The Persistent Radical Effect in Organic Synthesis

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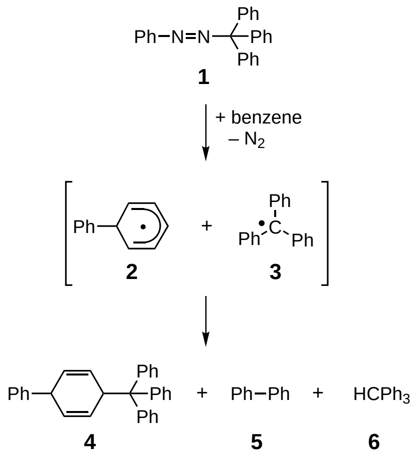
Abstract: The persistent radical effect (PRE) is a principle that explains the highly selective cross-coupling between a persistent and a transient radical when both species are formed at equal rates. In this paper, the concept of the PRE is briefly discussed. Applications of the PRE in different reactions such as Co-mediated radical addition and cyclization reactions, Kharasch reactions catalyzed by transition metals, the Barton reaction, and our nitroxide-mediated tin-free radical cyclizations are presented. Some future perspectives for the PRE in organic synthesis are also provided.

Keywords: C–C coupling · homogeneous catalysis · persistent radical effect · radicals · synthetic methods

Introduction

Back in the sixties, Perkins published an interesting paper on the thermal decomposition of phenylazotriphenylmethane (**1**) in benzene (Scheme 1).[1] As products *cis* and *trans*-1,4-dihydro-4-tritylbiphenyl (**4**), biphenyl (**5**), and triphenylmethane (**6**) were obtained. These products all derive from selective reaction of the intermediately formed cylohexadienyl radical **2** with the triphenylmethyl radical (**3**), either by disproportionation (→**5**, **6**) or by cross-coupling (→**4**). Interestingly, no products deriving from dimerization of radical **2** were observed. In a subsequent paper,[2] Perkins correctly suggested the reason for the highly selective cross-coupling reactions and for the discrimination of other possible reaction pathways: "The exceptional stability of triphenylmethyl radicals is probably responsible for the observed discrimination between possible product-forming steps in reactions of phenylazotriphenylmethane. This is because any trace occurrence of radical-destroying processes which do not involve triphenylmethyl radicals must give rise to a high stationary-state concentration of this stable species. The relatively high concentration of triphenylmethyl radicals can subsequently scavenge other radicals which are formed (with the exception of the very short-lived phenyl radical). Under stationary-state conditions, triphenylmethyl radicals are being formed at the same rate as that at which they are being converted into products. Hence, the relatively high concentration is maintained, and the scavenging effect continues throughout the reaction."



Scheme 1. Decomposition of phenylazotriphenylmethane in benzene.

About 20 years later, Huber noted that irradiation of dimethylnitrosamine in the gas phase neither leads to photoproducts nor to a decrease of starting material.[3] Thus, NO and the dimethylaminyl radical formed after initial N–N bond homolysis undergo highly selective cross-coupling to the starting nitrosamine. The similarities between the Perkins and the Huber processes was recognized by Fischer.[4] He formulated a general principle to explain unusual selectivities of radical reactions by internal suppression of fast modes. Later this principle was called the persistent radical effect (PRE) by Finke.[5]

The 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 (long lived) and the other transient and the two radicals are formed at equal rates. The initial buildup in concentration of the persistent species, caused by the self-termination of the transient radical, steers the reaction subsequently to follow a single pathway, that is, the cross reaction.

In the present concept paper we will discuss some selected examples[6] of the PRE in organic synthesis focussing on our

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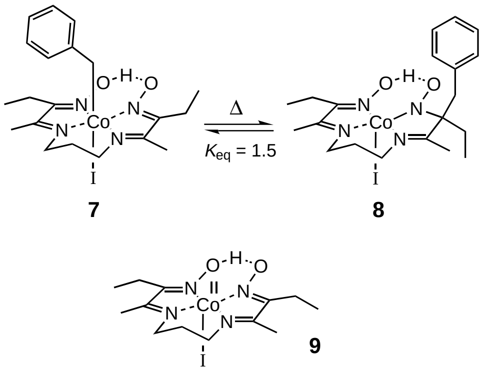
own work on the use of the PRE in tin-free radical cyclization reactions.[7] Regarding the PRE effect in the field of stable free-radical polymerization and atom-transfer radical polymerization, we refer to several nice review articles.[8]

Discussion

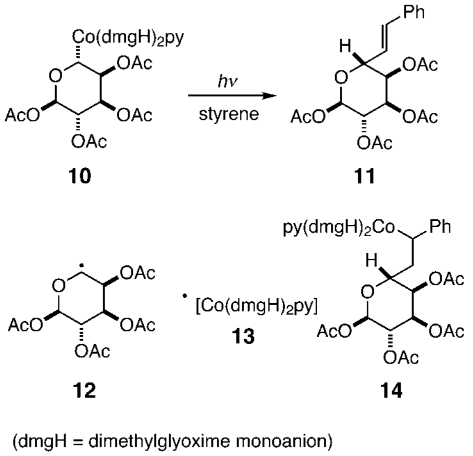
Processes mediated by transition metals: An extreme example of the PRE was published by Finke in 1992. He studied the isomerization of coenzyme B$_{12}$ model complex **7** to form **8** (Scheme 2).[5] He clearly showed that the apparently intramolecular reaction proceeds completely via intermolecular, freely diffusing radicals.[9] Thermal C–Co bond homolysis affords the persistent Co^{II} complex **9** and the transient benzyl radical in equal concentration. According to the PRE, the initial build up of the persistent Co species due to the formation of bibenzyl should lead to a highly selective cross-coupling (→**7**, **8**) and, thus, to a suppression of further bibenzyl formation. Indeed, Finke showed that the isomerization is a clean reaction and bibenzyl was formed in very small amounts (0.001 %) with respect to **7** and **8**.[10]



Scheme 2. Thermal isomerization of Co complex **7**.

Certainly, the isomerization described by Finke is of little preparative value; however, one can imagine using alkyl cobalt complexes as radical precursors in synthetically useful processes. Indeed, there are many reports of Co-mediated radical reactions[11] that follow the PRE principle. For example, Giese described several intermolecular radical addition reactions using glycosyl cobalt complex **10**.[12] For instance, irradiation of **10** in the presence of an excess of styrene in benzene afforded C-glycoside **11** (65 %, Scheme 3).

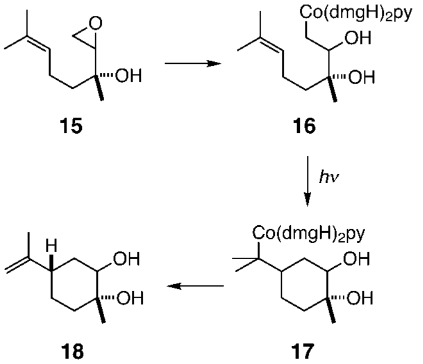
Abstract in German: *Der „Persistent Radical Effect“ (PRE) ist ein generelles Prinzip zur Erklärung der hochselektiven Bildung des Kreuzkupplungsprodukts aus einem langlebigen (persistenten) Radikal und einem kurzlebigen (transienten) Radikal. Dabei müssen die beiden Radikale gleichzeitig und in gleichen Mengen gebildet werden. In dieser Arbeit wird kurz das Prinzip des PRE erläutert. Anwendungen des PRE in verschiedenen Reaktionen wie Co-vermittelte radikalische Additions- und Cyclisierungsreaktionen, übergangsmetallkatalysierte Kharash Reaktionen, die Barton Reaktion und unsere neuen Nitroxid-vermittelten zinnfreien radikalischen Cyclisierungs-Reaktionen werden vorgestellt. Des Weiteren wird das Potential des PRE für zukünftige Anwendungen in der organischen Synthese dargestellt.*



Scheme 3. Co-mediated intermolecular radical addition reaction.

Reversible homolytic C–Co bond cleavage affords the transient glycosyl radical **12** and the persistent Co complex **13**. Intermolecular styrene addition onto radical **12** with subsequent reversible trapping of the intermediate benzylic radical with **13** affords complex **14**. Formal “dehydrocobaltation” eventually leads to the isolated product **11**.[13] Similar Co-mediated radical vinylations have been described by Branchaud[14] and Pattenden.[15]

In analogy, radical cyclization reactions have been performed. For example, epoxide opening in **15** with a nucleophilic Co^{I} reagent afforded alkyl–Co complex **16** as depicted in Scheme 4.[16] Isomerization of **16** under irradiation provides compound **17** (not isolated) which in turn undergoes “dehydrocobaltation” to form **18** (94 %). Formally, the transformation of **16** to **17** can be regarded as a cobalt-group transfer. However, as mentioned above, this process underlies the principle of the PRE and is not a chain reaction. Under special conditions the isomerized alkyl cobalt compounds can be isolated.[17] For additional reports on selective Co-mediated

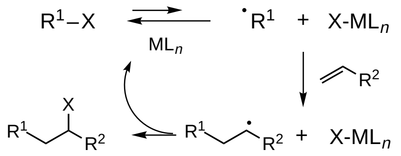


Scheme 4. Co-mediated radical cyclization reaction.

radical cyclization reactions that probably occur according to the principle of the PRE, we refer to two review articles.[11, 18]

In 1945, Kharasch first reported the radical addition of carbon tetrachloride to olefinic double bonds.[19] This reaction, often called the Kharasch addition, has found limited application in organic synthesis. This is mainly due to problems with telomerization and polymerization. About 30 years later, Minisci observed that upon addition of redox catalysts clean 1:1 adducts of CCl_4 with various olefins can be obtained.[20] Fe^{II} and Cu^{II} salts[21] were used as catalysts in those studies. Meanwhile, other catalysts derived from various metals, such as Ni[22] and Ru[23] among others, have also been used for these radical addition reactions. Although the mechanism of these reactions is still not entirely understood,[24] there are some reports pointing out the importance of the PRE in these transformations.[8g, 23c]

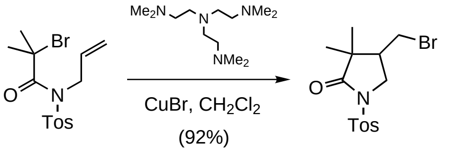
It is generally believed, that in the first step the redox-active metal ($[ML_n]$) abstracts a halogen atom from the starting material ($R^1{-}X$) to form the corresponding complex, which is a persistent radical, in its higher oxidation state ($[X{-}ML_n]$) along with the transient C-centered radical ($^{\bullet}R^1$, Scheme 5).



Scheme 5. Kharash reaction catalyzed by transition metals.

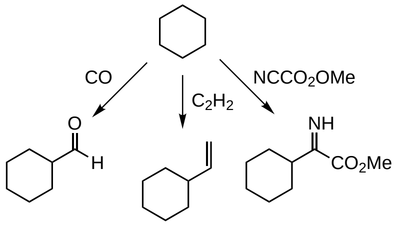
Indeed, van Koten was able to isolate a persistent Ru^{III} intermediate in such a process.[23c] Initial halogen abstraction is reversible. The transient radical can then add to an unsaturated group in an inter- or intramolecular reaction to form the corresponding radical adduct, which subsequently reabstracts the halogen atom from the oxidized metal compound $[X{-}ML_n]$ to form the halogen atom transfer product. In most of the cases this reabstraction is an irreversible process, since the adduct radical is generally less stable than the starting transient radical. However, if the adduct radical is as stable as the initial radical, halogen reabstraction is also reversible and polymerization can occur.[8f,g]

In Scheme 6 an example of an halogen-atom-transfer radical cyclization catalyzed by CuBr is presented.[25] A drawback of this chemistry is that the C–X bond of the starting material has to be activated.[26]



Scheme 6. Cu-catalyzed radical cyclization reaction.

In a series of papers, Hill showed that unactivated C–H bonds can be functionalized by using photoactivated polyoxotungstates as catalysts.[27] The mechanism, although not completely understood, is radical in nature. Thus upon irradiation of the decatungstate ion $[W_{10}O_{32}]^{4-}$, the corresponding reactive excited state abstracts an H atom from the unactivated alkane to generate the transient C-centered radical and the reduced decatungstate $[H]^+[W_{10}O_{32}]^{5-}$ ion. C–H activation is reversible. Reaction of the transient radical with radical acceptors such as CO,[28] ethene,[29] acetylene,[29] and methyl cyanoformate[30] affords the corresponding transient radical, which in turn is reduced by $[W_{10}O_{32}]^{5-}$ to form the functionalized alkane. The reactions are generally stopped at low conversions. Examples of such processes are depicted in Scheme 7. Fischer has shown that these reactions obey the principle of the PRE.[31] EPR and kinetic absorption spectroscopy experiments revealed the simultaneous formation of transient C-centered radicals and a persistent tungstate species ($[W_{10}O_{32}]^{5-}$) during the photoactivation of $[W_{10}O_{32}]^{4-}$ with organic substrates in solution.



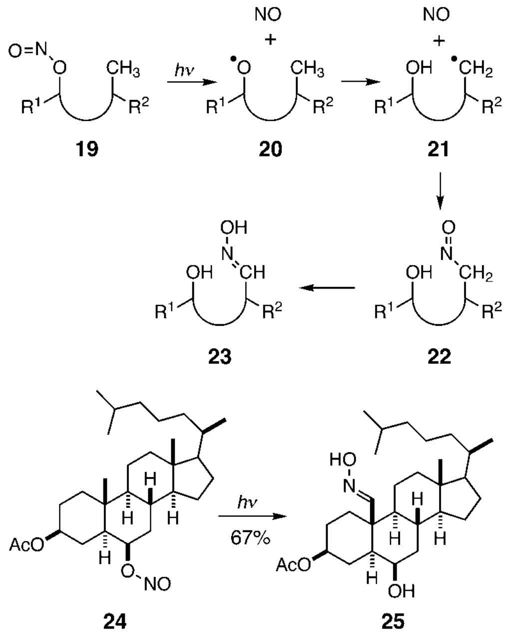
Scheme 7. C–H activation by polyoxotungstates. Conditions: R–H, CH_3CN, $[Bu_4N]_4[W_{10}O_{32}]$, *hν*.

We believe that many reactions based on transition metals with redox-active catalysts occur through radical processes, which function according to the principle of the PRE. Future work has to prove our hypothesis.

Metal-free processes: In 1960, Barton first described the remote fuctionalization of alkanes by photolysis of nitrite esters.[32] This reaction, now known as the Barton reaction, has found widespread application in synthesis, especially in the field of steroid modification.[33] The general reaction sequence is presented in Scheme 8. Photolysis of nitrite ester **19** affords the corresponding alkoxyl radical **20**, along with the persistent NO radical. Intramolecular H transfer, generally from the *δ*-carbon, generates a transient C-centered radical **21**, which according to the PRE undergoes highly selective cross-coupling with NO to form the nitroso compound **22**. Tautomerization eventually gives oxime **23**. As an example, the photochemical transformation of steroid **24** to **25** is also shown in Scheme 8.[34]

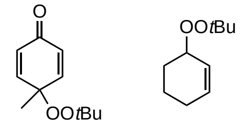
In addition to the typical Barton reaction, there are other radical processes involving the persistent NO radical that show high specifities for the formation of NO-trapping products. All of these reactions probably follow the kinetic scheme of the PRE. These include photochemical reactions of *N*-nitrosamines[3, 35] and photooxidations of alkanes by NOCl.[36]

Recently, Minisci reported the highly selective formation of mixed peroxides from *tert*-butyl hydroperoxide.[37] Transient C-centered radicals and the rather persistent *tert*-butyl hydroperoxyl radical were generated in equal concentration from



Scheme 8. Barton reaction.

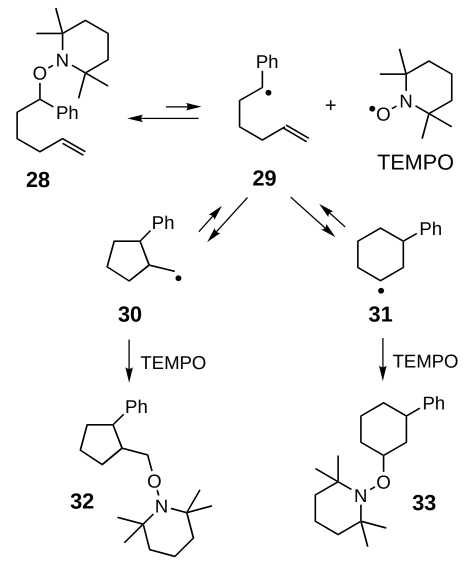
the corresponding precursor (*p*-cresol or cyclohexene) and *t*BuOOH by means of *tert*-butoxyl radicals. Selective cross-coupling of the transient carbon radical with the peroxyl radical provides the mixed peroxides **26** and **27**, respectively in high yield.



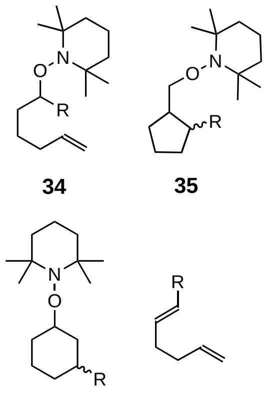
26 **27**

Very recently, we described our first application of the PRE in tin-free radical cyclization reactions.[7] We chose various nitroxides as the persistent species. It is well known that phenyl-substituted alkoxyamines derived from 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), such as **28**, have weak C–O bonds that can homolytically be cleaved.[38] Upon heating alkoxyamine **28**, a transient C-radical **29** and the persistent TEMPO radical are formed in equal concentration (Scheme 9). Hence, all the criteria of the PRE are fullfilled and high selectivity for the cross-coupling (back reaction) should be obtained. However, transient species **29** can also undergo 5-*exo* or 6-*endo* cyclization to form transients **30** and **31**. Trapping of these transient radicals with TEMPO affords **32** and **33**. TEMPO-trapping of **30** and **31** is irreversible, because the C–O bond in an alkoxyamine derived from TEMPO and a primary or secondary alkyl radical is too strong to be homolytically cleaved.[38] Indeed, heating of **28** in *t*BuOH (0.02 M) in the presence of camphorsulfonic acid (CSA, 10%)[39] for 24 h at 130 °C afforded the isomerized 5-*exo* product **32** (70%, *trans*:*cis* = 2.5:1) and the 6-*endo* product **33** (13%, diastereomeric ratio (*dr*) = 1:1) in a clean reaction.

We further showed that the isomerization works well for alkoxyamines with activated C–O bonds. Thus, all the α-(hetero)aryl-substituted TEMPO derivatives tested so far (**34a–d**), as well as the ester (**34e**), and nitrile (**34f**) derivatives, provided the corresponding cyclization products **35a–f** and **36a–f** in good yields (Table 1). Olefin **37a–f** was always formed as a side product in these isomerizations.



Scheme 9. Tin-free radical cyclization reaction using the PRE.



R	compound
4-BrC_6H_4	a
4-$CH_3OC_6H_4$	b
2-thienyl	c
2-pyridyl	d
tBuO_2C	e
NC	f
H	g
Me	h
PhS	i

Table 1. Isomerization of **34a–f**.

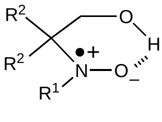
Starting material	**35** [%]	*dr* (**35**) (*trans*:*cis*)	**36** [%][a]	**37** [%]
34a	71	2.7:1	8	< 2[b]
34b	46	2.8:1	8	10
34c	67	2.1:1	11	5
34d	57	1.6:1	12	5
34e	67	1:1	< 2[b]	10
34f	61	1.1:1[c]	7	< 2[b]

[a] The 6-*endo* product was formed as a 1:1 mixture of the diastereoisomers. [b] In the 300 MHz ^1H NMR spectrum of the crude product, no signals of the corresponding compound were observed. [c] The relative configuration of the two isomers was not assigned.

No isomerization occurred with **34g** (R = H), **34h** (R = Me), and **34i** (R = SPh). It is likely that the C–O bond in **34g–i** is too strong to be effectively cleaved.[38]

From these results it is clear that the success of the reaction depends on the strength of the alkoxyamine C–O bond. Therefore, we studied the detailed kinetics of the C–O bond homolysis in various TEMPO-derived alkoxyamines. A rather good correlation of the rate constant (k_d) for the C–O cleavage with the C–H bond-dissociation energy (BDE) of the corresponding alkane was obtained ($\log(k_d)$ [s^{-1}] = $35.5(\pm 5.5) - 0.11(\pm 0.02)$ BDE(C–H) [$kJ\,mol^{-1}$]).[40]

The stability of the nitroxide evidently influences the BDE of the C–O bond of the corresponding alkoxyamine and, hence, the reactivity of the alkoxyamine. Based on results from Ingold and Beckwith on the stabilization of nitroxides by *intermolecular* H bonding,[41] we prepared new nitroxides capable of *intramolecular* H bonding (see **38**).[42] In addition to decreasing the trapping rate of the nitroxide with C-centered radicals, the H bonding should also influence the C–O bond homolysis rate (late transition state). In general, faster C–O homolysis rates and slower trapping rates will lead to a longer lifetime of the transient radical and, thus, to faster overall reaction rates. A series of new nitroxides,[43] with or without the capability of intramolecular H-bonding, was prepared and the corresponding alkoxyamines **39**–**41** tested in the isomerization reaction depicted in Scheme 9 for **28**.



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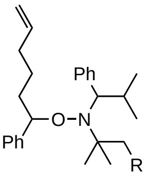
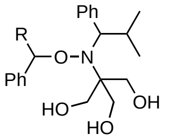
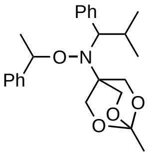


39 (R = OTBDMS)
40 (R = OH)



41 (R = $(CH_2)_3CH=CH_2$)
42 (R = CH_3)

Indeed, **40** was observed to isomerize faster (7 h; 12 h without CSA) than its silylated congener **39** (16 h with CSA). With **41**, reaction was already completed after 4 h (9 h without CSA). We further looked at the effect of intramolecular H bonding by measuring C–O homolysis rates of several alkoxyamines by means of EPR spectroscopy.[40] In agreement with our hypothesis, the homolysis rate of alkoxyamine **43** ($k = 1.5 \times 10^{-4} s^{-1}$) at 120 °C is about 40 times smaller than that for the H-bonding alkoxyamine **42** ($k = 5.6 \times 10^{-3} s^{-1}$).



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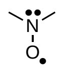

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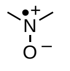

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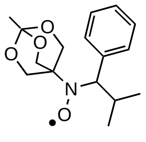
Furthermore, we also studied the EPR hyperfine coupling constants (a_N) of these nitroxides.[40] Nitroxides have two different resonance structures (see **44** and **45**).[44] Polar solvents as well as hydrogen bonding should stabilize structure **45** (compare also **38**). As a_N depends on the spin density on the nitrogen atom,[45] a_N will increase upon increasing the population of resonance structure **45**. Indeed, larger a_N values for nitroxides capable of intramolecular H bonding have previously been reported.[44, 46] The larger a_N of nitroxide **47** ($a_N = 14.88$ G), relative to that for nitroxide **46** ($a_N = 13.81$ G), strongly supports the occurrence of intramolecular H bonding in these compounds.



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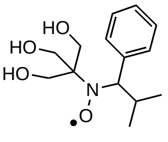

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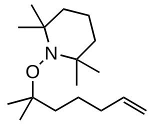

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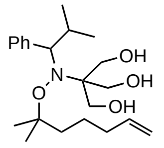

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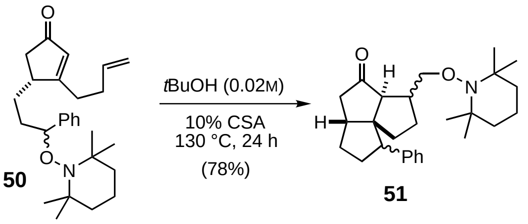
The advantage of our new alkoxyamines over the corresponding TEMPO-derivatives is exemplified by the failure of **48** to isomerize, whereas triol **49** could successfully be transformed into the corresponding isomerized alkoxyamine (52%). Finally, to document the potential of these tin-free radical cyclization reactions a cascade reaction is presented in Scheme 10. Alkoxyamine **50** was readily isomerized to the angular triquinane **51**, which was isolated in 78% yield as a mixture of stereoisomers.[7] Evidently, this new method can be applied to even more complicated tandem radical cyclization reactions with up to 5–6 consecutive isomerizations. Work along this line is underway.



Scheme 10. Radical cascade reaction using the PRE.

Future Outlook

We present here the application of the PRE in a series of different reactions. In principle, any persistent radical can be used to get highly selective cross-coupling with a transient radical when both species are generated in equal concentration. So far, various persistent radicals such as NO, different transition metal complexes, peroxyl radicals, and nitroxides have been used in processes that follow the kinetic scheme of the PRE. Certainly, there are many more persistent radicals that can be tested in similar transformations. Especially in the field of persistent species based on transition metals, we believe that there are great opportunities to apply the principle of the PRE. For nitroxide-mediated cyclization reactions, the design of even better nitroxides will allow the isomerizations to occur under milder conditions.

Furthermore, the knowledge gathered on the PRE in the field of synthetic organic chemistry should be directly applicable to stable free-radical polymerization.

Acknowledgement

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