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Photochemical Rearrangement of α-Chloro-Propiophenones to α-Arylpropanoic Acids: Studies on Chirality Transfer and Synthesis of (S)-(+)-Ibuprofen and (S)-(+)-Ketoprofen#,§

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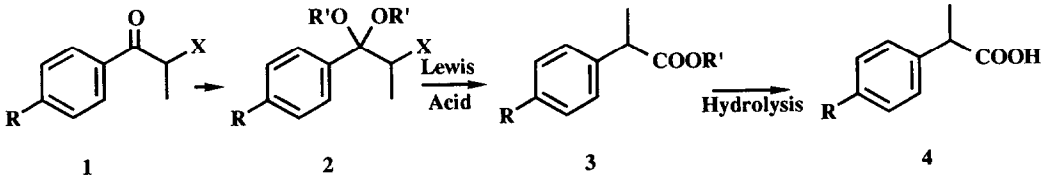
Abstract. *A new single-step efficient photochemical approach for α-arylpropanoic acids (4) from α-chloro-propiophenones (5) is described. It involves carbonyl triplet excited state directed 1,2-aryl migration of the aryl group which has been found to be highly dependent upon the nature of the aryl substituent. The mode of this rearrangement is probed by the study of the photobehaviour of a set of optically active α-chloro-propiophenones. The results suggest that the nature of the carbonyl triplets ($n,\pi^*/\pi,\pi^*$) plays an important role in the chirality transfer. This method finds application in the synthesis of optically active ibuprofen (4e) and ketoprofen (26), though in moderate optical yields.*

INTRODUCTION

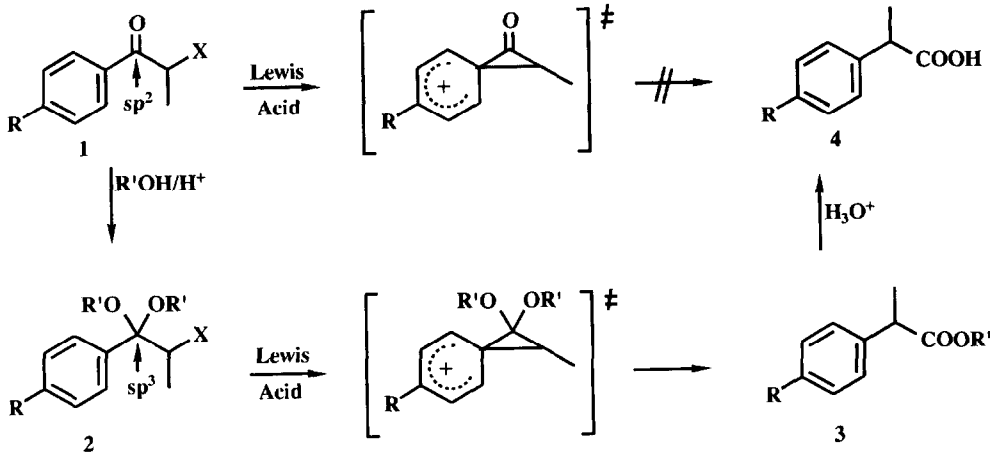
α-Arylpropanoic Acids have emerged as an important class of non-steroidal anti-inflammatory agents during the past two decades.[1,2] The numerous publications emanating from various research laboratories and the ever increasing number of patents in this area bear testimony to the frenetic synthetic efforts.[3,4] Despite the development of numerous methodologies for the synthesis of this class of drugs, Lewis acid-promoted rearrangement of acetals of α-substituted propiophenones via 1,2-aryl shift appears to be a method of general utility[5,6] (**scheme 1**).



1 2 3 4

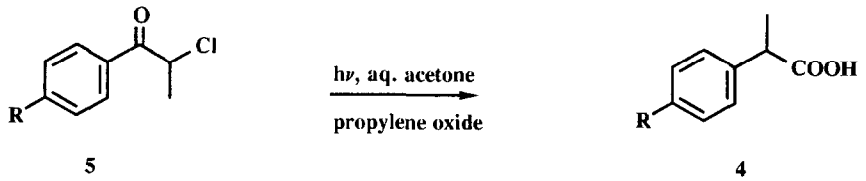
Scheme 1

As a special requirement it needs the masking of the carbonyl group (eg. acetal; $sp^2 \rightarrow sp^3$) to obviate the geometric constraint posed by the sp^2 carbonyl carbon in the attainment of the spirocyclopropyl-like transition state implicated in the transformation[7] (**scheme 2**). In fact, the earlier studies on unmasked propiophenones have shown that the reaction proceeds via the initial in situ derivatization of the carbonyl moiety.[8] In this context, we envisaged that an analogous hybridizational change in the excited carbonyl carbon[9] in **1** would promote the rearrangement and indeed found it to be the case. In our preliminary communication,[10] we reported a facile photochemicl transformation of *para*-substituted-α-chloro-propiophenones (**5**) into the corresponding α-arylpropanoic acids (**4**) (**scheme 3**).



Scheme 2

Encouraged by these initial findings, the photoreactions of α-bromo- and α-iodo-propiophenones were also investigated in order to assess the effect of these halogens on the photobehaviour. Interestingly, these ketones displayed entirely different photochemical transformations under similar conditions. In addition we have also briefly probed into the effect of *meta*-methyl and *meta*-benzyl groups on the photobehaviour and have shown for the first time that a key intermediate in the synthesis of another important anti-inflammatory agent, *viz.* ketoprofen,[11] can be made easily available by the photochemical transformation.



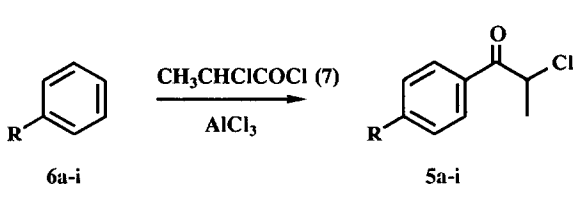
Scheme 3

Another important aspect addressed herein is the mode of 1,2-aryl migration in order to assess its potential in stereoselective synthesis of α-arylpropanoic acids, a topic of current interest.[12] In this context, it is pertinent to note that the 1,2-aryl migrations in the ground state reactions of this type of substrates have been thoroughly examined and found to be stereospecific in nature;[6,12] leading to a total inversion at the migration terminus, consistent with a S_N2 mechanism. This facet provided the impetus to develop methods for the asymmetric synthesis of α-arylpropanoic acids. We, therefore, synthesized a set of optically active α-chloro-propiophenones and investigated their photobehaviour with the objective of understanding the role of the excited state in chirality transfer to the products, i.e. α-arylpropanoic acids. The results thus obtained are unique in denoting that the chirality transfer is greatly influenced by the nature of the triplets involved $(n,\pi^*/\pi,\pi^*)$.

RESULTS AND DISCUSSION

Synthesis of α-chloro-, α-bromo- and α-iodo-propiophenones.

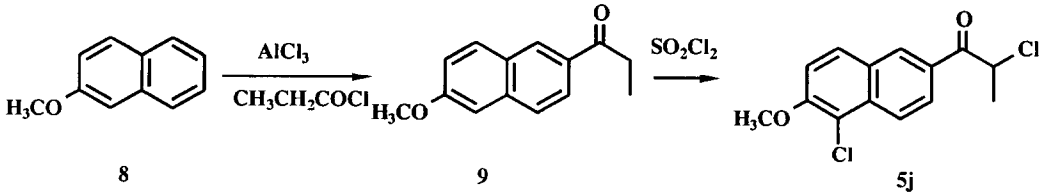
The starting α-chloro ketones **5a-i** were prepared by the Friedel-Crafts acylation of the corresponding aromatic hydrocarbons **6a-i** with α-chloropropionyl chloride[5,13] (**7**) (**scheme 4**). The chloro ketone **5j** was prepared by the Friedel Crafts reaction of 2-methoxynaphthalene (**8**) with propionyl chloride[14-15] followed by chlorination with sulfuryl chloride[16] (**scheme 5**). Grignard coupling of 2-bromo-6-methoxynaphthalene with **7** furnished[13] **5k**. The bromo ketone **10** was obtained[17] by treatment of the corresponding propiophenone with Br_2/CCl_4, while the iodo ketone **11** was prepared by the Finkelstein reaction of **5e** with NaI/acetone[18] (**figure 1**). These halo ketones displayed satisfactory spectral data (experimental). The UV data reveals that λ_{max} and extinction coefficients do not appear to be significantly affected by the substituents.



6a-i 5a-i

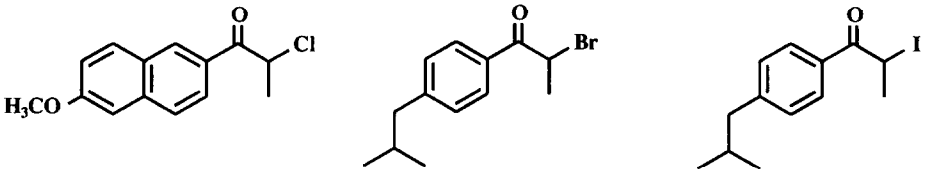
5	R	5	R
a	H	f	t-C_4H_9
b	CH_3	g	Cl
c	C_2H_5	h	Ph
d	n-C_3H_7	i	OCH_3
e	i-C_4H_9		

Scheme 4



8 9 5j

Scheme 5



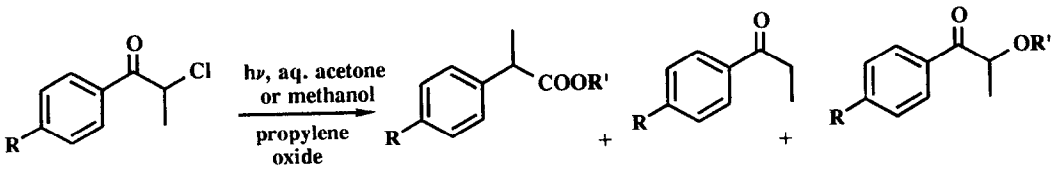
5k 10 11

Figure 1

Photolysis of chloro ketones 5a-k.

Irradiation of a solution of the chloro ketone (5 g) in 5% aq. acetone (acetone:water - 95:5, 250 mL) containing propylene oxide (5 mL) as an acid scavenger[19-21] was carried out employing a Hanovia 200 W medium pressure mercury vapour lamp (pyrex filter) almost till the disappearance of the starting material. The photoreaction was periodically monitored by GLC and ^1H NMR, especially at low conversions, to

detect and determine the nature of secondary photoreactions, if any. The neutral and acidic products from the photoreaction have been depicted in **scheme 6** and **Table I**. When the reactions were carried out in methanol, the corresponding methyl esters were obtained which were hydrolyzed to the acids. It was thought that irradiation of these substrates with a narrow band light source would lead to cleaner reaction products. However, similar results were obtained when the chloro ketones were irradiated at 300 nm in a Rayonet RPR 208 photoreactor.



5a-k

4a-k R' = H
12a-k R' = CH_3

13a-k

14a-k R' = H
15a-k R' = CH_3

Scheme 6

Table 1: Product distribution from the photolysis of α-chloro ketones[a] 5a-k

Entry	Substrate		Products					
			In aq. acetone			*In methanol*		
	5	R	4	13	14	4[b]	13	15
1	a	H	58	25	-	39[c]	30	-
2	b	CH_3	84	5	-	76	8	-
3	c	C_2H_5	82	6	-	74	9	-
4	d	*n*-C_3H_7	84	5	-	77	9	-
5	e	*i*-C_4H_9	74	10	-	65	15	-
6	f	*t*-C_4H_9	78	7	-	69	8	-
7	g	Cl	45	25	20	30	24	30
8	h	Ph	40	25	35	18	26	35
9	i	OCH_3	32	10	50	80	12	70
10	j		28	11	63	6	8	82
11	k		30	10	60	5	9	80

[a]Control experiments in the absence of light were carried out for all substrates. [b]After alkaline hydrolysis of the corresponding methyl ester **12**. [c]see ref 22.

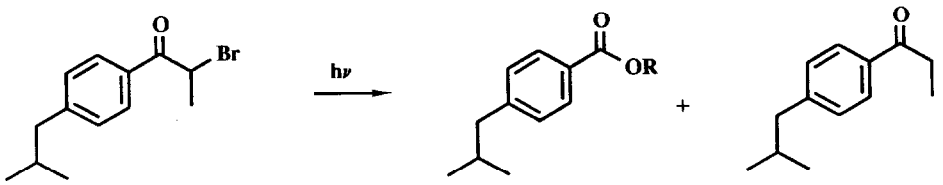
The results clearly reveal the occurrence of two distinct primary photoprocesses, *viz.* the 1,2-aryl migration leading to the acids **4** and the reduction of the C-Cl bond affording the corresponding propiophenones **13**. At the outset, a remarkable substituent effect on the propensity for 1,2-aryl migration to produce α-arylpropanoic acids/esters is noticed. The alkyl substituents favour the 1,2-aryl shift while in the methoxy substituted ketones **5i-k**, the solvolysis of C-Cl bond becomes the dominant pathway leading to

α-hydroxy/alkoxy ketones. However, the results from *para*-chloro- and *para*-phenyl-α-chloro-propiophenones (i.e. **5g** and **5h**) stand in between the two extremes. This significant effect of the substituents on the photoefficiency has been rationalized in terms of the different excited states involved (vide infra). It may be noted that the chloro ketone **5e** has led to a significant yield of the rearrangement product **4e** which is a well-known anti-inflammatory drug, *viz.* Ibuprofen. Thus, this photoreaction constitutes an efficient single step route to this drug.

The two primary processes appear to be solvent dependent, as can be evidenced from the results from the photolysis of **5a-k** in methanol. The alkyl substituted ketones underwent the 1,2-aryl rearrangement reaction to a less extent compared to that observed in aq. acetone; there was also a commensurate enhancement in the quantum of reduction products. Photosolvolysis of the C-Cl bond was the predominant process (entries 9-11) and it was at the expense of the rearrangement products. In this context, we assume that the high polarity of aq. acetone (95:5) is of importance rather than the triplet sensitization by acetone since, most of the known photochemistry of aryl alkyl ketones arises from the triplet excited state due to the well-known efficient intersystem crossing.[23] Thus, the products arising from the photolysis of these halo ketones could be deduced to arise from the triplet excited state. Nonetheless, this conjecture was confirmed when the irradiation of these ketones in the presence of piperylene led to no observable products.

Photolysis of α-bromo-4-(2-methylpropyl)propiophenone (10).

We next turned our attention to α-bromo and α-iodo-propiophenones in order to compare their photobehaviour with their α-chloro analogues. Interestingly, the 1,2-aryl rearrangement observed in the chloro ketones was conspicuously absent here. The bromo ketone **10** on photolysis in aq. acetone furnished an altogether different type of products, comprising the benzoic acid **16** (55%) and the reduction product **13e** (32%) (**scheme 7**). A similar result was noticed in the irradiation of **10** in methanol. The benzoate **17** and the reduction product **13e** were obtained as the principal photoproducts. The formation of benzoate finds precedence in the photochemistry of trichloroacetophenone and tribromoacetophenone.[24,25] The authors rationalized the formation of such products as arising from the nucleophilic attack of solvent (*eg.*CH_3OH) on the excited carbonyl carbon.

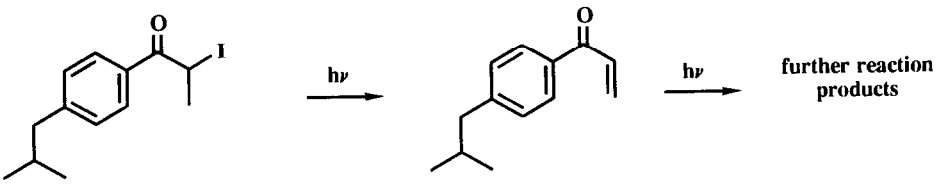


10 **16 R = H** **13e**
17 R = CH_3

Scheme 7

Photolysis of α-Iodo-4(2-methylpropyl)propiophenone (11)

The photobehaviour of **11** was rather interesting and showed marked difference compared to the corresponding α-chloro and α-bromo propiophenones. The formation of enone **18** as the only primary photoproduct (**scheme 8**) clearly reflects the propensity for the ionic cleavage of C-I bond, a typical feature of alkyl iodides.[26] However, the complete absence of solvolysis as well as the 1,2-aryl migration products is noteworthy.



11 18

Scheme 8

Synthesis of Optically Active α-arylpropanoic acids

As pointed out earlier, a synthetically useful methodology for an important class of α-arylpropanoic acids has emerged from this study. The single step method, particularly for ibuprofen, offers certain advantages over the existing ground state rearrangement reactions; it obviates the need for protection of the carbonyl group and hydrolysis step as well. It can be easily scaled up even up to 200 g level. Moreover, a series of experiments conducted in sunlight demonstrate that ibuprofen is readily obtained in a clean and convenient way in good yields (see experimental), obviating the use of photolamps.

Next, we became interested in learning about the mode of 1,2-aryl migration arising especially from the excited state of the carbonyl group when the corresponding ground state Lewis acid catalyzed transformation has received considerable attention from both mechanistic and preparative aspects.[12] In this context, we have examined the photobehaviour of some optically active α-chloro-propiophenones and the results obtained are interesting from a number of viewpoints. It appears that this study of the photobehaviour of optically active chloroketones is the first of its kind.

The optically active α-chloro ketones **5a,b**, **5e** and **5i** were obtained by the Friedel-Crafts acylation of the corresponding aromatic substrate with (*S*)-(+)-α-chloropropionyl chloride.[13,27] The chloro ketone **5k**, on the other hand, was prepared by the known[13] Grignard coupling of 2-bromo-6-methoxynaphthalene with (S)-(+)-**7**. The optical purity of these ketones was determined by comparison of their specific rotations with those reported [13,27] and also by HPLC on chiral columns. Irradiation of these optically active substrates was performed as described earlier using the Rayonet RPR 208 photoreactor fitted with 300 nm lamps. The results from these photolyses have been summarized in **Table 2**.

Table 2: Photolysis of optically active α-chloro-ketones (S)-(+)-5

Entry	Substrate	Products		
		(S)-(+)-4[a]		(±)-14
		Yield (%)	ee[b] (%)	Yield (%)
1	**5a**	55	20	-
2	**5b**	78	36	-
3	**5e**	70	40	-
4	**5i**	30	5	50
5	**5k**	28	6	60

[a]Average of three runs. [b]ee determined by ^{1}H NMR of corresponding methyl esters obtained by treatment of **4** with diazomethane.

The products essentially arose from the previously described photoprocesses of 1,2-aryl migration, solvolysis and reduction of the C-Cl bond. It should be mentioned that the type and extent of products remained the same as that obtained from the racemic substrates and therefore the table restricts itself to the magnitude of chirality transfer realized. The optical purity of the corresponding methyl esters obtained by treatment of the acids with diazomethane was determined by ^{1}H NMR employing the chiral shift reagent Eu(hfc)$_3$ as well as by a direct comparison of their specific rotations with those reported. Racemization of the products due to the possibility of internal return in chloro ketones **5** after the initial cleavage of the C-Cl bond was ruled out by determining their enantiomeric purity at different conversions (10-80%) by using HPLC with chiral columns. Similarly, the non-racemization of the acids **4** under the photolysis conditions was also confirmed by their separate irradiation, wherein their specific rotations remained unaltered.

The salient features of the results are:-

1. a remarkable substituent effect on optical yield is noticed; optical induction is maximum (40%) with *para*-alkyl groups while it gets considerably reduced with *para*-methoxy substituents (5%). In the case of the parent ketone (**5a**) the optical induction lies in between these two extreme cases.
2. A similar trend in the yields of rearrangement products i.e. α-arylpropanoic acids due to these groups is noteworthy.
3. The formation of (S)-(+)-**4** from (S)-(+)-**5** suggests that the 1,2-aryl migration proceeds with the inversion of configuration at the carbon bearing chlorine atom. It also suggests that the excited state induced aryl migration is not completely stereospecific, while all such thermal 1,2-migrations producing α-arylpropanoic acids are known to be completely stereospecific.[12]
4. Interestingly, the solvolysis products are racemic.
5. Therefore, these results do suggest that the quantum of optical induction is associated with the population of particular type of triplets in the lower energy states.

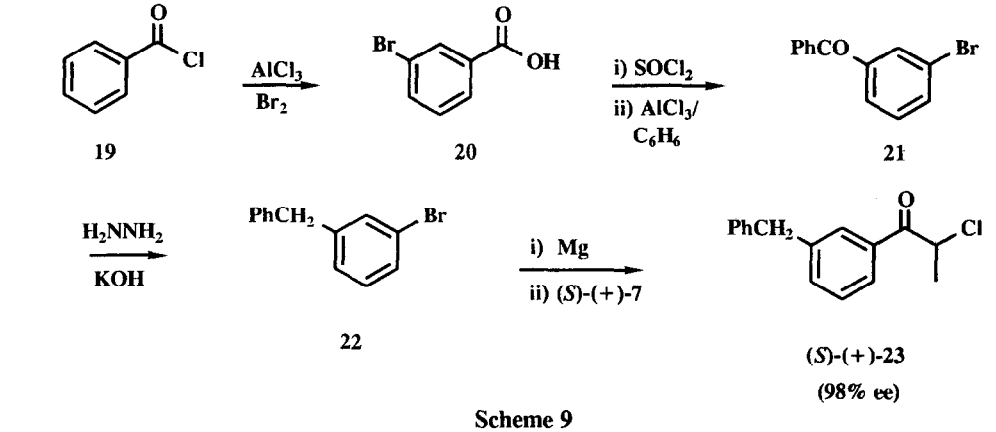
Pertinently, the rationalization of these results leading to the asymmetric induction in terms of Wagner's proposition[23] involving an α-ketocarbonium ion will be obviously inadequate. A preliminary plausible rationale, we believe, may be developed in terms of the known contribution of lower n,π^* and π,π^* triplets of alkyl aryl ketones, which are reported to be solvent and substituent sensitive.[23] The switch in photobehaviour may be attributed to the ionic character[28] of π,π^* triplets wherein the carbonyl carbon mostly remains in the sp^2 instead of sp^3 hybridization by virtue of resonance stabilization with the aryl group.[29] In this class of ketones, the phenomenon of "state switching" of these triplets due to the substituents is well recognized[28]. Viewed in this perspective, the higher optical induction (40%) obtained in *para*-alkyl-α-chloro-propiophenones **5b** and **5e** appears to be associated with the larger population of n,π^* states, while the involvement of essentially π,π^* triplets, being ionic in nature seem to cause considerable reduction in optical yield (6%) of α-arylpropanoic acid **5i** derived from *para*-methoxy-α-chloro-propiophenone. In other words, it denotes a unique influence of the nature of the excited triplets in chirality transfer in the phtobehaviour of these chiral alkyl aryl ketones.[30]

In this context, in principle, one also needs to note the formation of two diastereomeric triplet states upon excitation of the carbonyl chromophore (i.e sp^2 to sp^3) and their likely influence on the optical yield. As far as we are aware, practically no information seems to be available on this topic except one recent report. Inoue *et al.*[31] have recently observed a dramatic temperature effect on optical yields in their studies on photosensitized enantiodifferentiating *cis-trans* isomerization of cyclooctene. They postulate two diastereomeric excited states for the excited complex, the population of which varies with the temperature, which in turn seems to be responsible to give either *cis* or *trans*-cyclooctenes.

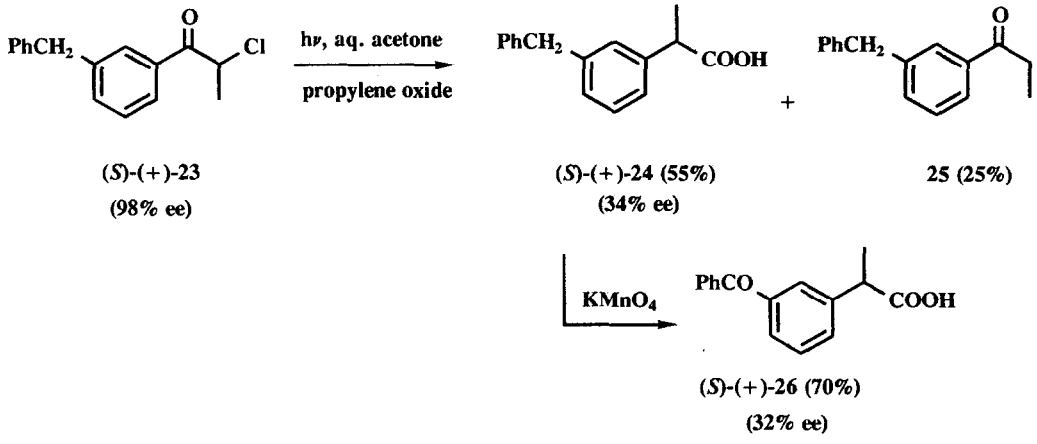
Reference may be made to another interesting paper by Meijer and Wynberg.[32] In their quest to synthesize a compound in which the optical activity is solely due to the presence of an excited state, they synthesized the optically active mono 1,2-dioxetane of 2,4-adamantanedione. On heating, the dioxetane was expected to decompose to the diketone in which selectively one carbonyl (originally masked as the 1,2-dioxetane) would be in the excited state. Due to the different stereoelectronic properties of the excited carbonyl group (out-of-plane geometry) as compared to its ground state, this diketone, which would be *meso* in the ground state, becomes chiral in the excited state. Such reasoning is very much in agreement with our basic assumption of an excited carbonyl carbon assuming an sp^3 configuration.

Synthesis of (S)-(+)-Ketoprofen (26)

After establishing the suitability of this photoreaction for the asymmetric synthesis of the well-known anti-inflammatory agents like ibuprofen and naproxen, it was prompting to check the efficacy of this method in the synthesis of another optically active agent of this class, *viz.* ketoprofen (**26**). Thus, photoreaction of (*S*)-(+)-*meta*-benzyl-α-chloro-propiophenone (**23**) was probed. (+)-**23** was prepared by the Grignard coupling of 3-benzylbromobenzene (**22**) with (S)-(+)-**7** (**scheme 9**). As the benzylic oxidation in the expected product could be easily achieved[33] it would lead to the required product **26**.



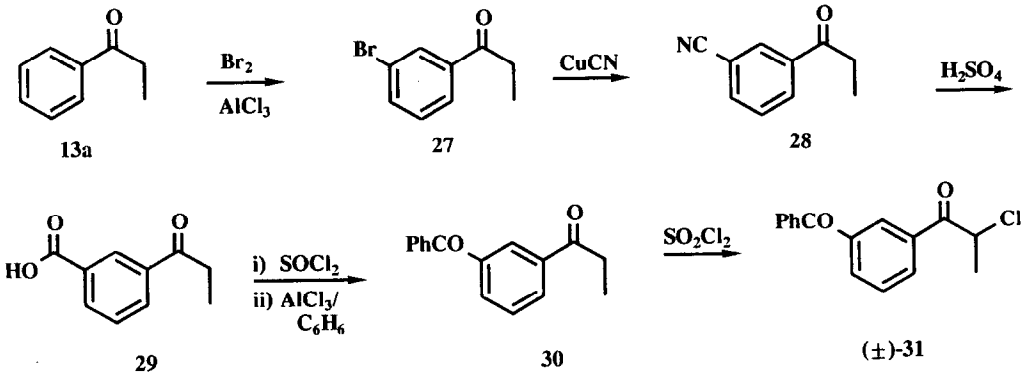
Scheme 9



Scheme 10

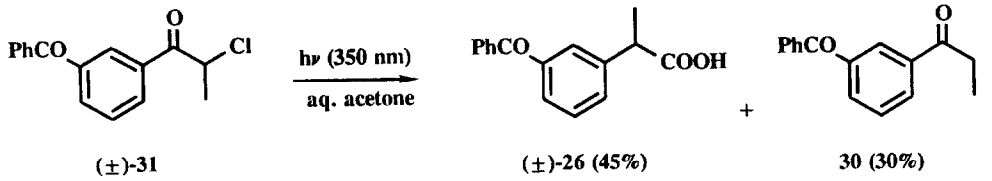
Irradiation of (*S*)-(+)-**23** under conditions described previously led to (*S*)-(+)-**24** in a good chemical yield although the asymmetric induction was just moderate (**scheme 10**). The photolysis afforded the reduction product to a small extent in addition to some unidentifiable ones, probably arising from α-cleavage reactions. The photoproduct **24** could be easily oxidized with $KMnO_4$ to ketoprofen **26** without any significant loss of enantiomeric purity.

It was interesting to check whether the direct transformation of *meta*-benzoyl-α-chloro-propiophenone **31** could lead to ketoprofen **26**, obviating the subsequent oxidation. Surprisingly, such a photoreaction resulted in a comparable yield (**schemes 11** and **12**).



Scheme 11

Such a comparable efficiency from two different substrates such as *meta*-benzyl- and *meta*-benzoyl-α-chloro-propiophenones is rather surprising. However, it may be noted that the photoreaction of the optically active benzoyl derivative could not be studied owing to the difficulty in obtaining the substrate. In this context, reaction of the optically active benzyl derivative holds promise for the synthesis of optically active ketoprofen.



Scheme 12

In summary, the present methodology represents a first meaningful example of aryl alkyl ketone photochemistry leading to therapeutically important compounds exemplified by ibuprofen and ketoprofen. We believe, the contrasting photobehaviour displayed by the *para*-alkyl and the *para*-methoxy substituents in α-chloro-propiophenones could serve as an alternative probe to study the different excited states of aryl alkyl ketones. An interesting phenomenon of chirality transfer associated with the nature of the excited states of aryl alkyl ketone photochemistry is noteworthy.[30]

EXPERIMENTAL

Synthesis of α-chloro-propiophenones 5a-k:

α-Chloro-4-(2-methylpropyl)propiophenone (5e). Typical Procedure: Isobutyl benzene (**6e**, 13.4 g, 0.10 mol) and 1,2-dichloroethane (75 mL) were placed in a three-necked 250 mL flask equipped with a mechanical stirrer (with an oil seal), a dropping funnel and an air condenser attached to a HCl gas scrubber. The flask was cooled in an ice-bath and powdered $AlCl_3$ (26.7 g, 0.20 mol) was added in small portions over a period of 10 min. Maintaining the temperature below 10 °C, α-chloropropionyl chloride (15.3 g, 0.12 mol) was added over a period of 1 h to the reddish brown solution. Stirring was continued at this temperature for 2 h and then the reaction mixture was gradually allowed to rise to room temperature. After stirring for 6 h at room temperature, the reaction mixture was poured onto 200 g crushed ice/water containing 5 mL HCl. Usual workup and concentration by rotary evaporation followed by distillation of the residue under reduced pressure gave **5e** as a pale yellow oil which solidified on keeping. **bp** 145-150 °C/2-3 mm, 19.1 g, 85%. **mp**: 52-53 °C [lit.[7] 53-54 °C] **IR** (nujol): 2950, 1695, 1610, 1425, 1355, 1265, 1175, 855 cm^{-1}. **^{1}H NMR**: 0.89 (d, J = 7 Hz, 6 H), 1.74 (d, J = 7 Hz, 3 H), 1.6-2.1 (m, 1 H), 2.52 (d, J = 7 Hz, 2 H), 5.15 (q, J = 7 Hz, 1 H), 7.23 (d, J = 9 Hz, 2 H), 7.90 (d, J = 9 Hz, 2 H). **MS**: m/z 226 (M^+, 3%), 224 (M^+, 9), 209 (8), 195 (2), 181 (11), 161 (100), 133 (10), 118 (19), 105 (7), 91 (12). **UV** (hexane): λ_{max} 322, ε 138.

α-Chloro-propiophenone 5a. **bp**: 90-95 °C/2 mm. **IR** (neat): 2960, 1700, 1605, 1465, 1360, 1270, 1215, 970, 820, 740, 720 cm^{-1}. **^{1}H NMR**: 1.75 (d, J = 7.5 Hz, 3 H), 5.23 (q, J = 7.5 Hz, 1 H), 7.2-7.5 (m, 2 H), 7.7-8.0 (m, 2 H). **MS**: m/z 170 (M^+, 2%), 168 (M^+, 6%), 134 (5), 105 (100), 77 (82). **UV** (hexane): λ_{max} 325, ε 75.

α-Chloro-4-methylpropiophenone 5b: **bp**: 87-89°C/2-3 mm **IR** (neat): 1690, 1615, 1455, 1385, 1275, 1195, 970, 855, 775 cm^{1-} **^{1}H NMR**: 1.67 (d, J = 7 Hz, 3 H), 2.38 (s, 3 H), 5.05 (q, J = 7 Hz, 1 H), 7.1 (d, J = 8 Hz, 2 H)), 7.73 (d, J = 8 Hz, 2 H). **MS**: m/z 184 (M^+, 10%), 182 (31), 119 (100), 91 (68), 77 (5). **UV**: λ_{max} 324, ε 86.

α-Chloro-4-ethylpropiophenone 5c: **bp** 135-8 °C/7-8mm. **IR:** 1695 cm^{-1}. ^{1}H NMR: 1.23 (t, J = 7 Hz, 3 H), 1.65 (d, J = 7 Hz, 3 H), 2.63 (q, J = 7 Hz, 2 H), 5.08 (q, J = 7 Hz, 1 H), 7.15 (d, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 2 H). **MS**: m/z 198 (M^+, 12), 196 (M^+, 36), 162 (8), 105 (40), 91 (100), 79 (45). **UV**: λ_{max} 324, ε 88.

α-Chloro-4-propylpropiophenone 5d: **bp** 123-5 °C/3-4 mm. **IR:** 1695 cm^{-1}. **^{1}H NMR:** 0.92 (t, J = 7.5 Hz, 3 H), 1.45-1.85 (m, 2 H), 1.72 (s, J = 7 Hz, 3 H), 2.63 (t, J = 7.5 Hz, 2 H), 5.15 (q, J = 7 Hz, 1 H), 7.16 (d, J = 8 Hz, 2 H), 7.83 (d, J = 8 Hz, 2 H). **MS**:, m/z 212 (M^+, 15%), 210 (M^+, 44), 176 (40), 119 (80), 105 (100), 91 (22).

α-Chloro-4-t-butylpropiophenone 5f: **bp**: 130-2 °C/2-3 mm. **IR**: 1700 cm^{-1}. **^{1}H NMR**: 1.33 (s, 9 H), 1.67 (d, J = 7 Hz, 3 H), 5.08 (q, J = 7 Hz, 1 H), 7.33 ((d, J = 9 Hz, 2 H), 7.83 (d, J = 9 Hz, 2 H). **MS**: m/z 224 (M^+, < 1%), 147 (100), 129 (9), 119 (23), 105 (15), 91 (48), 77 (21). **UV**: λ_{max} 321, ε 102.

α,4-Dichloro-propiophenone 5g: **mp**: 60-61 °C **IR** (nujol): 1695, 1605, 1460, 1270, 1110, 970, 865 and 795 cm^{-1}. **^{1}H NMR**: 1.75 (d, J = 7.5 Hz, 3 H), 5.1 (q, J = 7.5 Hz, 1 H), 7.3 (d, J = 8 Hz, 2 H), 7.8 (d, J = 8 Hz, 2 H). **MS**: m/z 204 (M^+, 3%), 202 (M^+, 6), 141 (42), 139 (100), 111 (55), 103 (9), 85 (5). **UV** λ_{max} 325, ε 114.

α-Chloro-4-phenylpropiophenone 5h: **mp**: 132-5 °C (ether: petroleum ether). **IR** (nujol): 1690, 1605, 1455, 1405, 1380, 1345, 1255, 1260, 1070, 1010, 965, 860 and 755 cm^{-1}. **^{1}H NMR**: 1.74 (d, J = 7.5 Hz, 3 H), 5.2 (q, J = 7.5 Hz, 1 H), 7.2-7.8 (m, 7 H), 8.05 (d, J = 9 Hz, 2 H). **MS**: m/z 246 (M^+, 2%), 244 (M^+, 6), 181 (100), 152 (54), 127 (6), 115 (3), 102 (4), 91 (5), 76 (12). **UV**: λ_{max} 328, ε 143.

α-Chloro-4-methoxypropiophenone 5i: **bp**: 100-105 °C/2-3 mm, **IR** (neat): 2980, 2940, 1695, 1605, 1545, 1445, 1355, 1305, 1265, 1170, 1060, 850 and 770 cm^{-1}. ^{1}H NMR: 1.65 (d, J = 7 Hz, 3 H), 3.8 (s, 3 H), 5.02 (q, J = 7 Hz, 1 H), 6.8 (d, J = 9 Hz, 2 H), 7.83 (d, J = 9 Hz, 2 H). **MS**: m/z 200 (M^+, 2%), 198 (M^+,6), 135 (100), 120 (3), 107 (11), 92 (15), 77 (19). **UV**: λ_{max} 326, ε 71.

α-Chloro-1-(5-chloro-6-methoxy-2-naphthyl)propanone 5j was prepared in two steps from **8**.

a. Nitrobenzene (65 mL) was placed in a 250 mL three-necked flask equipped with a dropping funnel, mechani-

cal stirrer with an oil seal and reflux condenser connected to a gas scrubber. The flask was cooled in an ice-bath and powdered $AlCl_3$ (15.4 gm, 0.115 mol) was added over a period of 10 min. Powdered 2-methoxynaphthalene (15.8 g, 0.100 mol) was then introduced in about 20 min. Maintaining an internal temperature of 15-25 °C, propionyl chloride (10.2 g, 0.110 mol) was added during 1 h.Stirring was continued at this temperature for 2 h and then at room temperature for 8 h. The reaction mixture was then poured onto 200 g ice/water containing 10 mL HCl. The organic layer was separated and nitrobenzene was steam distilled. The residue was extracted in EDC and the extract dried and concentrated. Methanol (150 mL) was added to the residue and the mixture was boiled, treated with charcoal and rapidly filtered hot. On cooling, the product, 1-(6-methoxy-2-naphthyl)propanone (**9**) crystallized out which was collected. **mp** 108-110 °C, [lit.[34] **mp** 109-110 °C] 17.1 g, 80%. **IR** (nujol): 1690, 1630, 1475, 1385, 1205, 1030, 820 cm^{-1} **^{1}H NMR** (90 M Hz): 1.24 (d, J = 7 Hz, 3 H), 3.07 (q, J = 7 Hz, 2 H), 3.87 (s, 3 H), 7.2-8.4 (m, 6 H).

b. A solution of **9** (10.7 g, 0.050 mol) and SO_2Cl_2 (17.0 g, 0.125 mol) in CCl_4 (100 mL) was stirred at 40-50 °C for 12 h. Excess SO_2Cl_2 and CCl_4 were distilled out and the residue was crystallized from CH_3OH (50 mL) to give the product **5j**, 12.1 g, 85%, **mp** 124-126 °C. **IR** (nujol): 1680, 1620, 1470, 1380, 1260, 1075, 810 cm^{-1}. **^{1}H NMR**: 1.79 (d, J = 7 Hz, 3 H), 4.04 (s, 3 H), 5.3 (q, J = 7 Hz, 1 H), 7.2-8.5 (m, 5 H). **MS**: m/z 284 (M^+, 9%), 282 (M^+, 14%), 221 (44), 219 (100), 204 (5), 191 (13), 176 (39), 161 (12), 148 (49), 141 (7), 126 (19), 113 (49), 99 (5), 87 (10), 75 (11).

α-Chloro-1-(6-methoxy-2-naphthyl)propanone 5k. In a 250 mL three necked flask equipped with a N_2 inlet and a reflux condenser were placed Mg turnings (2.40 g, 100 mmol) and dry THF (100 mL). 6-Bromo-2-methoxynaphthalene (19.00 g, 80 mmol) was added in small portions over a period of 20 min. The reaction mixture was gradually warmed up and was refluxed for 10 min. after the addition of 6-bromo-2-methoxynaphthalene was complete. In another three-necked 250 mL flask equipped with a N_2 inlet and a septum were placed α-chloropropionyl chloride (12.75 g, 100 mmol) and dry THF (70 mL). The reaction mixture was cooled to - 40 °C and the Grignard reagent, as prepared above, was transferred by a Cannula, under N_2 pressure, during 30 min. The mixture was stirred at this temperature for 4 h and then hydrolyzed with 5% ice-cold HCl (50 mL). The mixture was diluted with water and extracted with CH_2Cl_2 (2 x 100 mL). Usual workup and concentration yielded a solid which was crystallized from CH_3OH. **mp** 123-124 °C, 12.50 g, 63%. **IR** (nujol): 1690,1620, 1490, 1395, 1275, 1175, 1035, 865, 755 cm^{-1}. **^{1}H NMR**: 1.74 (d, J = 7 Hz, 3 H), 3.86 (s, 3 H), 5.3 (q, J = 7 Hz, 1 H), 7.0-8.50 (m, 6 H). **MS**: m/z 284 (M^+, 9%), 282 (14), 221 (44), 219 (100), 214 (5), 191 (13), 176 (39), 161 (12), 148 (49), 141 (7), 126 (19), 113 (49), 99 (5), 87 (10), 75 (11).

Synthesis of α-bromo and α-iodo-4-(2-methylpropyl)propiophenones

α-Bromo-4-(2-methyl-propyl)propiophenone[17] 10. Bromine (16.1 g, 102 mmol) in CCl_4 (20 mL) was added dropwise over a period of 1 h to a solution of **13e** in CCl_4 (80 mL). After stirring for another 1 h, the reaction mixture was poured over crushed ice. Usual workup afforded a pale yellow oil which was distilled under reduced pressure to yield **10** which solidified on keeping, 26 g, (85%). **mp** (CH_3OH) 65-6 °C. **IR:** 2955, 1690, 1610, 1420, 1265, 1255, 1160, 955, 865 cm^{-1}. **^{1}H NMR**: 0.90 (d, J = 7 Hz, 6 H), 1.6-2.1 (m, 1 H),1.82 (d, J = 7 Hz, 3 H), 2.50 (d, J = 7 Hz, 2 H), 5.13 (q, J = 7 Hz, 1 H), 7.1 (d, J = 8 Hz, 2 H), 7.8 (d, J = 8 Hz, 2 H). **MS**:, m/z 270 (M^+, 3), 268 (M^+, 4), 161 (100), 147 (8), 131 (7), 118 (18), 105 (7), 91 (21), 77 (8).

α-Iodo-4-(2-methyl-propyl)propiophenone[18] 11. A solution of **5e** (12.25 g, 100 mmol) in acetone (50 mL) was added to a suspension of NaI (30 g, 200 mmol) in acetone (100 mL) over a period of 30 min. Stirring was continued for 12 h after which the reaction mixture was poured in water. Usual workup and crystallization from CH_3OH yielded **11** as a pale yellow solid, 14 g, (86%). **mp** (CH_3OH) 55 °C. **IR:** 1690, 1615, 1450, 1345, 1235, 1090, 995, 945, 855, 765 cm^{-1}. **^{1}H NMR**: 0.90 (d, J = 7 Hz, 6 H), 1.6-2.1 (m, 1 H), 1.98 (d, J = 7 Hz, 3 H), 2.51 (d, J = 7 Hz, 2 H), 5.35 (q, J = 7 Hz, 1 H), 7.12 (d, J = 8 Hz, 2 H), 7.82 (d, J = 8 Hz, 2 H). **MS**:, m/z 316 ((M^+,8), 161 (100), 147 (5), 128 (12), 117 (21), 105 (7), 91 (8).

Photolysis of chloro ketones 5a-k.

1. ***In methanol. Typical Procedure:*** A solution of **5e** (5.0 g) in CH_3OH (250 mL) was placed in an immersion-well type photoreactor equipped with a Hanovia 200 W medium pressure mercury vapour lamp. Nitrogen was bubbled for 20 minutes and then propylene oxide (5 mL) was added. Photolysis was carried out and the reaction was monitored by GLC and ^1H NMR. The reaction mixture was maintained neutral to litmus by adding propylene oxide (1 mL) at 30 min intervals. When the starting material almost disappeared (3 h), the reaction mixture was concentrated and distilled under reduced pressure (4 g).

The total distilled product was refluxed with NaOH (2 g) in CH_3OH (30 mL) for 2 h. Excess CH_3OH was distilled off and the residue dissolved in water (100 mL). The aqueous layer was washed with ether and the ether layer kept aside for further workup. The alkaline extract was acidified with 10% H_2SO_4 and the oil that separated was extracted in ether. Concentration yielded an off-white solid which was identified as **4e** (3.4 g, 74%). The ether layer which was kept aside was concentrated and subjected to column chromatography over silica gel using 2% EtOAc in pet-ether for elution to yield a product which was identified as **13e**.

2. ***In aq. acetone. Typical Procedure:*** Photolysis of **5e** was carried out exactly as described above, the only difference being the change in solvent. Instead of CH_3OH, aq. acetone (acetone:water-95:5) was used. After the reaction was over (TLC and ^1H NMR), the reaction mixture was concentrated and the residue extracted in ether (100 mL). The ether layer was extracted with 5% $NaHCO_3$ and the alkali layer acidified with dil. H_2SO_4. The ether layer was kept aside for further workup. The oil that separated on acidification of the alkali layer was extracted in ether to afford on usual workup a solid residue. Crystallization from pet-ether afforded **4e** in 74% yield. The ether layer that was kept aside was concentrated and distilled under reduced pressure to yield **13e**.

In cases where the solvolysis products (**14** or **15**) were observed (by ^1H NMR), the work-up procedure was modified. When aq. acetone was used as solvent for photolysis, after extraction of the acidic products, the residue was chromatographed over silica gel to afford the propiophenones **13** and the solvolysis products **14**. When methanol was used as solvent, the total reaction mixture was chromatographed to separate the reaction products, *viz.* ester (**12**), propiophenone (**13**) and solvolysis product (**15**). Alkaline hydrolysis of the ester **12** afforded the corresponding α-arylpropanoic acid **4**.

Photolysis of the α-chloro ketones was also conducted utilizing the Rayonet RPR 208 photoreactor fitted with 300 nm lamps. In this case a solution of the chloro ketone (1 g) in aq. acetone or CH_3OH (50 mL) was filled in a pyrex tube, N_2 bubbled for 15 min, propylene oxide (3 mL) added and the tube was stoppered. The tube was placed in the photoreactor and irradiated for about 2-3 hours depending on the substrate. Workup of the reaction mixture was the same as described in the case of reaction in immersion-well type photoreactor.

Authentic samples of the known propiophenones were prepared[34] by the reaction of the appropriate hydrocarbon with propionyl chloride and $AlCl_3$ in 1,2-dichloroethane according to the procedure followed for the corresponding α-chloro-propiophenones **5** and were characterized by comparison of their spectral data with those reported.[34,35]

Spectral data of α-propanoic acids 4a-k

α-Phenylpropanoic acid 4a. **mp**: Low melting solid [lit.[36] 16 °C]. **IR** (nujol): 3400-2500, 1710, 1605, 1505, 1460, 1420, 1380, 1235, 1070, 945, 865 and 705 cm^{-1}. **^1H NMR**: 1.52 (d, J = 7 Hz, 3 H), 3.6 (q, J = 7 Hz, 1 H), 7.21 (m, 5 H), 8.3 (br. s, 1 H). **MS**: m/z 150 (M^+, 2%), 105 (100), 91 (27), 77 (70), 63 (9).

α-(4-Methylphenyl)propanoic acid 4b. **mp**: 38-39 °C (hexane) [lit.[36] 36-37 °C]. **IR** (nujol): 3500-2500, 1715 1620, 1525, 1465, 1415, 1385, 1295, 1235, 1190, 1085, 950, 820, 795 and 735 cm^{-1}. **^1H NMR**: 1.55 (d, 7 Hz, 3 H), 2.37 (s, 3 H), 3.72 (q, J = 7 Hz, 1 H), 7.0-7.3 (m, 4 H), 9.4 (br.s, 1 H). **MS**: m/z 164(M^+, 3%), 119 (100), 105 (15), 91 (60), 77 (32).

α-(4-Ethylphenyl)propanoic acid 4c. viscous oil. **IR**: 3300-2500, 1705, 1610, 1520, 1465, 1415, 1235, 1140, 835 cm^{-1} **^1H NMR**: 1.2 (t, J = 8Hz, 3 H), 1.47 (d, J = 7.5 Hz, 3 H), 2.58 (q, J = 8Hz, 2 H), 3.66 (q, J =

7.5 Hz, 1 H), 7.2 (s, 4 H). **MS**:, m/z (%): 178 (M^+, 19), 163 (5), 150 (7), 133 (100), 117 (28), 105 (86), 91 (40).

α-(4-propylphenyl)propanoic acid 4d. viscous oil. **IR:** **^{1}H NMR**: 0.9 (t, J = 7.5 Hz, 3 H), 1.4-1.8 (m, 2 H), 1.46 (d, J = 7 Hz, 3 H), 2,51 (t, J = 7.5 Hz, 2 H), 3.68 (q, J = 7 Hz, 1 H), 7.0-7.3 (m, 4 H), 8.4 (br.s, 1 H).

α-[4-(2-Methylpropyl)phenyl]propanoic acid 4e (Ibuprofen). **mp**: 76 °C (hexane) [lit.[34] 75-77 °C]. **IR** (nujol): 3300-2500, 1720, 1605, 1465, 1420, 1375, 1379, 1320, 1270, 1235, 1185, 1075, 1005, 940, 870 and 785 cm^{-1}. **^{1}H NMR**: 0.88 (d, J = 7 Hz, 6 H), 1.48 (d, J = 7 Hz, 2 H), 1.6-2.1 (m, 1 H), 2.47 (d, J = 7 Hz, 2 H), 7.2 (m, 4 H), 9.6 (br. s, 1 H). **MS**: m/z 206 (M^+, 34%), 163 (84), 161 (80), 145 (9), 119 (66), 117 (73), 107 (74), 91 (100), 77 (36).

α-(4-t-butylphenyl)propanoic acid 4f. viscous oil. **IR**: 3500-2500, 1710, 1615, 1515, 1465, 1415, 1375, 1295, 1235, 1120, 1070, 1030, 965, 855 cm^{-1}. **MS**:, m/z (%): 206 (M^+,35), 191 (100), 178 (13), 163 (62), 161 (54), 150 (23), 145 (75), 135 (29), 131 (45), 128 (25), 117 (49), 105 (73), 91 (48), 77 (41).

α-(4-Chlorophenyl)propanoic acid 4g. **mp**: 57 °C (hexane) [lit.[36] 57-58 °C]. **IR** (nujol): 3500-2500, 1705, 1490, 1450, 1440, 1400, 1375, 1220, 1090, 1010, 935, 865, 835, 795 and 755 cm^{-1}. **^{1}H NMR**: 1.49 (d, J = 7 Hz, 3 H), 3.71 (q, J = 7 Hz, 1 H), 7.27 (s, 4 H), 9.4 (br. s, 1 H). **MS**: m/z 186 (M^+, 6%), 184 (23), 141 (27), 139 (100), 103 (86), 77 (40).

α-Biphenylpropanoic acid 4h. **mp**: 146 °C (ether: petroleum ether) [lit.[36] 146.5°C]. **IR** (nujol): 3300-2600, 1710, 1600, 1455, 1365, 1290 and 755 cm^{-1}. **^{1}H NMR**: 1.55 (d, J = 7 Hz, 3 H), 3.77 (q, J = 7 Hz, 1 H), 7.1-7.65 (m, 9H), 8.6 (br.s, 1 H). **MS**: m/z 226 (M^+, 37%), 181 (100), 165 (34), 152 (16), 141 (5), 127 (8), 115 (8).

α-(4-Methoxyphenyl)propanoic acid 4i. **mp**: 57 °C (hexane) [lit.[36] 56-57 °C]. **IR** (nujol): 3500-2500, 1710, 1605, 1515, 1465, 1425, 1305, 1250, 1185, 1035, 950, 835 and 795 cm^{-1}. **^{1}H NMR**: 1.48 (d, J = 7 Hz, 3 H), 3.67 (q, J = 7 Hz, 1 H), 3.78 (s, 3 H), 6.8 (d, J = 9 Hz, 2 H), 7.2 (d, J = 9 Hz, 2 H), 9.3 (br. s, 1 H). **MS**: m/z 180 (M^+, 6%), 164 (40), 149 (4), 136 (6), 119 (100), 103 (21), 91 (69), 77 (26).

α-(6-Methoxy-5-chloro-2-naphthyl)propanoic acid 4j. **mp**: 151-153°C (acetone-hexane) [lit.[8] 158°C for (S)-(+)-**5j**]. **IR** (nujol): 3400-2500, 1700, 1600, 1470, 1385, 1280, 1245, 1070, 980, 900 and 805 cm^{-1}. **^{1}H NMR**: 1.56 (d, J = 7.5 Hz, 3 H), 3.58 (q, J = 7.5 Hz, 1 H), 3.99 (s, 3 H), 7.2-8.15 (m, 5 H), 9.3 (br. s, 1 H). **MS**: m/z 266 (M^+, 24%), 264 (74), 249 (4), 221 (37), 219 (100), 204 (6), 184 (60), 169 (17), 149 (39), 115 (17).

α-(6-Methoxy-2-naphthyl)propanoic acid 4k (Naproxen). **mp**: 151 °C (acetone-hexane) **IR** (nujol): 3300-2500, 1730, 1615, 1465, 1405, 1265, 1245, 1190, 1180, 1035, 905, 875 and 835 cm^{-1}. **^{1}H NMR**: 1.55 (d, J = 7.5 Hz, 3 H), 3.82 (q, J = 7.5 Hz, 1 H), 3.91 (s, 3 H), 7.1-7.8 (m, 6 H), 8.9 (br. s, 1 H). **MS**: m/z 230 (47), 215 (3), 185 (100), 176 (18), 153 (13), 141 (19), 141 (19), 115 (16).

Spectral data of propiophenones 13a-k was in agreement with that reported in literature. A typical example is given below.

4-(2-methylpropyl)propiophenone[34] (13e). **bp** 128-30 °/3-4mm. **IR**: 2960, 1690, 1605, 1465, 1410, 1225, 1180, 1015, 940, 855, 795 cm^{-1}. **^{1}H NMR**: 0.91 (d, J = 7 Hz, 3 H), 1.22 (t, J = 8 Hz, 3 H), 1.6-2.1 (m, 1 H), 2.53 (d, J = 7 Hz, 2 H), 2.98 (q, J = 8 Hz, 2 H), 7.2 (d, J = 9 Hz, 2 H), 7.9 (d, J = 9 Hz, 2 H). **MS**:, m/z 190 (M^+, 22), 175 (5), 162 (100), 147 (21), 133 (15), 119 (21), 105 (11), 91 (19), 77 (3). **UV**: λ_{max} 319, ϵ 155.

Preparation[5] and photolysis of the dimethyl acetal of 5e

A mixture of **5e** (2.245 g, 10 mmol), CH_3OH (10 mL), $HC(OCH_3)_3$ (10 mL) and pTsOH (10 mg) was refluxed for 12 h. Excess CH_3OH and $HC(OCH_3)_3$ were distilled off and the residue poured over dil. $NaHCO_3$. The oil that separated was extracted in hexane, washed with brine and dried over Na_2SO_4. Distillation under reduced pressure yielded the dimethyl acetal, 2.30 g, 85%. **bp** 124-7 °C/2-3 mm. **^{1}H NMR:** 0.90 (d, J = 7 Hz, 6 H), 1.30 (d, J = 7.5 Hz, 3 H), 1.81 (m, 1 H), 2.47 (d, J = 7 Hz, 2 H), 3.16 (s, 3 H), 3.32 (s, 3 H), 4.34 (q, J= 7.5 Hz, 1 H), 7.1-7.5 (m, 4 H).

Photolysis of this acetal under conditions described earlier and even in a Rayonet RPR 208 photoreactor fitted with 254 nm lamps for 12 h followed by its analysis by GLC and ^{1}H NMR indicated no traces of any reaction products.

Preparation of authentic samples of the solvolysis products 14 and 15. The α-chloro-propiophenones were converted to the corresponding α-hydroxy dimethyl acetals.[36] The α-hydroxy dimethyl acetals (2 mmol) were stirred in a two phase system consisting of 5% H_2SO_4 and CH_2Cl_2 (10 mL each) for 6 h. The organic layer was separated and worked up as usual to afford the α-hydroxy ketones **14g-k**. These displayed spectral data which was in agreement with that reported.[37]

The α-methoxy-propiophenones **15g-k** were prepared as follows. The α-hydroxy acetal, prepared as above, (2 mmol) in THF (5 mL) was added dropwise to a suspension of NaH (2.5 mmol) in THF (20 mL) at 0 °C. After 10 min, CH_3I (2.2 mmol) in THF (5 mL) was added slowly over a period of 10 min. Stirring was continued for 2 h, after which ice-cold water was carefully added to the reaction mixture. Extraction of the reaction mixture with ether and usual workup afforded the α-methoxy acetals which were subjected to acidic hydrolysis as described above for the α-hydroxy acetals **14g-k**. The spectral data of these α-methoxy ketones was in agreement with that reported.[38]

Photolysis of bromo ketone 10. Irradiation of **10** in aq. acetone at 350 nm was carried out under conditions described earlier in a Rayonet RPR 208 photoreactor equipped with 350 nm lamps. Work up in a manner as described earlier afforded two products **16** (55%) and **13e** (32%).

4-(2-Methylpropyl)benzoic acid 16. **mp** 105 °C. **IR**: 3300-2500, 1700 cm^{-1}. **^{1}H NMR:** 0.90 (d, J = 7 Hz, 6 H), 1.6-2.1 (m, 1 H), 2.55 (d, J = 7 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 8.07 (d, J = 8 Hz, 2 H), 9.31 (br, s, 1 H). **MS**: 178 (M^+, 24%), 133 (32), 119 (21), 105 (100), 91 (45), 79 (22).

Photolysis of iodo ketone 11. Irradiation of **11** in aq. acetone at 350 nm was conducted as described above. However, the irradiation was stopped when only 20% of the starting material had disappeared (^{1}H NMR). Concentration of the reaction mixture and column chromatography of the residue over silica gel (2% EtOAc in pet-ether) afforded **18**. **IR**: 1670 cm^{-1}. **^{1}H NMR**: 0.90 (d, J= 7 Hz, 6 H), 1.7-2.1 (m, 1 H), 2.5 (d, J= 7 Hz, 2 H), 5.86 (dd, J = 1.5 and 9 Hz, 1 H), 6.40 (dd, J = 1.5 and 16 Hz, 1 H), 7.18 (dd, J = 9 and 16 Hz, 1 H). **MS**: 188 (M^+, 5%), 161 (100), 146 (22), 133 (7), 119 (22), 105 (40), 91 (23).

Experiments utilizing sunlight.

A pyrex tube (60 cm X 1.5 cm) equipped with a facility for bubbling nitrogen was placed horizontally in a north-south direction in an open-air lab. The tube was filled with a solution of the α-chloro-propiophenone **5** (1 g) in either aq. acetone or CH_3OH (75 mL) and propylene oxide (3 mL) was added. A minute flow of N_2 was maintained and the reaction mixture was exposed to sunlight. Complete disappearance of the starting chloro ketones was observed in about 3-4 hours. The reaction mixture was then worked up as usual to afford the α-arylpropanoic acids in yields comparable to those obtained utilizing UV light. The composition of the other neutral products remained essentially the same.

A larger reactor facilitated the exposure of upto 100 g of the chloro ketone at a time. It consisted of a long tube (160 cm X 7.5 cm) with a provision for cooling its contents by circulating water through glass tubes placed at the center of the tubular reactor. Constant nitrogen flow was maintained throughout the course of the reaction which also served the purpose of stirring the reaction mixture. Utilizing this reactor, 100 g of the chloro ketone **5e** in aq. acetone (3000 mL) could be conveniently transformed into **4e**, *i.e* Ibuprofen, in about 3 days exposure to sunlight, the yield remaining essentially the same as that obtained using artificial light.

Synthesis of optically active α-chloro-propiophenones.

(S)-(+)-α-Chloropropionic acid. Prepared according to reported procedure.[39] **bp** 65-7 °C/4-5 mm. $[\alpha]_D^{25}$ -18.1°.
(S)-(+)-α-Chloropropionyl chloride (7). Prepared by treatment of the above α-chloropropionic acid with thionyl chloride.[13,39] **bp** 60 °C/100 mm.

Preparation of (S)-(+)-5a-b, 5e, 5i, and 5k. These compounds were prepared from the corresponding hydrocarbons and (*S*)-chloropropionyl chloride following the procedures employed for racemic **5a-k**. The optical rotations are given below (solvent, $CHCl_3$).

Substrate:	obsvd. $[\alpha]_D^{25}$	conc, c	Reported[13,27] $[\alpha]_D$
5a	+ 15.20°	1.00	+ 15.26°
5b	+ 39.20°	1.00	+ 39.80°
5e	+ 30.30°	1.00	+ 30.50°
5i	+ 49.90°	0.84	+ 50.20°
5k	+ 117.40°	1.00	+ 117.70°

Photolysis of optically active α-chloro-propiophenones

Irradiation of these ketones (1 g) in aq. acetone (50 mL) was carried out at 300 nm in a Rayonet RPR 208 photoreactor as described earlier. After the reaction was over, the reaction mixture was concentrated and extracted with ether. The ether layer was extracted with 5% $NaHCO_3$ and the alkali layer was cooled and acidified with 10% H_2SO_4. The α-arylpropanoic acids **4** that separated were re-extracted in ether, the ether layer washed with brine and dried over Na_2SO_4. Concentration of the ether extract and treatment of the residue with an ethereal solution of diazomethane followed by distillation under reduced pressure afforded the esters **12**. The enantiomeric excess of these methyl esters was determined by comparing their specific rotations with those reported and also by recording their ^1H NMR spectra in the presence of chiral shift reagent [(+)-Eu(hfc)$_3$, 60-90 mole %] and measuring the relative integration of the ester methyl group. A typical example is given below.

(S)-(+)-Methyl-2-[4-(2-Methylpropyl)phenyl]propanoate 12e. **IR** (neat): 2960, 1745, 1615, 1525, 1475, 1345, 1220, 1180, 1085, and 880 cm^{-1}. **^1H NMR**: 0.88 (d, J = 7 Hz, 6 H), 1.43 (d, J = 7 Hz, 3 H), 1.83 (m, 1 H), 2.4 (d, J = 7 Hz, 2 H), 3.56 (s, 3 H), 3.6 (q, J = 7 Hz, 1 H), 7.1 (m, 4 H). **MS**: m/z 220 (M^+, 38%), 177 (43), 162 (49), 145 (21), 131 (19), 118 (100), 105 (25), 91 (34), 77 (17). When the ^1H NMR spectrum was recorded in the presence of (+)-Eu(hfc)$_3$ (90 mol %), the signal for the methyl group of the ester which was observed at 3.56 δ in absence of the shift reagent, had shifted to 6.8 δ and split into two singlets. The ee was calculated from the relative integration of these two singlets.

Control Experiments: During photolysis of (*S*)-(+)-**5** aliquots were withdrawn at several intervals (10-80% completion as indicated by GLC and ^1H NMR) and analyzed by HPLC employing a chiral column and UV detector (313 nm). Column: Chiral Triacel (microcrystalline cellulose triacetate, particle size 7 μm). Dimensions 4 mm X 25 cm. From: Macherey-Nagel, Duren (FRG). Mobile phase CH_3OH-H_2O (75:25).

Optically active **4e** and **4k**, prepared by us in connection with some other work[40] were irradiated for 3 h under identical conditions and the enantiomeric composition determined by ^1H NMR using (+)-Eu(hfc)$_3$. It was found to be unaltered.

Synthesis of (*S*)-(+)-Ketoprofen (26).

Preparation of (*S*)-3-benzyl-α-chloro-propiophenone 23

3-Bromobenzophenone 21. was prepared from 3-bromobenzoic acid (**20**) by converting it to the acid chloride with $SOCl_2$ and its Friedel-Crafts reaction with $AlCl_3$ and benzene according to the procedure described for 3-benzoylpropiophenone (vide infra). **bp** 160-65 °C/2-3 mm. **IR**: 1690 cm^{-1}. **^{1}H NMR**:7.3-8.2 (m, 9 H). **MS**: m/z 262 (M^+, 16), 260 (M^+, 17), 182 (32), 155 (11), 105 (100), 77 (67).

3-Benzyl-bromobenzene*[41] *22. Hydrazine hydrate (1.442 g, 45 mmol) and KOH (2.243 g, 40 mmol) in ethylene glycol (10 mL) were added to **21** (2.50 g, 9.5 mmol) and heated for 2 h at 150±-5 °C. The temperature was then raised to 200 °C to remove excess hydrazine and heating was continued for another 4 h. The reaction mixture was then cooled to room temperature, diluted with dil HCl, extracted with ether and worked up as usual to give **22**. **^{1}H NMR**: 3.92 (s, 2 H), 7.1-7.5 (m, 9 H). **MS**: m/z 248 (M^+, 8), 246 (M^+, 8), 167 (100), 152 (32), 139 (11), 128 (7), 115 (19), 91 (57).

(S)-3-Benzyl-α-chloro-propiophenone 23. 3-Benzyl-bromobenzophenone (**22**) and (*S*)-(+)-α-chloropropionyl chloride were reacted according to the procedure employed for **5k** to afford (*S*)-**23**. It was found by chiral HPLC to be 98% optically pure. **mp** (CH_3OH) 133 °C. **IR**: 1690, 1660 cm^{-1}. **^{1}H NMR**: 1.82 (t, J = 7 Hz, 3 H), 4.23 (s, 2 H), 5.12 (q, J = 7 Hz, 1 H), 7.3- 8.35 (m, 9 H). $[\alpha]_D^{25}$ + 33.0° (c, 1, $CHCl_3$).

Photolysis of (*S*)-3-benzyl-α-chloro-propiophenone (23)

This was conducted exactly as reported for the optically active α-chloro-ketones **5**, in a Rayonet RPR 208 photochemical reactor fitted with 300 nm lamps. Two products were isolated, (*S*)-(+)-**24** (55%) and 3-benzylpropiophenone (**25**) (25%).

(S)-3-Benzyl-α-methyl-benzeneacetic acid (24). **IR**: 3400-2500, 1700 cm^{-1}. **^{1}H NMR**: 1.47 (d, J = 7 Hz, 3 H), 3.65 (q, J = 7 Hz, 1 H), 4.2 (s, 2 H), 7.2-7.8 (m, 9 H), 9.8 (br. s, 1 H). **MS**: m/z 240 (M^+, 81), 222 (4), 195 (98), 178 (21), 165 (42), 152 (13), 115 (21), 105 (17), 91 (100). **ee** 34% This was determined by recording the ^{1}H NMR of its methyl ester in the presence of chiral shift reagent (+)-Eu(hfc)$_3$.

3-Benzylpropiophenone (25). **^{1}H NMR**: 1.20 (t, J = 7 Hz, 3H), 2.96 (q, J = 7 Hz, 2 H), 4.21 (s, 2 H), 7.30-8.35 (m, 9 H).

3-Benzoyl-α-methyl-benzeneacetic acid (Ketoprofen, 26). The keto acid **24** (1 g) was dissolved in 1 N NaOH (20 mL) and $KMnO_4$ (2.6 g) in water (80 cc) was added. The reaction mixture was stirred overnight (16 h) at 20 °C and worked up as usual to obtain (*S*)-Ketoprofen (720 mg, 70%). $[\alpha]_D^{25}$ +17.1° {lit.[33] + 50.2°} **ee** 32%. This was determined by recording the ^{1}H NMR spectrum of its methyl ester in the presence of (+)-Eu(hfc)$_3$. **IR**: 3300-2500, 1700 cm^{-1}. **^{1}H NMR**: 1.45 (d, J = 7 Hz, 3 H), 3.67 (q, J = 7 Hz, 1 H), 7.3-8.30 (m, 9 H). **MS**: m/z 254 (M^+, 61%), 236 (7), 209 (52), 194 (8), 177 (61), 131 (11), 105 (100), 77 (83).

Preparation and photolysis of (±)-3-benzoyl-α-chloro-propiophenone

3-Cyanopropiophenone (28). A mixture of *3*-bromopropiophenone[42] (**27**) (21.3 g, 100 mmol), CuCN (10 g, 110 mmol) and DMF (75 mL) was refluxed with stirring for 6 h. The reaction mixture was poured hot into a mixture of $FeCl_3$ (10 g), water (60 mL) and conc. HCl (10 mL) and the mixture warmed to 70-80 °C and maintained at this temperature for 20 min; the reaction mixture was cooled and extracted with benzene. Usual workup afforded **28** as low melting solid, 14 g (86%). **IR**: 2250, 1690 cm^{-1}. **^{1}H NMR**: 1.22 (t, J= 7 Hz, 3 H), 2.98 (q, J = 7 Hz, 2 H), 7.3-8.1 (m, 4 H). **MS**: m/z 159 (12), 130 (100), 102 (44), 75 (150).

3-Hydroxycarbonyl-propiophenone (29). A solution of **28** (7.95 g, 50 mmol) in EtOH (20 mL) was added slowly to a cold solution of KOH (5 g) in EtOH (50 mL). The reaction mixture was refluxed for 2 h after which

EtOH was distilled off and the residue dissolved in water. The alkaline solution was extracted with ether to remove neutral impurities and then acidified with dil. H_2SO_4. The solid that separated was filtered and dried, **mp** 129 °C, 7 g, (78%). **IR:** 1.24 (t, J= 7 Hz, 3 H), 3.01 (q, J = 7 Hz, 2 H), 7.4-8.1 (m, 4 H), 9.21 (br. s, 1 H). **MS**: m/z 178 (M^+, 7%), 149 (100), 121 (19), 76 (8).

3-Benzoylpropiophenone (30). Thionyl chloride (4.7 g, 40 mmol) was added to a stirring solution of the acid prepared above (5.34 g, 30 mmol) in benzene (50 mL) at 0 °C. The reaction mixture was warmed gradually and then refluxed for 1 h. Excess $SOCl_2$ was distilled off and the remaining solution of the acid chloride in benzene was cooled to 0 °C in an ice-salt bath. Powdered $AlCl_3$ (6 g, 45 mmol) was added in portions over a period of 15 min and the reaction mixture stirred at this temperature for 2 h and was allowed to warm to room temperature and then stirred at 50 °C for 2 h. After cooling, it was poured over crushed ice and worked up as usual. Distillation under reduced pressure yielded the product as a colourless oil, 3.5 g, (88%). **bp** 180-85 °C/2-3mm. **IR:** 3060, 2980, 2920, 1690, 1650, 1600, 1450, 1280, 1220, 1185, 1125, 980, 780 cm^{-1}. **^{1}H NMR:** 1.2 (d, J = 7 Hz, 3 H), 2.95 (q, J = 7 Hz, 2 H), 7.2-8.27 (m, 9 H). **MS**: m/z 238 (21), 210 (34), 182 (25), 105 (100).

3-Benzoyl-α-chloro-propiophenone (31) was prepared by the reaction of 3-benzoylpropiophenone with SO_2Cl_2 in CCl_4 according to the procedure followed for **5j**. **mp** (CH_3OH) 88 °C. **IR**: 1690 cm^{-1}. **^{1}H NMR:** 1.83 (d, J = 7 Hz, 3 H), 5.15 (q, J = 7 Hz, 1 H), 7.4-8.35 (m, 9 H). **MS**: m/z 274 (M^+, 2%), 272 (M, 6), 236 (5), 209 (100), 181 (12).

Photolysis of 31. This was conducted at 350 nm in a Rayonet RPR 208 photoreactor according to the procedure described for the optically active chloro ketones **5**. The workup and isolation of the products also remains the same. Two products were obtained, (±)-ketoprofen (**26**, 45%) and 3-benzoylpropiophenone (**30**, 30%).

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