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Stereoselective intermolecular addition of ketyl radicals generated from ketones by photoinduced electron transfer

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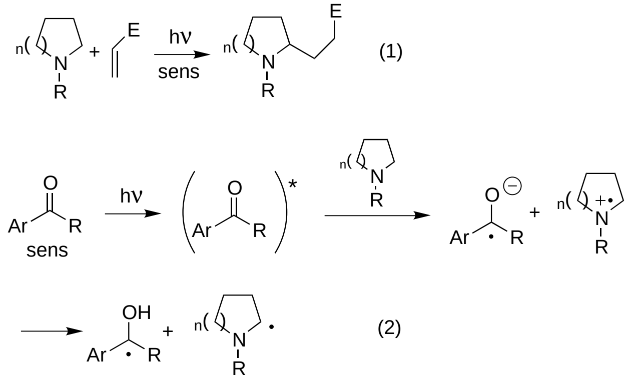
Abstract—Ketyl radicals were produced from ketones by photochemical electron transfer and subsequent proton transfer from tertiary amines. These radicals were stereoselectively added to (5*R*)-5-(−)-menthyloxy-2[5*H*]-furanone **1**. Due to their low reactivity, the α-aminoalkyl radicals which were generated at the same time were not added to **1**. The ketones were used in stoichiometric quantities. © 2001 Elsevier Science Ltd. All rights reserved.

Radical reactions have become an important tool in organic chemistry.[1] However, considerable efforts are still needed to improve the selectivity of these reactions.[2] Recently, we reported on an efficient photochemical method for the stereoselective radical addition of tertiary amines to electron deficient double bonds[3] (Scheme 1, Eq. (1)) and radical tandem reactions were successfully carried out under the same conditions.[4] The radical chain reaction was initiated by a single electron transfer followed by a proton transfer from the tertiary amine to the electronically excited sensitizer.[5] Nucleophilic α-aminoalkyl radicals and stable ketyl radicals were formed as intermediates (Scheme 1, Eq. (2)).[6,7] In the case of homogenous catalysis, the best results were obtained when aromatic ketones possessing electron donating substituents were used as sensitizers. The reaction could also be carried out under heterogenous conditions using inorganic semiconductors like TiO_2 and ZnS as sensitizers.[8]



Scheme 1.

During these investigations, we observed that some tertiary amines like *N*,*N*-dimethylbenzylamine **2** or triethylamine did not react or yielded complex mixtures in a slow reaction. Because of their oxidation potential, these amines should be as capable as tertiary amines like *N*-methylpyrrolidine to transfer an electron to an electronically excited ketone. The latter amine adds to electron deficient alkenes in a fast and clean reaction giving product yields up to 94%.[3] However, when the α-aminoalkyl radical is not reactive, the ketyl radical should be capable of adding to the electron deficient double bond (Scheme 2). Ketyl radicals are nucleophilic[7,9] and can easily add to electron poor alkenes in a stereoselective manner.[10,11] For this purpose, they have been most frequently generated by hydrogen abstraction from secondary alcohols used as solvent.

We wondered whether ketyl radicals which are generated by electron transfer from a tertiary amine onto an electronically excited ketone could add to electron deficient double bonds in the same way as ketyl radicals which are formed by hydrogen abstraction from alcohols.[12] In such a process, the ketyl source can be used in stoichiometric quantities instead of a large excess. In the context of organic synthesis, such an approach signifies that two electrophilic synthons are coupled by

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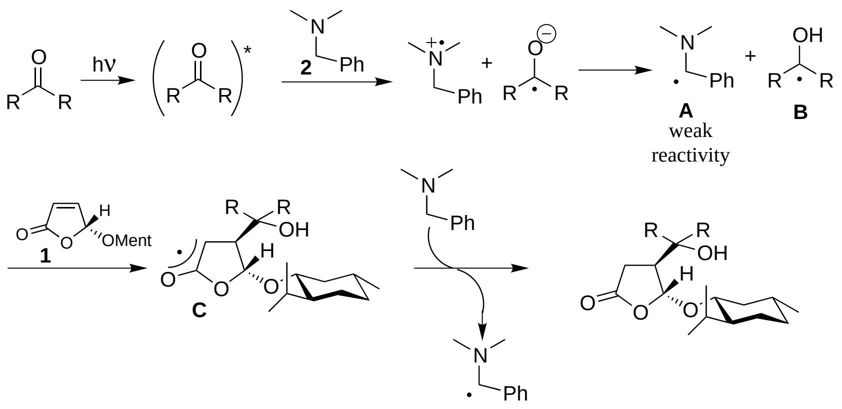


Scheme 2.

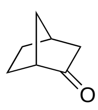
intervention of an umpolung step. In this case, however, no previous functionalization of the carbonyl group is necessary to invert the polarization.

We started our investigation by the irradiation of cyclic ketones in the presence of *N*,*N*-dimethylbenzylamine **2** or triethylamine in acetonitrile as solvent. (5*R*)-5-(–)-Menthyloxy-2[5*H*]-furanone **1** was used as the electron deficient olefin (Scheme 3, Table 1). In order to minimize side reactions, the concentration of the ketone was maintained low while the tertiary amine was used in large excess. The low concentration of the ketone caused inhibition of undesired reactions like pinacolization, while high concentrations of the tertiary amine favored the electron transfer to the excited ketone and slows down unimolecular side processes like Norrish reactions. In a typical reaction, a solution of **1** (1 mmol) and *N*,*N*-dimethylbenzylamine **2** (5 ml, ≈25 equivalents) in acetonitrile (50 ml in Pyrex tubes) was percolated with argon for 15 min before irradiation (Rayonet Chamber Reactor, $\lambda = 300$ mn). The solution of the ketone (1 equiv.) in acetonitrile (8 ml) was added in 15 equal portions each after 20 min. The reaction was monitored by TLC. The solvent and the amine were evaporated and the residue was subjected to flash chromatography (ethyl acetate/petroleum ether).

As previously determined by an application to asymmetric synthesis of natural products, the radical attack occurred specifically anti with respect to the menthyloxy substituent of **1**.[10] However, in the case of cyclobutanone (Table 1, entry 1), an unselective reaction was observed and the resulting complex mixture could not be analyzed. This result might be explained by the fact that cyclobutanone may undergo Norrish Type I reaction at its $^1n\pi^*$ and $^3n\pi^*$ state.[13] This reaction competes with electron transfer from the tertiary amine, which may occur at the $^1n\pi^*$ of aliphatic ketones. The latter hypothesis is supported by the fact that amines like diethylamine and triethylamine quench the fluorescence of aliphatic ketones.[14]

Apart from cyclopentanone (entry 2), the reaction rates were almost the same for triethylamine and *N*,*N*-dimethylbenzyamine **2** as electron donors, whereas the yields of the addition products were significantly better when **2** was used. When triethylamine was used as electron donor, considerable quantities of a complex mixture of mostly polymeric compounds was formed which could not be analyzed. The higher chemoselectivity of the reaction with **2** as an electron donor might be explained by the higher stability of the α-aminoalkyl radical **A** (Scheme 2). Undesired side reactions resulting from hydrogen abstraction of this intermediate are less frequent.

In the series of the investigated cyclic ketones, the best yields were obtained with cyclohexanone (entry 3). This observation is in contrast to results of the addition of ketyl radicals produced from secondary alcohols by hydrogen abstraction. In this case, the addition of 1-hydroxycyclopentyl radicals gave better yields.[10] Both ketones undergo the electron transfer at the $^1n\pi^*$ state, while α-cleavage most likely occurs at the $^3n\pi^*$ state. Consequently, the yield difference of these reactions can hardly be explained by a pronounced concurrent Norrish Type I reaction of cyclopentanone. For the moment, the reason for this behavior remains unclear. The yields of the reaction of higher homologues diminished (entries 4–6). This observation may be explained by the conformational mobility of the ketyl radicals, which increases the steric hindrance for the radical addition. Degradation instead of addition of the corresponding bicyclic ketyl radicals was also observed for norbornanone **3** and camphor **4**. In these cases, the steric hindrance of the corresponding ketyl radicals completely suppressed the radical addition.



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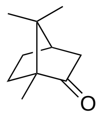

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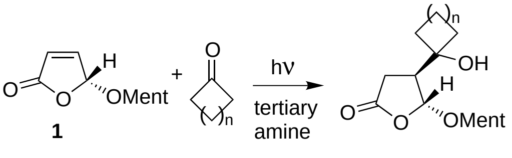


Scheme 3.

Table 1. Reaction of **1** with different cyclic ketones in the presence of tertiary amines (Scheme 3)

Entry	*n*	Amine **2**		Triethylamine	
		Conversion (%)[a]	Yield (%)[b]	Conversion (%)[a]	Yield (%)[b]
1	1	–	–[c]	–	–[c]
2	2	48	42	88	17
3	3	62	69	70	38
4	4	74	44	75	29
5	5	66	37	66	35
6	9	60	37	62	12

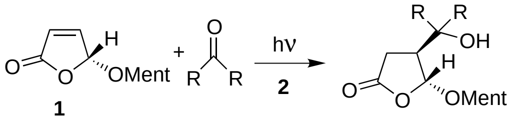
[a] Of **1**.
[b] With respect to the conversion of **1**.
[c] Complex mixture.

Under the optimized reaction conditions, we have carried out the reaction with linear ketones (Scheme 4, Table 2). Good results were observed with lower homologues like acetone and 3-pentanone (Table 2, entries 1 and 2). The yield for the addition of 3-hydroxypenthyl radical produced from ketones was as efficient as the addition of the same radicals produced from 3-pentanol.[10] In the case of linear ketyl radicals, the conformational mobility and the resulting steric hindrance play an important role, which explains why the addition of 3-pentanone was less efficient than that of acetone and why no reaction was observed in the case of 6-undecanone.

The results of our investigation can be explained by the mechanism depicted in Scheme 2. In a photochemical electron transfer process, α-aminoalkyl **A** and ketyl radicals **B** are produced. Both radicals are nucleophilic and can be added to electron deficient alkenes like **1**. Since **A** is less reactive than **B**, the addition of the ketyl radical **B** becomes competitive. The diminished reactivity of the α-aminoalkyl radicals can be attributed to greater mesomeric stabilization in the case of **A** or to conformational mobility in the case of the α-aminoalkyl radical produced from triethylamine. The reactivity of various α-aminoalkyl radicals was previously discussed.[3,4] The final product is formed by hydrogen abstraction of the oxoallyl radical **C** from **2**.

Until now, we were unable to isolate any final product resulting from the reaction of **A**. However, when we tried to carry out the reaction with aromatic ketones like **5** and **6** under the same reaction conditions, neither ketyl nor α-aminoalkyl radicals were added to **1**. Products **7** and **8**, which resulted from a radical coupling of the α-aminoalkyl radical **A** and the ketyl radical **D**, were isolated (Scheme 5).[15] Both radicals possess an aromatic and an electron donating substituent. This structural resemblance favored the photopinacolization like reaction.

In conclusion, we have reported a new method for the stereospecific addition of ketyl radicals to electron deficient alkenes. The ketyl radicals were produced by photoinduced electron transfer, followed by a proton transfer from the tertiary amine to the electronically excited ketones. The ketones were only needed in stoichiometric amounts. Their polarity was inverted by electron transfer. An umpolung by preceding functional group transformation as generally applied in synthesis was unnecessary.

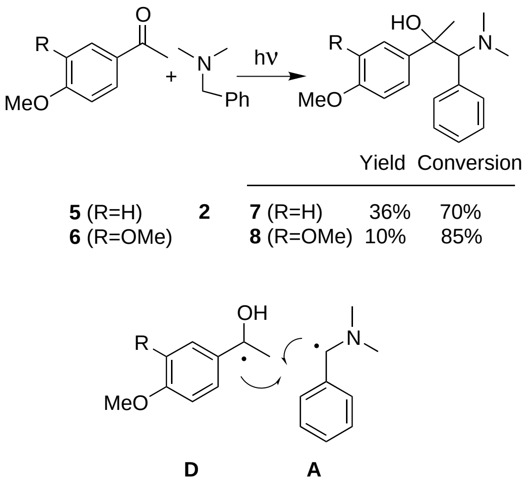


Scheme 4.

Table 2. Reaction of **1** with linear ketones in the presence of *N*,*N*-dimethylbenzylamine **2** (Scheme 4)

Entry	R	Conversion (%)	Yield (%)[a]
1	Me	34	73
2	Et	77	53
3	*n*-Pent	–	–

[a] With respect to the conversion of **1**.



Scheme 5. Reaction of aromatic ketones **5** and **6** with *N*,*N*-dimethylamine in the presence of furanone **1**. Yields are given with respect to the conversion of the ketone.

Acknowledgements

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