S Y N O P S I S

Part I. Studies of a Few Michael Reactions of Synthetic Utility under Phase Transfer Catalysis

A simple procedure for Michael condensations of a few selected CH acids (donors) with α,β-unsaturated ketones (acceptors), listed below, under phase transfer catalysis has been worked out. The method which is an extension of the one used by Yanovskaya[1] for α,β-unsaturated aldehydes consists in heating the donor and acceptor molecules in presence of benzyltriethylammonium chloride and anhydrous potassium carbonate in benzene at 60-80° is superior to conventional base-catalysed Michael reaction with regards to yields which are excellent except for highly hindered substrates. It is suggested that as the bulk of the acceptor molecule increases, the ion pair Q^+Nu^- (Q^+ stands for quaternary ammonium cation and Nu^- for the conjugate base of the CH acid) finds it difficult to approach

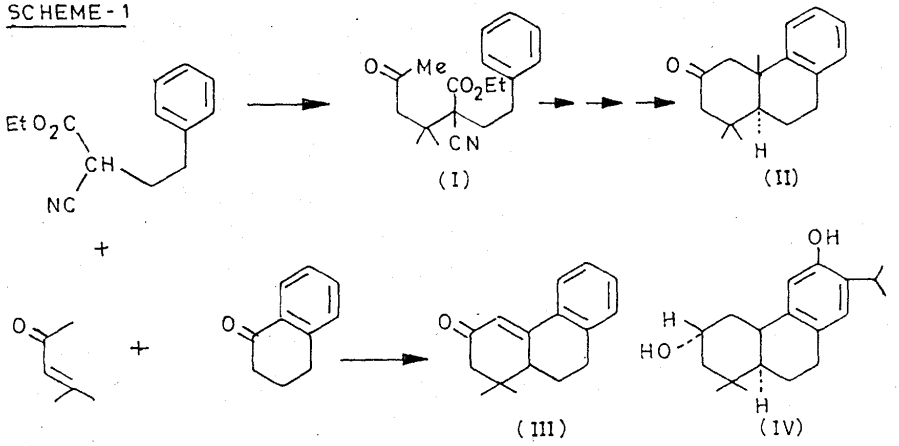
Donors	Acceptors
$NC-CH_2-CO_2Et$	$CH_3-COCH=CMe_2$
$EtO_2C-CH_2-CO_2Et$	$CH_2=CH-CO_2Et$
$C_6H_5CH_2CN$	$CH_3CH=CH-CO_2Me$
o-Me-$C_6H_4CH_2CN$	$(CH_3)_2C=CHCO_2Me$
$C_6H_5CH_2COCH_3$	

1. G.V. Kryshtal, V.V. Kulganek, V.F. Kucherov, and L.A. Yanovskaya, Synthesis, 1979, 107.

the crowded site of the acceptor molecule and the conventional metallic salt, $Na^{+}Nu^{-}$ is more effective. Some of the resulting products provide useful synthetic intermediates and have been used in the present laboratory for further synthesis.

A few recalcitrant Michael reactions, e.g., condensation of ethyl phenethylcyanoacetate and 3,4-dihydro-1(2H)-naphthalenone with mesityl oxide have also been carried out successfully under PTC giving respectively the products (I) and (III)

SCHEME-1



the former (I) is an intermediate for a projected synthesis of 2-oxopodocarpa-8,11,13-triene (II), the mother structure of salviol (IV),[2] a naturally occurring diterpene. The above procedure of Michael reactions under PTC may very well be a general one and is preferrable for its extreme simplicity.

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2. T. Hayashi, T. Handa, M. Ohashi, and H. Kakisawa, Chem. Commun., 1971, 541.

Part II. Studies on the Synthesis of 2-Oxopodocarpa-8,11,13-triene: Krapcho's Dealkoxycarbonylative Alkylation and Transposition of Ketonic Function

Carbanions generated *in situ* through de-ethoxycarbonylation of ethyl 2-cyano-3,3-dimethyl-5-oxohexanoate (V) and ethyl phenethylcyanoacetate (VI) by heating with lithium chloride in hexamethylphosphorus triamide (Scheme 2) according to Krapcho[3] have been submitted respectively to alkylation reaction with phenethyl bromide and to Michael addition with 4-methylpent-3-en-2-one (mesityl oxide) with a view to utilising the resultant 5-cyano-4,4-dimethyl-7-phenylheptan-2-one (VII) for a convenient synthesis of 2-oxopodacarpa-8,11,13-triene (II). The yields of the reactions are, however, poor (15-20%), presumably due to adverse steric effect of the geminal methyl groups in the substrate and adverse electronic effect of phenethyl bromide. Alkylation with benzyl chloride affords a mixture of mono- and di-alkylated products in somewhat better yield. Use of sodium hydride under phase transfer catalysis considerably improves the yield of alkylation of the above cyanoacetate (Va) (with keto group protected by cyclic acetal formation). The product (VIII) undergoes de-ethoxycarbonylation under Krapcho's condition but the resultant nitrile (IX) is found to be resistant to hydrolysis leading to an impasse. The reactions are shown schematically in Scheme 2.

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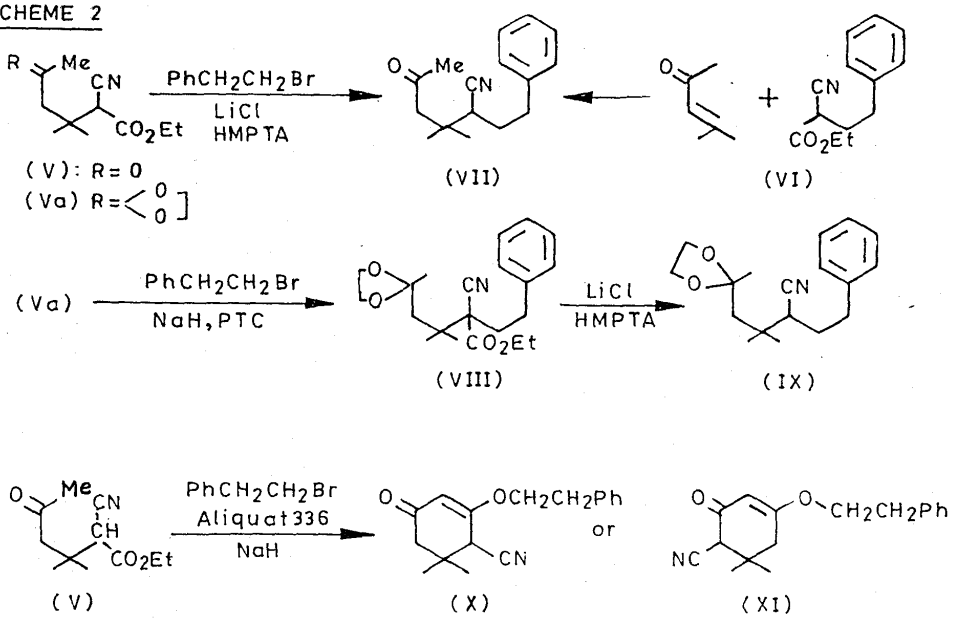
3. A.P. Krapcho, J.F. Weimaster, J.M. Eldridge, E.G.E. Jahngen, A.J. Lovey, and W.P. Stephens, J. Org. Chem., 1978, 43, 138.

SCHEME 2

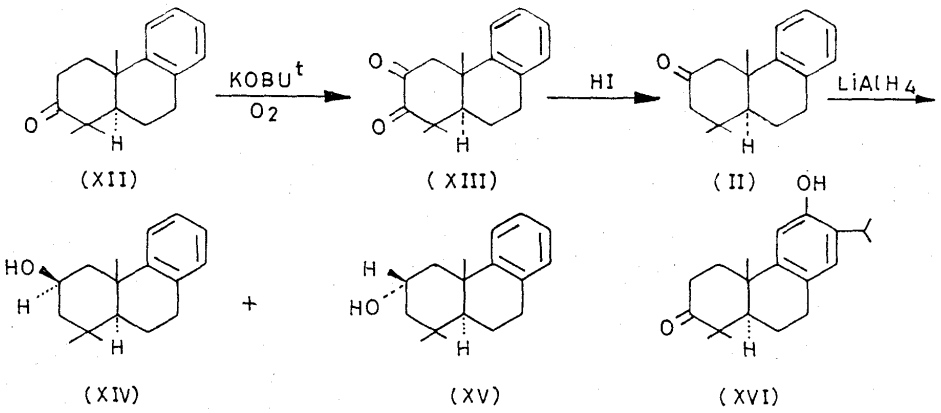


The ^{1}H-NMR spectrum of the ketocyano-ester (V) shows an AB-quartet for the keto-methylene protons with a pronounced ν_{AB} value (12 Hz). Alkylation of (V) with phenethyl bromide as shown in Scheme 2 affords an enol ether in 75% yield which may be represented by either of the structures (X) and (XI) both compatible with the ^{1}H-NMR spectrum.

2-Oxopodocarpa-8,11,13-triene (II) is finally synthesised from the easily accessible 3-oxo-derivatives (XII) by transposition of the ketonic function through a two step process, namely, oxidation with molecular oxygen in presence of potassium t-butoxide to 2,3-dioxoderivative (XIII) and its subsequent reduction

with boiling hydriodic acid[4] (Scheme 3). The ketone (II) on treatment with lithium aluminium hydride affords 2β (axial) (XIV) and 2∝ (equatorial) (XV) alcohols in a 60:40 ratio. The mixture could be converted into the more stable equatorial alcohol (XV) by equilibration through dichloro-alumino complexes.[5] The method if applied to the methyl ether of

SCHEME-3



hinokione (XVI), a ketonic diterpene of established structure would lead to a synthesis of salviol (IV) (see Part I).

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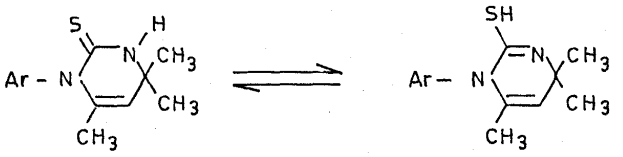
4. W. Reusch and R. Lemahieu, J. Amer. Chem. Soc., 1964, 86, 3068; E. Bailey, D.H.R. Barton, J. Elks, and J.F. Templeton, J. Chem. Soc., 1962, 1578.

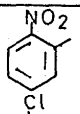
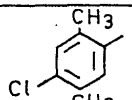
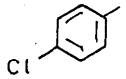
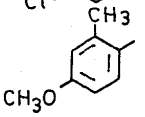
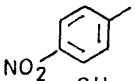
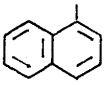
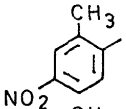
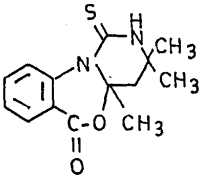
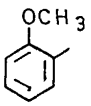
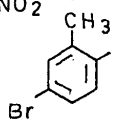
5. E.L. Eliel and D. Nasipuri, J. Org. Chem., 1965, 30, 3809.

Part III : Synthesis of 1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines : Their Alkylation under Phase Transfer Catalysis and Studies of their ^{1}H-NMR and ^{13}C-NMR Spectra

1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines (as XVII), alternatively, 3-arylpyrimidinethiols (as XVIII)[6] are easily accessible compounds, have potential biological importance, and some of them are used in rubber industry as vulcanisation accelerators. Fourteen of these compounds have been synthesised (a single step process)[6] and characterised by spectral data (particularly by ^{1}H-NMR and ^{13}C-NMR). Their structures as thiones (not as thiols as previously assumed) have been established by the following evidences:



(XVII) (XVIII)

	Ar		Ar		Ar
a		f		k	
b		g		l	
c		h		m	
d		i		n	
e		j			

(i) UV spectra which show peaks around 265nm characteristic of cyclic thiourea, (ii) IR spectra which show NH stretching frequency at 3400 cm^{-1}, (iii) ^{1}H-NMR spectra which exhibit the signal of the NH proton at δ 7.0 ppm exchangeable with D_2O, (iv) ^{13}C-NMR spectra in which carbon of C=S appear at δ 176.5 ppm similar to that reported in analogous compounds,[7] (v) melting points which are pretty high compared to the corresponding S-methylated products (see later), and finally, (vi) X'ray crystallography* of the compound (XVIIh) which shows the complete structure with S=C-NH unit.

The o-carboxy-derivative prepared from anthranilic acid proved to be a lactone having the structure (XVIIn), its structure being confirmed by ^{1}H-NMR. The 5-CH_2 protons are diastereotopic and give an AB-quartet.

Some of the thiones with bulky o-substituents (XVIIe, XVIIf and XVIIh) and the 1-naphthyl-derivative (XVIIm) show chemical non-equivalence for the geminal methyl groups in ^{1}H-NMR (as well as in ^{13}C-NMR). They have been studied by dynamic nuclear magnetic resonance in collaboration with Mr. N.P. Daw of the present laboratory. In the first two compounds (XVIIe and XVIIf), the free energies of activation (as determined from coalescence temperature)[8] for conformational inversion around aryl-nitrogen bond are found to be 97.9 and 100.24 kJ/mole respectively.

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6. R.A. Mathes, J. Amer. Chem. Soc., 1953, 75, 1747.
7. R. Faure, E.J. Vincent, G. Assef, J. Kister, and J. Metzger, Org. Magn. Reson., 1977, 9, 688.

*Through kind courtesy of Dr. G.D. Nigam, Department of Physics.

These thiones are capable of producing ambident anions (as $S=\underset{|}{C}-N^{-}$ & $^{-}S-\underset{|}{C}=N-$) with base. Their alkylation with methyl iodide and benzyl chloride under phase transfer catalysis has been investigated. It is found that alkylation takes place at sulphur giving thio-ethers with complete regioselectivity. The structures of the alkylated products as thio-ethers have been proved as follows :

(i) The UV spectra of the methylation products are entirely different from those of the starting thiones (XVII) and of the thiourea chromophore.

(ii) The IR spectra show a strong band at 1600 cm^{-1} which is absent in the spectra of the thiones and is possibly due to the C=N bond.

(iii) The ^{1}H-NMR spectra of the methylated products show a new methyl signal at δ 2.20-2.28 ppm (δ 15.1 ppm in ^{13}C-NMR) characteristic of $S-CH_3$. In ^{13}C-NMR, the C-2 peak at δ 150.0 - 150.4 ppm also supports the thio-ether structure.

(iv) The mass spectra are not diagnostic but certain characteristic features agree more to the thio-ether structure (see text).

Some of the thiones are being tested for their biological activity. That of the lactone (XVIIn) has been evaluated which is discussed.

8.(a) D. Nasipuri and S.K. Konar, J.C.S. Perkin II, 1979, 269; D. Nasipuri, P.K. Bhattacharya, and G.T. Furst, J.C.S.Perkin II, 1977, 356.

(b) D. Nasipuri, N.P. Daw, S. Banerjee, and Mita Dutta Gupta, J. Indian Chem. Soc. 1982, 59, 1379.

Part IV. Reduction of a Few Typical Cyclic Ketones with Some Alkoxyaluminium Dichlorides : Stereochemical Evidence for Single Electron Transfer Mechanism*

Alkoxyaluminium dichlorides, $ROAlCl_2$ with hydrogen at α-carbon are good reducing agents for ketones,[9] the reduction going supposely through a reversible H-transfer similar to Meerwein-Ponndorf-Verley (M-P-V) reaction. The one derived from bornan-2-exo-ol (XII) has proved particularly useful for its superior reactivity, high stereoselectivity (it affords the less stable epimeric alcohols in high excess), and virtual irreversibility of the reaction. Its optically active form has been successfully used for enantioselective reduction of a variety of ketones.[10] The results are interpreted on the basis of a cyclic mechanism (route-i, Scheme 4) or variations thereof.[11] In view of growing interest in the chemistry of complex hydrides, we have resumed the investigation with a host of these reagents (I)-(XII) (Table 1) and studied the stereochemistry of the reduction of a few typical ketones, shown in Table 1. 4-t-Butylcyclohexanone, an anancomeric system, represents unhindered cyclic ketones along with 2-, 3-, and 4-methylcyclohexanones; 3,3,5-trimethylcyclohexanone and norcamphor

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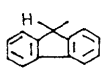
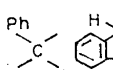
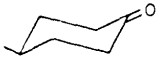
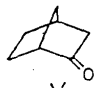
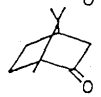
*The numbering of the structural formulae is independent of other parts.

9. E.L. Eliel and D. Nasipuri, J. Org. Chem., 1965, 30, 3809.

10. D. Nasipuri and P.R. Mukherjee, J. Indian Chem. Soc., 1974, 51, 171; and earlier papers.

11. D. Nasipuri and P.K. Bhattacharya, J.C.S. Perkin I, 1977, 576.

Table 1. Stereochemistry of reduction of cyclic ketones with alkoxyaluminium dichlorides and related reagents

Entry No.	Ketones	Relative percentage[a] of the thermodynamically more stable alcohols by reduction with:												
		$ROAlCl_2$[b] for R =											$LiAlH_4$	$Li-NH_3$
		 I	 II	III	 IV	 V	 VI	 VII	 VIII	 IX	 X	 XI	 XII[c]		
1		96-98 (95)[d]	90-95 (85)	80-85 (20)	85-88 (60)	87-89 (75)	75-90 (85)	70-72 (10)	70-75 (75)	-	95-97 (95)	55-60 (98)	8-10	89	98-99
2		84-88 (85)	75-80 (80)	-	-	-	-	-	-	-	-	-	10-11	81	99
3		89-92 (90)	78-80 (90)	-	-	-	-	-	-	-	-	-	8-9	88	94-95
4		80-88 (80)	-	-	-	-	-	-	-	-	-	-	2-3	70	99
5		75-95 (70)	83-85 (65)	-	-	63-65 (15)	22-32 (15)	- (0)	24-26 (40)	-	80-85 (70)	15-20 (20)	2	45	99
6		35-70 (45)	20-25 (50)	-	-	60-65 (20)	24-26 (20)	-	8-10 (20)	15-17 (70)	-	65-70 .(8)	3-5	9	9-32
7		75-78 (10)[e]	-	-	-	-	-	-	-	-	-	-	-	10	79-90
8		62-65 (20)[e]	-	-	-	-	-	-	-	-	-	-	5	79	-

[a]Percentages were determined from at least three experiments by GC conducted on 10% Carbowax and 15% FFAP columns (2m) using FID. [b]Treatment with 1.5 mol reagents for 15-20 min. at ambient temperature. [c]Taken from ref. 1. [d]Yields are in parenthesis. [e]Treatment with 2 mol reagents for 4 hr.

are moderately hindered, while camphor and menthone are highly so. The results are summarised in Table 1 along with a few literature data.

The reagents prepared in situ by the action of anhydrous $AlCl_3$ on lithium tetra-alkoxyaluminium in ether in presence of the ketone to be reduced are very reactive, specially the one (I) derived from fluorenol, the reduction being effected in 5-10 min. at 0°. The reactivity, however, diminishes with time and the reduction remains incomplete. The products are kinetically controlled and the possibility of equilibration of the alkoxyaluminium complexes[12] is eliminated by suitable control experiments.

The stereochemical results (Table 1) with the reagents (I) – (XI) fall under three main categories :

i) The unhindered cyclohexanones (entries 1-4) are reduced to the more stable equatorial alcohols preponderantly, in many cases more so than with $LiAlH_4$. Reagents (I) and (II) which are the bulkiest of all afford the highest ratio of such alcohols showing that 'Steric Approach Control' (SAC) appears to be ineffective.

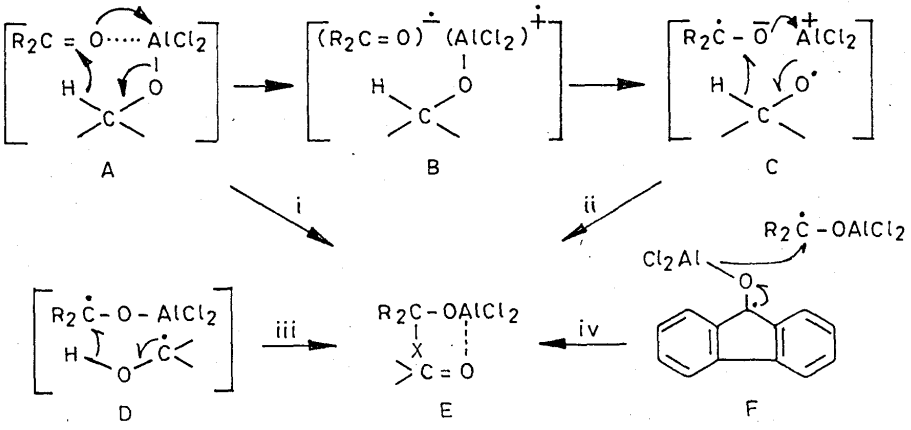
(ii) 3,3,5-Trimethylcyclohexanone and norcamphor (entries 5 and 6) give variable results with wider product-spreads, the four nonaromatic reagents (VI) – (IX) exhibit SAC to a much greater extent than the aromatic ones (I), (II), and (V) while the results with reagent (X) and (XI) are anomalous.

12. E.L. Eliel and M.N. Rerick, J. Amer. Chem. Soc., 1960,82, 1367.

iii) Camphor and menthone (entries 7 and 8) are reduced only with the reagent (I) giving menthol and borneol (stabler epimers) in high excess. Reagent (XII), the first to be investigated,[9] however, behaves quite differently furnishing the less stable alcohols almost to the exclusion of the other epimers.

The results in general and with reagents (I) and (II) in particular bear a close resemblance to those of dissolving metal reductions[13] (Table 1, last column) in which H is transferred from a H-donor (ROH or NH_4Cl) to an alkoxy anion radical or dianion.[14] This observation along with the recent findings of Ashby et al that aromatic ketones are reduced with metal hydrides[15] and alkoxides[16] through a radical intermediate formed by single electron transfer (SET) conform to the following mechanism (Scheme 4):

SCHEME-4



X = H or $AlCl_2$

The mechanism is similar to that proposed by Screttas and Cazianis[17] for M-P-V type reductions except in some minor details. The ketone first forms a complex (A) with the reagent which subsequently leads to a radical anion-radical cation pair (B) by single electron transfer and then to the radical species in (C). This in turn undergoes a rapid rearrangement from less stable O-centred radical to a more stable C-centred radical (D) and H is transferred (route iii) to $R_2\dot{C}-AlCl_2$ from $\dot{C}-OH$ (H-donor equivalent in $Li-NH_3$ reduction) to give the products (E, X = H). All these changes are reversible and take place within the solvent cage. The protonated ketyl in D being more acidic than the corresponding alcohol[18] also reacts with the reagent (e.g., I) to form dichloroaluminium ketyl (F) which can reduce $R_2\dot{C}-OAlCl_2$ by yet another route (iv) to furnish the product (E, X = $AlCl_2$). The stereochemistry of H-transfer

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13. J. W. Huffman and J.T. Charles, J. Amer. Chem. Soc., 1968, 90, 6486.

14. H.O. House, 'Modern Synthetic Reactions', 2nd Edn., W.A. Benjamin, 1972, 153.

15. E.C. Ashby, A.B. Goel, and R.N. DePriest, J. Amer. Chem.Soc., 1980, 102, 7779.

16. E.C. Ashby, A.B. Goel, and J. Argyropoulos, Tetrahedron Letters, 1982, 23, 2273.

17. C.G. Screttas and C.T. Cazianis, Tetrahedron, 1978, 34, 933.

18. C.G. Screttas, J.C.S. Perkin II , 1975, 165.

in route (iii) follows from the preferred conformation of $R_2\dot{C}\text{-}OAlCl_2$ which explains the formation of the more stable alcohols.[14]

Two other pathways (i) and (ii), both reversible and much more susceptible to SAC are also available, their contributions depending on the steric situation of the substrates and the stability of the intermediate radical species. For cyclic ketones, attack from either side of C = O is sterically hindered (due to axial H's in cyclohexanones), relatively speaking, and route iii (the least sterically demanding) predominates, particularly when $\dot{C}\text{-}OH$ in species (D) is stabilised by resonance which explains most of the results. The cases with intermediate and variable stereochemistry may be rationalised on the basis of two or more competing mechanisms. Since the results arise out of a balance between several mechanisms which can switch from one to the other very easily (a change from bornan-endo-2-ol to bronan-exo-2-ol in the reagents considerably alters the stereochemical pattern), a large product spread is observed. The atypical behaviour of the reagent (XII) (derived from bornan-2-exo-ol) may be attributed to its high propensity for collapsing into camphor molecule (relief of steric strain) which helps it react at an early stage via route (i) or route (ii).

No EPR signal, however, can be obtained when fluorenone or benzophenone is added to $ROAlCl_2$ (e.g., VI and IX) in tetrahydrofuran (THF) indicating that no ketyl is present in detectable amount. On the other hand, when $AlCl_2$ is replaced by Li, K, or MgCl in the reagents, strongly paramagnetic solutions result. This means that either the SET mechanism does not operate here (an unlikely proposition in view of the stereochemical results) or the radicals (as F) are destroyed on formation. We suggest that the ketyl (F) actually behaves as a mixture of fluorenone and $\dot{A}lCl_2$ and the latter readily couples with $R_2\dot{C}-OAlCl_2$ either directly (route iv) or through another SET.

As corroborative evidences, we have isolated norcamphor pinacol[13] in one of the equilibration experiment with norborneol-complexes in THF. 4-t-Butylcyclohexanone when reduced with the reagent (I) and its α-deuterated form shows the same stereochemistry (and reactivity), which is unusual if H is transferred from C rather than from O since such transfer is known to be more stereoselective[19,20] (also less reactive) for D than for H

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19. D. Nasipuri, C.K. Ghosh, and R.J.L. Martin, J. Org. Chem., 1970, 35, 657.

20. V.E. Althouse, E. Kaufmann, P. Loeffler, K. Ueda, and H.S. Mosher, J. Amer. Chem. Soc., 1961, 83, 3138.