Immobilization of TEMPO Derivatives in Saponite and Use of These Novel Hybrid Materials as Reusable Catalysts

Caren Röben,[a] Armido Studer,*[a] Wilhelm L. Hemme,[b] Hellmut Eckert*[b]

[a] Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstr. 40, 48149 Münster, Germany
Fax +49(251)8336523; E-mail: studer@uni-muenster.de

[b] Institut für Physikalische Chemie, Westfälische Wilhelms-Universität Münster, Corrensstr. 30, 48149 Münster, Germany
E-mail: eckerth@uni-muenster.de

Abstract: The letter describes a novel approach for immobilization of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) derivatives by cation-exchange reaction of TEMPO ammonium salts in a commercially available saponite. The organic–inorganic hybrid material is readily prepared and characterized by solid-state ^{1}H NMR spectroscopy. The hybrid material can be used as recyclable catalyst for oxidation of various alcohols. High catalytic activity for up to 10 runs is obtained. Leaching of the nitroxide salt out of the saponite occurs to a small extent. However, original high activity of the hybrid material can be restored by simply reloading the hybrid material with nitroxide salt by cation exchange.

Key words: alcohol oxidation, 2,2,6,6-tetramethylpiperidine-1-oxyl, TEMPO, catalyst immobilization, catalysis, solid-state NMR spectroscopy

Catalyst immobilization is a heavily investigated field of research.[1,2] Although homogeneous catalysis has been extremely successful in the past, several problems might occur by using homogeneous systems. Separation of the catalysts from the product is sometimes difficult and this is a particularly significant problem in the synthesis of pharmaceutical compounds which should ideally be completely free of catalysts. Moreover, for economic reasons catalyst recovery is an important issue if reactions are conducted by using expensive systems. Therefore, it is not surprising that for many industrially important catalytic reactions researchers have been trying to develop reusable catalysts.[1,2] Herein we report on immobilization of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) derivatives by using a simple cation-exchange process in commercially available saponites.[3] As a test reaction oxidation of alcohols will be discussed. Many reports on immobilization of TEMPO have appeared to date,[4,5] however, to the best of our knowledge the concept presented herein has not been applied for preparation of recoverable TEMPO-based catalysts.[6]

Nitroxides **1–3** (Figure 1) were readily prepared from commercially available 4-*N*-acetylamino-TEMPO or 4-oxo-TEMPO as described in the experimental section.[7]

Immobilization of **2** in saponite was recently reported by us.[8] Cation-exchange reactions with **1** and **3** were conducted analogously. To this end, commercially available saponite clay $\{Na_{0.46}[Si_{3.54}Al_{0.46}Mg_3O_{10}(OH)_2]\cdot nH_2O\}$ (Kunimine Chemical Co. Ltd, see Figure 2) with a cation-exchange capacity (CEC) of 100.43 milliequivalents per 100 grams of the clay was used.
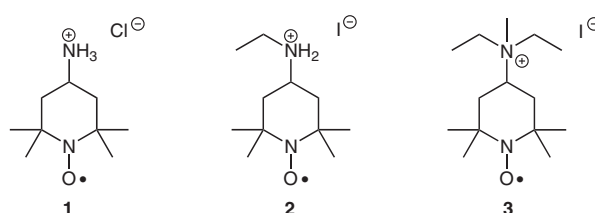
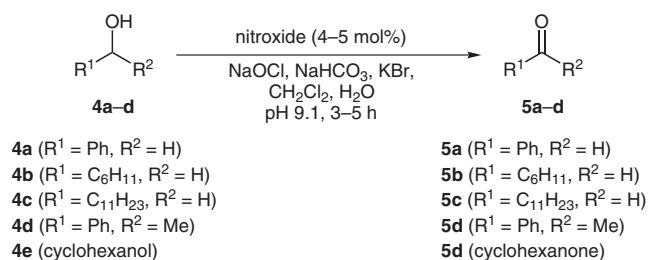**Figure 1** Nitroxides **1–3** used in the present study
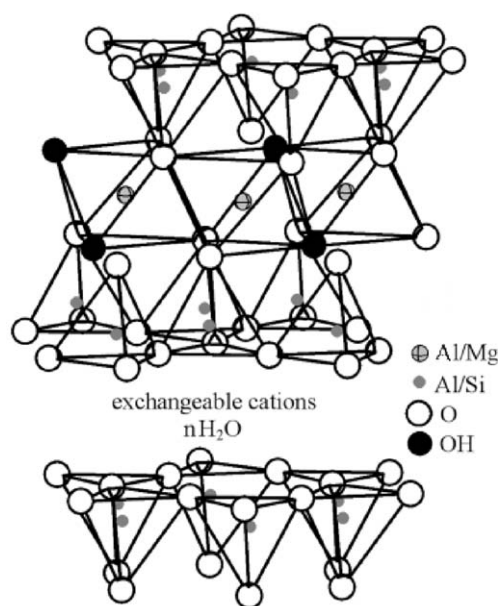
Figure 2 Saponite structure[9]

The intercalation was carried out by suspending the clay under stirring in an aqueous solution of the nitroxide salts **1–3** for 4 hours at room temperature. The amount of intercalated material was readily quantified by CHN elemental analysis. Moreover, solid-state ^{1}H NMR measurements were carried out to further analyze the novel organic–inorganic hybrid materials (see the discussion below). The CHN analysis showed that cation-exchange capacity

(CEC) was highest for the hybrid **3**@saponite prepared with the diethylmethylammonium salt **3** (CEC = 74%). The monoethyl salt **2** provided a slightly lower CEC (69%) whereas a significantly lower loading was achieved for **1**@saponite (CEC = 45%). Hence, the extent of alkylation of the amino group influenced cation-exchange process to a large degree.

As first test reaction, we studied oxidation of benzyl alcohol (**4a**) to benzaldehyde (**5a**) under typical Anelli conditions (Scheme 1).[10] Reactions were conducted with **1**@saponite, **2**@saponite, and **3**@saponite by using 4–5 mol% of nitroxide at room temperature for 3–5 hours.

4a (R^1 = Ph, R^2 = H)   **5a** (R^1 = Ph, R^2 = H)
4b (R^1 = C$_6$H$_{11}$, R^2 = H)   **5b** (R^1 = C$_6$H$_{11}$, R^2 = H)
4c (R^1 = C$_{11}$H$_{23}$, R^2 = H)   **5c** (R^1 = C$_{11}$H$_{23}$, R^2 = H)
4d (R^1 = Ph, R^2 = Me)   **5d** (R^1 = Ph, R^2 = Me)
4e (cyclohexanol)   **5d** (cyclohexanone)

Scheme 1   Oxidation of various alcohols

We were very pleased to observe that hybrid **1**@saponite was catalytically active, and a quantitative oxidation of benzyl alcohol was achieved. After reaction the clay material was rinsed with dichloromethane and then reused without further purification. This procedure was repeated nine times. We found quantitative oxidation of **4a** for runs 2–4; however, for the fifth run the yield dropped to 89% (Figure 3). Probably slow leaching of the nitroxide catalyst out of the saponite was occurring during the reaction. This assumption was further supported by the observation that the yield steadily decreased in runs 6–10 from 84–54%.

A better result was obtained with **2**@saponite where we got quantitative conversion for 10 runs. With **3**@saponite the yield was also quantitative for the first 10 runs. With this material we decided to go beyond these 10 runs. Dis-
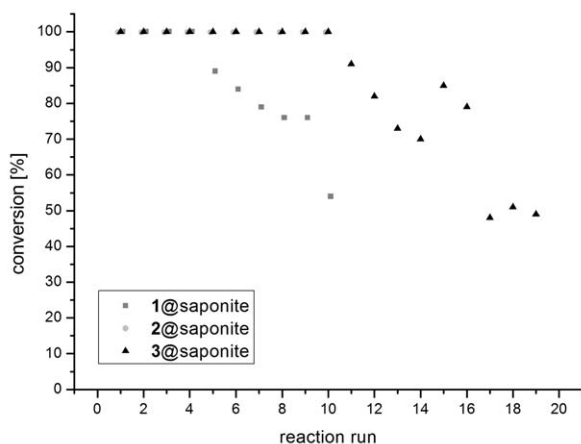
Figure 3   Oxidation of **4a** to **5a** by using **1**@saponite, **2**@saponite, and **3**@saponite

appointingly, the 11th run showed a slight decrease in yield (91%). Yield further dropped to around 80% in run 16. We then stored the catalyst system **3**@saponite for three days at 4 °C without adding any solvent and found that activity further decreased to around 50% for runs 17–19.

It seemed that for all three materials tested nitroxide leaching was occurring. This was not really surprising since reactions were conducted in the presence of different salts (NaOCl, NaHCO$_3$, and KBr). It is obvious that cations present in these salts will undergo cation-exchange reactions with our hybrid materials. To get an idea about nitroxide leaching induced by cation exchange we analyzed the cation-exchange capacity of the material obtained after 10 reactions (for **1**@saponite and **2**@saponite) and 19 reactions (for **3**@saponite), respectively.

The CHN analysis on 'used' **1**@saponite revealed a CEC of 8% after 10 runs. Hence, more than 80% of nitroxide **1** were extracted by cation exchange during 10 runs. Slower exchange was occurring for **2**@saponite where we found a CEC of 18% after 10 runs (75% were extracted). The slowest leaching was observed for nitroxide **3**. After 19 reactions, CHN analysis showed a CEC of 30% amounting to about 40% of the initial loading. Clearly, leaching was also occurring with nitroxide salt **3**; however, the latter was exchanged far more slowly than its congeners **1** and **2**. We believe that the lower water solubility of **3** as compared to **1** and **2** might be the reason for the slower cation exchange and hence the reduced leaching rate. In addition, under the applied conditions the ammonium salts **1** and **2** can undergo deprotonation which would lead to TEMPO derivatives which at least in the nitroxide form (not at the oxoammonium oxidation state) are present as noncationic compounds which do not efficiently interact with the saponite host material.

Solid-state ^{1}H NMR spectroscopy can also be used to monitor catalyst leaching, as illustrated in Figure 4 at the example of **3**@saponite. For uncharged saponite two resonances appear in the spectra: the 0.5 ppm peak can be attributed to the structural hydroxy group, while the signal near δ = 3.9 ppm arises from molecular H$_2$O in the interlayer space.[8] In the loaded material, this signal appears greatly enhanced (presumably due to additional water uptake) as well as significantly broadened, caused by strong dipolar interactions with the unpaired electrons of the nitroxide guest species. Owing to this broadening effect, the signals attributed to the *N*-alkyl species of **3**, occurring in the 5–10 ppm region, are partially obscured by the water resonance and only detectable in the form of a high-frequency shoulder in the inclusion compound. In contrast, the signals of the four β-methyl groups near –28 ppm are clearly observable, albeit significantly broadened, in the catalyst, and their intensity can be used to follow the catalyst cycling process.

Figure 4 clearly illustrates that the matrix material (saponite) is not destroyed under the reaction conditions applied, and can be discharged and re-charged reversibly.

Hence, simple reloading by renewed cation exchange upon adding a nitroxide salt should also restore the initial catalytic activity of our hybrid material. This of course would render our approach even more attractive.
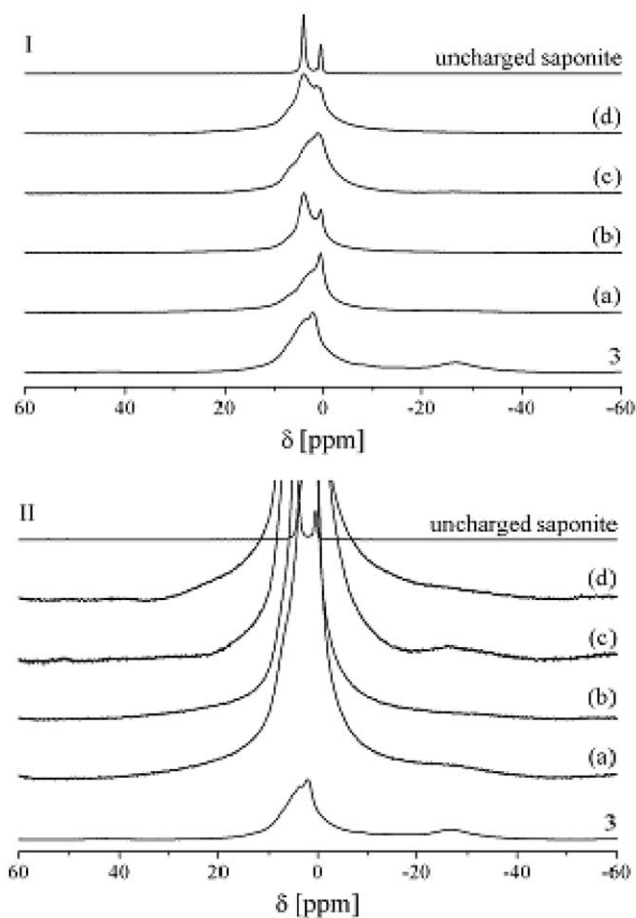
Figure 4 Normalized (I) and enhanced (II) ^{1}H MAS-NMR spectra of **3**@saponite before (a) and after 19 reaction cycles (b), subsequent re-charging (c) and exposure to 10 additional reaction cycles (d). Included are reference spectra of **3** and uncharged saponite.

Indeed, subjection of **3**@saponite (used for 19 runs) to **3** under the cation-exchange conditions described above for 4 hours provided a 'refreshed' organic–inorganic hybrid material with a CEC of 84%. Interestingly, recharging afforded a slightly higher catalyst loading (84% vs. 74% CEC). The reloaded hybrid catalyst was then used for 10

Table 1 Oxidation of Alcohols **4b–e** with **2**@saponite

Entry[a]	Alcohol	Time (h)	Product	Yield (%)
1	**4b**	3.5	**5b**	>99[a]
2	**4c**	5	**5c**	>99[a]
3	**4d**	3.5	**5d**	>95[b]
4	**4e**	3.5	**5e**	>95[b]

[a] Determined by GC analysis.
[b] Determined by ^{1}H NMR spectroscopy.

runs for oxidation of benzyl alcohol, resulting in quantitative yields for these 10 runs.

We finally tested whether other substrates can be oxidized with our hybrid catalyst. These studies where conducted with **2**@saponite. We found that oxidation of cyclohexylmethanol **4b** to **5b** was slightly slower. Quantitative conversion was achieved in 3.5 hours (Table 1, entry 2). Similar results were observed for oxidation of cyclohexanol (**4e**) and benzylic alcohol **4d** showing that also secondary alcohols can be oxidized with our immobilized nitroxides (entries 3 and 4). Oxidation of dodecanol **4c** was slower. In order to get quantitative formation of **5c** five hours were required (entry 2).

In conclusion we showed that TEMPO ammonium salts were readily immobilized by cation exchange into saponites. Importantly, the nitroxide salts were easily prepared and saponite used is commercially available. Preparation of the hybrid material is readily performed without using any special equipment. The hybrid materials can be analyzed by solid-state ^{1}H NMR spectroscopy and elemental analysis. Cation-exchange capacities of up to 85% were achieved. Highest loadings were obtained with the tetraalkylammonium salt **3** whereas nitroxides containing dialkyl- or alkylammonium salt moieties such as **2** and **1** were immobilized to a lower extent. The novel inorganic–organic hybrid materials were successfully used as reusable catalysts for oxidation of various alcohols. All materials showed high activity under typical oxidation conditions by using NaOCl as a stoichiometric oxidant. Catalyst recovery was easy to perform. With **2**@saponite and **3**@saponite quantitative oxidation of benzyl alcohol was obtained for 10 runs. However, nitroxide leaching was observed leading to reduced yields for subsequent runs. Importantly, in contrast to most immobilization methods known, the catalyst system is readily 'refreshed' by recharging with nitroxide salt by cation-exchange reaction diminishing the 'leaching' problem. The reloaded catalyst showed excellent activity.

4-Ammonia-2,2,6,6-tetramethyl-piperidine-1-oxyl Radical Chloride (1)

4-Amino-2,2,6,6-tetramethyl-piperidine-1-oxyl radical (1.61 g, 9.39 mmol) was diluted in Et_2O (30 mL) and was washed with HCl (aq, 1 M, 3×5 mL). The aqueous layers were combined, and the solvent was removed under reduced pressure. Compound **1** was obtained as red solid and was used without further purification.

IR (neat): 2926 (br s), 2365 (m), 2356 (m), 2339 (m), 1622 (m), 1611 (m), 1522 (m), 1479 (m), 1391 (s), 1352 (w), 1243 (m), 1223 (w), 1178 (w), 1095 (m), 1057 (w9, 1018 (w), 953 (w), 886 (w), 744 (m) cm^{-1}.

HRMS (ESI$^+$): m/z calcd for [M – Cl]$^+$: 172.1570; found: 172.15685.

4-Ethylammonia-2,2,6,6-tetramethyl-piperidine-1-oxyl Radical Iodide (2)

4-Amino-2,2,6,6-tetramethyl-piperidine-1-oxyl radical (700 mg, 4.09 mmol) was dissolved in ethyl iodide (5.00 mL, 62.5 mmol) and was stirred at r.t. for 72 h. The resulting solid was filtered off. Recrystallization (MeCN–PhMe) gave **2** as red crystalline solid (913 mg, 2.79 mmol, 68%).

IR (neat): 2971 (s), 2947 (s), 2850 (m), 2823 (m), 2361 (w), 1572 (w), 1441 (m), 1321 (w), 1369 (w), 1329 (w), 1314 (w), 1243 (m), 1192 (m), 1031 (m), 923 (w) cm^{-1}.

HRMS (ESI$^+$): m/z calcd for [M – I]$^+$: 200.1883; found: 200.1900.

4-Diethyl-methyl-ammonia-2,2,6,6-tetramethyl-piperidine-1-oxyl Radical Iodide (3)

Iodomethane (2.30 mL, 36.9 mL) was added to 4-diethylamino-2,2,6,6-tetramethylpiperidine-1-oxyl radical (677 mg, 2.98 mmol). The mixture was stirred 12 h at r.t. The resulting solid was suspended in Et_2O (10 mL), filtered off and washed with Et_2O (5×10 mL). Recrystallization (MeCN–PhMe) gave **3** as a red crystalline solid (836 mg, 2.27 mmol, 76%).

IR (neat): 2992 (w), 2361 (w), 1608 (m), 1478 (m), 1454 (s), 1438 (m), 1410 (w), 1396 (w), 1370 (m), 1345 (m), 1329 (m), 1273 (m), 1244 (s), 1202 (s), 1184 (m), 1135 (w), 1101 (w), 1018 (s), 923 (w), 898 (s), 827 (s), 795 (m) cm^{-1}.

HRMS (ESI$^+$): m/z calcd for [M – I]$^+$: 242.2351; found: 242.2353.

General Procedure for the Intercalation of TEMPO Salts into Layered Saponite Clay (GP1)

The intercalation was carried out by suspending the clay (500 mg, 1.1 mmol, 0.5 mequiv) in an aqueous solution of the nitroxide ammonium salt (60 mL, 1.25 mmol) and stirring for 4 h at r.t. That means that 1.25 mmol of nitroxide was offered to saponite clay, corresponding to 250% CEC. The clay was filtered off and dried for 48 h in vacuo. The amount of intercalated material was quantified by CHN elemental analysis.

General Procedure for Oxidation Reactions of Alcohols by Using TEMPO Ammonium Salts that Are Immobilized into Layered Saponite Clay (GP2)

The immobilized TEMPO ammonium salt (4.1–5.0 mol%) was added to a reaction vessel which was equipped with a frit to filter off the reaction mixture directly. A solution of the alcohol (0.400 M, 1.0 equiv) and hexadecane (0.400 M, 1.0 equiv; as internal standard) in CH_2Cl_2, a solution of KBr (aq, 0.500 M, 0.10 equiv) and a solution of NaOCl (0.350 M, buffered with $NaHCO_3$ to a pH of 9.1, 1.25 equiv) were added at 0 °C. The reaction mixture was then shaken for 3–5 h at 0 °C. The reaction was stopped simply by filtering off the catalyst from reaction mixture and washing with CH_2Cl_2 (3×2 mL). The phases were separated and the organic layer was dried over $MgSO_4$. The conversion was determined by means of GC

chromatography or ^{1}H NMR spectroscopy. The catalyst was subsequently reused.

Typical Oxidation of Benzyl Alcohol Using Catalyst System 1@saponite

According to **GP2** with **1**@saponite (45% CEC, 0.45 mmol/g, 50.0 mg, 22.5 μmol **1**, 4.5 mol%), 1.25 mL of a solution of benzyl alcohol (0.400 M, 0.500 mmol) and hexadecane (0.400 M, 0.500 mmol) in CH_2Cl_2, KBr (aq, 0.500 M, 0.100 mL, 50.0 μmol) and NaOCl (aq, 0.350 M, buffered with $NaHCO_3$ to a pH of 9.1, 1.79 mL, 0.627 mmol). The reaction mixture was then shaken for 3 h. The conversion of the reaction was determined by means of GC chromatography. The catalyst was reused 10 times.

References

(1) Immobilization of catalysts: (a) Fraile, J. M.; García, J. I.; Mayoral, J. A. *Chem. Rev.* **2009**, *109*, 360. (b) Trindade, A. F.; Gois, P. M. P.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 418. (c) Akiyama, R.; Kobayashi, S. *Chem. Rev.* **2009**, *109*, 594.

(2) Immobilization of organocatalysts: (a) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401. (b) Benaglia, M. *New J. Chem.* **2006**, *30*, 1525. (c) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367. (d) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666.

(3) Review on the use of TEMPO in synthesis: (a) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979. Reviews on immobilization of catalyst into nanostructured supports, see: (b) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Pires, E. *Chem. Soc. Rev.* **2009**, *38*, 695. (c) Fraile, J. M.; García, J. I.; Mayoral, J. A. *Chem. Rev.* **2009**, *109*, 360.

(4) Immobilization of TEMPO: (a) Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795. (b) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271. (c) Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* **2001**, *66*, 8154. (d) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 102. (e) Weik, S.; Nicholson, G.; Jung, G.; Rademann, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 1436. (f) Ciriminna, R.; Bolm, C.; Fey, T.; Pagliaro, M. *Adv. Synth. Catal.* **2002**, *344*, 159. (g) Ansari, I. A.; Gree, R. *Org. Lett.* **2002**, *4*, 1507. (h) Testa, M. L.; Ciriminna, R.; Hajji, C.; Garcia, E. Z.; Ciclosi, M.; Arques, J. S.; Pagliaro, M. *Adv. Synth. Catal.* **2004**, *346*, 655. (i) Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C.; Hayes, W. *J. Org. Chem.* **2004**, *69*, 6851. (j) Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G. *Org. Lett.* **2004**, *6*, 441. (k) Ferreira, P.; Hayes, W.; Phillips, E.; Rippon, D.; Tsang, S. C. *Green Chem.* **2004**, *6*, 310. (l) Gilhespy, M.; Lok, M.; Baucherel, X. *Chem. Commun.* **2005**, 1085. (m) Jiang, N.; Ragauskas, A. *Tetrahedron Lett.* **2005**, *46*, 3323. (n) Holczknecht, O.; Cavazzini, M.; Quici, S.; Shepperson, I.; Pozzi, G. *Adv. Synth. Catal.* **2005**, *347*, 677. (o) Benaglia, M.; Puglisis, A.; Holczknecht, O.; Quici, S.; Pozzi, G. *Tetrahedron* **2005**, *61*, 12058. (p) Geneste, F.; Moinet, C.; Ababou-Girard, S.; Solal, F. *New J. Chem.* **2005**, *29*, 1520. (q) Kubota, J.; Ido, T.; Kuroboshi, M.; Tanaka, H.;

Uchida, T.; Shimamura, K. *Tetrahedron* **2006**, *62*, 4769.
(r) Vugts, D. J.; Veum, L.; al-Mafraji, K.; Lemmens, R.;
Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Hanefeld,
U.; Orru, R. V. A. *Eur. J. Org. Chem.* **2006**, 1672.
(s) Gheorghe, A.; Cuevas-Yañez, E.; Horn, J.; Bannwarth,
W.; Narsaiah, B.; Reiser, O. *Synlett* **2006**, 2767.
(t) Gheorghe, A.; Matsuno, A.; Reiser, O. *Adv. Synth. Catal.*
2006, *348*, 1016. (u) Luo, J.; Pardin, C.; Lubell, W. D.; Zhu,
X. X. *Chem. Commun.* **2007**, 2136. (v) Mason, B. P.;
Bogdan, A. R.; Goswami, A.; McQuade, D. T. *Org. Lett.*
2007, *9*, 3449. (w) Karimi, B.; Biglari, A.; Clark, J. H.;
Budarin, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7210.
(x) Gheorghe, A.; Chinnusamy, T.; Cuevas-Yañez, E.;
Hilgers, P.; Reiser, O. *Org. Lett.* **2008**, *10*, 4171. (y) Dobbs,
A. P.; Penny, M. J.; Jones, P. *Tetrahedron Lett.* **2008**, *49*,
6955. (z) Subhani, M. A.; Beigi, M.; Eilbracht, P. *Adv.
Synth. Catal.* **2008**, *350*, 2903.

(5)   (a) Schätz, A.; Grass, R. N.; Stark, W. J.; Reiser, O. *Chem.
Eur. J.* **2008**, *14*, 8262. (b) Kuroboshi, M.; Goto, K.;
Tanaka, H. *Synthesis* **2009**, 903. (c) Lindner, J.-P. B.;
Röben, C.; Studer, A.; Stasiak, M.; Ronge, R.; Greiner, A.;
Wendorff, H.-J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8874.

(6)   Intercalation of cationic nitroxides in clays: (a) Grauer, Z.;
Waterman, K. C.; Turro, N. J. *Langmuir* **1987**, *3*, 59.
(b) Fujita, W.; Awaga, K. *J. Chem. Soc., Chem. Commun.*
1995, 739. (c) Caneschi, A.; Gatteschi, D.; Sangregorio, C.;
Vaz, M. G. F.; Costantino, U.; Nocchetti, M.; Vivani, R.
Inorg. Chim. Acta **2002**, *338*, 127. (d) Miwa, Y.; Drews,
A. R.; Schlick, S. *Macromolecules* **2006**, *39*, 3304.

(7)   Rey, P.; Rassat, A. *Nouv. J. Chim.* **1983**, *7*, 531.

(8)   Hemme, W. L.; Fujita, W.; Awaga, K.; Eckert, H. *Dalton
Trans.* **2009**, 7995.

(9)   Grim, R. E. *Applied Clay Mineralogy*; McGraw-Hill: New
York, **1962**.

(10) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org.
Chem.* **1987**, *52*, 2559.