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Intermolecular Radical Addition and Addition/Cyclization Reactions of Alkoxyamines onto Nonactivated Alkenes

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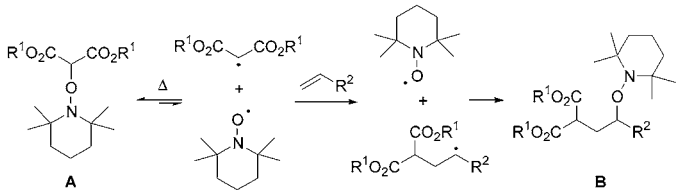
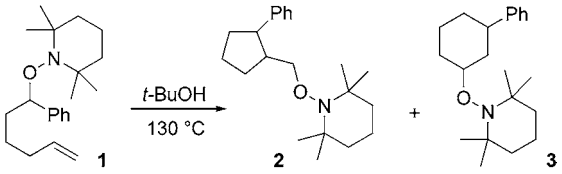
ABSTRACT



Alkoxyamines A, which are readily prepared from commercially available starting materials, undergo efficient thermal radical carboaminoxylations onto various nonactivated alkenes to provide 1,4-functionalized malonates B in good to excellent yields. The experiments are very easy to conduct. The carboaminoxylations can be combined with radical cyclization and fragmentation processes.

Recently, we published our first results on environmentally benign radical alkoxyamine isomerization reactions.[1] These processes are controlled by the so-called Persistent Radical Effect (PRE).[2] For example, alkoxyamine **1** was readily isomerized to the corresponding cyclized alkoxyamines **2** (70%) and **3** (13%) upon simple heating in *t*-BuOH (Scheme 1).

Scheme 1. PRE in Radical Cyclization Reactions



Since the N−O bond can be cleaved with various methods, these alkoxyamine isomerizations can formally be regarded as intramolecular carbohydroxylations (without N−O cleavage as intramolecular carboaminoxylations).

Transition-metal-catalyzed[3] or ionic additions[4] of alcohols onto C−C double bonds are well established in organic synthesis. However, alcohol additions, where the C−O bond inserts into the multiple bond (carbohydroxylation), have rarely been investigated to date.[5] Herein we present our first results on intermolecular radical alkoxyamine additions onto nonactivated double bonds.

Alkoxyamines have found widespread application as regulators/initiators for living radical polymerizations.[6] To circumvent polymerization in our planned bimolecular processes, the stability of the starting and the product alkoxyamine has to be tuned carefully. We have previously

(1) Studer, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1108. See also: Allen, D. A.; Fenwick, M. F.; Henry-Riyad, H.; Tidwell, T. T. *J. Org. Chem.* **2001**, *66*, 5759. Leroi, C.; Fenet, B.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 1079.

(2) (a) Studer, A. *Chem. Eur. J.* **2001**, *7*, 1159. (b) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581.

(3) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270 and references therein.

(4) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, 2001.

(5) (a) Nakamura, H.; Sekido, M.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6838. (b) Monteiro, N.; Balme, G. *Synlett* **1998**, 746. (c) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785.

(6) Hawker, C. J.; Bosman, A. W.; Hart, E. *Chem. Rev.* **2001**, *101*, 3661.

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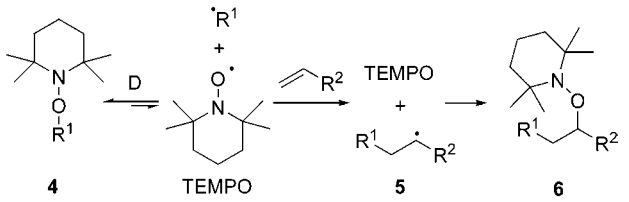
shown that the C−O bond dissociation energy correlates with the C-radical stability.[7] Alkoxyamines derived from nonstabilized C-radicals have strong C−O bonds and are therefore prevented from undergoing C−O bond homolysis. Thus, thermal reversible homolysis of an alkoxyamine **4** derived from a stabilized radical R^1 will generate R^1, which in turn can react with an olefin $CH_2{=}CHR^2$ to afford radical adduct **5** (Scheme 2). If **5** is a nonstabilized radical, irreversible

Scheme 2. PRE in Intermolecular Addition Reactions



trapping with TEMPO will eventually provide **6**. 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.[8]

The first experiments were performed using 1-octene as a radical acceptor. The reactions were conducted in *t*-BuOH (1 M, sealed tube) at 135 °C with a 5-fold excess of the olefin. However, none of the desired products were obtained using the alkoxyamines **7** and **8**. The intermolecular addition of the stable radicals derived from **7** and **8** to 1-octene is too slow to compete with TEMPO trapping. We therefore studied the intermolecular addition of the more reactive tertiary butyl radical using alkoxyamine **9**. Tertiary alkyl radicals react with 1-octene about 2 orders of magnitude faster than secondary benzylic radicals.[9] However, addition did not occur. The activation energy for efficient C−O bond homolysis in **9** is too large.[7] Furthermore, tertiary alkyl-TEMPO compounds are not sufficiently stable under the applied conditions (see below). Malonic ester derivatives

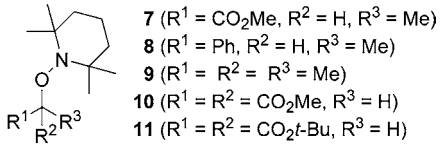
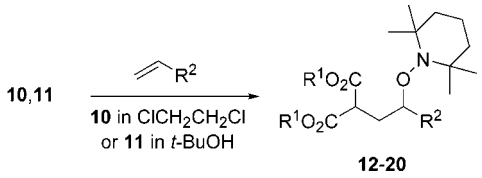


Figure 1. Various alkoxyamines studied.

have successfully been used in atom transfer reactions.[10] Malonyl radicals are reactive in intermolecular addition reactions[9] and, due to their stability, should be readily generated with our method. TEMPO-derivative **10** was easily prepared via enolate oxidation using $CuCl_2$ in the presence of TEMPO (see Supporting Information). Pleasingly, reaction of **10** with 1-octene (5 equiv) in *t*-BuOH at 135 °C for 3 days afforded **12** in 35% yield (Table 1, run 1). As a side

Table 1. Reaction of **10** and **11** with Various Olefins (5 equiv) at 135 °C for 3 days



run	R^1	R^2	compd	solvent	yield (%)
1	Me	C_6H_{13}	**12**	*t*-BuOH	35[a]
2	Me	C_6H_{13}	**12**	MeOH	25
3	Me	C_6H_{13}	**12**	CH_3CO_2Et	55
4	Me	C_6H_{13}	**12**	DMF	46
5	Me	C_6H_{13}	**12**	C_6H_5Cl	63
6	Me	C_6H_{13}	**12**	$C_6H_5CF_3$	64
7	Me	C_6H_{13}	**12**	$ClCH_2CH_2Cl$	66
8	*t*-Bu	C_6H_{13}	**13**	*t*-BuOH	54
9	*t*-Bu	C_6H_{13}	**13**	*t*-BuOH	72[b]
10	*t*-Bu	C_6H_{13}	**13**	*t*-BuOH	76[c]
11	Me	CH_2CH_2Ph	**14**	$ClCH_2CH_2Cl$	49
12	Me	OBu	**15**	$ClCH_2CH_2Cl$	78
13	*t*-Bu	OBu	**16**	*t*-BuOH	69[b]
14	Me	$(CH_2)_3OCO_2Me$	**17**	$ClCH_2CH_2Cl$	42
15	*t*-Bu	$(CH_2)_3OCO_2Me$	**18**	*t*-BuOH	38[b]
16	Me	$(CH_2)_3OTBDMS$	**19**	$ClCH_2CH_2Cl$	70
17	*t*-Bu	$(CH_2)_3OTBDMS$	**20**	*t*-BuOH	55[b]

[a] Transesterification product formed in 36%; see text. [b] Reaction for 5 days. [c] Performed with 10 equiv of 1-octene.

product the corresponding *tert*-butyl methylmalonate derived from monotransesterification of **12** with *t*-BuOH was formed in 36% yield (see Supporting Information). To circumvent the transesterification, the experiment was repeated in MeOH; however, a lower yield was obtained (25%, run 2). Experiments in ethyl acetate, DMF, trifluorotoluene, chlorobenzene, and dichloroethane provided good results (runs 3−7). We further studied the reaction using di-*tert*-butyl malonate **11** in *t*-BuOH as a solvent. Product **13** was isolated in 54% yield along with 40% yield of **11** (run 8). Reaction for 5 days under otherwise identical conditions afforded **13** in an excellent yield (72%, run 9). Reaction time can be decreased if 10 equiv of 1-octene is used (3 days, 76%, run 10). Thus, the best results were obtained using malonate **10** in $ClCH_2$-CH_2Cl or **11** in *t*-BuOH. These two protocols were used for the following studies.

The reaction with 4-phenyl-1-butene (→ **14**), butyl vinyl ether (→ **15**,**16**), $CH_2{=}CH(CH_2)_3OCO_2Me$ (→ **17**,**18**), and $CH_2{=}CH(CH_2)_3OTBDMS$ (→ **19**,**20**) provided the corresponding addition products in moderate to good yields,

(7) Marque, S.; Fischer, H.; Baier, E.; Studer, A. *J. Org. Chem.* **2001**, *66*, 1146. See also: Marque, S.; Fischer, H.; LeMercier, C.; Tordo, P. *Macromolecules* **2000**, *33*, 4403.

(8) Formal long-lived radicals due to degenerate processes: Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.

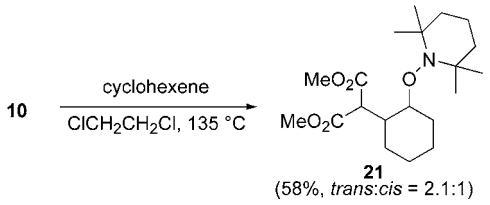
(9) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1341.

(10) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. Review: Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, 72

documenting the generality of our method (runs 11−17). It is not surprising that the highest yields were obtained with the most nucleophilic olefin (butyl vinyl ether), since the malonyl radical is electrophilic in nature.[9] Starting TEMPO-malonate could not be recovered in these experiments. Some decomposition of **10** and **11** occurs under the applied conditions.

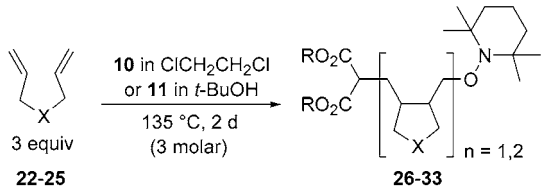
Carboaminoxylations onto terminally substituted olefins can also be performed, as shown for the reaction of **10** with cyclohexene to provide **21** (Scheme 3, 58%).

Scheme 3. Thermal Addition of **10** to Cyclohexene



We next studied intermolecular additions followed by cyclization reactions. Various dienes **22**−**25** (3 equiv) were reacted with malonates **10** and **11** under slightly modified conditions (→ **26**−**33**, Scheme 4, Table 2).[11]

Scheme 4. Addition/Cyclization Reactions

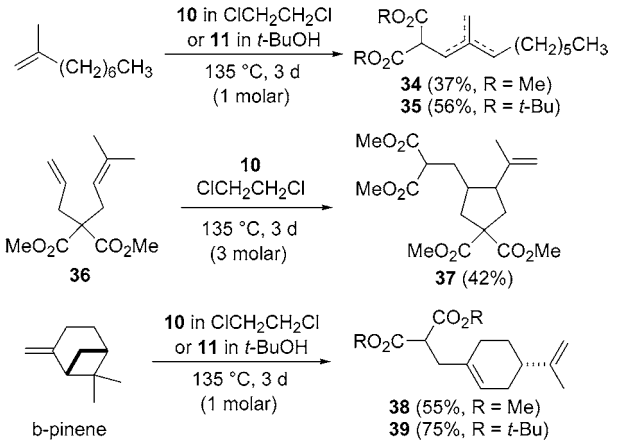


Addition/cyclizations with **10** in $ClCH_2CH_2Cl$ afforded **26**, **28**, **30**, and **32** in moderate to good yields as a *cis*/*trans* mixture of isomers.[12] In *t*-BuOH with **11**, we always observed telomerization as a side reaction ($n = 2$). It is known that the reaction of TEMPO with a C-centered radical is slower in polar protic solvents.[13] Therefore, in *t*-BuOH, telomerization can compete with TEMPO trapping of the primary C-radical formed after cyclization.

We also investigated reactions leading to tertiary alkoxyamines. We found that the product alkoxyamines always undergo elimination of TEMPOH under the reaction conditions.[14]

The elimination products are also useful compounds for further synthetic manipulations. For example, reaction of **11** with 2-methyl-1-nonene provided **35** in 56% yield, unfortunately, as a mixture of regioisomers (Scheme 5).[15] Similarly, **34** was isolated in 37% yield. However, regioselective elimination can also be obtained. For example, addition/cyclization of **10** using acceptor **36** provided cyclization/regioselective elimination product **37** (42%, *cis*/*trans* = 2.4:1). We also studied an example comprising an addition/fragmentation sequence. Thus, reaction of β-pinene with **11** afforded the addition/fragmentation/regioselective elimination product **39** in good yields (75%). In analogy, **38** was prepared starting from malonate **10** (55%).

Scheme 5. Addition/Elimination Reactions



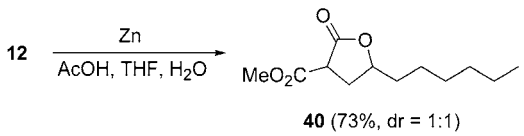
Finally, for a single case, we also conducted the reductive C−O bond cleavage ("deprotection"). Carboaminoxylation product **12** was treated with activated Zn in AcOH/THF/H_2O (Scheme 6). As expected, the secondary alcohol liberated underwent lactonization under the reaction conditions to provide lactone **40** in 73% yield as a 1:1 mixture of isomers.

Table 2. Intermolecular Addition/Cyclization Reactions

starting material	X	R	product ($n = 1$)	(%)	*cis*:*trans*[a]
22	$C(CO_2Me)_2$	Me	**26**	68	
22	$C(CO_2Me)_2$	*t*-Bu	**27**	40[b]	2.2:1
23	O	Me	**28**	33[c]	1.8:1
23	O	*t*-Bu	**29**	37[d]	1.7:1
24	NTos	Me	**30**	49	1.3:1
24	NTos	*t*-Bu	**31**	42[e]	1.5:1
25	$C(CH_2CH_2O)_2CMe_2$	Me	**32**	36	2.3:1
25	$C(CH_2CH_2O)_2CMe_2$	*t*-Bu	**33**	34[f]	2.1:1

[a] Determined by HPLC or NMR. [b] Consisted of 10% telomer was isolated as a side product. [c] Performed with 6 equiv of **23**. [d] Consisted of 12% telomer was isolated as a side product. [e] Consisted of 23% telomer was isolated as a side product. [f] Consisted of 12% telomer was isolated as a side product.

Scheme 6. Reductive N−O Bond Cleavage with Subsequent Lactonization



(11) Reactions under the above-described optimized conditions provided lower yields.

In conclusion, we have presented efficient radical carboaminoxylations of various nonactivated C−C double bonds to provide synthetically useful functionalized malonates. It is important to note that the malonyl radical precursors can be *readily prepared in one step in high yield starting from commercially available TEMPO and dialkyl malonates*. Furthermore, the reactions *are very easy to conduct.* Simple mixing of the starting materials and heating allows the preparation of functionalized malonates in a single operation. The carboaminoxylations can be combined with radical cyclization and fragmentation reactions. N−O bond cleavage can be performed under standard conditions to provide γ-butyrolactones.

Acknowledgment. We thank the Fonds der Chemischen Industrie (Ph.D. stipend to C.W.) and the Swiss Federal Office for Education and Science (D12/0005/98) for funding.

Supporting Information Available: Experimental procedures and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034994K

(12) Diastereoisomers could not be separated. The relative configuration was assigned on the basis of literature reports on similar cyclizations: Amrein, S.; Studer, A. *Helv. Chim. Acta* **2002**, *85*, 3559.

(13) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983.

(14) We currently believe that elimination occurs via an ionic-type process from the corresponding tertiary alkoxyamines. Since C−O bond homolysis in these tertiary alkoxyamines is not efficient, radical disproportionation is less likely. For a discussion, see: Ananchenko, G. S.; Fischer, H. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 3604.

(15) For **34**, exomethylene:$\beta\gamma$-unsaturated:$\gamma\delta$-unsaturated = 3.9:1:1.2. For **35**, exomethylene:$\beta\gamma$-unsaturated:$\gamma\delta$-unsaturated = 1.1:1:0.4. The $\beta\gamma$- and γ,δ-unsaturated compounds were obtained as a *trans*/*cis* mixture of isomers.