Chain propagation determines the chemo- and regioselectivity of alkyl radical additions to C–O vs. C–C double bonds†

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Investigations into the selectivity of intermolecular alkyl radical additions to C–O vs. C–C-double bonds are described. Therefore, a photoredox-initiated radical chain reaction is explored, where the activation of the carbonyl-group through an in situ generated Lewis acid – originating from the substrate – enables the formation of either C–O or the C–C-addition products. α,β-Unsaturated aldehydes form selectively 1,2-, while esters and ketones form the corresponding 1,4-addition products exclusively. Computational studies lead to reason that this chemo- and regioselectivity is determined by the consecutive step, i.e. an electron transfer, after reversible radical addition, which eventually propagates the radical chain.

Introduction

Radical chemistry has been investigated for decades and, owing to the high reactivity of open-shell species, represents a complementary approach to classical closed-shell chemistry towards the synthesis of organic molecules.1 Considering that the selectivity of radical reactions is essential for targeted synthesis,2 numerous attempts to control these highly reactive intermediates have been made.3 Especially recent advances in controlled radical generation by means of photoredox catalysis have further expanded the field of selective radical reactions.4

Owing to their high reactivity, radicals usually undergo only low activation barrier pathways. Selective radical reactions are therefore often enabled by rapid, innate chains (usually requiring fast and exothermic steps) or efficient transformations to long-lived (non-radical) intermediates (i.e. radical-polar crossover). To enable efficient chains, a polarity match of radical and reaction partner has to be given, otherwise non-productive side reactions with lower activation barriers will be the preferred pathways for these “impatient” intermediates.5

Amongst the elementary steps within radical chain reactions, radical additions to different π-bonds,6 which represent
an efficient means to C–C bond formation, are quite well understood. In principle, selectivity in radical additions for two competitive reaction steps is determined by the difference in activation barriers: this kinetic control is usually governed by a polarity match between an electrophilic radical and a nucleophilic double bond, or vice versa. It is, however, rather challenging to control such a selectivity, when multiple addition sites with matching polarity and, in turn, similarly low barriers are available. As an example, the classical Minisci-type addition of nucleophilic radicals to electron-deficient heterocycles such as pyridine often yields a mixture of 2- and 4-substitution. In such systems, as well as e.g. for benzene rings or asymmetrical dienes, it remains challenging to predict the site selectivity of the radical addition of a given radical (see Fig. 1).

Building on our recent study on the radical addition to carbonyls, in which aromatic aldehydes and ketones act as radical acceptors for alkyl radicals under Brønsted acid activation, we investigated the selectivity of the radical addition to the C–O vs. C–C double bond in Michael acceptors.

Results and discussion

To investigate the selectivity of the radical addition to C–O vs. C–C double bonds, Michael acceptors were chosen as radical acceptors. To enable an overall redox-neutral transformation, silyl ketene acetals were applied as radical precursors. In combination with an oxidizing photoredox catalyst, these
substrates form amphiphilic alkyl radicals\(^1\) after single electron oxidation, which subsequently can add to \(\pi\)-bonds.

Irradiating silyl ketene acetal 1 in the presence of the photocatalyst [Ir(dF-CF\(_3\)-ppy)\(_2\)(dtbpy)]PF\(_6\) (PC-1) and different Michael acceptors 2, an unexpected chemoselectivity switch was observed: whereas the addition to \(\alpha,\beta\)-unsaturated esters and ketones afforded the Giese-type 1,4-addition product, the reaction of \(\alpha,\beta\)-unsaturated aldehydes selectively formed allylic alcohols as products of a formal 1,2-addition. To rationalize this switch in reactivity, experimental and computational mechanistic analyses were conducted.

Mechanistic studies

As a first model system the reaction between trimethyl silyl ketene acetal 1 (1a) and methyl acrylate (2a) was investigated in detail. In the absence of either light or photocatalyst, no product was detected, which corroborates a photochemical reaction pathway.

In steady-state absorption measurements, the photocatalyst was observed; whereas the addition to \(\alpha,\beta\)-unsaturated esters and ketones afforded the Giese-type 1,4-addition product, the reaction of \(\alpha,\beta\)-unsaturated aldehydes selectively formed allylic alcohols as products of a formal 1,2-addition. To rationalize this switch in reactivity, experimental and computational mechanistic analyses were conducted.

Mechanistic analyses were conducted. Volmer analysis and nanosecond-transient absorption spectroscopy (ns-TAS) suggest an effective quenching of the electronically excited state of PC-1 by silyl ketene acetal 1. Upon irradiation PC-1 gives rise to a MLCT triplet state featuring a 2.49 ± 0.06 \(\mu\)s lifetime. In ns-TAS experiments, the latter is effectively quenched when silyl ketene acetal 1 is added and gives rise to newly developing transient absorption features. A comparison with the spectro-electrochemical measurements (see ESI for further details\(^\dagger\) infers the reduction of PC-1 to afford PC-1\(^*\)\(^\dagger\). The underlying electron transfer from the silyl ketene acetal 1 to photoexcited catalyst PC-1 occurs with diffusion-controlled dynamics: \(k_{\text{ET}} = (1.25 \pm 0.02) \times 10^9 \ \text{L mol}^{-1} \text{s}^{-1}\). A high quantum yield (\(\varphi = 15.6\)) suggests that this quenching step initiates an efficient chain reaction.\(^\dagger\) Considering that the addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf, without irradiation) did not lead to product formation, a radical pathway rather than a Lewis-acid-mediated mechanism is likely to be operative.

With these results in hand, we propose the following general mechanism (see Fig. 2): silyl ketene acetal 1 is oxidized by photocatalyst PC-1. The resulting radical cation A then fragments to the respective \(\alpha\)-carbonyl radical B,\(^\dagger\) which adds to the Lewis-acid-activated \(\alpha,\beta\)-unsaturated carbonyl C to yield radical cation D.\(^\dagger\) Intermediate D is readily reduced by the excess of silyl ketene acetal 1,\(^\dagger\) which closes the radical chain cycle and yields intermediate E. Removal of the trimethylsilyl group by aqueous or fluoride workup leads to the final product.

Additional support for such a reaction mechanism came from further mechanistic experiments (see ESI for further details\(^\dagger\)): upon addition of TEMPO to the reaction mixture, TEMPO adducts of intermediates B and D could be detected, while intermediate E was identified by means of ESI-MS. Furthermore, experiments using deuterated reaction solvent excluded the possibility of a hydrogen atom transfer (HAT)

Fig. 3 (A) 1,2- vs. 1,4-Addition to \(\alpha,\beta\)-unsaturated aldehydes (B) 1,2- vs. 1,4-Addition to \(\alpha,\beta\)-unsaturated esters and the subsequent electron transfer step towards product E. Calculated for cinnamaldehyde and methyl cinnamate with trimethyl silyl ketene acetal (B3LYP-D3/def2-TZVPP/CPCM(MeCN)).
event from a solvent molecule. Overall, the thermodynamic feasibility of the chain propagation step was supported by the calculated redox potentials, which underline that oxidation of silyl ketene acetal 1 by intermediate D is feasible ($E_1 = +0.46$ V vs. SCE, $E_D = +0.96$ V vs. SCE).  

For $\alpha,\beta$-unsaturated aldehydes the observed 1,2-addition can be rationalized by an analogous hole catalysis mechanism ($E_D = +1.63$ V vs. SCE). Here, photocatalyst and light are required for the reaction to proceed as well. Notably, the addition of TMSOTf (without irradiation) leads to exclusive formation of the 1,4-addition product. Since no 1,2-addition product was observed under these Lewis acid conditions, a radical pathway rather than a Lewis-acid-mediated mechanism is likely to be operative under the standard reaction conditions. For $\alpha,\beta$-unsaturated ketones, however, a competing Lewis-acid-mediated chain reaction could not be fully excluded.

To understand the difference in behaviour of $\alpha,\beta$-unsaturated aldehydes and esters, a computational analysis of the proposed radical chain processes was conducted. Density functional theory calculations were performed at the B3LYP-D3/def2-TZVPP/PCM(MeCN) level. Activation barriers for the electron transfer steps were estimated using the four-point approximation to Marcus–Hush theory (see ESI for further details†). Although not widely established, this method was applied to different cases in organic chemistry to estimate electron transfer barriers. Therefore, we believe that this methodology should result in a reasonable estimation of the electron transfer activation barrier (see Fig. 3).

For $\alpha,\beta$-unsaturated aldehydes (see Fig. 3A), a highly oxidizing radical cation $D_4$ can be formed via a reversible radical $C$–$O$ addition, which can undergo a fast electron transfer as a consecutive reaction. Crucial for the selectivity is the electron transfer barrier, which is seemingly lower for the 1,2-addition.

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**Reaction scope**

1) [Ir(dF-CF3ppy)2(dbbpy)]PF$_6$ (PC-1, 1.0 mol%)  
2) TBAF or water  

| Esters | Ketones | Aldehydes |
|--------|---------|-----------|
| ![Image of esters](image1.png) | ![Image of ketones](image2.png) | ![Image of aldehydes](image3.png) |

**Fig. 4** Scope of the 1,4-radical addition to $\alpha,\beta$-unsaturated esters and ketones and the 1,2-radical addition to aldehydes. Standard conditions: Michael acceptor (2, 0.4 mmol), silyl ketene acetal (1, 0.6 mmol), PC-1 (0.004 mmol), MeCN (0.1 M), 16 h, 455 nm LEDs, workup with TBAF. (a) Workup with HCl 0.5 mmol scale, 1 (3.0 eq.). (b) Preformation of 1 without purification and subsequent coupling, 0.5 mmol scale. (c) Addition of TMSOTf (in the absence of light) showed product formation.
product ($\Delta G^2 = 3.8$ kcal mol$^{-1}$) than for the respective 1,4-addition product ($\Delta G^2 = 11.8$ kcal mol$^{-1}$). As such, we propose that, in a Curtin–Hammett-type scenario, the electron transfer is the selectivity determining step, which accounts for the 1,2-over 1,4-preference. This conclusion is in agreement with the computed redox potentials, since the 1,2-addition product ($E_D = +1.63$ V vs. SCE) shows a higher oxidation potential than the 1,4-addition product ($E_D = +1.21$ V vs. SCE) and therefore undergoes a faster electron transfer. For $\alpha,\beta$-unsaturated esters, a different selectivity is observed (see Fig. 3B). Here, a rather high activation barrier is calculated in all cases. This reaction was shown to be applicable for the preparation of aldehydes, although full conversion could not be achieved in secondary and tertiary $\alpha$-unsaturated aldehydes (1,2-addition product) in the acceptor were well tolerated. Furthermore, diverse and highly functionalized aldehydes could be derived from the subsequent electron transfer step, which propagates the radical chain. The control of regioselectivity of radical additions through a consecutive step represents a previously underestimated strategy which shows potential for further reaction design towards switchable selective radical additions.

Conclusions

With this method, a radical alternative to the well-studied ionic Mukaiyama–Michael/Aldol-reaction was developed. This variant does not require any external Lewis acid, allowing for good functional group tolerance and for the generation of quaternary carbon centers under mild reaction conditions. $\alpha,\beta$-Unsaturated esters and ketones show a high selectivity towards the 1,4-addition products, while $\alpha,\beta$-unsaturated aldehydes form the 1,2-addition product exclusively. Computational studies suggest that the high regio- and chemoselectivity of the reaction is not determined by the radical addition itself, but by the subsequent electron transfer step, which propagates the radical chain. The control of regioselectivity of radical additions through a consecutive step represents a previously underestimated strategy which shows potential for further reaction design towards switchable selective radical additions.

Conflicts of interest

There are no conflicts to declare.

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