo, in the presence of Co(I) species, what are formally S_N2' as well as S_N2 substitutions (although electron transfer reactions can not be excluded). In those cases, steric factors strongly influence the site of attack, presumably due to the relatively large bulk of the cobalt (I) species.

Two previously unexamined aspects of our reactions (Scheme 1) are their stereochemical and regiochemical behaviour. The knowledgement of the details of these aspects of our reactions is important from the synthetic and mechanistic points of view. Here we report an study on the regiochemistry and the stereochemistry of the reaction of $(acac)_2Co$ with alkylating agents.

RESULTS AND DISCUSSION: STEREOCHEMICAL STUDIES

a) Enantiospecificity or racemization.

The selected alkylating agent was *(S)*-(-)-1-bromo-1-phenylethane,[13] **1**. This product was prepared with 68% e.e. by reaction of (R)-(+)-1-phenylethanol with phosphorus tribromide at -10°C. The enantiomeric excess (e.e. = 68%) was determined from its specific rotation. The reaction between **1** and $(acac)_2Co$ (80°C, [RX] = 2.92M in $CHCl_3$) led to the C-alkylation product, **2** (Scheme 2). This product showed non-zero specific rotation ($[\alpha]^{25}_D = 3.52°$) although the value was small. The corresponding data for the homochiral compound is not known, therefore complexation with homochiral shift reagents was attempted in order to study the complexes by NMR techniques. This approach failed due to insufficient peak separation. Cyclodextrins have been used in chiral analysis.[14] Among the requirements to observe chiral discrimination and enantioselective complexation are the presence of an aromatic ring and that at least one chiral center substituent must form a strong interaction with the hydroxy groups in the cyclodextrin rim.[15] Our product fulfills the requirements, and the NMR spectrum in the presence of β-CD showed a splitting of the band corresponding to one of the methyl groups, with separation enough to safely establish the enantiomeric excess by simple integration. This analysis led to a value e.e = 9±1%. The Scheme 2 reaction was repeated and the chiral analysis led to e.e = 8±1%. Therefore, the reaction works with ≈ 90% racemization, but a residual optical activity (e.e ≈ 10%) is present in the final alkylation enantioisomers mixture.

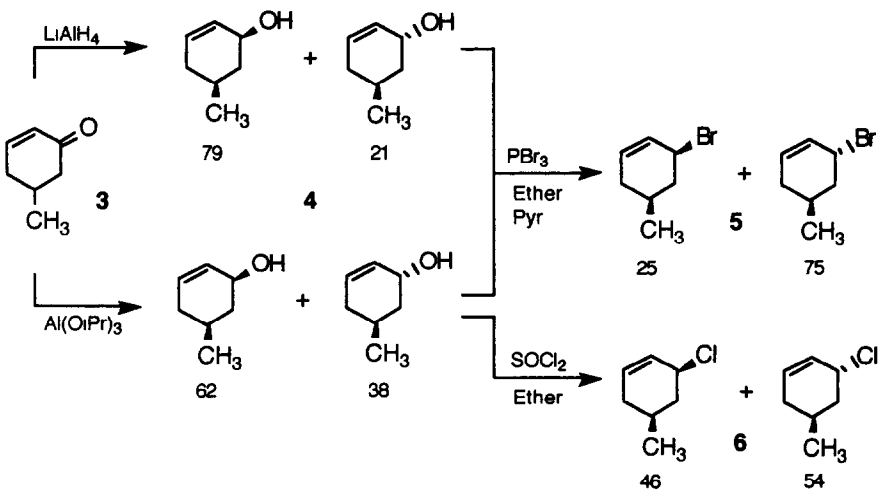


Scheme 2

b) Diastereospecificity or configurational equilibration at carbon.

The use of homochiral 1-bromo-1-phenylethane indicated partial racemization, but no practical ways of knowing if the process happened with predominant retention or inversion of configuration existed in this system. Therefore, alkylating agents able of producing diastereomeric alkylation products, depending on the stereospecificity or stereoselectivity of the process, were used in this part of the work. The selected system was that of 5-methyl-2-cyclohexenyl constitution

The 3-bromo-5-methylcyclohexene, **5**, was prepared from 5-methyl-2-cyclohexenol[16], **4**, obtained by reduction of 5-methyl-2-cyclohexen-1-one[17], **3**. In order to get different diastereomeric mixtures of products **5**, 5-methyl-2-cyclohexen-1-one, **3**, was reduced by two different procedures. The use of $LiAlH_4$ led to *cis/trans* (79:21) diastereomeric mixture of alcohols **4**, in 91% yield, while the Meerwein-Ponndorf-Verley reduction (aluminium isopropoxide) gave rise to a *cis/trans* mixture (62:38) in 87% yield. The substitution of the hydroxy group by bromide was carried out following the very mild method[13] used in the preparation of chiral 1-bromo-1-phenylethane with known e.e.. However in the present case, both starting alcohol diastereomeric mixtures gave rise to the same diastereomeric mixture of bromides, *cis/trans* (25:75) in a 67% total yield (scheme 3). The isomeric ratio was obtained from G.C., and assignement (Table 1) of the signals of the ^{13}C NMR spectrum allowed to establish the major and minor components.



Scheme 3

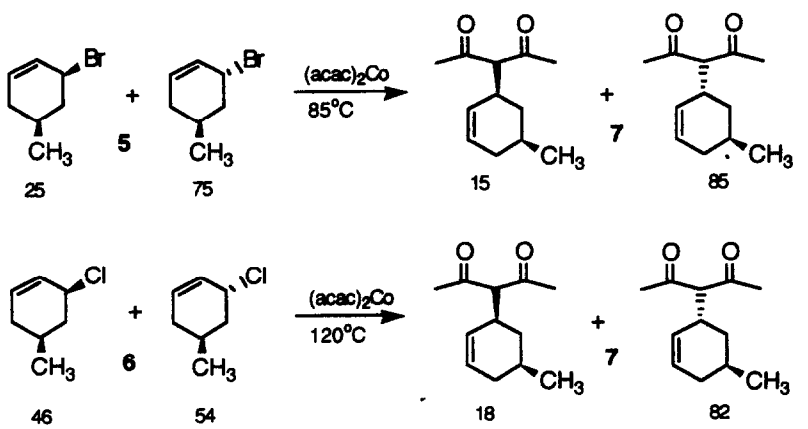
The 3-chloro-5-methylcyclohexene,[18] **6**, was prepared in 65% yield, as diastereomeric mixture *cis/trans* (46:54) treating the *cis/trans* (62:38) 5-methyl-2-cyclohexen-1-ol with thionyl chloride in ether (scheme 3). The obtained *cis/trans* ratio does not correspond to the configurational equilibrium, and the isomers ratio did not permit the major and minor isomers to be stablished from NMR analyses. Heating the mixture of chlorides at 120°C a ratio *cis/trans* of 33:67 was obtained. This ratio (G.C.) allowed a confident NMR analysis.

Kitching *et al.*[19] state that the methyl group in *cis* -3-chloro-5-methylcyclohexene shows a lower δ value in ^{1}H NMR. This tentatively, indicated that the *trans* isomer was the major isomer in both diastereomeric chloride mixtures. This conclusion was confirmed by ^{13}C NMR analyses. In Table 1, the ^{13}C NMR chemical shifts, and the corresponding assignments for the obtained diastereomeric mixtures of products **5** and **6** are described. Assignments follow simple chemical shift considerations, off resonance decoupled spectra and comparison with previous assignments for the related acetates.[20]

Table 1. ^{13}C NMR Chemical Shifts (δ) for 5-bromo-5-methylcyclohexenes, **5**, and 3-chloro-5-methylcyclohexenes, **6**, in $CDCl_3$

Product	Substituents situation	C-3	C-4	C-5	C-6	CH_3
5, *cis*	eq,eq	48.18	43.17	30.42	32.92	21.57
5, *trans*	ax,eq - eq,ax	49.10	40.40	23.86	33.46	21.30
6, *cis*	eq,eq	56.59	42.25	29.52	33.03	21.68
6, *trans*	ax,eq - eq,ax	55.85	40.00	23.27	33.50	21.29

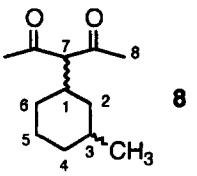
The main configurational diagnosis peaks have been those corresponding to C-5. The γ-gauche effect is evident, and in the cases where the halogen atom can be in axial situation (*trans* isomer) a strong shift to higher field (≈ 6 ppm) is observed. The C-3 chemical shifts give more ambiguous information in those cases. It is known[21] that a carbon atom bearing a halogen substituent in axial position appears at lower fields (Δδ ≈ 2.6 for bromine and ≈ 0.3 for chlorine, in cyclohexanes) with respect to a carbon atom bearing a halogen in equatorial position (this effect is opposite to the observed for oxygen based substituents[20]). The same is observed in our cases (Table 1), but the effect is reduced to Δδ = 0.92 ppm for bromine due to the γ-gauche effect that the C-5 methyl induces on C-3 (*trans* isomer) and that will result in a shift to higher field for the C-3 absorption. In the case of chlorine, this γ-gauche effect is stronger enough to invert the normal situation, the C-3 of the *trans* isomer appearing at slightly higher field than the corresponding carbon in the *cis* isomer.



Scheme 4

The reaction between $(acac)_2Co$ and the mixture *cis/trans* (26:74)-3-bromo-5-methylcyclohexenes, **5**, in high concentrated chloroform solution, and at 85°C led to a diasteromeric mixture *cis/trans* (15:85) 3-(5-methyl-2-cyclohexenyl)pentane-2,4-diones, **7**, in 90% total yield (scheme 4). The corresponding reaction carried out with the diastereomeric mixture *cis/trans* (54:46) 3-chloro-5-methylcyclohexenes, **6**, in the same concentration conditions but at 120°C led to a diasteromeric mixture *cis/trans* (18:82), **7**, in 71% total yield (scheme 4). The isomer ratios were established by ^1H NMR and gas chromatography, and the major and minor components identification in the mixtures was carried out by ^{13}C NMR after hydrogenation to the corresponding saturated cyclohexanes, **8**. The configurational assignments in substituted cyclohexanes are better known than in the cyclohexenes. For the halogenated derivatives **5** and **6**, the configurational assignments had to be performed on the cyclohexenes due to the lability of the carbon-halogen bond in the usual hydrogenation conditions. The ^{13}C NMR of the mixture **8**, shows two sets of peaks of very different intensity. In table 2, the assignments are shown. There is still a certain ambiguity in the assignement of some peaks. However, it can be concluded that the major isomer shows a *trans* configuration. Thus, the C-1 and C-3 chemical shifts (δ values) are smaller (higher field) in the major isomer. This is expected for a relative configuration with an axial component of the substituents placed on those carbons (*trans* isomer). This conclusion can be confirmed by consideration of the C-3 and C-7 chemical shifts. In these cases, the absorption must appear at higher field if the relative configuration is of the axial-equatorial / equatorial-axial type. This is the case for the major isomer, thus assigned to the *trans* configuration.

Table 2. ^{13}C NMR Chemical Shifts (δ) for 3-(3-methylcyclohexyl)pentane-2,4-dione, **8**, in $CDCl_3$



8

Product	Substituents position	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	CH_3
8, *trans*	eq,ax - ax,eq	29.40	36.63	27.02	33.69	20.08 or 20.49	32.95	73.79	29.60	20.49 or 20.08
8, *cis*	eq,eq	30.33 or 32.29	39.45	35.29 or 30.33	34.61 or 38.57	25.70	38.57 or 34.61	76.66	29.57	22.50

The results of Scheme 4 indicate that no diastereospecificity is observed in these reactions since a very similar final alkylation mixture (scheme 4) is obtained starting from different diastereomeric mixtures of alkylation agents.

A very fast starting halide equilibration in the presence of the metal would explain the observed results. This was investigated and the results are shown in Table 3. Thus, when a mixture *trans/cis* (49:51) of 3-chloro-5-methylcyclohexenes, **6**, was left in chloroform at 120°C, equilibration to the thermodynamic mixture happened in about 15 min., however upon addition of $CoCl_2(PPh_3)_2$ (0.1 eq.) the equilibration was almost instantaneous.

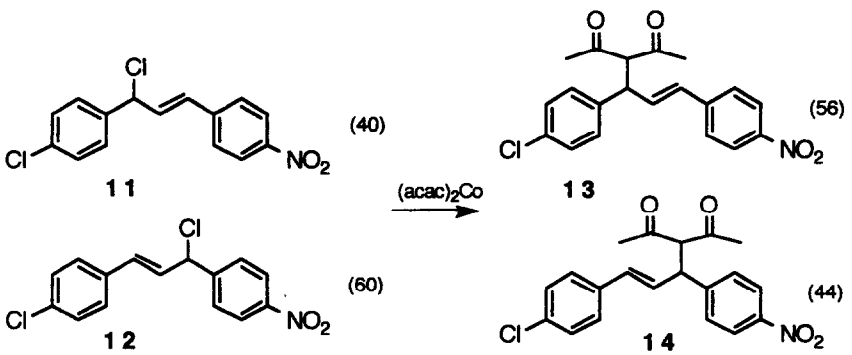
Table 3. Evolution with Time of a Mixture *trans/cis* of 3-Chloro-5-methylcyclohexenes, **6**, (2.92M) in Chloroform at 120°C.

Time (min)	0	5	10	15
trans/cis (without additive)	49:51	53:47	58:42	67:33
trans/cis (with $CoCl_2(PPh_3)_2$, 0.1eq.)	49:51	67:33	67:33	67:33

These results suggest that in the presence of cobalt species, a rapid isomerization of the starting halides occurs, competing with the alkylation process. The described results suggest that the system is under Curtin-Hammett[22] preequilibrium conditions. If the starting materials equilibration is faster than the alkylation reaction, the final products ratio is only determined by the free energy difference between the transition states leading to the final alkylation products.

RESULTS AND DISCUSSION: REGIOCHEMICAL STUDIES

Cobalt(I) species have been observed to undergo S_N2 and S_N2' reactions in front of allylic halides.[12] It is known that steric factors have strong influence on the site of attack. Therefore, in order to establish the regiochemistry of our reactions (minimizing the steric influence), reagents **11** and **12** were used as alkylating agents (scheme 5). There are several examples in the literature (Pd chemistry) on the use of such reagents. Thus, Keinan and coworkers studied a few examples of the reactions of 3-phenyl-1-(4-X-phenyl)-2-propen-1-ol acetates with polymethylhydrosiloxane (hydride donor),[23] alkoxytributylstannanes (alkoxy group donors),[24] and allenyltributylstannane (propargyl group donor),[25] under Pd(0) catalysis. One of us has studied similar reactions with carbon nucleophiles, finding a strong regioselectivity in the allylation reactions.[26]

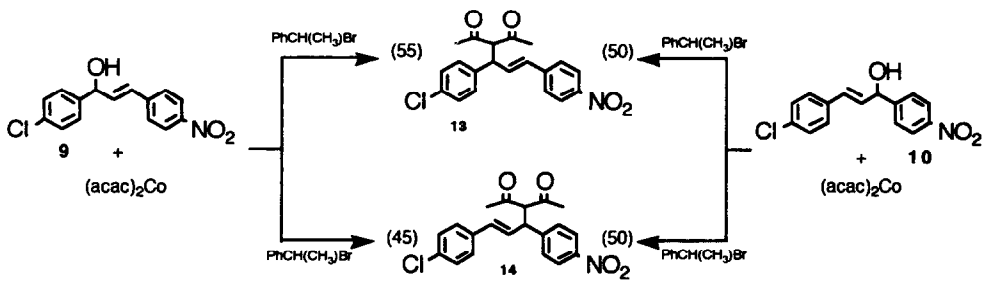


Scheme 5

Attempts to prepare pure samples of the chlorides **11** and **12** starting from the corresponding alcohols **9** and **10** failed, giving rise in all the cases to a mixture 40:60 of the products **11** and **12**. This ratio was established from the ^1H NMR spectrum of the mixture, and the major isomer was identified as **12** and the minor as **11**, after reductive ozonolysis of the mixture and analysis of the resulting aldehydes. This mixture was reacted with $(acac)_2Co$ in the usual concentration conditions, leading to a mixture of the C-alkylation products **13** and **14** in a molar ratio 56:44, with a yield of 84% (Scheme 5). This ratio was also obtained from the ^1H NMR spectrum of the mixture, and the regioisomers identification was again achieved by reductive ozonolysis, and analysis of the resulting aldehydes. The starting chlorides seem to equilibrate at a

fast rate, therefore, the Curtin-Hammett principle must be again applied to explain the observed results. The final outcome of the reaction depends only on the free energies of the transition states involved in the production of each final alkylation product. If a common intermediate of the free radical or cation type were involved, a stronger regioselectivity[26] (perhaps the appearance of only one final isomer) would be expected, considering the alkylating system used.

The fast equilibration of the starting chlorides **11** and **12**, precluded any interpretation on the regiospecificity of the process. Therefore, we decided to use alcohols as alkylating agents. In the preceding paper[1] the alkylation of $(acac)_2Co$ with alcohols and acetates in the presence of the corresponding bromides has been reported. We decided to try this approach using the 3-(4-X-phenyl)-1-(4-Y-phenyl)-2-propen-1-ol systems (**9**,**10**) and 1-bromo-1-phenylethane to elicit the reaction. In this case pure samples of the alcohols were used. Starting from alcohol **9**, a final ratio of the alkylation products **13** and **14** of 55:45 was obtained (overall yield 81%). On the other hand, when the reaction was carried out starting from the isomeric alcohol **10**, the ratio was 50:50, and the yield was only 26% (Scheme 6). The weak regiospecificity which is observed, suggesting the starting materials equilibration has been slowed down enough to start breaking the Curtin-Hammett conditions. However, it is impossible to say if the observed ratios are the result of regiospecific S_N2 - S_N2' contributions in every case, or are partially due to starting material equilibration.



Scheme 6

It is interesting to notice that the reaction starting from **10** is slower than the reaction starting from **9**. Considering the stability of the starting alcohols must be very similar, and that no steric effects are present, the observed important rate difference argues again against the operativity of a common intermediate.

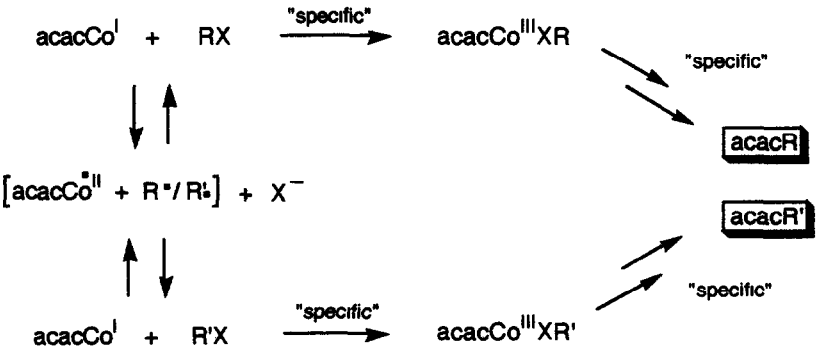
CONCLUSIONS

From the synthetic point of view, the conclusion of the above experiments is that our reactions show an almost complete lack of stereo- and regiospecificity, and also a low stereo- and regioselectivity. However, these results can be significant and merit some extra discussion from the mechanistic point of view.

The present results can be justified by the general mechanistic scheme proposed in the preceding paper[1]. From those results, we concluded that no free radicals were involved in the propagation cycle of the mechanism (Scheme 1). This interpretation is now supported by the regiochemical experiments described in this paper. The probability of metal-metal interchange is very low in our case, due to the fact we seem to be in a cycle where the Co(I) and the Co(III), that would exchange the alkyl ligand, are both transients and therefore their concentrations are expected to be very small. In our cases, the starting halides seem to equilibrate, in the presence of cobalt complexes, at a rate comparable (or faster) to the alkylation rate. This suggest that in most cases, the systems are in Curtin-Hammett conditions.[22] In this situation, the starting material equilibration would be faster than the following reaction of the individual isomers. The proportion of the final products would be governed only by the free energy difference between the transition states leading

to the final products and would be independent of the initial proportions of the starting isomers, thus justifying the observed lack of specificity and selectivity.

The results of the reaction of $(acac)_2Co$ with 1-bromo-1-phenylethane of known enantiomeric excess, and with the allylic alcohols **9** and **10** take now a mechanistic significance since the non complete racemization (≈ 9% e.e. in the alkylation product) observed in the first case, and the very weak regiospecificity observed in the second case can be interpreted in terms of a S_N2 (plus SN2' in the second case) oxidative addition reaction contending with the fast racemization of the starting material in the presence of the metal complex (Scheme 7). Therefore, our results support the existence of a competence between a specific (probably S_N2) oxidative addition (that leads to the final product through reductive elimination), and a reversible "inner sphere electron transfer / caged radical pair" mechanism, that is responsible for the configurational and allylic equilibration of the starting material (together with the cyclization of the radical clocks and the formation of radical dimers, reported in the preceding article[1]) but that does not lead to the alkylation product . In Scheme 7 the mechanistic proposal for the oxidative addition step is shown. Configurational, and allylic equilibration would occur in the radical pair stage.



[RX, R'X stereo- or regioisomers]

Scheme 7

EXPERIMENTAL

All melting points are uncorrected. ^1H NMR were recorded at 80 or 400 MHz and the ^{13}C NMR at 20 or 100 MHz. The GC analyses were performed using a HP-Crosslinked Dimethylsilicone Gum 12m x 0.2mm x 0.33m film thickness capillary column. (S)-1-bromo-1-phenylethane,[13] **1**; 5-methyl-2-cyclohexen-1-one,[17] **3**; 1-(4-chlorophenyl)-3-(4-nitrophenyl)-2-propen-1-ol,[27] **9**; 3-(4-chlorophenyl)-1-(4-nitrophenyl)-2-propen-1-ol,[27] **10**; were prepared following the literature procedures.

Preparation of the cis/trans 5-methyl-2-cyclohexenol, 4 , in different ratios. Product **4**, was prepared as diastereomeric mixtures *cis/trans* (79:21, 91% yield) and (62:38, 87% yield) by $LiAlH_4$[16] and aluminium isopropoxide[28] reduction respectively of 5-methyl-2-cyclohexen-1-one, **3**, following the described literature methods. Identification of the *cis* isomer in the mixture was done by comparison of its spectroscopic constants with an authentical sample.[20]. The ratio was established by G.C.

Preparation of 3-bromo-5-methylcyclohexene, 5. Cis/trans (79:21) 5-methyl-2-cyclohexenol (2.7 g, 0.024 mol), **4**, 15 mL of anhydrous ether, and 4.4 mL of dried pyridine were placed in a round-bottomed flask. The stirred mixture was immersed in a bath at -20°C. Next, a solution of PBr_3 (2.5 mL, 0.026 mol) in

anhydrous ether was added dropwise for 1h. The stirring was maintained one additional hour at -10°C and two days at 5°C. The mixture was poured into ice/water. The organic layer was washed with cold saturated bicarbonate solution. The residue obtained after ether evaporation was distilled to give 2.8 g (67% yield) of *cis/trans* (26:74) 3-bromo-5-methylcyclohexene, bp 100-110°C 25 Torr (lit[18] 74-75°C 15 Torr): IR (film) 3034, 2954, 2925, 1457, 1436, 1267, 1185, 1123, 1095, 1046, 1022, 992, 960, 852 cm^{-1}; ^1H NMR ($CDCl_3$) 2.00 (3H), 1.42-2.48 (5H), 4.73-4.94 (1H), 5.57-6.03 (2H); ^{13}C NMR ($CDCl_3$), *cis* isomer (eq,eq) 21.57, 30.42, 32.92, 43.17, 48.18, 129.66, 129.77; *trans* isomer (eq,ax / ax,eq) 21.30, 23.86, 33.46, 40.41, 49.18, 128.36, 130.68; MS m/e (relative intensity) 95 (M-79, 84), 93(23), 82(94), 80(100), 79(77), 67(53), 55(35). Isomeric identification was based in the analysis of the ^{13}C NMR spectrum as explained before. The isomer ratio was established by G.C.. When the reaction was repeated starting from the mixture *cis/trans* (62:38) of alcohol **4**, the same final diastereomeric mixture of product **5** was obtained.

Preparation of 3-chloro-5-methylcyclohexene, 6. Cis/trans (63:37) 5-methyl-2-cyclohexenol, **4**, (2.71 g, 0.024 mol), freshly distilled $SOCl_2$ (1.74 mL, 0.024 mol), and 30 ml of anhydrous ether were introduced in a 50 mL round-bottomed flask. When bubbling finished, the ether and $SOCl_2$ were evaporated at room temperature under reduced pressure. The residue was distilled to give 2.02g (65% yield) of *cis/trans* (46:54) 3-chloro-5-methylcyclohexene, **6**, bp 61-64°C 27 Torr (lit[18] 60-62°C, 25 Torr): ^1H NMR ($CDCl_3$) 0.99-1.01 (3H), 1.5-2.3 (5H), 4.60-4.66 (1H), 5.68-5.90 (2H); ^{13}C NMR ($CDCl_3$) *cis* isomer (eq,eq) 26.68, 29.52, 33.03, 42.25, 56.59, 129.15, 129.81; trans isomer (eq,ax / ax,eq) 21.29, 23.27, 33.50, 40.00, 55.58, 127.18, 131.34; MS m/e (relative intensity) 132 (M+2, 6), 130 (M, 15), 95 (100), 94 (36), 88 (11), 79 (72), 77 (33), 67 (47), 53 (27). The isomer ratio was established by G.C..

Preparation of a mixture of 3-chloro-3-(4-chlorophenyl)-1-(4-nitrophenyl)-1-propene, 11, and 3-chloro-1-(4-chlorophenyl)-3-(4-nitrophenyl)-1-propene, 12. Thionyl chloride (0.5 mL, 6.9 mmol) was slowly added (30 min) over 1-(4-chlorophenyl)-3-(4-nitrophenyl)-2-propen-1-ol,[27] **9** (2.00 g, 6.9 mmol), placed in a round-bottomed flask in a ice/water bath with magnetic stirring. The mixture was left 6 h. at room temperature. After evaporation of the volatile products, 2.03 g. (95% yield) of a mixture 40:60 of products **11** and **12** was obtained. The identification of the major and minor isomer in the mixture was carried out by ozonization and determination of the resulting aldehyde ratio. Thus, in a 50 mL ozonization reactor, 0.5 g (1.62 mmol) of the **11/12** mixture in 40 mL of anhydrous CH_2Cl_2 was introduced. The solution was cooled to -70°C and a O_3 flux of 4 mmols/h was passed through for 6 h. After that, argon was bubbled through the solution for 10 min, and 0.3 mL (3.24 mmol) of dimethyl sulfide was added. The solution was left at room temperature for 1 h, washed with water, and after solvent evaporation, the residue was directly analyzed by G.C. using authentical samples of 4-nitrobenzaldehyd and 4-chlorobenzaldehyd as standards. From this analysis a ratio **11/12** of 40:60 is obtained. Product **11** ^1H NMR ($CDCl_3$) 5.66 (d, J = 7.9Hz, 1H), 6.39 (dd, J = 7.9Hz, J = 15.6Hz, 1H), 6.58 (d, J = 15.4Hz, 1H), 7.35 (s, 4H), 7.60, 7.63, 8.19, 8.23 (AA'BB', 4H); product **12** ^{1}HNMR ($CDCl_3$) 5.60 (d, J = 6.7Hz, 1H), 6.58 (dd, J = 6.7 Hz, J = 15.9Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 7.28 (s, 4H), 7.48, 7.51, 8.14, 8.17 (AA'BB', 4H); mixture **11/12** IR (KBr) 1599, 1520, 1492, 1345, 1091, 850, 825 cm^{-1}; ^{13}C NMR ($CDCl_3$) 61.78, 123.86, 127.29, 127.98, 128.19, 128.65, 128.77, 128.93, 130.06, 132.02, 132.89, 133.67, 134.25, 134.44, 137.82, 141.92, 146.70, 147.23, 147.54.

This reaction was repeated in different conditions: 0°C, -20°C, in the presence of pyridine, and using N-chlorosuccinimide/dimethyl sulfide as chlorinating agent. In all cases, a mixture 40:60 of **11/12** was obtained.

Reaction of $(acac)_2Co$ with 1-bromo-1-phenylethane , 1, (e.e. 68%). The reaction was carried out as previously described[1] for the racemic halide. The obtained 3-(1-phenylethyl)pentane-2,4-dione, **2**, showed a $[\alpha]^{25}_D = 3.52°$. The e.e was stablished by ^1H NMR analysis of the complex with β-cyclodextrin. A mixture of β-cyclodextrin and racemic **2**, in a molar ratio 3.6:1.0, was sonicated in deuterium oxide. After filtration,

the 1H NMR spectrum was recorded. The signal that appears at 1.91 ppm, is split enough (0.15 ppm) for reliable separate integration. The integration values were compared with those obtained when the product **2** from the reaction with optically active **1**, was used. From them an e.e of 8% was obtained. The whole process, starting from the reaction of **1**, with $(acac)_2Co$ was repeated, an e.e. of 9% being obtained.

*Reaction of $(acac)_2Co$ with 3-bromo-5-methylcyclohexene, **5**.* In a 25 mL sealed reactor, 1.80 g (0.01 mol) of *cis/trans* (25:75) 3-bromo-5-methylcyclohexene, **5**, 1.32 g (0.005 mol) of $(acac)_2Co$ and 3.4 mL of chloroform were introduced ([**5**] = 2.92M). The mixture was left at 85°C for 2 h, washed with 1M HCl and with water. After solvent evaporation, the residue was distilled, bp 70°C 0.2 Torr, affording 1.75 g (95% yield) of 3-(5-methyl-2-cyclohexenyl)pentane-2,4-dione, **7**. This product was obtained as a diastereomeric *cis/trans* (15:85) mixture. The isomers ratio was established by G.C. and ^1H NMR, and their identification, was carried out (see above) by 13C NMR of the saturated mixture (*vide infra*). The spectra description corresponds, unless otherwise stated, to the major isomer, *trans* **7**: IR (film) 3024, 2953, 2924, 2912, 1724, 1690, 1456, 1442, 1259, 1190, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) 0.72 (d, J = 7.5Hz, 3H), 0.78-2.28 (m, 5H), 2.12 (s, 3H), 2.16 (s, 3H), 3.00 (broad, 1H), 3.58 (d, J = 12.5Hz, 1H, isomer *cis*), 3.66 (d, J = 12.5Hz, 1H, isomer *trans*), 5.19-5.72 (m, 2H); ^{13}C NMR ($CDCl_3$) 21.14, 24.28, 29.03, 30.31, 33.22, 33.65, 34.47, 74.58, 126.31, 129.34, 203.38, 203.58; MS m/e (relative intensity) 195 (M+1, 8), 194 (M, 2), 151, (36), 101 (25), 95 (25), 93 (13), 79 (11), 67 (10), 43 (100).

*Reaction of $(acac)_2Co$ with 3-chloro-5-methylcyclohexene, **6**.* *Cis/trans* (46:54) 3-chloro-5-methylcyclohexene, **6** (0.50 g, 3.83 mmol), $(acac)_2Co$ (0.492 g, 1.91 mmol), and 1.3 mL of chloroform ([**6**] = 2.92M) were placed in a 25 mL sealed reactor. The mixture was heated at 120°C for 2 h. Next, it was washed with 1N HCl and with water. Following the procedure reported in the previous paragraph, 0.50 g (71% yield) of 3-(5-methyl-2-cyclohexenyl)pentane-2,4-dione, **7**, was isolated. The diastereomeric ratio resulted to be *cis/trans* (18:82) in this case.

*Preparation of 3-(3-methylcyclo-hexyl)pentane-2,4-dione, **8**. Hydrogenation of 3-(5-Methyl-2-cyclohexenyl)pentane-2,4-dione, **7**.* 3-(5-Methyl-2-cyclohexenyl)pentane-2,4-dione, **7** (0.20 g, 1 mmol), and 10 % Pd/C (0.020 g) in 50 mL of ethanol were introduced in a 150 mL round-bottomed flask . The mixture was hydrogenated at room temperature and atmospheric pressure for three hours. The solution was filtered through celite and after solvent evaporation, 0.140 g (71% yield) of 3-(3-methylcyclohexyl)pentane-2,4-dione, **8**, bp 75°C 0.2 Torr was obtained: ^1H NMR ($CDCl_3$) 0.9 (d, J=6.1Hz, 3H), 1.09-2.10 (m, 9H), 2.2 (s, 6H), 2.24-2.76 (m, 1H), 3.45 (d, J = 10.9Hz, 1H, isomer *cis*), 3.75 (d, J = 10.9Hz, 1H, isomer *trans*); ^{13}C NMR ($CDCl_3$) unambiguous signals of isomer *cis*, 22.50, 25.70, 29.57, 39.45, 76.66; unambiguous signals of isomer *trans*, 27.02, 29.40, 29.60, 32.95, 33.69, 36.63, 73.79; other signals, 20.08, 20.49, 30.33, 32.29, 34.61, 38.57, 203.95, 204.07; MS m/e (relative intensity) 154 (2), 153 (1), 136 (22), 121 (11), 111 (15), 101 (96), 97 (11), 96 (14), 95 (12), 85 (13), 81 (26), 55 (16), 44 (12), 43 (100).

*Reaction of $(acac)_2Co$ with the mixture of 3-chloro-3-(4-chlorophenyl)-1-(4-nitrophenyl)-1-propene, **11**, and 3-chloro-1-(4-chlorophenyl)-3-(4-nitrophenyl)-1-propene, **12**.* In a 25 mL sealed reactor, 0.448 (1.45 mmol) of the mixture (40:60) of **11** and **12**, 0.187 g (0.73 mmol) of $(acac)_2Co$, and 5 mL of $CHCl_3$ were introduced. The mixture was left at 100°C for 24 hours. Next, it was washed with 1M HCl and several times with water. After solvent evaporation, 0.473 g (88% yield) of an oil identified as a mixture (56:44) of the alkylation products 3-(1-(4-chlophenyl)-3-(4-nitrophenyl)-2-propenyl)pentane-2,4-dione, **13** and 3-(3-(4-chlorophenyl)-1-(4-nitrophenyl)-2-propenyl)pentane-2,4-dione, **14** (the ratio was established from the 1H NMR spectrum and the identification of the major and minor isomers was done by ozonization of the mixture, see following paragraph). The oil was purified by chromatography through silica-gel using hexane / ethyl acetate as eluent. **13/14** Mixture: IR (film) 1732, 1707, 1598, 1517, 1492, 1347, 1246, 1184, 1183, 1094,

854, 823 cm^{-1}; MS m/e (relative intensity) 371 (1), 330 (13), 329 (14), 328 (35), 311 (13), 226 (12), 192 (13), 191 (14), 189 (10), 125 (21), 43 (100); calculated for $C_{20}H_{18}ClNO_4$: C, 64.62; H, 4.85; N, 3.77; found: C, 64.72; H, 5.03; N, 3.66; product **13**: ^1H NMR ($CDCl_3$) 1.95 (s, 3H), 2.23 (s, 3H), 4.30 (d, J = 11.4Hz, 1H), 4.35 (dd, J = 8.2Hz, J = 11.4Hz, 1H), 6.32 (dd, J = 8.2Hz, J = 15.9Hz, 1H), 6.44 (d, 15.9 Hz, 1H), 7.17, 7.19, 7.23, 7.25 (AA'BB', 4H), 7.38, 7.40, 8.11, 8.13 (AA'BB', 4H); product **14**: ^1H NMR ($CDCl_3$) 1.97 (s, 3H), 2.24 (s, 3H), 4.38 (d, J = 11.6Hz, 1H), 4.45 (dd, J = 8.1Hz, J = 11.6Hz, 1H), 6.10 (dd, J = 8.1 Hz, J = 15.7Hz, 1H), 6.39 (d, J = 15.7Hz, 1H), 7.18, 7.20, 7.29, 7.32 (AA'BB', 4H), 7.41, 7.43, 8.17, 8.19 (AA'BB', 4H).

The mixture **13/14** was ozonized to identify the regioisomers. Thus, in a 50 mL ozonization reactor, 0.138 g (0.371 mmol) of the **13/14** mixture in 40 mL of CH_2Cl_2 were introduced. The solution was cooled to -70C and a O_3 flux of 4 mmols/h was passed through for 6 h. After that, argon was bubbled through the solution for 10 min, and 0.046 g (0.742 mmol 0.05 mL) of dimethyl sulfide was added. The solution was left at room temperature for 1 h, washed with water, and after solvent evaporation, the residue was directly analyzed by G.C. using authentical samples of 4-nitrobenzaldehyde and 4-chlorobenzaldehyde as standards. From this analysis a ratio **13/14** of 56:44 is obtained.

*Reaction of $(acac)_2Co$ with 1-(4-chlorophenyl)-3-(4-nitrophenyl)-2-propen-1-ol, **9**, in the presence of 1-bromo-1-phenylethane.* In a 10 mL round-bottomed flask, 0.592 g (2.04 mmol) of alcohol **9**, 0.378 g (2.04 mmol) of 1-bromo-1-phenylethane, 0.525 g (2.04 mmol) of $(acac)_2Co$ and 2 mL of chloroform were introduced. The mixture was refluxed for 6 h and after that it was diluted with 25 ml of chloroform. The organic solution was washed with 1M HCl and with water several times. After solvent evaporation, 1.075 g of residue was obtained. Direct integration of the ^1H NMR resulted in a ratio of alkylation products **13/14** of (55:45). This result was confirmed after column chromatography (silica-gel, hexane-ethyl acetate). 0.357g of 3-(1-phenylethyl)pentane-2,4-dione, and 0.705 g (89% yield) of a mixture (55:45, 1H NMR) of the alkylation products **13/14** were obtained.

*Reaction of $(acac)_2Co$ with 3-(4-chlorophenyl)-1-(4-nitrophenyl)-2-propen-1-ol, **10**, in the presence of 1-bromo-1-phenylethane.* The process described in the previous paragraph was repeated starting from the isomeric alcohol **10**. After working up, 0.21 g (26% yield) of the mixture **13/14** were obtained, in a 50:50 ratio.

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