Efficient Catalytic Asymmetric Alkylations. 3.[1] A Kinetic and Mechanistic Study of the Enantioselective Phase-Transfer Methylation of 6,7-Dichloro-5-methoxy-2-phenyl-1-indanone

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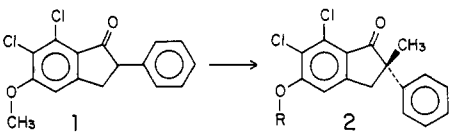
The phase-transfer methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone by MeCl in 50% NaOH/toluene using substituted *N*-benzylcinchoninium halides has provided the methylated indanone **2** in ee's up to 94%. The effects of solvent, alkylating agent, temperature, and catalyst were investigated: nonpolar solvents gave higher ee's than polar solvents; MeCl gave a higher ee than did MeBr and MeI; and temperature had little effect on the reaction. A Hammett plot of log ee/ee_0 vs. σ for the *N*-benzylcinchoninium halide catalysts gave a reaction constant ρ of 0.21 with an ee range of 60% to 94%, demonstrating that substituents with increasing electron-withdrawing power improve catalyst selectivity. A kinetic and mechanistic study of the reaction has revealed several unusual features. In 50% NaOH/toluene these include the following: (1) the indanone **1** is deprotonated at the interface to form the sodium enolate as a separate solid phase; (2) the substituted *N*-benzylcinchoninium catalysts are extracted into the organic layer as dimers; and (3) the kinetic order in MeCl is 0.7 and in catalyst is 0.55. In 30% NaOH/toluene the following obtain: (1) no solid enolate is formed; (2) an order in catalyst of 0.5 was found for the chiral methylation pathway, while an order of 1.0 was found for the racemic methylation pathway.

Much recent synthetic methodology has been devoted to developing and understanding asymmetric reactions in an effort to provide direct, efficient, and economical routes to target compounds. Carbon–carbon bond-forming reactions of enolates are one important area of asymmetric synthesis. The stereospecific alkylation of ketones has been approached in three ways: (1) the three-step sequence involving preparation of a chiral intermediate (imine, hydrazone, etc.), alkylation of the intermediate, and hydrolysis of the alkylated intermediate to the ketone;[2] (2) reaction of an enolate with an alkylating agent having a chiral leaving group;[3] and (3) phase-transfer alkylation involving a chiral catalyst.[4] Work on the chiral auxiliary route began in the 1960s,[5] but only in the last decade has success (≥90% ee) been achieved.[2] Despite these achievements, some drawbacks are inherent in this approach. The procedures require three steps and the use of stoichiometric quantities of chiral auxiliaries, which often must be synthesized. Using the chiral leaving group approach, Duhamel[3b,c] has methylated the Schiff base of methyl glycinate with ee's up to 70%. The method appears to be limited to ketones or esters having a functional group in the α-position capable of chelating with Li^+. Catalytic chiral phase-transfer alkylations offer a potentially simple, one-step alternative. However, development of this route has not met with the same success as the chiral auxiliary route. Optical yields of 15% have been reported for the alkylation of cyclic β-keto esters using ephedrinium halides as catalysts,[4] but even these modest yields have been disputed since it was shown that catalyst decomposition products account for most of the optical rotation in the isolated products.[6] A bona fide optical yield of 19% was obtained for the solid–liquid phase-transfer alkylation of potassium phthalimide,[7] but ee's of only 2–3% were found under similar conditions for carbanion alkylations.[7]

Scheme I



98%, 94% e.e.

2. R=CH_3
3. R=H
4. R=CH_2COOEt
5. R=CH_2COOH

Despite these inauspicious reports in the literature, the rewards in terms of synthetic simplicity, yield, and cost prompted us to explore the chiral phase-transfer route as the key step in the preparation of the uricosuric (*S*)-indacrinone (**5**). In a preliminary paper we described the outcome of these studies which culminated in the first efficient, catalytic, enantioselective methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone (Scheme I).[1a] Enantiomeric excesses up to 94% were achieved with catalysts derived from substituted *N*-benzylcinchoninium halides (**6**) under liquid/liquid conditions using 50% NaOH/toluene. The high enantioselectivity was rationalized in terms of a tight ion pair (Figure 1) between the catalyst and indanone enolate.

CPK molecular models, the single-crystal X-ray structure, and molecular modeling studies of the *N*-benzylcinchoninium ion suggest that a preferred conformation may be that in which the quinoline ring, the C_9–O bond,

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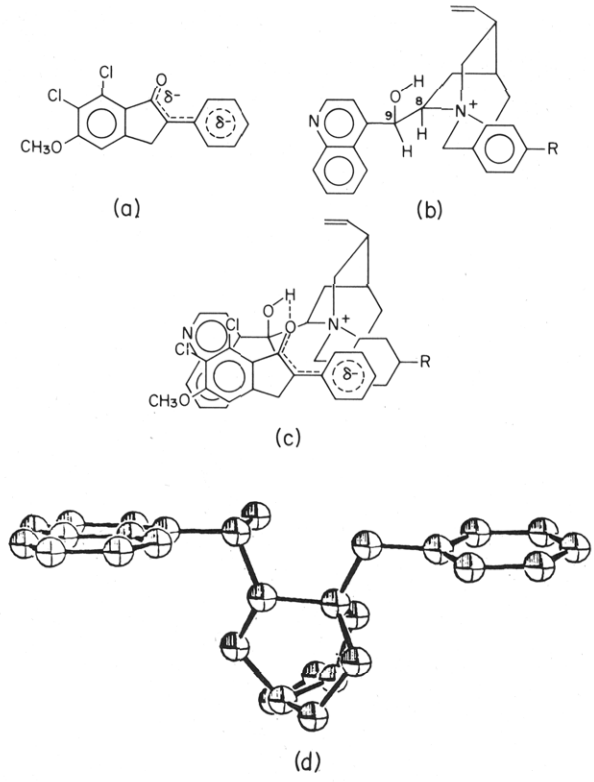


Figure 1. Ion pairing between the indanone anion (a) and the *N*-benzylcinchoninium halide (b) to form a complex (c). (d) ORTEP depiction of *N*-benzylcinchonium halide revealing planar surface.

and the *N*-benzyl group all lie in one plane (Figure 1d). The anion of **1** also has an almost planar structure with the negative charge delocalized into the 2-phenyl ring (Figure 1a). Both molecules in their nearly planar conformations fit naturally on top of each other, providing π-interaction between the benzyl group of the catalyst and the 2-phenyl group of **1** on the one side and between the quinoline and methoxydichlorobenzene moieties on the other (Figure 1c). The C_9-hydroxyl provides a directional handle for the ionic attraction via hydrogen bonding to the indanone anion. The alkylating agent can only alkylate from the front side and form the (*S*)-(+)-6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone (**2**).

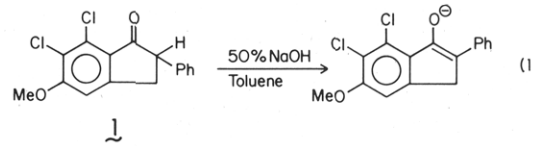
As we began to examine this reaction in more depth, it became clear that the mechanism was more complex than that of a simple phase-transfer reaction.

Initial experiments with *N*-[*p*-(trifluoromethyl)-benzyl]cinchoninium bromide (*p*-CF_3BCNB) and MeCl demonstrated some unusual behavior of the chiral alkylation: (a) the ee dropped from 90% to 0% when the catalyst mol % was reduced from 10% to 2.5%, (b) the ee was increased at higher dilution and constant molar ratios of reactants to catalyst, and (c) the reaction was zero order in indanone. To further probe these findings, the concentrations of reactants, product, and catalyst were followed throughout a reaction. These measurements revealed several abnormal aspects about the reaction. For example, although the substituted *N*-benzylcinchoninium halide catalysts are completely insoluble in toluene, millimolar quantities of the catalyst are present throughout the reaction in the toluene layer. In addition, the amount of methylation is minimal (20%) during the first 6 h, and then rapid and complete reaction occurs within the next 3 h. At the 6-h point, however, the amount of starting material in the toluene layer is 5% and the amount of product is 20%, leaving 75% of the mass balance unaccounted for! Our studies aimed at understanding these unusual features have led to an unraveling of the complex mechanism of the reaction, described in the following sections.

Results and Discussion

A. Kinetics and Mechanism. Phase-transfer alkylations require three primary steps: deprotonation of the substrate, transfer of the substrate anion into the organic phase, and alkylation in the organic phase.[8] This section describes our studies aimed at understanding these steps in the chiral phase transfer methylation. It is divided into two major parts, one describing reactions in 50% NaOH/toluene and the other for reactions in 30% NaOH/toluene, because there are major mechanistic differences between the two media. Each section is divided into the three basic steps of the phase-transfer reaction.

1. 50% NaOH. Step 1. Enolate Anion Formation: Evidence for Interfacial Deprotonation. The solubility of indanone **1** in toluene is about 16 mM, so when the standard 10 mmol of indanone is charged with 125 mL of toluene in these reactions, only about 20% dissolves. Therefore, we would expect the toluene layer to stay saturated in indanone for the first 80% of the methylation and then begin to drop off. However, the indanone concentration drops to about 10^{-4} M early in the reaction and remains at a low level throughout the course of the methylation. Apparently, the indanone in the toluene layer reacts nearly completely with the 50% aqueous NaOH to form the sodium enolate as a solid phase suspended in the two liquid layers (eq 1). The FTIR spectrum of this



suspended phase showed that the carbonyl peak at 1700 cm^{-1} was absent and two new peaks at 1525 and 1565 cm^{-1}, due to the enolate anion, had appeared. The location of these peaks is in accord with the literature spectra of enolates.[17] As further confirmation, the anion was prepared in a Me_2SO solution by using NaOMe and again produced a spectrum lacking the carbonyl stretch and containing peaks at 1530 and 1563 cm^{-1}.

The deprotonation of indanone **1** is a liquid–liquid interfacial reaction since the reaction occurs in the absence of a phase-transfer catalyst and since indanone **1** is insoluble in 50% aqueous NaOH. No deprotonation occurs when solid indanone is stirred for several days with 50% NaOH and no organic solvent.

There has been a long-standing controversy about whether the deprotonation step in phase-transfer reactions occurs at the interface (Makosza mechanism) or whether it occurs in the organic phase after the catalyst extracts HO^- into the organic phase (Starks mechanism).[8] While the latter mechanism earlier found more support from studies involving kinetics, dependence on NaOH concentration and stirring rates, and the effectiveness of lipophilic vs hydrophilic catalysts,[9] more recent studies favor the interfacial mechanism: (1) Makosza has shown that at elevated temperatures, some two-phase alkylations and

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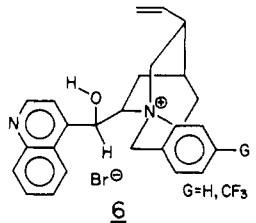
condensations can occur without a catalyst;[10] (2) Dehmlow has found that two-phase Wittig reactions give the same yields with and without catalyst;[11] and (3) some D/H exchange can occur in two-phase systems without catalyst.[12] Our finding is clear-cut evidence that interfacial deprotonation occurs under phase-transfer conditions and that the Makosza mechanism is operative. However, this interfacial deprotonation is not the rate-limiting step, since complete deprotonation has occurred when methylation is only 20% complete. If this is true of other phase-transfer reactions, then evidence presented in favor of the Starks mechanism, such as kinetic orders of unity in reactants and lack of dependence on stirring speed, is no longer valid support since these data would also support the Makosza mechanism where the alkylation step in the organic layer is still the rate-determining step. From the lack of deuterium isotope effects in phase-transfer reactions, Rabinovitz and co-workers have likewise concluded that interfacial deprotonation is occurring but is not the rate-limiting step.[13a] They have also recently reviewed phase-transfer reactions and have concluded that compounds that have a pK_a such as indanone 1 should react by an interfacial mechanism.[13b]

Step 2. Anion Extraction into the Organic Phase: Nature of the Catalyst in the Organic Phase. One important property of phase-transfer catalysts is that they have some solubility in both water and organic solvents so that they can act as an anion shuttle between the two phases. However, the solubilities of the *N*-benzylcinchoninium halides are so low in toluene that they cannot be detected by LC ($<10^{-5}$ M) after vigorous stirring of the solid in the solvent for several hours. Yet, in the quenched toluene layer of the phase-transfer reactions, the catalyst is present, as detected by LC, in millimolar quantities. Some transformation of the catalyst must be occurring that makes the catalyst more soluble under phase-transfer conditions.

For *N*-benzylcinchoninium bromide (BCNB) and *N*-[*p*-(trifluoromethyl)benzyl]cinchoninium bromide (*p*-CF_3BCNB) the species in the toluene layer appears to be a dimer of the catalyst (**6**) and its zwitterionic oxide (**7**), based on the experiments described below.



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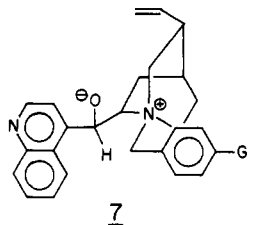

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1. Stirring BCNB or *p*-CF_3BCNB (100 mg) in toluene (10 mL)/50% NaOH (8 mL) produced a clear solution in 0.5 h. HPLC assay of the toluene layer indicated that nearly all of the catalyst was in the toluene layer, while titration showed that half of the catalytic species was basic. By microanalysis, the solid isolated from the toluene layer had one Br per two catalyst molecules. All these data are consistent with the dimeric species, with the zwitterion being the basic species.

2. In several phase-transfer reactions using 50% NaOH, the toluene layer was analyzed for total catalyst and for basicity. In all cases the basicity was about half the molarity of the total catalyst present, suggesting that the catalyst was also present as the dimer under actual reaction conditions. The basicity of the toluene layer cannot be due to the indanone enolate since LC assay of the quenched toluene solution shows indanone to be present in toluene in concentrations of less than 10% that of the catalyst.

3. It is possible that HO^- is a counterion for the half of the catalyst in toluene that is basic. Arguments against this include (a) tetraalkylammonium salts with HO^- as counterion are typically 1000-fold less soluble than with Br^- as counterion in organic solvents,[14] and we know that the catalyst with Br^- as counterion is insoluble in toluene, (b) tetraalkylammonium ions with HO^- counterion generally carry four molecules of water per catalyst ion with them into the organic solvent,[14] yet we can make 20 mM solutions of the *p*-CF_3BCNB dimer in toluene with a water content of only 7 mM, and (c) if HO^- is present, then quenching of the toluene solution with a dry acid should produce a mole of water for each mole of quenched HO^-. Quenching 20 mM solutions of the catalyst in toluene gives a slight rise in water content by KF titration (1–2 mM) but far less than that needed to account for the total basicity.

4. Reacting the dimer formed in the toluene layer with MeI gave about equal amounts of the methyl ether **8** and unreacted catalyst. Since only the zwitterion is expected to react with MeI, the approximately 50% reaction is further evidence for the dimer.

In summary, the pathway for the catalyst to enter the organic layer is outlined below. A small amount of catalyst dissolves in the aqueous layer (eq 2) where it is partially deprotonated by the strong base (eq 3). The dimer between the catalyst and zwitterion is then extracted into the organic layer (eq 4). The last equilibrium lies to the right, which tends to make the dimer build up in the organic phase even though the first equilibrium is highly unfavorable.

$$(Q\text{–}OH)^+(Br^-)_{solid} \rightleftharpoons (Q^+\text{–}OH)_{aq} + (Br^-)_{aq} \quad (2)$$

$$(Q^+\text{–}OH)_{aq} + (OH^-)_{aq} \rightleftharpoons (Q^+\text{–}O^-)_{aq} + H_2O \quad (3)$$

$$(Br^-)_{aq} + (Q^+\text{–}OH)_{aq} + (Q^+\text{–}O^-)_{aq} \rightleftharpoons (Q^+OH\cdots{}^-O\text{–}Q^+Br^-)_{org} \quad (4)$$

We have shown that the indanone 1 is deprotonated at the interface to form a solid enolate and that the catalyst is extracted into the organic layer as a dimer. Before methylation can occur, the indanone enolate must enter the organic phase. Three mechanisms, among which we cannot distinguish, are possible: (1) dissolution of a small amount of Na^+ Ind^- in the aqueous layer followed by liquid/liquid extraction (eq 5), (2) solid/liquid extraction of the solid enolate present at the interface (eq 6), and (3) deprotonation of residual indanone in the toluene layer by the catalyst zwitterion portion of the dimer to form the catalyst–indanone complex (eq 7). In support of the third

$$(Na^+\ Ind^-)_{aq} + (Q^+\text{–}OH\ Br^-)_{tol} \rightleftharpoons (Q^+\text{–}OH\ Ind^-)_{tol} + NaBr \quad (5)$$

$$(Na^+\ Ind^-)_{solid} + (Q^+\text{–}OH\ Br^-)_{tol} \rightleftharpoons (Q^+\text{–}OH\ Ind^-)_{tol} + NaBr \quad (6)$$

$$(Ind\text{–}H)_{tol} + (Q^+\text{–}O^-)_{tol} \rightleftharpoons (Q^+\text{–}OH\ Ind^-)_{tol} \quad (7)$$

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Table I. Rates of Methylation for Preformed Enolate Reactions[a]

entry	initial catalyst charged, mmol	initial indanone charged, mmol	[catalyst]$_{tol}$,[b] mM	[MeCl]$_{tol}$,[c] M	stirring rate, rpm	10^6k,[d] mol L^{-1} s^{-1}
1	1.0	10	6	0.56	1200	3.7
2	1.0	20	4.5	0.56	1200	4.1
3	0.50	10	2.5	0.56	1200	3.2
4	0.50	5.0	2.9	0.56	1200	2.8
5	0.25	10	0.65	0.56	1200	1.9[e]
6	0.25	2.5	1.5	0.56	1200	1.5
7	0.125	1.25	0.9	0.56	1200	1.2
8	1.0	10	5	1.68	1200	7.5
9	1.0	10	6	1.12	1200	6.7
10	1.0	10	6	0.22	1200	2.3
11	1.0	10	6	0.16	1200	1.5
12	2.0	20	11	0.56	1200	5.4
13	1.0	10	6	0.56	500	3.9
14	1.0	10	5	1.68	500	8.1

[a] Reaction conditions: 125 mL of toluene, 25 mL of 50% aqueous NaOH, and indanone were stirred together until the level of indanone in toluene dropped to $\sim 10^{-4}$ M (1–5 h depending on initial charge of indanone). Then, the specified amounts of *p*-CF_3BCNB catalyst and MeCl were added to start the reaction. [b] Measured level of *p*-CF_3BCNB catalyst in toluene layer (LC assay). [c] Charged amount of MeCl, assuming all dissolved in toluene layer. [d] Zero-order rate of formation of methylindanone, assuming the reaction occurs in the 125-mL toluene layer. [e] Reaction stops at 70% conversion due to complete catalyst decomposition.

mechanistic proposal (eq 7), LC measurements indicate that 10^{-4} M indanone remains in the toluene layer after deprotonation with 50% NaOH. Also, the orange color of the indanone enolate is formed on addition of indanone 1 to a solution of catalyst dimer in toluene, indicating that the zwitterion is sufficiently basic to deprotonate indanone 1.

Step 3. Chiral Methylation in the Organic Phase. In the last two sections we have shown that the indanone enolate is formed at the interface, that the catalyst dimerizes to form a toluene-soluble species, and that the catalyst extracts enolate into the toluene layer. The last step is the chiral methylation in the organic layer. As described in the first part, the kinetics of the methylation are complex, as there is an induction period in some cases and also a high sensitivity of rate and ee to the catalyst/indanone ratio. To eliminate these complications, the enolate anion was allowed to form before the catalyst and MeCl were added. Figure 2 shows a comparison of two reactions, curve A with all reagents added at once and curve B with the enolate preformed before addition of catalyst and MeCl.

Since the kinetics are simplified when the enolate is preformed, an in depth study of the effect of catalyst level, MeCl concentration, the stirring rate, and the temperature on the rates and ee of the reaction was made, and the results are tabulated in Table I. Of note is that the isomer ratio remains essentially *unchanged at 96/4* (+/−) when the indanone/catalyst ratio is altered, when the concentration of MeCl is varied 10-fold, and when the stirring rate is slowed from 1200 to 500 rpm.

a. Level of Charged Indanone. Examination of the first six entries of Table I shows that at a constant catalyst concentration, the rate of methylation is nearly independent of the amount of charged indanone, which is present as the sodium enolate. Having a larger amount of enolate decreases the amount of catalyst in the toluene layer. The level of indanone (either as neutral and/or enolate) in the toluene layer is about 10^{-4} M when the other reagents are added, but the level increases as the reaction proceeds. The total indanone concentration in toluene increases to 0.5 mM when 2.5 mmol of enolate are present and 1.5 mM when 20 mmol of enolate are present. These numbers could reflect the concentration of catalyst–enolate ion pair in solution. It is possible that the low level of indanone assayed in the toluene layer during these reactions is because during the time that the sample is taken from the autoclave, centrifuged, and quenched, the enolate could be reacting with MeCl. The following control experiment ruled this out. The reaction was run under the conditions of entry 1, Table I, except that no MeCl was added. The level of indanone assayed in the toluene layer was about 0.5 mM, a value similar to that in the presence of MeCl.

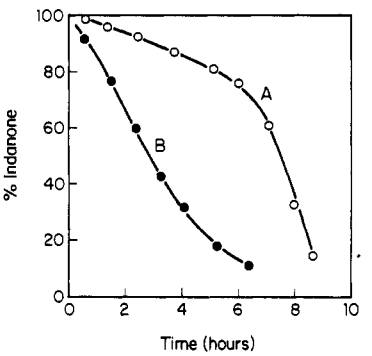

Figure 2. Rate of reaction of indanone 1 with MeCl in 50% NaOH/toluene with 10% *p*-CF_3BCNB as catalyst at 20 °C: initial vs delayed catalyst charge.

b. Stirring Rate. Slowing the rate of stirring from 1200 to 500 rpm had no effect on the rate or the ee (entry 13, Table I). This means that the rate-determining step is occurring in the toluene layer and is not an interfacial process involving transport of the solid enolate into the organic phase. By tripling the concentration of MeCl (entry 14) we hoped to speed the methylation to the point where interfacial transport would become rate-determining, but the rate of stirring still had no effect on the rate or ee.

c. Catalyst Level. A bilogarithmic plot of the rate constant for methylation vs the amount of charged catalyst has a slope of 0.56 ± 0.05.

The points chosen for the plot are those in which the ratio of indanone to catalyst was always constant at 10 (entries 1, 4, 6, 7, and 12 of Table I), as this ratio had some effect on the level of catalyst in toluene and on the rate of reaction. A plot using the concentration of catalyst in the toluene layer (instead of the amount charged) gives a similar slope. An order of <1 in catalyst has been reported in the literature for other phase-transfer reactions, and the ordinary explanation is that the rate of interfacial deprotonation is competitive with the rate of alkylation. In our case, the lack of dependency of the reaction rate on the

Table II. Rates of Methylation Using 30 wt % NaOH at 20 °C[a]

entry	initial catalyst charged, mmol	initial indanone charged, mmol	$[catalyst]_{tol}$,[b] mM	$[MeCl]_{tol}$,[c] M	$10^6 k_o$, M s^{-1}	ee, %
1	2.0	10	13	0.56	2.2	55
2	1.0	10	6.5	0.56	1.6	64
3	0.50	10	3.3	0.56	0.90	70
4	0.25	10	1.8	0.56	0.54	78
5	0.20	10	1.1	0.56		78
6	0.25	2		0.56	0.52	
7	0.50	5	3.3	1.68	2.15	69
8	0.50	5	3.3	0.56	0.82	72
9	0.50	5	3.3	0.28	0.43	72
10	0.50	5	2.9	0.135	0.20	75
11	0.50	5	3.3	0.56	0.77[d]	69

[a] Reaction conditions: 125 mL toluene, 25 mL of 30% aqueous NaOH, 1200 rpm, with *p*-CF_3BCNB as catalyst. [b] Concentration of catalyst in toluene layer. [c] Concentration of MeCl in toluene layer. [d] 500 rpm.

stirring speed suggests that an interfacial reaction is not rate-determining. A more plausible explanation is that the catalyst in toluene is a dimer or higher aggregate that must dissociate prior to complexation with the indanone anion. If the rate has a first-order dependence on the monomer, the amount of monomer is very small, and the equilibration between dimer and monomer is fast, then the order in total catalyst should be 0.5, within experimental error of the observed 0.55.

d. MeCl Concentration. The dependence of the rate on MeCl is also less than first order, as a five-point plot of log *k* vs log MeCl concentration had a slope of 0.67 ± 0.06. This would suggest that a step prior to methylation is competitive with methylation, but our other evidence argues against an interfacial step being rate-determining. Also, a curved plot of log *k* vs log [MeCl] would be expected if another reaction not involving MeCl were competitive with methylation.

e. Comparison with Aliquat 336 as Catalyst. The orders of less than unity in catalyst and MeCl for the chiral methylations using the preformed enolate method with *p*-CF_3BCNB prompted us to determine whether this was a general phenomenon for preformed enolate reactions or if this was a peculiarity of the asymmetric process.

For the standard phase-transfer catalyst, Aliquat 336, the order in catalyst is near 1.0, in contrast to the order of 0.55 for *p*-CF_3BCNB. We postulated that the order in *p*-CF_3BCNB near 0.5 was caused by the catalyst existing as an unreactive dimer which had to dissociate before reacting. Since Aliquat 336 would not dimerize, an order of 1.0 would be expected for it.

The order in MeCl is 1.04 ± 0.04, again contrasting with the order of 0.7 found with *p*-CF_3BCNB as catalyst. The order near 1.0 shows that the reaction with MeCl is the only rate-limiting step with Aliquat as catalyst, while an order of <1 shows that another step, perhaps an extraction, must be competitive with methylation when *p*-CF_3BCNB is catalyst (although the stirring speed did not affect the rate of reaction).

These results are in accord with the only other kinetic analysis of a phase-transfer reaction involving a nucleophile in the solid phase. Yadav and Sharma[15] studied the phase-transfer reaction of solid sodium benzoate and acetate with $PhCH_2Cl$ in toluene finding that the reactions were first order in catalyst and alkyl halide. Also, similar to our results using *p*-CF_3BCNB as catalyst, they found that stirring speed had little effect on the reaction rate.

2. 30% NaOH. Major differences in the three steps required for a phase-transfer reaction (anion formation, extraction, and alkylation) occur when the aqueous base is diluted from 50% NaOH to 30% NaOH, as discussed below.

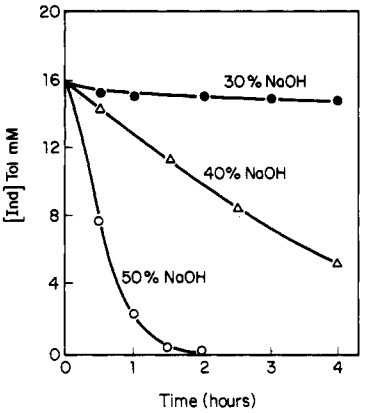

Figure 3. Rate profile for interfacial deprotonation of indanone 1 in toluene/aqueous NaOH mixtures at 20 °C and 1200 rpm.

Indanone Enolate Formation. Dependence of NaOH Concentration. In contrast to reactions in 50% NaOH/toluene, little enolate is formed in the reactions with 30% NaOH. Figure 3 shows how the rate of interfacial deprotonation of indanone is dependent on the concentration of NaOH. For these reactions, a saturated solution of indanone in toluene (2 mmol in 125 mL) was stirred at 20 °C and 1200 rpm with 25 mL of aqueous NaOH and with no catalyst present. Halving the concentration of NaOH from 19 (50 wt %) to 9.5 M (30 wt. %) essentially stops formation of solid enolate while the reaction with 13.5 M (40 wt %) proceeds about 5-fold slower than that at 19 M (50 wt %).

This unusual dependence of the rate on small changes in NaOH concentration is probably related to the amount of unsolvated HO^- present. The literature studies suggest that the solvation shell for HO^- is three molecules of water per HO^- ion.[16] At 19 M NaOH, there are only 2.2 mol of water per HO^- mol, so some ions will not be fully solvated and, therefore, strongly basic. At 9.5 M NaOH, there are 5 mol of water per mole of HO^-, providing full solvation of all ions.

An alternate way of viewing the situation is that rapid deprotonation still occurs at the interface, but the free water is more acidic than indanone so that reprotonation occurs; that is, with 30% NaOH an equilibrium exists that

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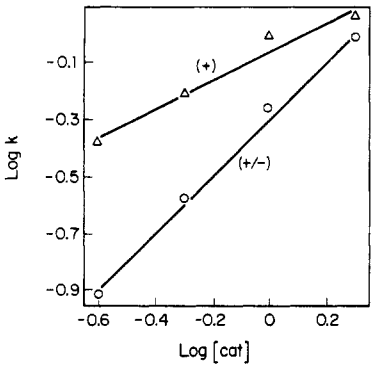


Figure 4. Plot of log k vs log [catalyst] for chiral phase-transfer alkylation with MeCl in 30% NaOH/toluene using p-CF_3BCNB as catalyst at 20 °C. The slope for (+)-methylation is 0.5 and for racemic methylation is 1.0.

disfavors the deprotonated indanone. In line with this is the observation that when the enolate is formed in 50% NaOH/toluene, it is completely reprotonated when enough water is added to the mixture to dilute the aqueous layer to 30% NaOH.

Chiral Methylation. A study of the variables affecting the methylation in 30% NaOH/toluene was carried out, and the results are shown in Table II. Since enolate is not formed as a solid layer in this media, all reagents were added at the beginning of the experiment.

a. Level of Indanone. The reactions are zero order in indanone. Most of the reactions in Table II were run at levels where much of the indanone was not soluble in the toluene (2 mmol is soluble in 125 mL), so the toluene layer stays saturated in indanone until the latter stages of the reaction. Experiment 7 of Table II was run where all the indanone was initially all in solution and this reaction was still zero order in indanone concentration. Also, the rate of reaction was no different from that in which 80% of the indanone initially charged was out of solution (entry 4). Therefore, the amount of indanone had no effect on the rate of reaction.

b. MeCl Concentration. A five-point plot of log k vs log [MeCl] has a slope of 0.94 ± 0.02. The slope of nearly 1 indicates that the methylation is the sole rate-determining step.

c. Stirring Rate. One run at 500 rpm gave the same rate of reaction as the run at 1200 rpm (entries 9 and 13).

d. Catalyst Concentration. The data in Table II show that the ee of the reaction decreases as the catalyst concentration increases. On the basis of these ee's, rates of formation of the (+)-isomer and racemic product can be calculated. The log of these rates are plotted vs log [catalyst] in Figure 4.

The figure clearly shows that formation of racemic material has a different mechanism from formation of (+)-product. The order of about 0.5 for catalyst for the chiral process is similar to that order found with 50% NaOH and is consistent with a mechanism in which a catalyst dimer must dissociate to the monomer to catalyze the reaction. The order of 1 for formation of racemic product would be consistent with the undissolved dimer or aggregate catalyzing a nonspecific methylation. However, this rationale does not explain why the catalyst dimer or aggregate does not catalyze a racemic reaction in 50% NaOH/toluene.

Other factors which may be important for the reactions in 30% NaOH are as follows: (1) The level of water in toluene is three to four molecules per molecule of catalyst, while in the 50% NaOH reactions there was about one molecule of water per catalyst molecule. Hydration of the catalyst hydroxyl group may lower its ability to form a tight ion pair with the enolate and reduce its tendency to form a dimer with itself. (2) Neutral indanone is present in the toluene layer; it could possibly form aggregates with catalyst or indanone enolate.

Table III. Enantioselectivity as a Function of Substituent Effects in *N*-Benzylcinchoninium Halide Catalysts 6

6, G	counterion	ee, %	6, G	counterion	ee, %
H	Cl	79	m-Cl	Br	89
H	Br	83	p-CF_3	Br	94
p-MeO	Cl	70	m-CF_3	Cl	87
p-Me	Cl	75	m-CF_3	Br	94
p-F	Cl	87	p-NO_2	Cl	30
p-Cl	Cl	88	3,4-Cl_2	Cl	94
m-Cl	Cl	91	3,4-Cl_2	Br	92

B. Parameters Controlling the Enantioselectivity of the Chiral Phase-Transfer Methylation. Parameters influencing the enantioselectivity of the reaction include catalyst structure, solvent, temperature, and methylating agent.

1. Dependence of Enantioselectivity on Catalyst. Substituted *N*-benzylcinchoninium catalysts **6** provided the best enantioselectivity in the phase-transfer methylation. Table III shows enantioselectivity as a function of substituents in the benzyl group of the catalyst. All the reactions were carried out by first stirring the indanone 1 (10 mmol) with 25 mL of 50% NaOH and 125 mL of toluene at 1200 rpm, 20 °C, in a 300-mL autoclave. Complete formation of the sodium indanone enolate as a finely dispersed solid phase occurred in 5 h, at which time 10 mol % catalyst and 70 mmol of MeCl were charged. Complete methylation required from 7 h with *N*-[*p*-(trifluoromethyl)benzyl]cinchoninium bromide (p-CF_3BCNB) to 36 h with *N*-benzylcinchoninium chloride (BCNC).

Inspection of Table III shows that electron-attracting groups in the benzyl moiety of the catalyst increase the ee of the reaction, with a Hammett plot being roughly linear and having a ρ value of 0.21 ± 0.02. The positive ρ value may be explained based on the ion pair hypothesis shown in Figure 1. The electron-withdrawing substituents make the benzyl group and the positive nitrogen center more electron-poor, increasing the interaction with the electron-rich enolate anion. This increased interaction stabilizes the ion pair orientation which leads to (+)-methylation over other orientations which lead to racemic or (−)-methylation.

Table III also shows that changing the catalyst counterion from Cl^- to Br^- gave only small differences in ee, with no trends observable.

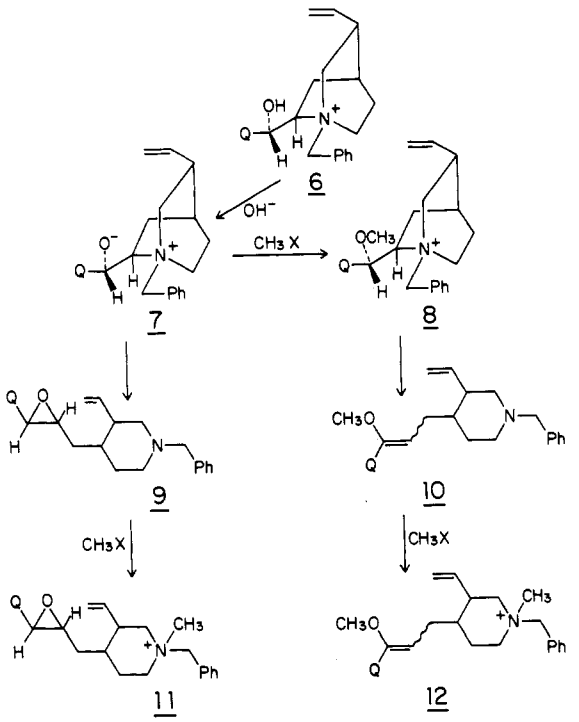
Hydrogenation of the vinyl group to an ethyl group in the catalyst caused no change in ee.

Several catalysts other than *N*-benzylcinchoninium halides were tried, and none proved as successful: *N*-benzylquinidinium, *N*-methylcinchoninium, and *N*-methyl-, *N*-benzyl-, and *N*-dodecylephedrinium bromides all gave ee's of <25%.

2. Effect of Solvent, Methylating Agent, and Temperature on Enantioselectivity. A limited survey of the effect of solvent, methylating agent, and temperature on enantioselectivity was done. The reactions were carried out as described in the previous section by allowing the enolate to preform before the methylating agent and *N*-[*p*-(trifluoromethyl)benzyl]cinchoninium bromide (p-CF_3BCNB) were added.

The highest ee's were obtained in the nonpolar, polarizable solvents toluene and tetralin (92% ee). The ee decreases to 83% in the more polar solvent, 1,2-dichlorobenzene, a trend previously observed by Wynberg.[18] This

Scheme II



trend supports the tight ion pair hypothesis for enantioselectivity (Figure 1), since more polar solvents would disrupt the tightly oriented ion pair required for (+)-methylation. In the nonpolar, nonpolarizable solvents (hexane, cyclohexane), poor solubility of the indanone 1 slows the reaction rates and lowers the ee.

Of the methylating agents, MeCl clearly gave the highest enantioselectivity (MeCl, 92%; MeBr, 68%; MeI, 36%; Me_2SO_4, 36%; Me_3PO_4, no reaction). Based on HPLC assay on a chiral Pirkle column, the ee remains constant throughout the reaction with MeCl and MeBr with catalyst levels above 10 mol %.

Over the temperature range of 0–40 °C, changes in ee were too small to be detected, remaining in the 92–94% range with MeCl as alkylating agent in toluene.

C. Catalyst Degradation. Dehmlow has shown that β-hydroxy ammonium catalysts react to form oxiranes under the basic conditions used for phase-transfer reactions. Under the conditions used for the chiral phase-transfer methylation (50% NaOH/toluene/MeCl/20 °C), the *N*-benzylcinchoninium halides form some oxirane **9** but primarily decompose by alkylation and elimination (Scheme II) to form the enol ether **10**. The oxirane **9**, methyl ether **8**, and enol ether **10** were independently prepared and characterized. Under the reaction conditions the methyl ether **8** is rapidly converted to the enol ether, confirming the degradation pathway shown in Scheme II.

When MeI is used as alkylating agent in the phase-transfer methylation, the oxirane **9** and the enol ether **10** are methylated to form the new quaternary ammonium salts **11** and **12**. Although chiral, these compounds only catalyze the racemic methylation of indanone **1** to form (±)-2-methylindanone **2**. This in part accounts for the low enantioselectivity in the chiral alkylation (ee 36%) when MeI is the alkylating agent. With MeBr, alkylation of tertiary amines **9** and **10** is slow relative to alkylation of indanone **1**. Methyl chloride does not alkylate **9** and **10** under the reaction conditions; therefore, when the catalyst has completely decomposed to **9** and **10**, the phase-transfer alkylation of indanone **1** stops. Consistent with the low reactivity of MeBr and MeCl toward **9** and **10** is the observation that the ee's remain constant throughout the reaction.

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Summary

This detailed study of the first efficient chiral PTC methylation has revealed a number of key and unexpected results. These include interfacial deprotonation of the indanone, presence of the catalysts as toluene-soluble dimers under the reaction conditions resulting in a reaction order of 0.5 for the catalysts, and an ordered response of the ee to the electron-withdrawing ability of the substituents present in the *N*-benzylcinchoninium ion catalysts. A second, and equally efficient, application of this technique to the Robinson annulation of indanones via alkylation was recently reported.[1b] Current studies relate to the application of polyether cocatalysts in chiral PTC alkylations,[19a] the structural nature of the catalyst dimers,[19b] and efforts to characterize the substrate–catalyst complexes.

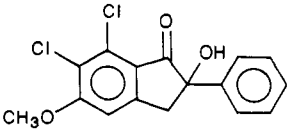
Experimental Section

A. Autoclave Reactions. The chiral methylations were carried out in an Autoclave Engineers 300-mL stirred autoclave controlled to ±0.5 °C with a high capacity Haake recirculating bath. The impeller of the stirrer was positioned at the organic/aqueous interface to provide optimal phase mixing. The stirring speed was periodically calibrated by tachometry. Samples were added to and removed from the autoclave via a dip tube extending to the bottom of the autoclave. Methyl chloride was metered into the autoclave by measuring the pressure drop of a 1-L holding vessel.

A typical experiment for a preformed enolate reaction is described below. Under a nitrogen atmosphere, a slurry of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone (3.07 g, 10 mmol) in 125 mL toluene was charged to the autoclave along with 50% aqueous NaOH (25 mL). The mixture was stirred for 3 h at 1200 rpm and 20 °C. HPLC assay at this point showed the indanone level in toluene to be 0.03 mg/mL. Then, a slurry of *N*-[*p*-(trifluoromethyl)benzyl]cinchoninium bromide (0.53 g, 1.0 mmol) in 2 mL of toluene and MeCl (3.5 g, 70 mmol) was added. Complete reaction occurred in 8 h.

B. Assays. 1. Progress of Reaction. The rates of reaction were monitored by HPLC assay of indanone **1** and the methylated product **2**. The samples were taken from the autoclave directly into a quench solution of AcOH in MeOH. The eluent for the HPLC assay on an Altex C18 column was 40% CH_3CN/60% water containing 0.05 M $Me_4N^+H_2PO_4^-$ at pH 2. The flow rate was 1.5 mL/min, and the column temperature was 70 °C. Under these conditions, the various catalysts eluted in 3–5 min, the starting indanone at 10 min, and the product methyl indanone at 15 min.

2. Toluene Layer. To assay the toluene layer, samples were taken into a septum-capped centrifuge tube under nitrogen and centrifuged to separate the emulsified aqueous and organic layers. Failure to keep the sample under a nitrogen atmosphere resulted in production of the oxidized indanone **13**. After centrifugation,



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the toluene layer was diluted in MeOH and quantitatively assayed by the HPLC system described above for catalyst, indanone 1, and methylindanone 2. The basicity of the toluene layer was determined by adding a weighed amount of the toluene layer to water and titrating with standardized acetic acid to a phenolphthalein end point.

C. Determination of Enantiomeric Excess. The (+/-) isomer ratio of the methylindanone 2 was determined by NMR from 10 mL of reaction sample worked up as follows: washed with 2 × 5 mL of 4 N HCl and then 5 mL of H_2O; concentrated and flushed with 2 × 10 mL of $CHCl_3$ to remove all toluene; 100 mg of residue plus 100 mg of tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium (III) in 0.5 mL of $CDCl_3$.

D. Catalyst Preparation. The catalysts were prepared from cinchonine (Fluka) and the appropriate benzyl halide in refluxing toluene or isopropyl alcohol. The bromides required 1-2 h reflux, while the chlorides required 24-48 h reflux for complete reaction.

Commercial cinchonine usually contains 15% of dihydrocinchonine, which forms the dihydro analogue of the catalyst during the reaction. The catalytic activity of this analog is very similar to that of the title catalyst. Therefore the presence of dihydrocinchonine does not present a problem.

E. Catalyst Dimer. 1. Preparation and Characterization of the Dimer. *p*-CF_3BCNB (76 mg) was added to toluene (10 mL) and 50% NaOH (8 mL) and stirred for 0.5 h until the solution was clear. HPLC of the toluene layer showed that all the catalyst had dissolved in toluene (14.3 mM). The toluene layer (2.16 mL) was added to 25 mL of water and titrated to a phenolphthalein end point with 1.11 mL of 13.8 mM HOAc, giving a basicity of 7.1 mM in the toluene layer. Similarly, catalyst (450 mg), benzene (20 mL), and 50% NaOH (10 mL) were stirred for 0.5 h. The benzene layer was separated, dried over 4A powdered sieves, filtered, concentrated to approximately 5 mL, and stored overnight. The resulting solid was filtered, washed with 1 mL of benzene, and dried to afford 213 mg of crystalline (microscopy) catalyst dimer, mp 120-125 °C dec. Anal. Calcd for $C_{54}H_{55}N_4BrF_6O_2$ (dimer): C, 65.8; H, 5.6; N, 5.7; Br^-, 8.1. Anal. Calcd for $C_{27}H_{28}N_2BrF_3O$ (monomer): C, 60.8; H, 5.3; N, 5.25; Br^-, 15.0. Found: C, 65.8; H, 6.0; N, 5.2; Br^-, 7.6.

BCNB (95 mg) was added to toluene (10 mL) and 50% NaOH (8 mL) and stirred at room temperature for 5 h. HPLC of the toluene layer showed all the catalyst had dissolved (20.4 mM). The toluene layer (0.64 mL) in 20 mL of water was titrated with 1.99 mL of 3.45 mM HOAc, giving a basicity in toluene of 10.7 mM. Similarly, catalyst (550 mg), benzene (20 mL), and 40% NaOH were stirred for 3 h. The benzene layer was separated, dried over 4A powdered sieves, filtered, and concentrated to 5 mL. After 2 h at 25 °C the resulting solid was filtered, washed with 1 mL of benzene, and dried at 25 °C (1 mm) to afford 74 mg of dimer. Anal. Calcd for $C_{52}H_{57}N_4BrO_2$ (dimer): C, 73.5; H, 6.7; N, 6.6; Br, 9.4. Anal. Calcd for $C_{26}H_{29}N_2BrO$ (monomer): C, 67.1; H, 6.0; N, 6.0; Br, 17.2. Anal. Calcd for $C_{52}H_{57}BrN_4O_2 \cdot {}^1/_2C_6H_6 \cdot 3H_2O$ (dimer benzene hemisolvate trihydrate: presence of $^1/_2$ mol of C_6H_6 confirmed by NMR; H_2O by Karl Fisher analysis): C, 70.0; H, 7.1; N, 5.9; Br, 8.5. Found: C, 70.3; H, 6.7; N, 6.2; Br, 8.3.

2. Methylation of Catalyst Dimer. *p*-CF_3BCNB (1.28 mmol) was stirred 1 h in 50 mL of toluene and 50 mL of 50% NaOH. The toluene layer (45 mL) was separated, MeI (2.8 g) was added, and the solution was aged 43 h. A precipitate was recovered (0.23 g), which showed, by ^1H NMR, 40% starting material (6) and 60% of the methyl ether 8. HPLC also gave a 60/40 ratio. Evaporation of the solution gave an additional 0.26 g, which showed, by LC, 68% catalyst 6 and 32% methyl ether 8. Overall, then, 87% of material was recovered; 55% was catalyst 6 and 45% was methyl ether 8, in line with the proposed dimeric species in toluene.

Registry No. 1, 60769-26-8; 2, 88494-66-0; 6 (G = H)·Cl^-, 69221-14-3; 6 (G = H)·Br^-, 85653-34-5; 6 (G = *p*-MeO)·Cl^-, 110097-80-8; 6 (G = *p*-Me)·Cl^-, 110097-81-9; 6 (G = *p*-F)·Cl^-, 110097-82-0; 6 (G = *p*-Cl)·Cl^-, 110097-83-1; 6 (G = *m*-Cl)·Cl^-, 110097-84-2; 6 (G = *m*-Cl)·Br^-, 110097-85-3; 6 (G = *p*-CF_3)·Br^-, 95088-20-3; 6 (G = *m*-CF_3)·Cl^-, 110097-86-4; 6 (G = *m*-CF_3)·Br^-, 110097-87-5; 6 (G = *p*-NO_2)·Cl^-, 110097-88-6; 6 (G = 3,4-Cl_2)·Cl^-, 110171-18-1; 6 (G = 3,4-Cl_2)·Br^-, 110171-19-2; 6 (G = *p*-CF_3) dimer, 110097-90-0; 6 (G = H) dimer, 110097-93-3; 8, 110097-91-1.

Reactions of *N*-Chlorobenzylalkylamines with Sodium Methoxide in Methanol. Steric Effects in Elimination Reactions[1]

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Reactions of *N*-chlorobenzylalkylamines in which the alkyl group is Me, Et, *i*-Pr, *t*-Bu, and *sec*-Bu with MeONa-MeOH have been investigated kinetically. The eliminations are quantitative and regiospecific, producing only benzylidenealkylamines. The reactions are first order in base and first order in substrate, and an E2 mechanism is evident. The relative rates of elimination at 25 °C are 1/0.5/0.3/0.2/0.01 for Me/Et/*i*-Pr/*sec*-Bu/*t*-Bu alkyl substituents, respectively. The results are attributed to repulsive interaction between the alkyl group and the base in the transition state. Hammett ρ and k_H/k_D values decreased, but the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values increased with bulkier alkyl substituents. Changes in the transition-state parameters with the substrate steric effect are interpreted with variation in structure of the imine-forming transition states.

Steric and electronic effects are among the most important factors that influence organic reaction pathways. It is well-known that the rate of S_N2 reaction decreases with steric hindrance in the substrate. In contrast, there is considerable controversy regarding the explanation of the effect of alkyl groups on reaction rates and orientation in elimination reactions.[2-6] From a series of reactions of $RCH_2C(X)Me_2$ and $RCH_2CH(X)Me$ (X = Br, I, OTs, S^+Me_2, SO_2CH_3, N^+Me_3), Brown concluded that the steric effects are the cause of the observed effects of alkyl groups on the rate and orientation in both E1 and E2 reactions.[2] On the other hand, Ingold proposed that the inductive and electromeric effects of the R groups dominate the E2 reactions of RCH_2CH_2X (X = S^+Me_2, N^+Me_3) compounds and the steric effect is insignificant except when the alkyl

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