TUTORIAL REVIEW

CSR
www.rsc.org/csr

Tin-free radical chemistry using the persistent radical effect: alkoxyamine isomerization, addition reactions and polymerizations

Armido Studer
Department of Chemistry, Philipps-University Marburg, 35032 Marburg, Germany.
E-mail: studer@uni-muenster.de; Fax: +49 (0)251 8336523; Tel: +49 (0)251 8333291

Received 19th December 2003
First published as an Advance Article on the web 18th May 2004

In this tutorial review applications of alkoxyamines as C-radical precursors for the conduction of tin-free radical reactions are presented. These processes are controlled by the Persistent Radical Effect. A brief introduction on the Persistent Radical Effect is provided. In addition, the use of microwave irradiation to conduct thermal radical reactions is discussed. Finally, the use of alkoxyamines as initiators/mediators for the controlled/living radical polymerization is highlighted.

Introduction

The Persistent Radical Effect (PRE) is a general principle that explains the highly specific formation of the cross-coupling product R^1–R^2 between two radicals R^1 and R^2 when one species is persistent (R^1) and the other transient (R^2) and the two radicals are formed at equal rates.[1] At first glance, the highly selective coupling between two reactive intermediates sounds surprising. One would expect non-selective statistical reaction between the two different radical intermediates. The reason behind this interesting reactivity lies in the reluctance of the persistent radicals to undergo homo-coupling. Therefore, the persistent radicals can only disappear *via* a cross-reaction with a transient radical. The transient species, however, can also react in a homo-coupling process to form R^2–R^2 and the corresponding disproportionation products. This in turn leads to a build up of the persistent radical and hence to the highly selective cross-coupling reaction.

To further clarify this picture a simulation of a simple system obeying the principle of the PRE is described below. Three reactions are considered: 1) Homolysis of starting material R^1–R^2 generates the two radicals R^1 (persistent) and R^2 (transient) at equal rates (rate constant for the homolysis $k_h = 1 \times 10^{-3}$ s^{-1}, initial concentration of R^1–R^2 = 1 M). 2) The radical R^1 is a persistent species and does not undergo homo-coupling; however, it can react with R^2 to reform the starting material R^1–R^2 (rate constant for the cross-coupling $k_c = 1 \times 10^9$ s^{-1}). 3) Homo-coupling of the transient radical R^2 delivers dimer R^2–R^2 (rate constant for the dimerization $k_d = 1 \times 10^9$ s^{-1}). In Fig. 1 the concentration evolution of the four different species (starting R^1–R^2, persistent R^1, transient R^2, and dimer R^2–R^2) as a function of time is drawn.† Very early in the reaction ($t < 10^{-4}$ s) roughly equal amounts of R^1 and R^2 are present in the reaction mixture. Since the radical concentrations are very low ($< 10^{-7}$ M) cross- and homo-coupling reactions play a minor role. After this initial period, radical–radical reactions are starting to become important. Hence, the formation of significant amounts of dimer can be observed. This in turn leads to a consumption of transient radical R^2. Indeed, radical R^2 reaches a maximum concentration after 1.4 milliseconds and afterwards its concentration is steadily decreasing. However, at the same time the concentration of persistent R^1 is slowly increasing. This leads to a build up of the persistent radical. Since the cross-coupling is a fast reaction, the dimerization will be suppressed and the cross-coupling to form R^1–R^2 will become the dominant process. In fact, due to the dominant cross-reaction (regeneration of the starting material) the concentration of the starting R^1–R^2 is decreasing very slowly. After 10^3 s only 0.014% of starting R^1–R^2 was transferred to dimer R^2–R^2 and persistent R^1. After 115 days under these conditions one would still observe 99.7% of starting material!

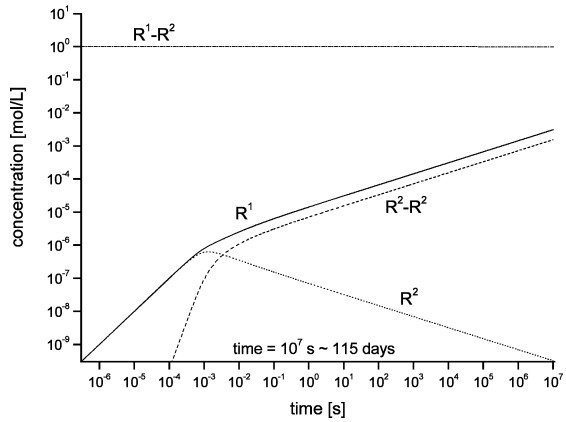


Fig. 1 Simulation of the first 115 days of a reaction obeying the principle of the PRE.

Now the question arises whether the PRE can be used to control radical reactions. Indeed, there are meanwhile several reports on the

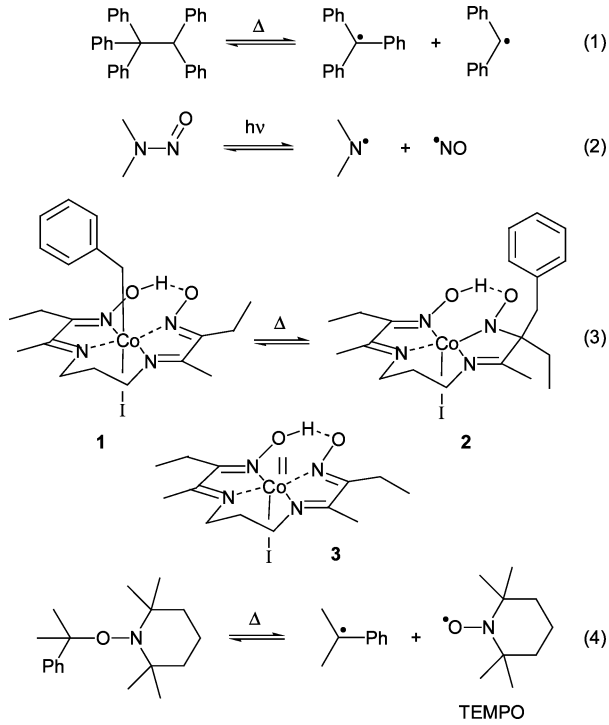
† The simulation was conducted using PowerSim, a program for modeling non-linear dynamics: http://www.powersim.com.

Armido Studer received his Diploma in 1991 and his PhD in 1995 from the ETH Zürich under the direction of Professor Dieter Seebach. He continued his scientific education as a Swiss National Science Foundation Postdoctoral Fellow at the University of Pittsburgh with Professor Dennis P. Curran, where he worked on fluorous phase chemistry. In 1996 he started his independent career at the ETH Zürich. In 2000, he was appointed as Associate Professor of Organic Chemistry at the Philipps-University in Marburg, and in 2004 as full professor at the Westfälische Wilhelm University at Münster, Germany. His current research interests focus on the development of new synthetic methods in free radical chemistry.

DOI: 10.1039/b307652k

application of this kinetic phenomenon in organic synthesis.[1,2] Due to space limitations only a few examples are discussed herein. For a more comprehensive compilation of data on the use of the PRE in organic synthesis we refer to two review articles.[1,2]

To the best of our knowledge, the first report describing unusual selectivities between persistent and transient radicals was published by Bachman and Wiselogle back in 1936.[3] They noticed that pentaphenylethane at 100 °C in *o*-dichlorobenzene has an unexpectedly long lifetime. After heating for two hours only 2% of tetraphenylethane was observed and 87% of the starting pentaphenylethane was recovered. However, in the presence of a radical scavenger such as O_2 the starting material was quantitatively consumed within a few minutes, showing that C–C-bond homolysis is indeed occurring under the applied conditions. Thus, the thermal C–C-homolysis leads to the persistent triphenylmethyl radical and the transient diphenylmethyl radical, which in the absence of O_2 undergoes dimerization to form tetraphenylethane. This leads to an increase of the concentration of the persistent species and this in turn makes (according to the PRE) the cross-reaction of the triphenylmethyl and the diphenylmethyl radical to become the dominant process [Scheme 1, eqn. (1)].



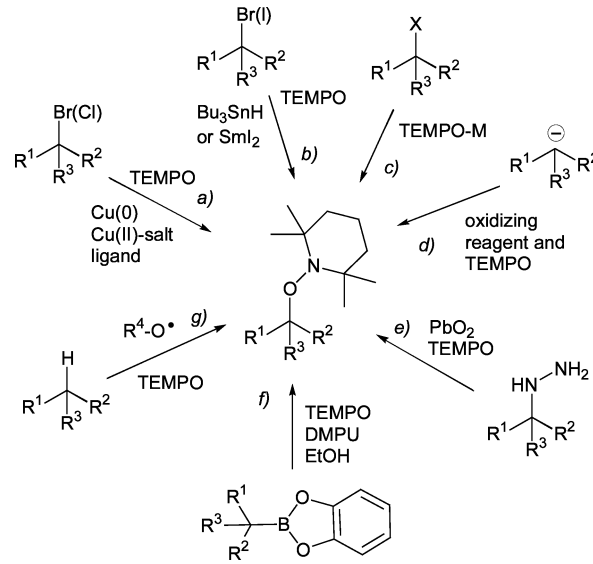
Scheme 1 Unexpected long lifetimes of reactive starting compounds.

Another example describing an unusual long lifetime of a reactive starting compound was published by Huber.[4] He showed that the irradiation of dimethylnitrosamine in the gas phase does not lead to a significant decrease of the starting material. The photochemically generated persistent NO radical and the transient dimethyl aminyl radical undergo (steered by the PRE) a highly selective cross-reaction to regenerate the starting nitrosamine [eqn. (2)]. In a seminal paper, Fischer carefully looked at the kinetics behind the principle of the PRE.[5] A few years later Finke coined the term PRE while studying the thermal isomerization of coenzyme B_{12} model compound **1** [eqn. (3)].[6] Thermal C–Co-bond homolysis leads to the persistent Co(II)-complex **3** and the transient benzyl radical. The benzyl radical undergoes cross-coupling with **3** to from either **1** or its isomer **2**. Despite the occurrence of reactive intermediates, the isomerization is a very clean reaction, again guided by the PRE. In the last example of this series the thermal homolysis of cumyl–TEMPO is discussed [eqn. (4)].[7] Thermal C–O-bond homolysis affords the persistent 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) and the transient cumyl radical. Dimerization (or disproportionation) of the cumyl radicals leads to a buildup of the TEMPO concentration and eventually to a highly selective cross-reaction of TEMPO with the cumyl radical. The reversible thermal C–O-bond homolysis of similar alkoxyamines has successfully been used to control free radical polymerizations.[1,8] This issue will be discussed in more detail below.

About 5 years ago, we started a project to apply the PRE-mediated reversible alkoxyamine homolysis for the generation of C-centered radicals to conduct environmentally benign radical reactions. Most of the radical reactions are still conducted using toxic tin hydrides. Many drawbacks are associated with tin-based radical chemistry. The toxicity of organostannanes necessitates special handling in disposal. Moreover, it is often tedious to remove the organotin by-products. Many research groups are meanwhile involved in the development of new tin-free radical chemistry.[9] In this tutorial article we will give a short overview on the use of alkoxyamines in tin-free radical chemistry.

Environmentally benign radical alkoxyamine isomerizations

The starting alkoxyamines can readily be prepared using different methods. The most useful procedures are presented in Scheme 2.

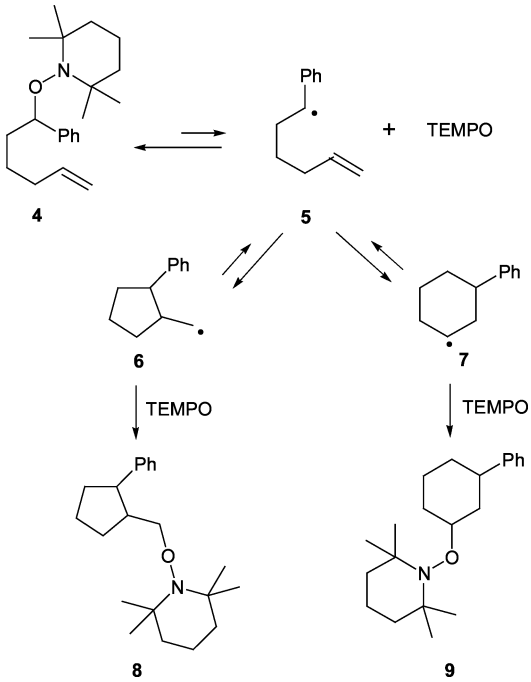


Scheme 2 Various methods for the preparation of alkoxyamines.

For activated halides (bromides as well as chlorides) the method of choice is the reaction of the halide with a catalytic amount of a copper(II) salt such as $Cu(OTf)_2$ in the presence of Cu(0) and TEMPO.[10] To solubilize the intermediately formed reactive Cu(I)-species a ligand such as 4,4′-*tert*-butyl-2,2′-bipyridine has to be added (route a). Non-activated alkyl or aryl halides can be converted to the corresponding alkoxyamines using tin hydride or SmI_2 in the presence of TEMPO (route b). The C-radical generated with stannyl radicals or SmI_2 is trapped with TEMPO to form the corresponding alkoxyamine.[11] The alkoxyamine moiety can also be introduced *via* a nucleophilic substitution process using metalated TEMPOH (route c).[12] One-electron oxidation of enolates or other C-metalated species in the presence of TEMPO provides the corresponding alkoxyamines. These reactions can be conducted with various oxidizing reagents (route d).[13,14] The oxidation of alkyl hydrazines in the presence of TEMPO has successfully been used for the preparation of alkoxyamines (route e).[13] Moreover, alkylcatecholboranes have been used as precursors for the preparation of TEMPO-derived alkoxyamines (route f).[15] Reaction of alkanes bearing activated C–H-bonds with reactive alkoxyl radicals in the presence of TEMPO provides the corresponding alkoxyamines (route g).[12,13] The methods presented are not restricted to the preparation of TEMPO-derived alkoxyamines. For most of the

procedures described above TEMPO can readily be replaced by other stable nitroxides.

In 2000 we published our first results on the use of TEMPO-derived alkoxyamines as radical precursors for the conduction of tin free radical cyclization reactions.[16] As an example the isomerization of alkoxyamine **4** is depicted in Scheme 3. The reaction was



Scheme 3 PRE-mediated isomerization of alkoxyamine **4**.

performed in *t*-BuOH at 130 °C. Reversible C–O-bond homolysis affords the transient C-radical **5** and the persistent TEMPO. Along with the back reaction to reform **4**, which is a degenerative process, the benzylic radical **5** can undergo a 5-*exo* or a 6-*endo* cyclization to form radicals **6** and **7**, respectively. Highly selective PRE-mediated trapping of these radicals with TEMPO eventually leads to the isolated isomerization products **8** (70%, *trans : cis* = 2.5 : 1) and **9** (13%, dr = 1 : 1). Unfortunately, the isomerization is a slow process. Fastest isomerizations (24 h) were obtained in the presence of 10% camphorsulfonic acid. Other solvents such as *tert*-butylbenzene, *N*,*N*′-dimethyl-*N*,*N*′-propylene urea (DMPU), DMF, H_2O and ionic liquids turned out to be less suited to conduct these radical reactions.

We found that the isomerization works well for alkoxyamines derived from stabilized C-centered radicals. Thus, various benzylic alkoxyamines **10** (aryl = 4-BrPh, 4-MePh, 2-thienyl, 2-pyridyl) were successfully isomerized in moderate to good yields (46–71%, Fig. 2). Moreover, isomerization could be accomplished with ester **11** (57%)[17] and nitrile **12** (61%), whereas alkoxyamines **13–15** were reluctant towards radical cyclization.

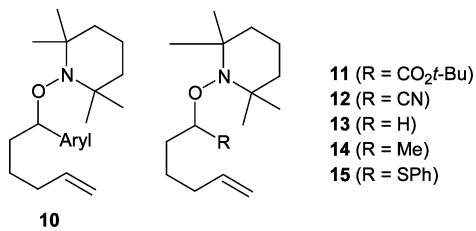


Fig. 2 Some alkoxyamines studied in the isomerization.

It is obvious that the success of the reaction depends on the C–O-bond strength of the starting alkoxyamine. We therefore started to measure the rate constant k_d for the C–O-bond homolysis of various TEMPO-derived alkoxyamines. The rate constants were determined by kinetic EPR experiments.[18] Details of these experiments, which were performed in collaboration with S. Marque and H. Fischer at the University of Zürich, can be found in the original literature. We got a satisfactory correlation between the C–O-homolysis rate constant and the stability of the leaving C-radical.[19] In Fig. 3 the logarithm of the experimentally determined rate

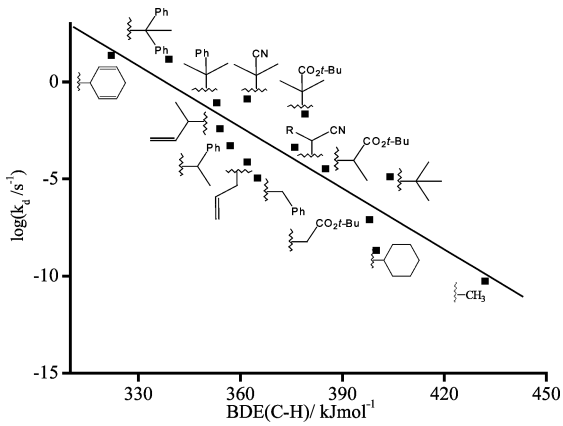
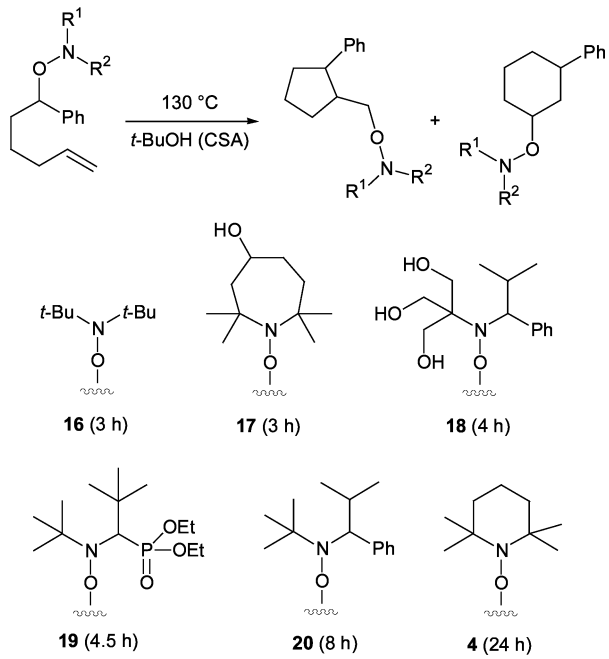


Fig. 3 Rate constants log(k_d) for the C–O-bond homolysis of TEMPO derivatives *vs.* BDE(C–H) of the corresponding alkane.

constants are depicted *versus* the bond dissociation energies (BDE) of the corresponding hydrocarbons. Alkoxyamine isomerizations work well if k_d is larger than $\sim 10^{-5}$ s^{-1} and if BDE is smaller than $\sim$390 kJ mol^{-1}. Thus, by simply looking at the BDE of the alkane one can judge whether a PRE-mediated isomerization reaction using TEMPO as the persistent species is feasible or not.

We then started to test other nitroxides to conduct these alkoxyamine isomerizations. It is clear that the structure and the stability of the nitroxide (steric and electronic effects) will alter the reactivity of the corresponding alkoxyamine. Meanwhile more than 30 different nitroxides have been tested in our group. Only a few will be discussed in the present article. As a model reaction to judge the efficiency of a nitroxide we studied the 5-*exo*/6-*endo* type isomerization shown in Scheme 4. The reactions were conducted in *t*-BuOH at 130 °C and the time necessary to get complete conversion was determined. Yields ranging from 50 to 80% were obtained.

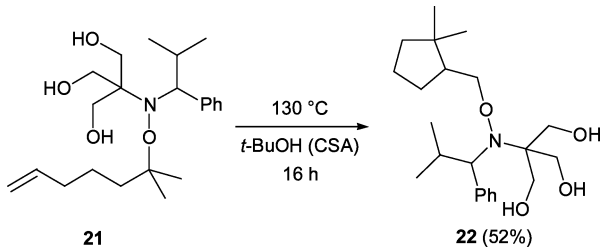


Scheme 4 Effect of the nitroxide on the alkoxyamine isomerization.

Sterics play an important role in these processes. Thus, the sterically highly hindered di-*tert*-butylnitroxide derived alkox-

yamine **16** isomerized in just 3 h. We further found that in cyclic nitroxides the ring size influences the C–O-bond dissociation energy (BDE) of the corresponding alkoxyamines.[20] The BDE increases from 7- to 6- to 5-membered cyclic systems. For alkoxyamine **17** bearing a 7-membered cyclic nitroxide isomerization was completed within 3 h, but for the 6-membered TEMPO-derivative **4** reaction took 24 h. However, a further increase of the ring-size (8-membered ring) of the nitroxide does not lead to a smaller BDE of the corresponding alkoxyamine.

We found that nitroxides capable of forming intramolecular H-bonds[18] are well suited for our PRE-mediated radical processes. For instance, alkoxyamine **18** isomerized in 4 h, whereas for the corresponding non-H-bonding system **20**, 8 h were necessary to get complete conversion under the same conditions. Phosphonate **19**[21] isomerized in 4.5 h. With the most efficient nitroxides it is also possible to generate tertiary alkyl radicals.[16,22] As example, the isomerization of alkoxyamine **21** to **22** is depicted in Scheme 5. The



21 **22** (52%)

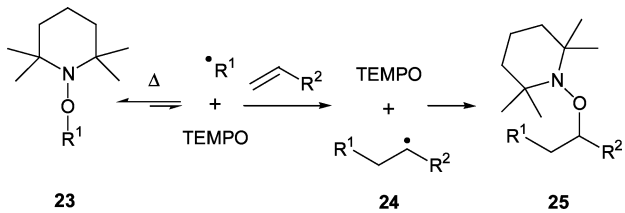
Scheme 5 Isomerization of a tertiary alkoxyamine.

same reaction using TEMPO as nitroxide component does not work. The C–O-bond in the TEMPO-derived tertiary alkoxyamine is too strong to be cleaved under the applied conditions.

To conclude this section, one can state that readily available TEMPO-derived alkoxyamines can be used in thermal radical isomerization reactions if stabilized radicals are involved in the processes. However, for the generation of less stabilized radicals, such as *tert*-alkyl radicals, more sophisticated alkoxyamines are necessary.

Intermolecular radical addition and addition/cyclization reactions of alkoxyamines onto non-activated alkenes

Our next goal was the application of the above presented concept to intermolecular reactions. The general reaction scheme is depicted below. Reversible thermal C–O-bond homolysis of an alkoxyamine **23** will generate R^1 and TEMPO (Scheme 6). Reaction of R^1 with

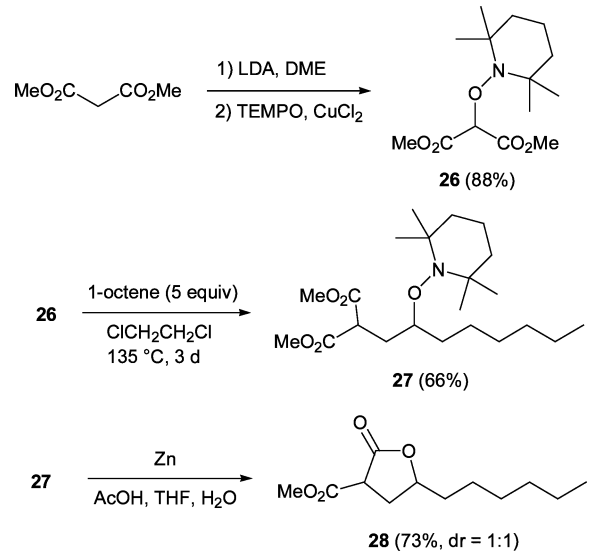


23 **24** **25**

Scheme 6 Intermolecular alkoxyamine additions.

an olefin CH_2=CHR[2] will afford radical adduct **24**, which will be trapped by TEMPO to eventually provide **25**. Since the generation of radical R^1 is a reversible process, it has a longer formal lifetime, and the method should particularly be useful for slow intermolecular radical additions. In order to succeed, several issues have to be considered. The generation of radical R^1 is only an efficient process if R^1 is a stabilized radical, as discussed in the previous section. However, stabilized radicals are in general not reactive in intermolecular addition reactions. Furthermore, trapping of **24** has to be efficient in order to circumvent telomerization (oligomerization, polymerization).

It is well known that malonyl radicals are stable. Moreover, they are reactive in intermolecular addition reactions.[23] Thus, malonyl-TEMPO **26**, which is readily prepared in a single operation from commercially available dimethyl malonate and TEMPO, should add to non-activated olefins according to Scheme 6. The synthesis of **26** is presented in Scheme 7. Indeed, heating of **26** and 1-octene

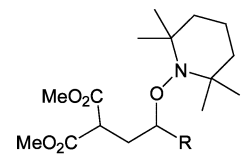


Scheme 7 Synthesis of **26** and its thermal addition onto 1-octene.

(5 equiv) in $ClCH_2CH_2Cl$ for 3 days afforded the desired alkoxyamine addition product **27** in 66% yield (Scheme 7).[24] The reaction can also be conducted in C_6H_5Cl, $C_6H_5CF_3$ and CH_3CO_2Et. Yields ranging from 55–64% were obtained.

The intermolecular addition of **26** onto 1-octene is a carboaminoxylation of a non-activated olefin, a process not known in the literature so far. Furthermore, the N–O-bond in the product alkoxyamine can be readily cleaved using activated Zn, as shown in Scheme 7. N–O-cleavage and subsequent lactonization provided **28** in 73% yield as a 1 : 1 mixture of diastereoisomers. Thus, our addition can formally be regarded as a radical carbohydroxylation process. Again, a useful reaction of which only a few examples are known in the literature to date.

We have shown that the radical carboaminoxylation is a general reaction. Various non-activated olefins were used as radical acceptors in this process. In Fig. 4 some carboaminoxylation



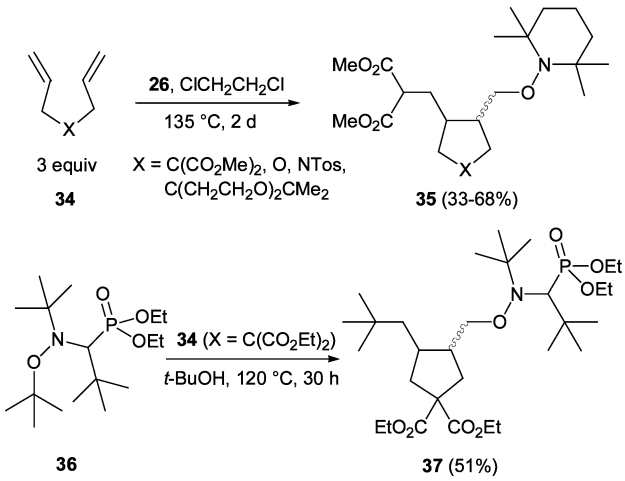
29 (49%, R = CH_2CH_2Ph)
30 (78%, R = OBu)
31 (42%, R = $CH_2CH_2CH_2OCO_2Me$)
32 (70%, R = $CH_2CH_2CH_2OTBDMS$)
33 (64%, R = *N*-Phthalimide)

Fig. 4 Some alkoxyamines prepared by the thermal radical carboaminoxylation.

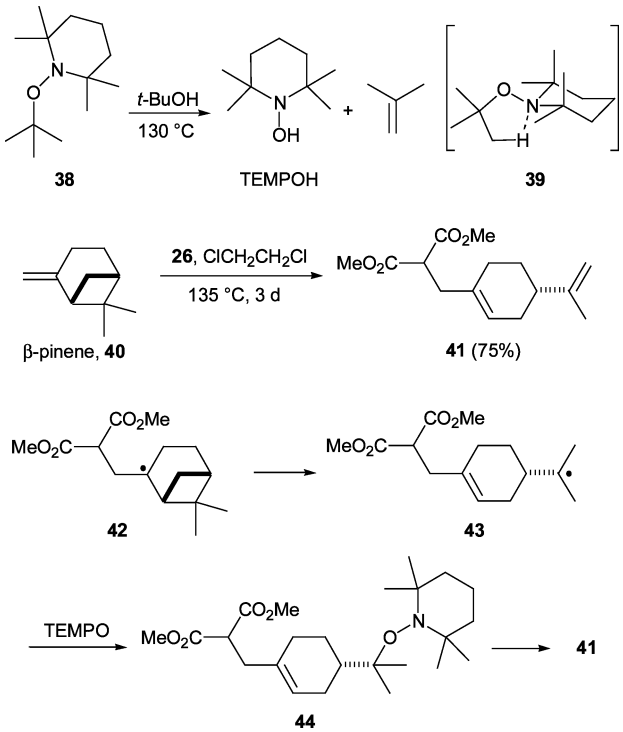
products **29–33** are presented showing that the applied conditions are compatible with different functional groups such as arenes, acetals, carbonates and silyl ethers.

The radical carboaminoxylation can also be combined with a cyclization reaction. Various olefins **34** were successfully reacted with malonate **26** to provide the corresponding addition/cyclization products **35** (Scheme 8). Moderate to good yields were obtained for these reactions. Unfortunately, the cyclizations are not stereoselective. Recently, Ciufolini reported similar addition/cyclization reactions using alkoxyamine **36**.[22] An example is presented in Scheme 8 (→ **37**). In agreement with our work, Ciufolini showed that tertiary alkyl radicals can be generated from the corresponding alkoxyamines if sophisticated nitroxides are used.

During our investigations we found that tertiary TEMPO-derived alkoxyamines are not stable under the standard reaction conditions (*t*-BuOH, 130 °C). For example, prolonged heating of alkoxyamine **38** leads to the formation of isobutylene and TEMPOH (Scheme 9).



Scheme 8 Addition/cyclization reaction using the PRE.



Scheme 9 Elimination of TEMPOH in *tert*-alkyl-TEMPO derivatives.

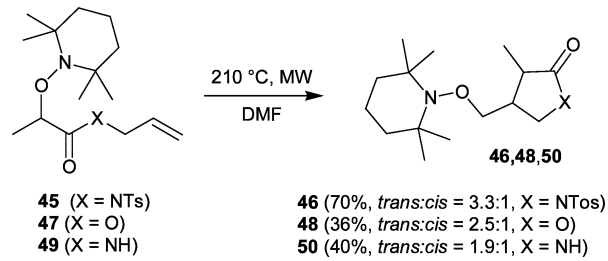
Two mechanisms can be considered for this elimination process.[25] Thermal C–O-bond homolysis affords TEMPO and the *tert*-butyl radical. Disproportionation will eventually lead to TEMPOH and isobutylene. In addition, a concerted process (see **39**) would directly lead to the elimination products. Since the C–O-bond in tertiary TEMPO-derived alkoxyamines is strong,[18] we think that at least for **38**, the ladder mechanism is operative under the applied conditions (130 °C). The elimination process can be integrated in radical cascade reactions. Reaction of β-pinene (**40**) with **26** afforded the ring-opening/elimination product **41** in 75% yield. This interesting cascade comprises the following steps. Malonyl radical addition leads to the tertiary radical **42**, which undergoes β-fragmentation to generate **43**. PRE-mediated selective trapping of **43** with TEMPO affords alkoxyamine **44**, which regioselectively eliminates TEMPOH to finally give **41**.

Microwave-assisted free radical chemistry using the PRE

A serious limitation of the alkoxyamine isomerizations/additions presented above is the long reaction time necessary to get high conversions. For the intermolecular additions it takes up to 3 days to get quantitative conversion. We therefore conceived the idea of using microwave (MW) induced heating to conduct these thermal processes.[26,27]

As a model reaction we first examined the carboaminoxylation of 1-octene with alkoxyamine **26** to give adduct **27**.[28] Various solvents were tested. The best result was obtained in DMF. Heating a 0.07 molar solution of **26** in DMF at 180 °C for 10 min afforded **27** in 63% yield. The same reaction under classical conditions took 3 days (see Scheme 7). Hence, a 430-fold acceleration was achieved upon switching to microwave irradiation. The carboaminoxylations were performed in sealed tubes using professional laboratory microwave equipment. The experimental setup allowed the exact temperature control inside the vessel. MW experiments in PhCOMe, $C_6H_4Cl_2$ and DMSO provided slightly lower but still satisfactorily yields (53–62%). Under the optimized conditions (DMF, 180 °C, 10 min) various non-activated olefins were reacted with malonate **26**. In most of the cases even better yields were obtained, compared to the yields obtained using classical heating (→ **29** (71%), **30** (84%), **31** (70%), **32** (78%), **33** (72%)). The reaction of β-pinene (**40**) with **26** under MW conditions afforded the addition/fragmentation/elimination product **41** in 94% yield in just 10 minutes.

We also studied alkoxyamine isomerizations using MW-induced heating. Isomerization of alkoxyamine **4** to give **8** (51%, *trans : cis* = 3.8 : 1) and **9** (*trans : cis* = 1 : 1) was completed within 2.5 minutes at 180 °C. Moreover, we found that difficult radical cyclizations can be conducted using MW irradiation. For these isomerizations the reaction conditions were modified. The reactions were best conducted at 210 °C for 2.5 min (Scheme 10). For



Scheme 10 MW-induced heating for the conduction of difficult radical alkoxyamine isomerizations.

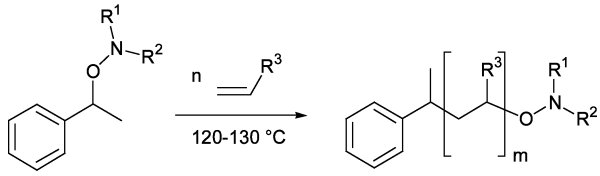
example, allyl tosyl amide **45** could efficiently be isomerized to **46** (70%). A lower yield was obtained for the cyclization of ester **47** (→ **48**). For the isomerization of amide **49** addition of CSA was necessary for a successful isomerization. Furthermore, the reaction time had to be increased (12 min). Amide **50** was isolated in 40% yield (*trans : cis* = 1.9 : 1). It is important to note that the alkoxyamines **45**, **47** and **49** can not be isomerized using classical heating, documenting the power of MW-induced heating to conduct these radical alkoxyamine isomerizations.

To conclude these two sections, difficult alkoxyamine additions or isomerizations can either be performed using sophisticated nitroxides under comparably mild conditions or using MW heating with commercially available TEMPO as nitroxide component under harsh conditions.

Alkoxyamines as initiators/mediators for the controlled/living radical polymerization

Well-defined polymers with polydispersities below the theoretical limit for a conventional radical polymerization (1.5) can nowadays be prepared by controlled/living radical polymerization. Nitroxide-mediated polymerizations (NMP) belong to this category.[1,8] The NMP can also be called Stable Free Radical Polymerization (SFRP). The NMP process is controlled by the persistent radical effect. In analogy to our alkoxyamine additions discussed in the previous sections, the control of the polymerization in the NMP is based on the reversible formation of a dormant alkoxyamine from

the corresponding nitroxide and the chain growing polymer radical. Mediated by the PRE, the concentration of free radicals remains low during the entire polymerization, thus ensuring a very low fraction of irreversible termination *via* polymer radical dimerization/disproportionation. The equilibrium constant between the nitroxide-capped polymer and the free nitroxide and polymer radical, respectively, is therefore of great importance in these processes.[1] In the context of this tutorial review, NMP can be regarded as a multiple intermolecular radical carboaminoxylation process. The polymerizations are generally conducted in bulk at 120–130 °C and an alkoxyamine, often derived from the styryl radical, is used as the initiator/mediator (Scheme 11).



Scheme 11 Nitroxide mediated controlled/living radical polymerization.

In seminal work, it was shown that TEMPO can be used as nitroxide component to control the polymerization of styrene.[29,30] Meanwhile many reports on the use of styryl–TEMPO **51** as an initiator/mediator for the controlled polymerization of styrene and styrene derivatives have appeared in the literature (Fig. 5).[1,8] However, this initiator is only suitable for the polymerization of styrene derivatives. Unfortunately, the polymerization of acrylates cannot be performed with **51** in a controlled manner.

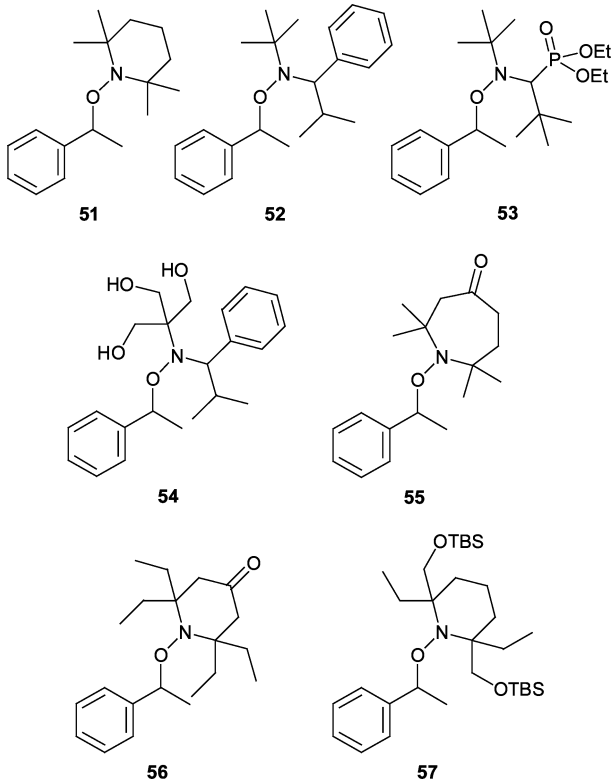


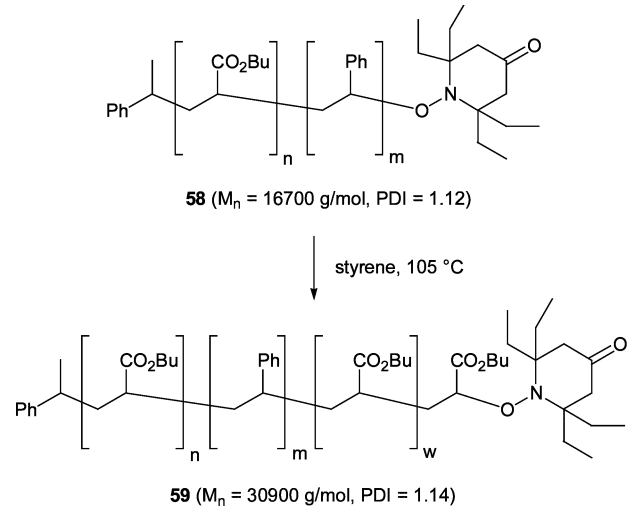
Fig. 5 Alkoxyamines for NMP.

Many groups in industry as well as in academia are working on the development of new alkoxyamines for the controlled/living radical polymerization of acrylates. Hawker, Braslau and coworkers first showed that alkoxyamine **52**, derived from a non-cyclic nitroxide, is able to mediate the controlled acrylate polymerization.[31] Tordo and coworkers successfully used phosphonate **53** for the controlled/living polymerization of *n*-butyl acrylate.[32] Polydispersities below 1.2 were obtained with alkoxyamines **52** and **53**. Moreover, block copolymers can readily be prepared using **52** and **53**.

It is obvious that nitroxides, which are highly efficient to conduct PRE-mediated isomerizations and carboaminoxylations, should also be good candidates for controlled/living radical polymerizations. We therefore tested most of our nitroxides, designed for the application in organic synthesis as mediators in the controlled polymerization of styrene and *n*-butyl acrylate.

Nitroxides capable of forming intramolecular H-bonds, which turned out to be highly efficient persistent species in radical isomerizations (see Scheme 5), have been shown by Hawker to be excellent mediators for the *n*-butyl acrylate polymerization (*e.g.* **54**).[33] We have discussed above how ring enlargement in cyclic nitroxides leads to an increase of the rate constant for the C–O-bond homolysis of the corresponding alkoxyamines. This should also increase the mediator efficiency of these alkoxyamines in polymerizations. Indeed, the 7-membered alkoxyamine **55** is a good initiator/mediator for the styrene polymerization.[20] Acceptable results have also been obtained for the preparation of low-molecular weight poly(*n*-butyl acrylate). The sterically highly hindered tetraethyl–TEMPO-derivative **56** is probably the most efficient mediator/regulator known to date.[34] Styrene and *n*-butyl acrylate can be polymerized at temperatures as low as 90 °C. Polydispersities below 1.2 were obtained using **56**.

Moreover, we have shown that block copolymers are readily prepared with the sterically hindered alkoxyamine **56** (Scheme 12).



Scheme 12 Preparation of triblock copolymer **59** using macroinitiator **58**.

Gel permeation chromatography traces (GPC-traces) of the macroinitiator diblock copolymer **58** and the product triblock copolymer **59** documenting the highly controlled/living character of the **56**-mediated polymerization are presented in Fig. 6. Furthermore,

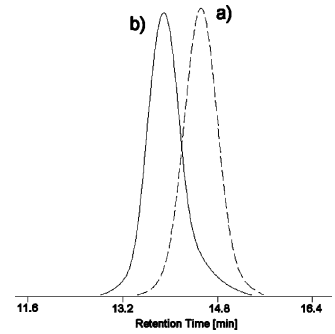


Fig. 6 GPC-traces of **58** (trace a) and product **59** (trace b).

we have found that alkoxyamine **57**, which is easier to prepare than **56**, is as efficient a mediator/regulator for the styrene and acrylate polymerization as **56**.[35] Thus, the careful design of nitroxides for PRE-mediated radical isomerizations allowed us to develop new highly efficient alkoxyamines for the controlled/living radical polymerization.

Summary and outlook

The PRE-mediated thermal reversible alkoxyamine homolysis is a highly efficient method for the clean generation of C-radicals. This method can be used to conduct environmentally benign tin-free radical reactions. Cyclizations and intermolecular additions can be performed using this approach. The reactivity of the alkoxyamines can be tuned *via* the structure of the nitroxides. In addition, we have shown that microwave-induced heating can be applied to perform these thermal radical reactions. So far microwaves have found scant applications in free radical chemistry. We believe that microwaves can also be used to speed up other typical radical reactions. Studies in this direction are ongoing.

The alkoxyamines can also be used as initiators/mediators for the controlled/living radical polymerization of styrene, styrene derivatives and acrylates.[1,8] Alkoxyamines, which turned out be highly efficient for the conduction of PRE-mediated isomerizations, are also efficient mediators in polymerizations. Hence, the radical isomerizations can be regarded as assays to find new efficient alkoxyamine polymerization mediators. We have shown that our new alkoxyamines can be used for the preparation of triblock copolymers. These polymer mediators will be used in the future for the preparation of complex polymer architectures. Moreover, polymer brushes should be readily prepared using our systems. Thus, these PRE-mediated processes are general and can be used for organic synthesis, for polymer chemistry and also for material science.[8]

I thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for funding. Moreover, I would like to thank my coworkers K. Jantos, C. A. Knoop, C. Müller, T. Schulte, C. Wetter and K. Woithe for their important contributions to the projects discussed in this tutorial review. Furthermore, Professor H. Fischer and Dr S. Marque are acknowledged for a fruitful collaboration and many helpful discussions.

References

1 H. Fischer, *Chem. Rev.*, 2001, **101**, 3581.
2 A. Studer, *Chem. Eur. J.*, 2001, **7**, 1159.
3 W. E. Bachmann and F. Y. Wiselogle, *J. Org. Chem.*, 1936, **1**, 354.
4 G. Geiger and J. R. Huber, *Helv. Chim. Acta*, 1981, **64**, 989.
5 H. Fischer, *J. Am. Chem. Soc.*, 1986, **108**, 3925.
6 B. E. Daikh and R. G. Finke, *J. Am. Chem. Soc.*, 1992, **114**, 2938.
7 T. Kothe, S. Marque, R. Martschke, M. Popov and H. Fischer, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1553.
8 C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, 2001, **101**, 3661.
9 A. Studer and S. Amrein, *Synthesis*, 2002, 835.
10 K. Matyjaszewski, B. E. Woodworth, X. Zhang, S. G. Gaynor and Z. Metzner, *Macromolecules*, 1998, **31**, 5955.
11 R. Braslau and M. O. Anderson, in *Radicals in Organic Synthesis*, eds. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, **Vol. 2**, p. 127.
12 C. J. Hawker, G. G. Barclay, A. Orellana, J. Dao and W. Devonport, *Macromolecules*, 1996, **29**, 5245.
13 R. Braslau, L. C. Burrill II, M. Siano, N. Naik, R. K. Howden and L. K. Mahal, *Macromolecules*, 1997, **30**, 6445.
14 U. Jahn, P. Hartmann, I. Dix and P. G. Jones, *Eur. J. Org. Chem.*, 2001, 3333 and references cited therein.
15 C. Ollivier, R. Chuard and P. Renaud, *Synlett*, 1999, 807.
16 A. Studer, *Angew. Chem., Int. Ed.*, 2000, **39**, 1108.
17 For a similar isomerization see: D. A. Allen, M. F. Fenwick, H. Henry-Riyad and T. T. Tidwell, *J. Org. Chem.*, 2001, **66**, 5759.
18 S. Marque, H. Fischer, E. Baier and A. Studer, *J. Org. Chem.*, 2001, **66**, 1146.
19 Upon considering steric and polar effects the correlation can be improved: S. Marque, *J. Org. Chem.*, 2003, **68**, 7582.
20 T. Schulte and A. Studer, *Macromolecules*, 2003, **36**, 3078.
21 S. Grimaldi, J.-P. Finet, A. Zeghdaoui, P. Tordo, D. Benoit, Y. Gnanou, M. Fontanille, P. Nicol and J.-F. Pierson, *Polym. Prepr.(Am. Chem. Soc., Div. Polym. Chem.)*, 1997, **38**, 651.
22 C. Leroi, B. Fenet, J.-L. Couturier, O. Guerret and M. A. Ciufolini, *Org. Lett.*, 2003, **5**, 1079.
23 J. Byers, in *Radicals in Organic Synthesis*, eds. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, **Vol. 1**, p. 72.
24 C. Wetter, K. Jantos, K. Woithe and A. Studer, *Org. Lett.*, 2003, **5**, 2899.
25 G. S. Ananchenko and H. Fischer, *J. Polym. Sci. Part A: Polym. Chem.*, 2001, **39**, 3604.
26 L. Perreux and A. Loupy, *Tetrahedron*, 2001, **57**, 9199.
27 P. Lidström, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225.
28 C. Wetter and A. Studer, *Chem. Commun.*, 2004, 174.
29 D. H. Salomon, E. Rizzardo and P. Cacioli, *US Pat.* 4 581 429,1985; *P. Eur. Pat. Appl. 135280*, 1985.
30 M. K. Georges, R. P. N. Veregin, P. M. Kazmeier and G. K. Hamer, *Macromolecules*, 1993, **26**, 2987.
31 D. Benoit, V. Chaplinski, R. Braslau and C. J. Hawker, *J. Am. Chem. Soc.*, 1999, **121**, 3904.
32 S. Grimaldi, J.-P. Finet, F. Le Moigne, A. Zeghdaoui, P. Tordo, D. Benoit, M. Fontanille and Y. Gnanou, *Macromolecules*, 2000, **33**, 1141.
33 E. Harth, B. Van Horn and C. J. Hawker, *Chem. Commun.*, 2001, 823.
34 C. Wetter, J. Gierlich, C. A. Knoop, C. Müller, T. Schulte and A. Studer, *Chem. Eur. J.*, 2004, **10**, 1156.
35 C. A. Knoop and A. Studer, *J. Am. Chem. Soc.*, 2003, **125**, 16327.