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Synthesis of Functionalized Aliphatic Acid Esters via the Generation of Alkyl Radicals from Silylperoxyacetals

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Abstract: We describe a catalytic method for the synthesis of a variety of functionalized aliphatic acid esters using silylperoxyacetals, which are versatile alkyl radical precursors with a terminal ester moiety. In the presence of an appropriate transition-metal catalyst, the in situ generation of alkyl radicals and the subsequent bond-forming process proceeds smoothly to afford synthetically valuable aliphatic acid derivatives. The present method can be applied to the efficient synthesis of a pharmaceutically important 1,1-diarylalkane motif. In addition, a novel strategy for the synthesis of structurally diverse hydroxy acid derivatives via a C–O bond formation process that utilizes TEMPO has been developed.

Aliphatic acids and their derivatives are ubiquitous fundamental structural motifs that have found a variety of applications, from biologically active molecules[1] to monomer units in material science (Figure 1).[2] Since most of these compounds contain various functional groups on their aliphatic carbon chains, the development of a universal strategy for the synthesis of functionalized aliphatic acid derivatives is of great importance. Thus, given the outstanding ability of radical species to serve in diverse carbon–carbon or carbon–heteroatom bond-forming reactions, the generation and functionalization of alkyl radical intermediates may potentially represent an attractive solution to this problem.[3] Although many protocols that use well-designed precursors for the generation of alkyl radicals have been developed so far, very few of these precursors lead to alkyl radicals with terminal carboxy or ester groups. For example, Schaafsma and coworkers have reported that a single-electron oxidation of a cyclopropanone hemiacetal affords a transient alkoxy radical that immediately induces a strain-releasing ring-opening via β-scission to generate a terminal

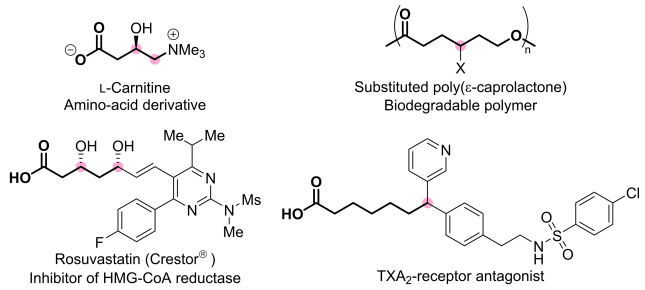
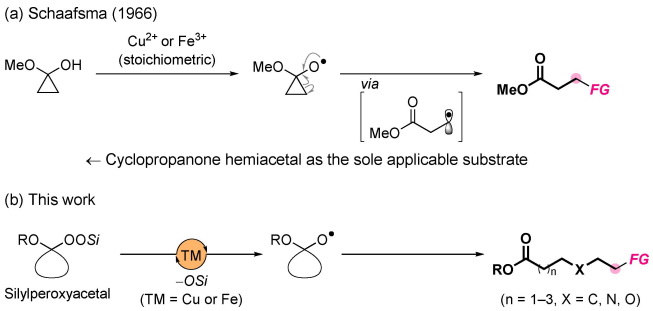


Figure 1. Selected examples of functionalized aliphatic acid derivatives.

ester moiety (Scheme 1a).[4] While this process was successfully merged with further transformations such as dimerization, chlorination, or radical conjugate addition to provide functionalized aliphatic acid esters, the same strategy could not be applied to other hemiacetal species, probably due to their unstable nature and the lack of strain energy required to promote the ring-opening process.[5]

Recently, synthetic methods for the generation of alkyl radicals from alkylsilyl peroxides via β-scission and subsequent functionalization in the presence of transition-metal catalyst have been developed.[6] Using these methods, a variety of functional groups can be introduced to the in situ generated alkyl radicals, which have a terminal keto group, to provide the corresponding aliphatic ketone derivatives. In addition, we have prepared acetal-derived alkylsilyl peroxides from sugar derivatives.[6f] These compounds can be transformed into polyoxygenated linear formyl esters via an iron-catalyzed C–C bond cleavage/C–C bond formation sequence. As part of these ongoing studies, we herein report a practical approach for the synthesis of functionalized aliphatic acid esters via a radical process (Scheme 1b). This method uses silylperoxyacetals, an underexplored class of alkylsilyl peroxides prepared from readily



Scheme 1. Synthesis of aliphatic acid esters via radical functinoalization (FG = functional group).

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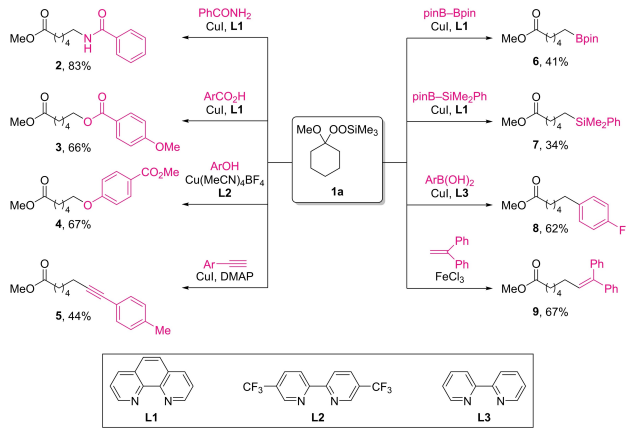
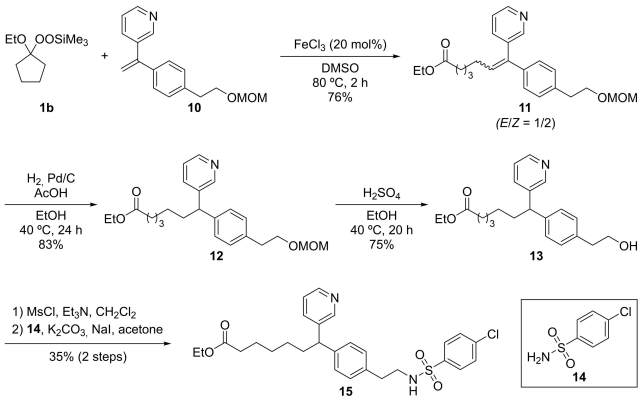
available cyclic ketones. The versatility of these compounds as a precursor for aliphatic acid esters was investigated by applying them in a series of radical functionalizations.[7] Furthermore, the synthesis of hydroxy acid derivatives via the iron-catalyzed aminooxygenation of the in situ generated alkyl radicals was also demonstrated.

We commenced our study using silylperoxyacetal **1a** (Scheme 2), which is prepared from cyclohexanone in three steps (for details, see the Supporting Information). First, the applicability of **1a** as an alkyl radical precursor in a variety of transition-metal-catalyzed radical functionalizations was evaluated. As shown in Scheme 2, **1a** could be used in a variety of bond-forming reactions (C–N, C–O, C–C, C–B, and C–Si bonds).[6] The reaction of **1a** with benzamide using a CuI/1,10-phenanthroline (**L1**) catalytic system furnished the corresponding amide product **2** in high yield. The formation of a C–O bond was also possible via the coupling with a benzoic acid derivative or a phenol derivative to afford **3** and **4**, respectively. An arylacetylene could also be used as a coupling partner resulting in the formation of a C_{sp3}–C_{sp} bond and providing alkynylated ester **5** in 44% yield. In addition, radical borylation and silylation reactions furnished the corresponding products **6** and **7**, albeit in moderate yields. The copper-catalyzed formation of a C_{sp3}–C_{sp2} bond using phenylboronic acid afforded arylated ester **8** under mild reaction conditions. In addition to copper catalysts, the iron salt $FeCl_3$ was also found to facilitate the generation of an alkyl radical from **1a**, and the subsequent addition to diphenylethylene furnished **9** in good yield.



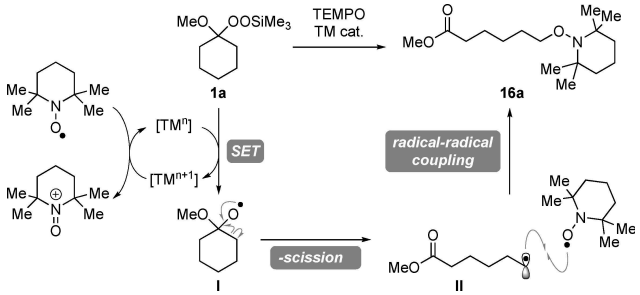
Scheme 2. Transition-metal-catalyzed functionalizations using silylperoxyacetal **1a**. For detailed reaction conditions, see the Supporting Information.



Scheme 3. Synthesis of TXA_2-receptor antagonist derivative **15**.

One of the products **9** can be regarded as a precursor of an aliphatic acid with a 1,1-diarylalkane structure, an important motif that exists in a number of biologically active compounds.[8] Thus, we attempted to construct the substructure of a potent thromboxane A_2 (TXA_2)-receptor antagonist (Figure 1) using an iron-catalyzed radical addition to the corresponding diarylethylene (Scheme 3).[6f] Starting from a silylperoxyacetal containing a five-membered ring (**1b**), the reaction with diarylethylene **10** in the presence of a catalytic amount of $FeCl_3$ gave the desired alkene **11** in good yield as a mixture of *E* and *Z* isomers. The isomers were reduced efficiently using a catalytic amount of palladium on carbon under an atmosphere of hydrogen gas to furnish 1,1-diarylalkane **12**. The subsequent deprotection of the *para*-substituent on the aryl ring of **12** resulted in the formation of **13**. Mesylation of **13**, followed by the nucleophilic substitution with sulfonamide **14**, afforded **15**, which is an ethyl ester derivative of a TXA_2-receptor antagonist. These results demonstrate that various functionalized aliphatic acid esters, including a pharmaceutically relevant motif, can be efficiently synthesized by our method using silylperoxyacetals.

Having confirmed the utility of silylperoxyacetals as precursors for aliphatic acids, we next investigated expanding the scope of valuable aliphatic acid derivatives that can be created using our method. Hydroxy acids are an attractive synthetic target due to the crucial roles they play in the metabolic system and in functional materials such as surfactants or biodegradable plastics.[9] While the previously described methods for the formation of C–O bonds using **1a** can provide the corresponding hydroxy acid derivatives such as **3** and **4** (Scheme 2), these products present a potential problem for further transformations as it is challenging to selectively deprotect the benzoyl or aryl groups while keeping the ester moiety intact. Thus, the introduction of an alternative oxygen source that can be selectively and flexibly transformed would be preferrable. In this regard, we focused on the formation of a C–O bond via the reaction of alkyl radicals with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).[10] As outlined in Scheme 4, a single-electron transfer (SET) from a suitable transition-metal catalyst to silylperoxyacetal **1a** would form alkoxy radical **I**. The subsequent ring-opening of **I** via β-scission would generate alkyl



Scheme 4. Proposed mechanism for the reaction of **1a** with TEMPO.

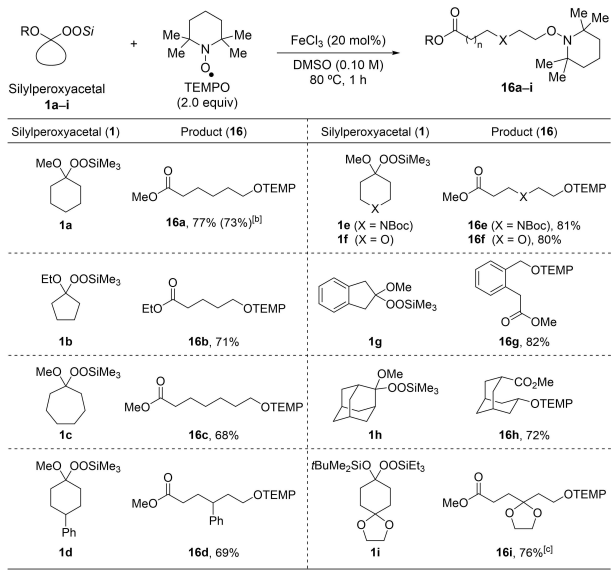
radical **II**, which can react with TEMPO to furnish the desired product **16a**. In this catalytic system, TEMPO can also act as a reducing reagent for the transition-metal catalyst. We also thought that the weak N–O bond of the resulting TEMPO adduct could be selectively cleaved giving access to various oxygen functionalities (hydroxy, formyl, or carboxyl groups) depending on the reaction conditions used.[10b,f]

The optimization of the reaction conditions was carried out using silylperoxyacetal **1a** and 2.0 equivalents of TEMPO. The screening of transition-metal catalysts, ligands, and solvents revealed that $FeCl_3$ efficiently promotes the desired reaction in DMSO at 80 °C without the need for an external ligand, affording TEMPO adduct **16a** in high yield within an hour. It should be noted that the use of $FeCl_2$ instead of $FeCl_3$ also gave **16a** in a good yield (see S26 in the Supporting Information). These results indicate that both Fe(II) and Fe(III) species would be involved in the catalytic cycle, which is consistent with the proposed mechanism described in Scheme 4. Under the optimal conditions, the reactivity of a series of cyclic silylperoxyacetals was investigated (Table 1). In general, the reactions proceed smoothly to furnish the corresponding TEMPO adducts **16** as hydroxy acid derivatives in good to high yields. Not only was six-membered cyclic silylperoxyacetal **1a** reactive under these conditions, but five- and seven-membered derivatives **1b** and **1c** were also active. The desired products **16a–c** were obtained in good yield regardless of the difference in the strain energy of the ring systems. The reaction of silylperoxyacetal **1d** also worked well to give the corresponding phenyl-substituted product **16d**. Several functional groups such as cyclic ether (**1e**), *N*-*tert*-butoxycarbonyl amine (**1f**), and cyclic acetal (**1i**) moieties were well tolerated, and the corresponding products **16e**, **16f**, and **16i** were obtained in good to high yields. In addition, silylperoxyacetals **1g** and **1h**, derived from 2-indanone and 2-adamantanone, respectively, gave structurally unique hydroxy acid derivatives **16g** and **16h**.

Subsequently, we conducted the reactions using acyclic silylperoxyacetals **1j–1l** (Table 2). When **1j**, derived from isopentyl methyl ketone, was used isopentyl-substituted alkoxyamine **16j** was selectively obtained in 43% yield. Moreover, silylperoxyacetals prepared from aliphatic aldehydes could also be applied to this transformation. For example, the reaction of citronellal-derived peroxyacetal **1k** successfully furnished the corresponding TEMPO adduct **16k** without affecting the terminal olefin moiety. Notably, a deoxyribose-derivative **1l**, which contains both a silyl-protected acetal and a free hydroxy moiety, could be transformed into erythritol derivative **16l** in moderate yield, indicating that our method has the potential to be applied to the functionalization of complex molecules.

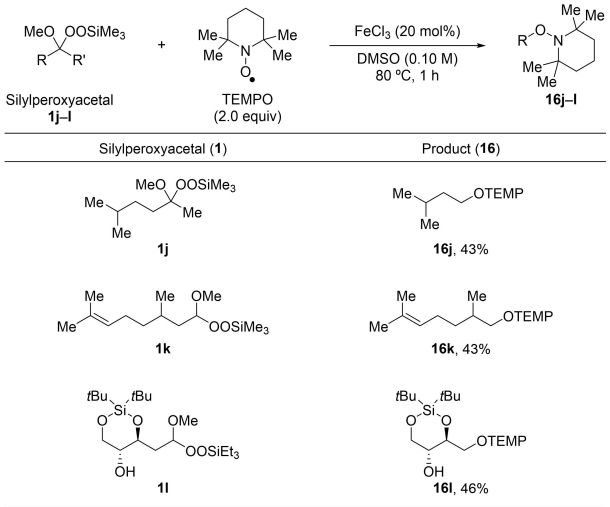
Depending on the C–C bond that is cleaved via the β-scission of the alkoxy radical intermediate, two possible products are potentially formed during the reactions that use unsymmetric silylperoxyacetals **1m–1o** (Scheme 5). In these cases, we observed that the cleavage of the C–C bond occurs in a highly regioselective manner. Specifically, the reaction of 2-

Table 1. Scope with respect to cyclic silylperoxyacetals.[a]



[a] Reaction conditions: **1** (0.10 mmol), TEMPO (0.20 mmol), and $FeCl_3$ (20 mol%) in DMSO (1.0 mL) at 80 °C for 1 h under N_2 atmosphere. Yields of isolated products are shown. [b] 1.1 g of **1a** was used. [c] The reaction was quenched with $[nBu_4N]F$, followed by the addition of MeI.

Table 2. Scope with respect to acyclic silylperoxyacetals.[a]



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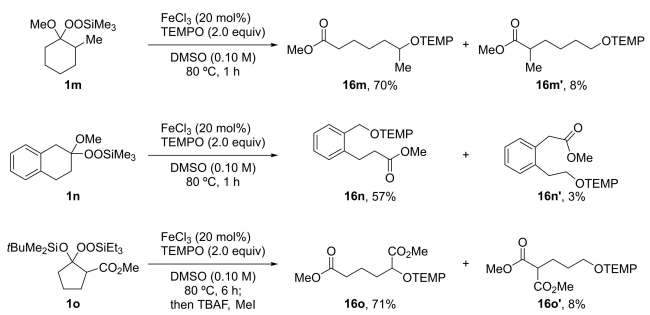
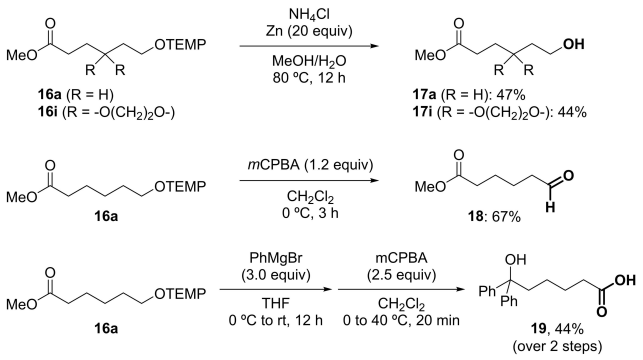


Scheme 5. Reactions of unsymmetric silylperoxyacetals with TEMPO.



Scheme 6. Subsequent transformations of the TEMPO adducts **16a** and **16i**.

methyl-substituted silylperoxyacetal **1m** selectively afforded **16m** because the C–C bond cleavage occurs at the more substituted bond of the acetal center. An aryl-fused silylperoxyacetal **1n** also showed high regioselectivity, furnishing **16n** via the trapping of TEMPO at the benzylic position. It is also noteworthy that the reaction of **1o**, which contains an electron-withdrawing methoxycarbonyl group at the 2-position, also proceeded smoothly via the selective cleavage of the C–C bond at the more substituted bond of the acetal center affording **16o** in a good yield.

Finally, we conducted transformations of the obtained TEMPO adducts to demonstrate their synthetic utility (Scheme 6). As expected, the N–O bond of the product could be cleaved under both reductive and oxidative conditions, affording the corresponding alcohols **17a** and **17i** or aldehyde **18** without affecting the terminal ester moiety. In addition, the conversion of the ester moiety via a Grignard reaction without removing the N–O bond of the TEMPO moiety was also possible. The subsequent oxidative cleavage of the N–O bond furnished hydroxy acid **19**, which bears a tertiary alcohol moiety. These results demonstrate the general utility of our method for the synthesis of a broad range of hydroxy acid derivatives.

In conclusion, we have presented a method for the synthesis of functionalized aliphatic acid esters. Using silylperoxyacetals, i.e., alkyl radical precursors that bear an ester moiety, a broad range of functionalized aliphatic acid esters were efficiently synthesized via the transition-metal-catalyzed generation and subsequent functionalization of alkyl radicals. As a practical application of the present method, the synthesis of a pharmaceutically relevant molecule containing a 1,1-diarylalkane structure was demonstrated. In addition, the development of an iron-catalyzed aminooxygenation of the in situ generated alkyl radicals allowed for the synthesis of structurally diverse hydroxy acid derivatives.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–C bond cleavage · β-scission · alkyl radicals · silylperoxyacetals · iron-catalysis · hydroxy acids

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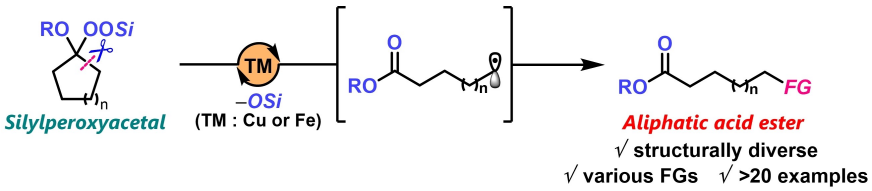

A catalytic method to access functionalized aliphatic acid esters using silylperoxyacetals as alkyl radical precursors with a terminal ester moiety is described. The reaction proceeds via the in situ generation and subsequent functionalization of alkyl radicals, affording synthetically valuable aliphatic acid derivatives. A novel strategy for the synthesis of hydroxy acid derivatives via a C–O bond formation process is also developed.

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