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Microflow Radical Carboaminoxylations with a Novel Alkoxyamine

Inga C. Wienhöfer,[†] Armido Studer,*[,†] Md. Taifur Rahman,[‡] Takahide Fukuyama,[‡] and Ilhyong Ryu*[,‡]

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstrasse 40, 48149 Münster, Germany, and Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

studer@uni-muenster.de; ryu@c.s.osakafu-u.ac.jp

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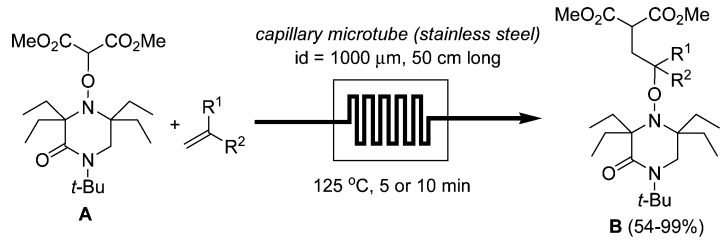
ABSTRACT



Highly efficient thermal radical carboaminoxylations of various olefins by using the novel alkoxyamine A to give adducts of type B are described. It is reported that these radical addition reactions can be performed in a microflow reaction system. As compared to conventional batch reaction setup, significantly higher yields are obtained by running carboaminoxylations using the microflow system under analogous conditions.

Microreactor technology has gained increased attention during the past few years and has been used to conduct different types of reactions.[1−3] However, only few reports on the use of microreactors to conduct radical chemistry have appeared to date.[4] Herein we present radical carboaminoxylations[5] by using either classical batch or microflow technology. Importantly, these radical reactions are performed without the need of toxic trialkyl tin compounds.[6] Moreover, we introduce a novel alkoxyamine for highly efficient radical carboaminoxylation reactions.[7]

We have shown that various alkoxyamines undergo thermal radical addition reactions to various unactivated

[†] Westfälische Wilhelms-Universität.
[‡] Osaka Prefecture University.

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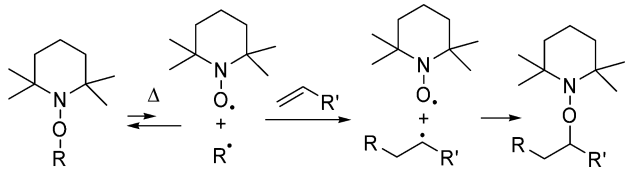
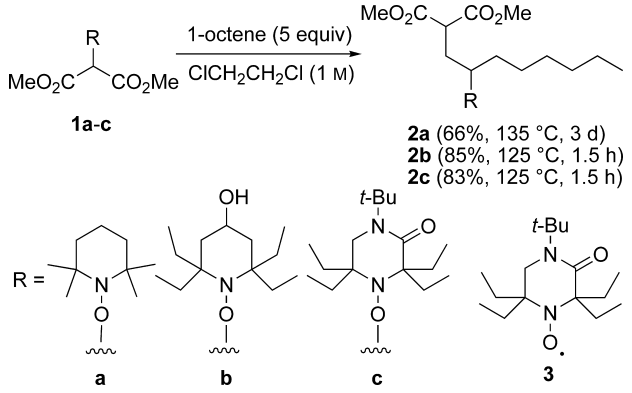
olefins. Radical generation occurs by C−O-bond homolysis in these processes. The C-radical adds to the olefin, and the thus formed adduct radical is eventually trapped by the nitroxide (aminoxyl radical) to form the corresponding alkoxyamine product (Scheme 1).[5]

Scheme 1. Intermolecular Radical Alkoxyamine Additions by Using TEMPO-Derived Alkoxyamines



Intermolecular reactions, which we call radical carboaminoxylations, occurred efficiently by using alkoxyamines derived from malonates.[5,6] The structure of the nitroxide moiety in the alkoxyamine heavily influenced reaction outcome. Hence, alkoxyamine **1a** bearing a TEMPO moiety (TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical)[8] reacted with 1-octene to give the corresponding adduct **2a** in 66% yield (3 d, 135 °C), whereas alkoxyamine **1b**, bearing a sterically more demanding nitroxide moiety, reacted far more efficiently and **2b** was isolated in 85% yield in far shorter reaction time and lower temperature (1.5 h, 125 °C, Scheme 2).[7e] Since the nitroxide of alkoxyamine **1b** was

Scheme 2. Radical Carboaminoxylation of 1-Octene



difficult to prepare, we were looking for an alternative readily accessible sterically highly demanding nitroxide. The bulky nitroxide **3** has recently been introduced as a readily prepared efficient regulator for nitroxide-mediated radical polymerization.[9] We therefore decided to test **3** in radical carboaminoxylation reactions. Alkoxyamine **1c** was easily prepared from dimethylmalonate and **3** (see Supporting Information). We were pleased to observe that **1c** reacted as efficiently as **1b** and product **2c** was isolated in 83% yield (1.5 h, 125 °C). As previously shown, activation energy E_a for C−O-bond homolysis of an alkoxyamine correlates well with the reaction outcome of the corresponding radical carboaminoxylation. For malonates **1a** and **1b** we reported activation energies of 140.0 and 124.9 kJ/mol, respectively.[7e] For **1c** we measured (see Supporting Information) a value of 128.8 kJ/mol, which shows that the novel, readily available bulky alkoxyamine **1c** compares well with the highly efficient **1b**. Therefore, all further studies were performed by using alkoxyamine **1c**.

To document substrate scope, various olefins were reacted with **1c** under optimized conditions. Results are summarized in Figure 1. Reactions with unactivated olefins (→ **4a**−**c**),

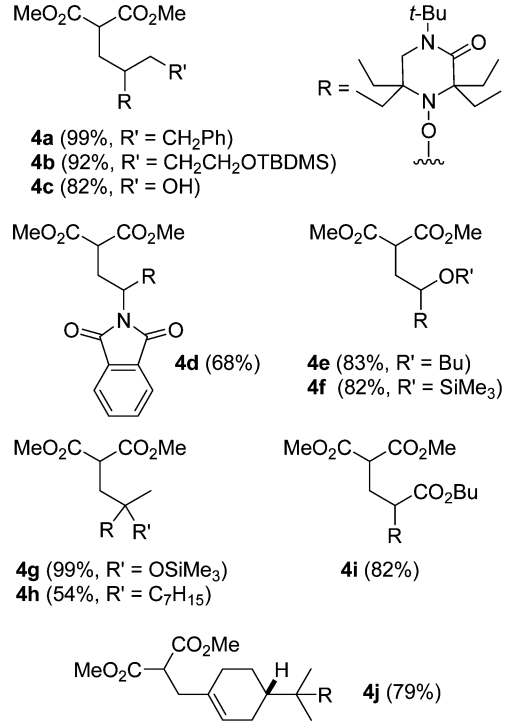


Figure 1. Products of carboaminoxylations with **1c**. Conditions: olefin (5 equiv, **4i** 1.05 equiv), $ClCH_2CH_2Cl$ (1 M), 2 h, 125 °C.

vinylphthalimide (→ **4d**), and vinyl ethers (→ **4e,f**) occurred with high yields. Interestingly, even tertiary sterically

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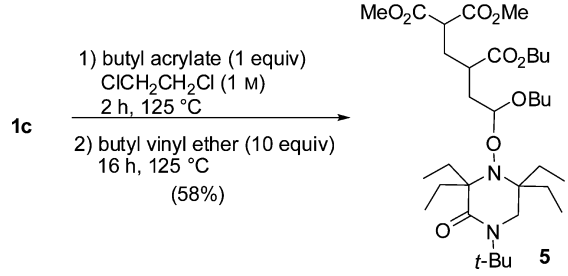
hindered stabilized radicals were efficiently trapped with **3** as shown in the synthesis of **4g** and **4h**.[10] The electron-poor *n*-butyl acrylate also underwent radical addition to give **4i** in 82% yield.[11] Radical carboaminoxylation of *β*-pinene with **1c** afforded adduct **4j** resulting from malonyl radical addition, fragmentation, and nitroxide trapping.[12]

Radical carboaminoxylations could also be performed in water as a solvent.[13] Mixing of 1-octene (5 equiv) with **1c** in H_2O (1 M) for 2 h in a sealed tube at 125 °C afforded **2c** in 78% yield. By analogy, **4a** (98%) and **4d** (54%) were successfully prepared in water. Interestingly, reaction also worked under neat conditions. Hence, stirring of 1-octene (5 equiv) and **1c** at 125° for 2 h gave **2c** in 82% isolated yield, and heating a mixture of vinylphthalimide (5 equiv) and **1c** for 2 h at 125 °C afforded **4d** in 50% yield.

Radical cascade reactions could be conducted as a one-pot process. To this end, **1c** was first allowed to react with *n*-butyl acrylate (1 equiv) in $ClCH_2CH_2Cl$ for 2 h (125 °C). After evaporation of the solvent the reaction vessel was charged with butyl vinyl ether (10 equiv), and heating was continued for 8 h. Compound **5** was isolated in 58% yield as a mixture of isomers (Scheme 3).[14]

Scheme 3. Cascade Reaction



Importantly, all radical carboaminoxylations were performed without addition of any reagents by mixing the two reactants. Therefore, this chemistry should be well suited to be conducted in a microflow system. As a typical solvent for the microflow system we chose DMSO (Figure 2).

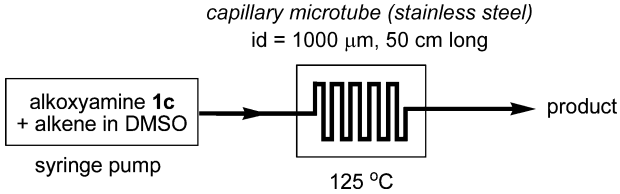


Figure 2. Setup of the microflow system (DMSO, 0.07 M).

Reactions were performed in a capillary microtube (stainless steel) at 125 °C by feeding a mixture of alkoxyamine and olefin in a flow system (2 equiv of olefin; 5 or 10 min residence time in the reactor). For comparison, we repeated all experiments by using conventional batch reaction technique under otherwise identical conditions (residence time in flow reactor = reaction time in batch system). Results are summarized in Table 1.

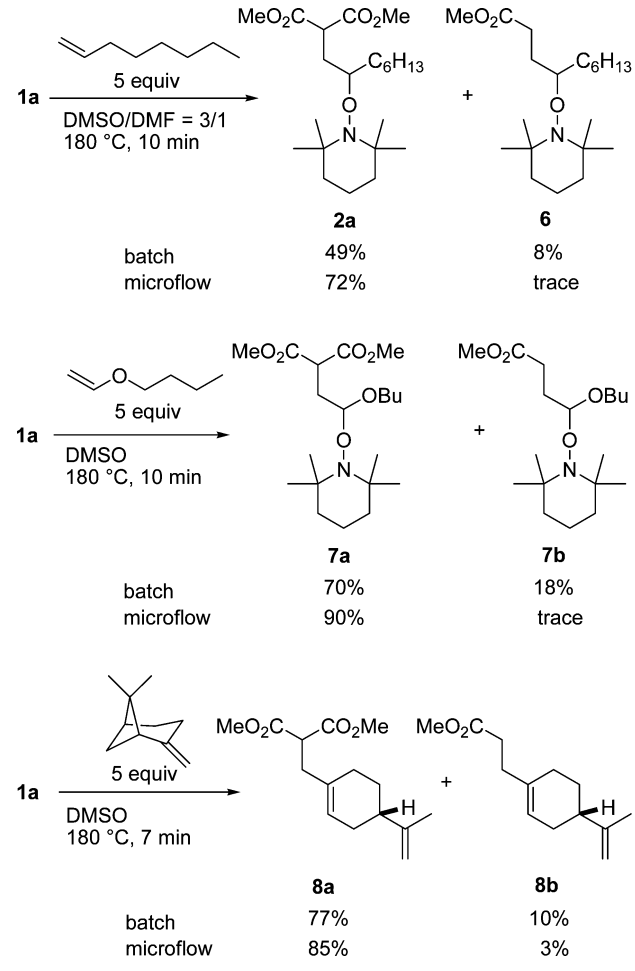
Table 1. Batch and Microflow Radical Carboaminoxylations

entry	alkene	time [min]	no.	batch yield [%]	microflow yield [%]
1	1-octene	10	**2c**	45	73
2	1-octene[a]	10	**2c**	72	95
3	4-phenyl-1-butene	5	**4a**	31	65
4	4-phenyl-1-butene	10	**4a**	55	86
5	*β*-pinene	5	**4j**	60	77
6	2-methyl-1-nonene	5	**4h**	60	81
7	butyl vinyl ether	5	**4e**	65	93
8	vinylphthalimide	5	**4d**	58	68[b]

[a] 5 equiv. [b] Telomer resulting from addition of 2 equiv of vinyl phthalimide was obtained as side product in 13% yield.

It turned out that carboaminoxylations proceeded very efficiently in DMSO as a solvent. In the batch system, reaction of 1-octene (2 equiv) with **1c** for 10 min provided **2c** in 45% yield (entry 1). Increasing the amount of 1-octene

Scheme 4. Batch and Microflow Carboaminoxylations with **1a**



to 5 equiv further increased yield (entry 2). To our delight, yields were further improved upon switching to the flow system. Thus 10 min residence time in the flow reactor resulted in a 95% isolated yield of **2c** (entry 2). Similar results were achieved in the carboaminoxylation of 4-phenyl-1-butene (entries 3 and 4). For the more reactive butyl vinyl ether as a radical acceptor, a 93% isolated yield was achieved with 5 min reactor residence time. Importantly, for all reactions studied, yields were higher in the microflow system as compared to yields achieved in the batch reaction under comparable conditions (entries 1−8), documenting the power of microflow technology to conduct these radical addition reactions.

High thermal efficiency of a microflow system over a batch system led us to reexamine TEMPO-malonate addition chemistry,[7c] which requires higher temperatures to undergo effective addition to alkenes. Scheme 4 shows results of both batch and microflow reactions of **1a** with three different olefins, which were conducted at 180 °C. In all cases examined, microflow reactions constantly gave better yields of alkene addition products **2a**, **7a**, and **8a** over batch reactions. It is noteworthy that microflow reactions gave negligible formation of byproducts **6**, **7b**, and **8b**, which would be obtained by further thermal decomposition reactions of the initially obtained addition products. Thus, in turn of microflow reactions, high-speed cooling down (fast product removal from the reactor) would allow for such selective reactions.

In summary, we presented a novel, readily available alkoxyamine that underwent a highly efficient radical carboaminoxylation reaction to various olefins. Radical carboaminoxylations were for the first time conducted by using microflow technology. Importantly, as compared to conventional batch reaction setup, microflow technology delivered substantially higher yields under comparable conditions.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Along with **4h**, olefins deriving from hydroxylamine elimination were isolated in 32% as mixture of regioisomers and an unidentified side product (see Supporting Information).

(11) Radical carboaminoxylation on electron-poor olefins, see: Dufils, P.-E.; Chagneux, N.; Gigmes, D.; Trimaille, T.; Marque, S. R. A.; Bertin, D.; Tordo, P. *Polymer* **2007**, *48*, 5219.

(12) Along with **4j**, an olefin deriving from hydroxylamine elimination was isolated in 8% (see Supporting Information).

(13) Reactions in water: (a) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725. (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. Radical chemistry in water: (c) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674.

(14) As a side product **4e** was formed in 25% yield.