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# Free-radical carbo-oximation of olefins and subsequent radical-ionic cascades

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ABSTRACT

A sequential carbo-formylation cascade has been developed, involving a free-radical carbo-oximation process, followed by the hydrolysis of the oxime ether. For this purpose, we designed a new SEM *O*-protected sulfonyl oxime, which enable both rapid radical addition and hydrolysis under mild conditions. The resulting aldehyde-esters were then engaged in various nucleophilic cascades, such as Sakurai allylations or domino-Mukaiyama aldol condensation/lactonizations. Addition of an amine and TMSCN similarly led after Strecker reaction/lactamization to α-cyano-piperidinones in good overall yield. Finally, a Pictet–Spengler/lactamization sequence was devised, which open a new entry toward the tricyclic core of eburnan alkaloids.



## 1. Introduction

Addition of functionalized carbon fragments across the olefinic π-system offers a straightforward access to valuable intermediates for organic synthesis. Such a transformation may be handled through a multicomponent approach, using organometallic catalysis.[1] Several studies have thus been reported, although their scope of application is restricted by the nature of the added fragments.[1] Free-radical multicomponent reactions (MCR) are more flexible and fulfill some of the stringent criteria for an efficient carbo-functionalization of olefins.[2] Radical MCRs have thus attracted a considerable attention. Addition of carbon-radical species across the π-system of electron-deficient olefins is a well documented and reliable transformation.[3] In contrast, it is only recently that addition of carbon fragments across the π-bond of non-activated olefins through free-radical pathways has received intense scrutiny, resulting in the description of useful transformations, such as for instance carbo-alkynylation,[4] carbo-allylation,[2,5] and carbo-alkenylation of olefins.[5d,e,6,7] These processes also illustrate the importance of the influence of polar effects in free-radical MCRs.[2c] Such reactions proceed through the preliminary addition of an electron-poor radical issued from **A** to the less hindered end of an olefin **B**, forming a new nucleophilic radical, which can then be trapped by an electrophilic partner **C** (Fig. 1).[7] Various electrophilic species may be envisioned, but sulfones including vinyl-,[7,8] alkynyl-,[4,7] and allylsulfones[5d,7,9] hold a prominent place, due to the efficient β-fragmentation of the sulfonyl moiety.[10] Sulfones also allow the incorporation of other $R^3$ substituents on the olefinic backbone (CN, SPh, Cl, $N_3$, etc.…).[7,11]

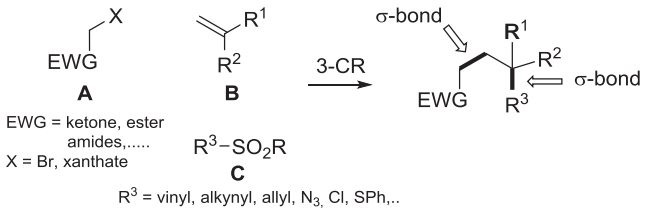


**Fig. 1.** Free-radical 3-component processes with sulfones.

Pioneering studies by Kim and co-workers[12] showed that sulfonyl oximes are also excellent radical acceptors, enabling the incorporation of an oxime onto a carbon framework. Based on this work, we recently developed a free-radical formal [2+2+2]-process involving sulfonyl oximes as electrophilic radical traps.[13] Addition, of a nucleophilic alkyl radical or an allylzinc species onto the oxime, issued from the 3-component reaction, led to the one-pot formation of 5,6-disubstituted piperidinones in good yields and high diastereoselectivities. The present work describes our studies on the generalization of this carbo-oximation of olefins as a formal carbo-formylation process. Carbo-formylation of an olefin under radical conditions has been described by Ryu et al. using carbon monoxide as the radical trap.[14] The use of Kim's sulfonyl oxime **1a** constitutes a more practical surrogate to toxic CO,[12,15] which generally requires

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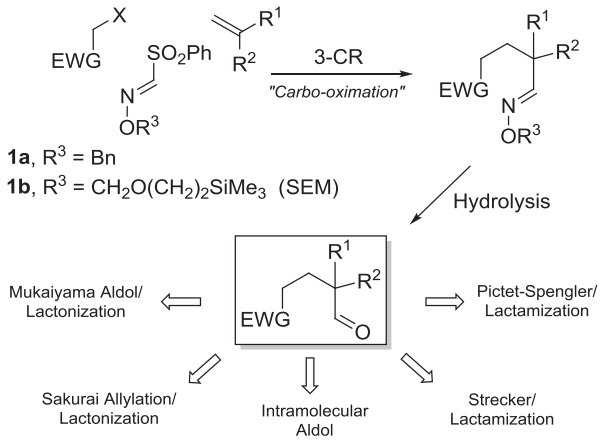
relatively high pressure, and therefore specific autoclave equipment.[14] We report herein the synthesis and the use in multicomponent reactions of the new SEM-protected sulfonyl oxime **1b**, which enables facile hydrolysis of the oxime under mild conditions. We finally describe the post-functionalization of the carboformylation products, which provides a rapid access to lactones, after Mukaiyama aldol or Sakurai allylation reactions or more complex piperidinones using Pictet–Spengler processes (Scheme 1).

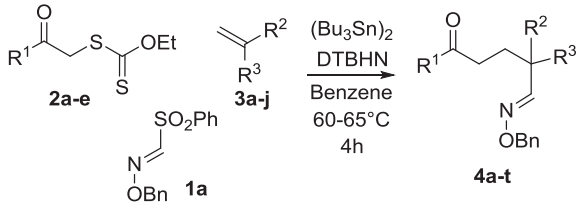



**Scheme 1.** 3-Component carbo-oximation and post-functionalization.

## 2. Results and discussions

The 3-component carbo-oximation process was first carried out using Kim's sulfonyl oxime **1a**[12a] (2 equiv), an excess of the olefin **3** (5 equiv), a xanthate precursor **2** (1–1.2 equiv), and $(Bu_3Sn)_2$ (1.5 equiv) in benzene (degassed) as a solvent. The reaction was initiated using di-*tert*-butylhyponitrite (DTBHN) (10 mol %). The results are summarized in Table 1 below. Generally good and reproducible yields of the 3-component adducts were obtained (60–80%). The final oximes **4a**–**t** were easily isolated through chromatography over silica gel. A broad variety of substituents on the olefin is compatible with the reaction conditions, including electron-rich olefins, such as allylsilanes (**3f**, entry 7) and enol ethers (**3b**, entry 2,6,8), but also simple alkyl olefins (**3c**–**d**, entry 3–4). Trisubstituted olefins also reacted well leading to tertiary formaldoximes (entries 10–12, 20). In contrast, vinyl-phthalimide **3e** (entry 5) led to a poor yield. The scope of the xanthate precursors was investigated and functional groups, such as esters, ketones, and thioesters, all provided the desired products in good yields showcasing the tolerance of the process towards the nature of the xanthate.[16] Activated esters bearing good leaving groups, such as $C_6F_5O$ performed also well under the reaction conditions (entry 6). Although the present work based on phenylsulfonyl oximes generates undesired stannylated by-products, this procedure was found more efficient, in terms of yields, than the one using ethylsulfonyl oximes, which does not require the use of $(Bu_3Sn)_2$.[7,13a]

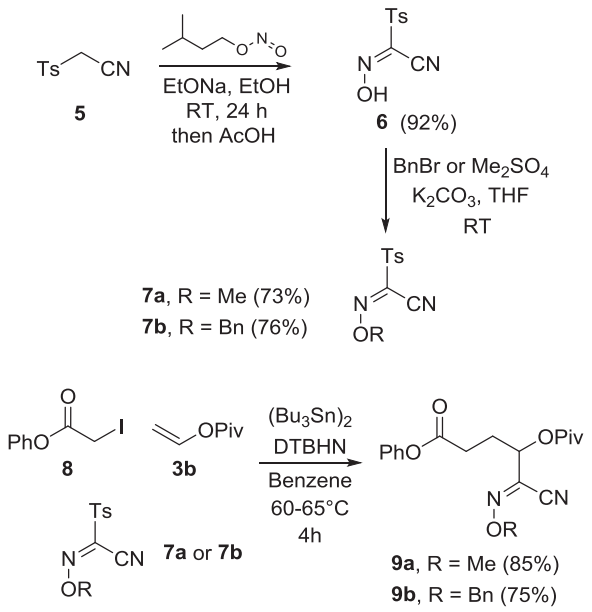
**Table 1**
Free-radical carbo-oximation of olefins with sulfonyl oxime **1a**




| Entry | Xanthate **2** | $R^1$ | Olefin | $R^2$ | $R_3$ | Product | Yield[a] |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | PhO | **3a** | OAc | Me | **4a** | 72 |
| 2 | **2a** | PhO | **3b** | OPiv | H | **4b** | 70 |
| 3 | **2b** | EtO | **3c** | $C_6H_{13}$ | H | **4c** | 64 |
| 4 | **2a** | PhO | **3d** | $-(CH_2)_5-$ | | **4d** | 73 |
| 5 | **2a** | PhO | **3e** | NPht | H | **4e** | 32 |
| 6 | 2c[b] | $(C_6F_5)O$ | **3b** | OPiv | H | **4f** | 64 |
| 7 | **2d** | Me | **3f** | $CH_2SiMe_3$ | H | **4g** | 60 |
| 8 | **2d** | Me | **3b** | OPiv | H | **4h** | 61 |
| 9 | **2d** | Me | **3c** | $C_6H_{13}$ | H | **4i** | 60 |
| 10 | **2d** | Me | **3d** | $-(CH_2)_5-$ | | **4j** | 68 |
| 11 | **2d** | Me | **3g** | $-(CH_2)_4-$ | | **4k** | 67 |
| 12 | **2d** | Me | **3h** | Et | Et | **4l** | 61 |
| 13 | **2e** | PhS | **3f** | $CH_2SiMe_3$ | H | **4m** | 68 |
| 14 | **2e** | PhS | **3b** | OPiv | H | **4n** | 71 |
| 15 | **2e** | PhS | **3c** | $C_6H_{13}$ | H | **4o** | 71 |
| 16 | **2e** | PhS | **3d** | $-(CH_2)_5-$ | | **4p** | 74 |
| 17 | **2e** | PhS | **3g** | $-(CH_2)_4-$ | | **4q** | 66 |
| 18 | **2e** | PhS | **3h** | Et | Et | **4r** | 69 |
| 19 | **2e** | PhS | **3i** | $(CH_2)_3OTBDMS$ | H | **4s** | 58 |
| 20 | **2e** | PhS | **3j** | $(CH_2)_2OTBDMS$ | Me | **4t** | 72 |

[a] Isolated yield after chromatography over silica gel.
[b] The α-bromoester was used instead of the xanthate.

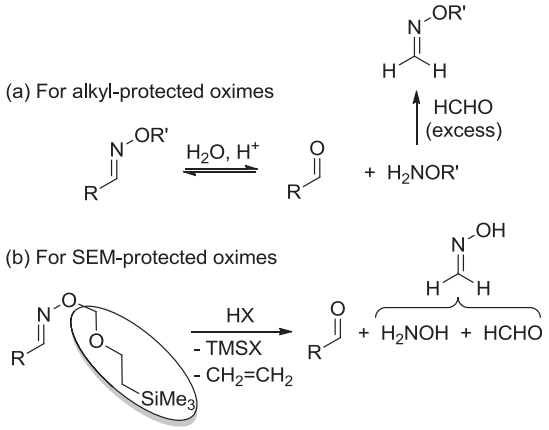
The reaction was extended to new sulfonyl oximes **7a**–**b**, readily available from the corresponding α-sulfonyl nitrile **5**. The treatment of the latter with isoamyl nitrite under basic conditions[12,17] led to the desired oxime **6**, which was *O*-protected[18] to afford **7a**–**b** in good overall yield (Scheme 2). The carbo-oximation of vinyl pivalate **3b** under the conditions described above, with oxime ethers **7a**–**b** and iodoester **8** gave the desired nitriles **9a**–**b** in excellent yields.




**Scheme 2.** Synthesis of oximes **7a**–**b** and their 3-CR reactions.

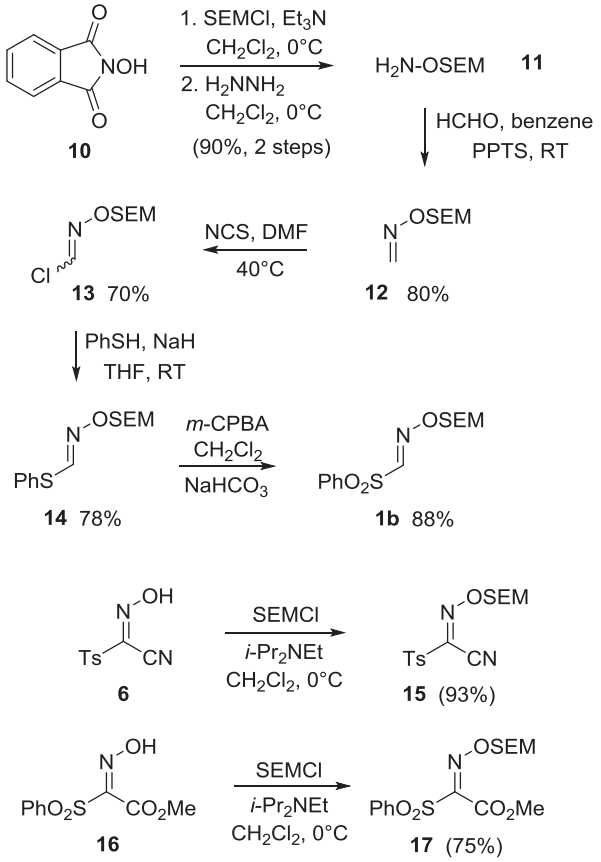
Hydrolysis of oxime ethers (Bn, Me) often requires rather harsh conditions, producing the desired aldehyde along with the reactive hydroxylamine $H_2NOR'$ (Scheme 3, pathway (a)). As the reaction is formally reversible, excess aqueous formaldehyde is generally employed to trap $H_2NOR'$ and shift the equilibrium in the desired direction.[12,15] Although these conditions have a broad scope, the presence of large quantities of aqueous formaldehyde may not be compatible with other functional groups in the substrate. We thus designed a second generation of oxime ethers, which could be converted into the corresponding aldehyde under mild conditions, without the recourse to aqueous formaldehyde (Scheme 3, pathway (b)). It was foreseen that the SEM (2-(trimethylSilyl)EthoxyMethyl ether) group[19] should be well adapted for this purpose. Its deprotection typically achieved with Brønsted acids, such as TFA[20] would produce the desired aldehyde, a silylated derivative, ethylene (both likely volatile by-products), but also an equivalent of

formaldehyde and $H_2NOH$. It was anticipated that formaldehyde and hydroxylamine would condense to form the formaldoxime, overall acting as a driving force towards the clean formation of the desired aldehyde. Trans-oximation between deprotected oxime and formaldehyde may also occur.



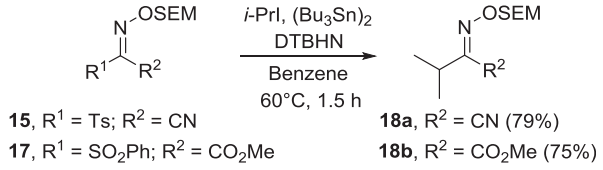

**Scheme 3.** Hydrolysis of oxime ethers.

We prepared the corresponding sulfonyl oxime **1b** using the six-steps sequence depicted below (Scheme 4).[12a] The SEM-protected hydroxylamine **11**, which is not commercially available was prepared from *N*-hydroxyphthalimide **10** in two-steps.[21] Formylation of **11** afforded the formaldoxime ether **12**, which was then chlorinated to give **13**. Introduction of the sulfonyl group was carried out through a two-steps sequence via the intermediate thioxime ether **14**. The required sulfonyl oxime **1b** was finally obtained in a 35% overall yield in six steps from **10** on a multigram scale. Simple O-protection with SEMCl[18] was also performed with readily available oxime **6** and **16**, providing the corresponding SEM-oxime ethers **15** and **17** in excellent yields.



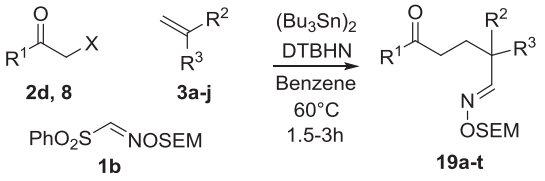

**Scheme 4.** Preparation of sulfonyl oxime SEM ethers **1b**, **15**, and **17**.

The compatibility of these new oximes toward radical conditions using tin as a mediator, was tested with the addition of isopropyl iodide onto oximes **15** and **17**. The latter were found to be slightly more reactive than the benzylated analogue **1a**, leading to the desired products **18a**–**b** in good yield in less than 1.5 h. With these results in hand, the three-component process was then studied using iodide **8** or xanthates **2d** as radical precursors, a range of olefins **3** as above and sulfonyl oxime **1b**. Better yields were consistently obtained using 2 equiv of oxime (Table 2). The scale-up of the reaction required the reaction to be performed using a 0.4–0.5 M concentration in iodide or xanthate, in order to get three-component adducts in good yields. The reaction conditions were found to be compatible with esters (entry 2–3, 16, 20), silyl ethers (entry 10), Boc protected amines (entry 12), but surprisingly, no reaction was observed when a free OH group was present in the olefin (entry 11). Similarly, no reaction was observed with styrenes, vinyl ethers (entry 14), and allylic acetates, which is surprising as these olefins were shown to be compatible partners, for instance, in carbo-alkenylation,[6] a multicomponent process run under similar conditions (Scheme 5).




**Scheme 5.** Radical additions to SEM sulfonyl oximes **15** and **17**.

**Table 2**
Free-radical carbo-oximation of olefins with SEM sulfonyl oxime **1b**

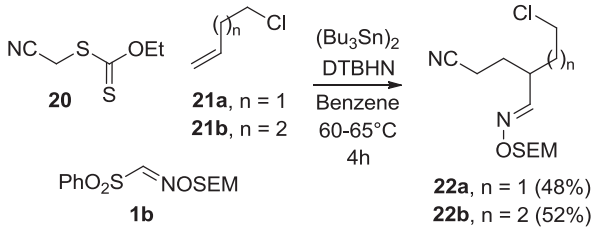



| Entry | Xanthate or iodide **2** | $R^1$ | Olefin | $R^2$ | $R^3$ | Product | Yield[a] |
|---|---|---|---|---|---|---|---|
| 1 | **8** (X=I) | PhO | **3f** | $CH_2SiMe_3$ | H | **19a** | 82[c] |
| 2 | **8** (X=I) | PhO | **3b** | OPiv | H | **19b** | 76[b] |
| 3 | **8** (X=I) | PhO | **3b** | OPiv | H | **19b** | 73[c] |
| 4 | **8** (X=I) | PhO | **3c** | $C_6H_{13}$ | H | **19c** | 54[b] |
| 5 | **8** (X=I) | PhO | **3c** | $C_6H_{13}$ | H | **19c** | 69[c] |
| 6 | **8** (X=I) | PhO | **3d** | $-(CH_2)_5-$ | | **19d** | 62[b] |
| 7 | **8** (X=I) | PhO | **3d** | $-(CH_2)_5-$ | | **19d** | 77[c] |
| 8 | **8** (X=I) | PhO | **3g** | $-(CH_2)_4-$ | | **19e** | 48[b] |
| 9 | **8** (X=I) | PhO | **3g** | $-(CH_2)_4-$ | | **19e** | 69[c] |
| 10 | **8** (X=I) | PhO | **3k** | $(CH_2)_2OTBDPS$ | Me | **19f** | 76[c] |
| 11 | **8** (X=I) | PhO | **3l** | $(CH_2)_2OH$ | Me | — | 0 |
| 12 | **8** (X=I) | PhO | **3m** | $-(CH_2)_2NBoc(CH_2)_2-$ | | **19g** | 61[c] |
| 13 | **8** (X=I) | PhO | **3n** | $-(CH_2)_2O(CH_2)_2-$ | | **19h** | 68[c] |
| 14 | **8** (X=I) | PhO | **3o** | OEt | H | — | 0 |
| 15 | **8** (X=I) | PhO | **3h** | Et | Et | **19i** | 78[c] |
| 16 | **8** (X=I) | PhO | **3p** | $(CH_2)_2OBz$ | Me | **19j** | 80[c] |
| 17 | **2d** (X=xanth.) | Me | **3f** | $CH_2SiMe_3$ | H | **19k** | 68[c] |
| 18 | **2d** (X=xanth.) | Me | **3c** | $C_6H_{13}$ | H | **19l** | 52[c] |
| 19 | **2d** (X=xanth.) | Me | **3d** | $-(CH_2)_5-$ | | **19m** | 74[c] |
| 20 | **2d** (X=xanth.) | Me | **3b** | OPiv | H | **19n** | 64[c] |

[a] Isolated yield after chromatography over silica gel.
[b] 1 equiv of oxime **1b** was used.
[c] 2 equiv of oxime **1b** was used.

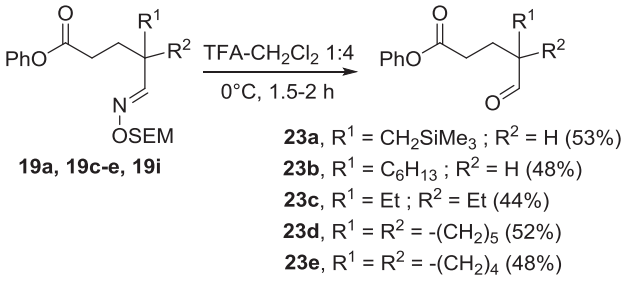
The reaction was next extended to α-cyano xanthate **20**,[16] which was shown to react with chloro-olefins **21a**–**b**. This last result demonstrates that the tin-mediated process is compatible with the

presence of halogens, leading to the desired 3-component products **22a**–**b**, albeit in moderate yields (Scheme 6).



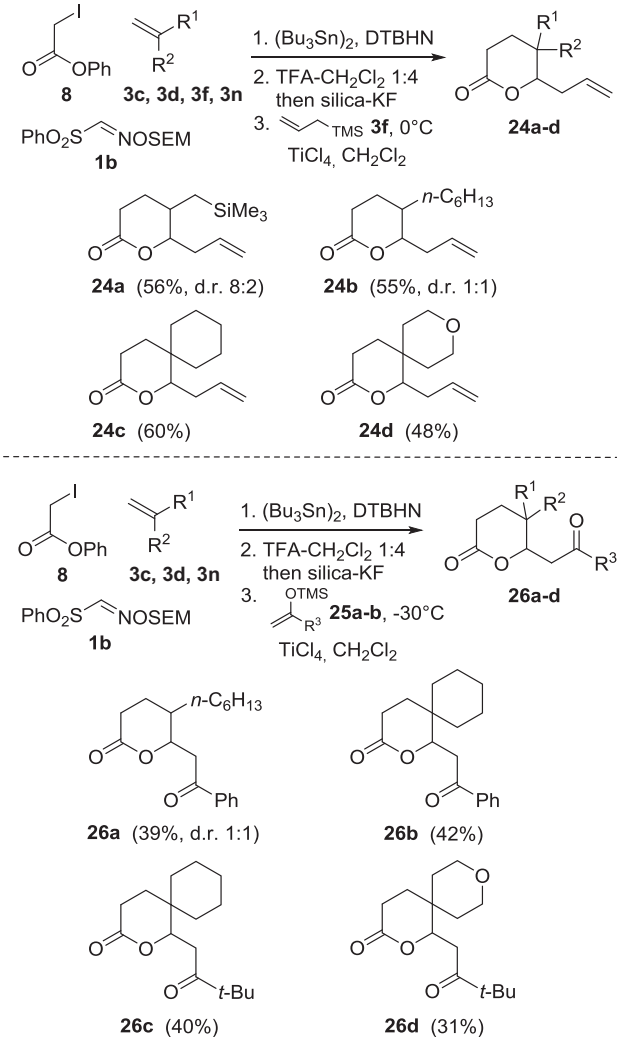

**Scheme 6.** Radical additions of α-cyano xanthates to SEM sulfonyl **1b**.

We then studied the conversion of these SEM-oximes into the corresponding aldehydes under various conditions. Fluoride sources (CsF, TBAT, TBAF),[19,20] and acidic conditions were investigated to trigger the conversion of oximes **19** into their corresponding aldehydes. While fluoride sources led to no reaction,[22] efficient deprotection was observed using TFA in $CH_2Cl_2$ (1:4 ratio) or HF–pyridine. At 0 °C, the conversion was complete within two hours and the crude yield of the aldehyde, after work-up, typically reached 70–80%. Our attempt to purify aldehyde-esters **23a**–**e** through chromatography led to some loss of material, but reasonable isolated yields (ca. 40–60%) were however obtained (Scheme 7). In most cases, aldehydes were pure enough to be used in subsequent transformations without further purification (vide infra).




**Scheme 7.** Hydrolysis of 3-component products **19**.

We next evaluated the further transformation of **23a**–**e**, resulting overall from a formal carbo-formylation of olefins. The functional groups embedded in **23a**–**e**, should provide, via simple transformations, an access to functionalized cyclic substrates in a limited number of operations. For instance, addition of a nucleophile onto aldehydes **23** should provide an alcohol, which would lactonize under suitable conditions, to afford 5,6-disubstituted lactones. Hosomi–Sakurai allylation[23] and Mukaiyama aldol[24] processes were first selected for this purpose using, respectively, allyltrimethylsilane **3f** and silyl enol ethers **25a** ($R_3$=Ph) and **25b** ($R_3$=*t*-Bu) as nucleophiles (Scheme 8). Since the purification of the aldehydes was inevitably hampered by some degradation on silica gel, preliminary studies were designed as to carry out the following sequence: free-radical 3-CR/oxime hydrolysis/Sakurai reaction in a single pot, without purification of any intermediates. Such a protocol however did not produce the desired products in reasonable yield. The free-radical process likely generates various by-products, which interfere with the subsequent transformations. To address this drawback, the 3-component products **19** were hydrolyzed using the method described above (using a 1:4 TFA–$CH_2Cl_2$ mixture) and the resulting crude materials were purified through a short pad of silica gel doped with KF,[25] in order to remove tin residues. The intermediate aldehydes were then isolated in reasonable overall yields over two-steps (ca. 50%), and importantly, pure enough to be used in subsequent Sakurai and Mukaiyama reactions. Hosomi–Sakurai allylations conducted on these purified materials, in the presence of a stoichiometric amount of $TiCl_4$, produced the

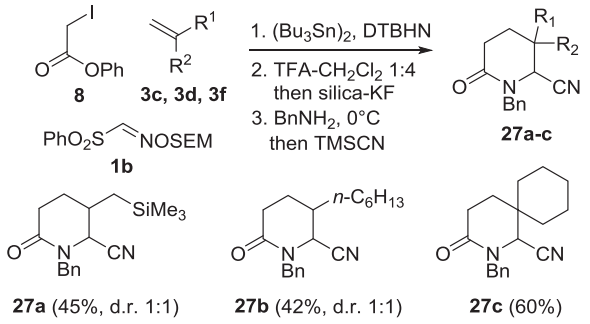



**Scheme 8.** Free-radical-3CR/oxime hydrolysis/Sakurai allylation or Mukaiyama aldol/lactonization cascades.

expected lactones **24a**–**d** in good overall yield (50–60%) in three steps from iodide **8**. These overall yields indicate that the allylation step proceeds very efficiently (>90%), albeit with poor diastereocontrol (Scheme 8). This two-pot operation was next extended to the Mukaiyama aldol, again using as originally described,[24] $TiCl_4$ to mediate the reaction. Ketolactones **26a**–**d** were obtained with slightly lower overall yields from **8** (30–40%), illustrating the somewhat lower efficiency of the silyl enol ether **25a**–**b** addition.

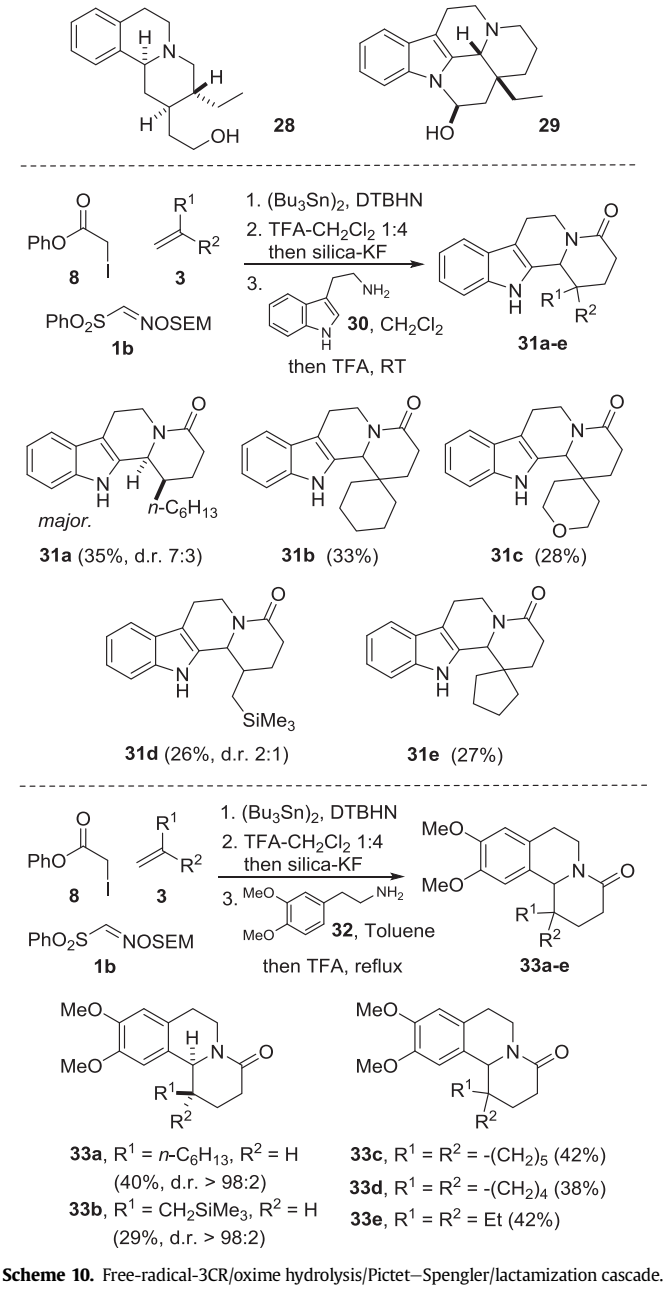
We next evaluated the behavior of these aldehydes with primary amines in order to determine their level of performance in Strecker[26] and Pictet–Spengler[27] protocols. Treatment of aldehydes, issued from the multicomponent process between iodide **8**, olefins **3** and sulfonyl oxime **1b**, with benzylamine and then TMSCN[28] provided the expected cyano-amides **27a**–**c** (Scheme 9). The latter are versatile intermediates in particular for the generation of highly reactive acyl-iminium species.[29] Cyano-amides **27a**–**c** were isolated in 40–60% overall yield in three steps/two-pot operation from **8**.

With the objective of accessing more complex structural motifs, our aldehydes were submitted to a Pictet–Spengler-lactamization cascade.[30] The tricyclic framework obtained using this strategy is present in many bioactive compounds including natural alkaloids, such as protoemetinol **28**[31] and eburnamine **29**.[32] In practice, the aldehydes resulting from the free-radical 3-component reaction/oxime ether hydrolysis were reacted with tryptamine **30** in $CH_2Cl_2$ at room temperature, leading to the



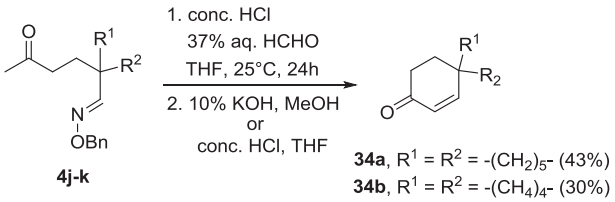

**Scheme 9.** Free-radical-3CR/oxime hydrolysis/Strecker/lactamization cascade.

corresponding imine intermediate, which did not required to be isolated. In situ addition of TFA then triggered the Pictet–-Spengler-lactamization cascade,[33] generating the tricyclic compounds **31a**–**e** in reasonable overall yield over three steps (Scheme 10). Diastereocontrol was again poor, with major isomer possessing the *cis* relative configuration as determined by $^1$H NMR. The Pictet–Spengler-lactamization tandem process was then extended to less reactive homoveratrylamine **32**. The aldehydes issued from the free-radical 3CR were reacted with **32** following, as above, a one-pot protocol, without isolation of the imine intermediate. The imine preformation required heating in toluene at reflux for 2 h. TFA was then added to the resulting imine and heating was then continued for a further 3 h. The desired tricyclic substrates **33a**–**e** were isolated in 29–42% overall yields over three steps from iodide **8**. It is noteworthy that **33a** and **33b** were obtained as single isomers. The *cis*-configuration is likely the result of an iminium-enamine equilibrium during the Pictet–Spengler process, due to relatively harsh acidic conditions. This contrasts with the stereocontrol obtained for **31a** issued from the same reaction with tryptamine, but under milder conditions.




**Scheme 10.** Free-radical-3CR/oxime hydrolysis/Pictet–Spengler/lactamization cascade.

Finally, a combination between the free-radical carbo-oximation/oxime hydrolysis cascade and an intramolecular aldol reaction was envisaged, which would offer a straightforward access to γ-substituted cyclohexenones.[34] It was anticipated that hydrolysis under acidic conditions of SEM-protected oximes **19k**–**n** bearing a methyl ketone (Table 2), followed by treatment of the resulting keto-aldehyde with a base would produce the desired cyclohexenones (Scheme 11). Unfortunately, all our efforts to hydrolyze oximes **19k**–**n** using various conditions (TFA–$CH_2Cl_2$, HCl, PTSA) met with failure. The presence of the methyl ketone in these compounds likely interferes with the hydrolysis process. Alternatively, the hydrolysis of the oxime benzyl ether in 3-component adducts **4j**–**k** (Table 1), using an excess of formaldehyde was attempted.[12,15] To our delight, under these conditions, the corresponding aldehydes were formed in 50–60% isolated yield. These were then treated either with base (KOH, MeOH) or with acid conditions (conc. HCl in THF), affording in each case reasonable yields of the desired γ,γ-substituted cyclohexenones **34a**–**b**.




**Scheme 11.** Oxime hydrolysis/intramolecular aldolisation cascade.

## 3. Conclusion

In summary, a sequential carbo-formylation protocol involving a 3-component radical carbo-oximation–hydrolysis process was developed. In order to avoid *trans*-oximation, which interferes with the hydrolysis of the oxime ether, a new SEM-O-protected sulfonyl oxime was prepared, and successfully used in the 3-component radical carbo-oximation process. Its hydrolysis under mild conditions allowed the carbo-oximation/oxime hydrolysis to be carried out in a single pot. The resulting aldehydes were then elaborated further, through a series of cascade reactions based on the distinct and enhanced reactivity of the aldehyde over the ester functional group. Sakurai allylation and Mukaiyama aldol reactions on the aldehydes, immediately followed by spontaneous lactonization, led to a series of lactones in good overall yield. In a similar fashion, a Strecker reaction offered a straightforward access to cyano-piperidinones, precursors of useful acyl-iminium reagents. A Pictet–Spengler-lactamization cascade on these aldehyde-esters with tryptamine and homoveratrylamine was also devised, which delivered a number of piperidinones bearing polycyclic framework

found for instance in eburnan alkaloids. All these cascades were carried out using a three-step sequence from readily available material, in a two-pot operation, thus limiting the number of purification steps.

## 4. Experimental section

### 4.1. General procedure for the three-component carbo-oximation with sulfonyl oxime (1a) (Table 1). Three-component adducts (4a–t)

To a solution of xanthate **2a**–**e** (0.21 mmol, 1.2 equiv), sulfonyl oxime **1a** (0.42 mmol, 2 equiv), $(Bu_3Sn)_2$ (1.5 equiv), and the alkene **3a**–**j** (4–5 equiv) in degassed benzene (1.8 mL, 0.1 M relative to **1a**) at 60 °C was added DTBHN (di-*tert*-butylhyponitrite) (5 mol %) every 90 min. After usually 2–4 additions, TLC indicated complete consumption of the oxime component. Concentration in vacuo, followed by purification by flash chromatography (silica gel with 10% KF (w/w), Petroleum ether/EtOAc) afforded oxime **4a**–**t** as colorless oils.

*4.1.1. 4-Acetoxy-5-benzyloxyimino-4-methyl-pentanoic acid phenyl ester (**4a**).* Compound **4a** was obtained according to the general procedure described above from xanthate **2a** (64 mg, 0.25 mmol, 1 equiv), sulfonyl oxime **1a** (138 mg, 0.5 mmol, 2 equiv), isopropenyl acetate **3a** (0.16 mL, 1 mmol, 4 equiv), $(Bu_3Sn)_2$ (0.19 mL, 0.38 mmol), and DTBHN (4 mg, 0.04 mmol, 10 mol %) added by 5 mol % portion every 1.5 h, in degassed benzene (1.5 mL). Concentration in vacuo, followed by purification by flash chromatography (silica gel with 10% KF (w/w), Petroleum ether/EtOAc 95:5→90:10) afforded oxime **4a** as a colorless oil (106 mg, 72%). $R_f$=0.22 (Petroleum ether/EtOAc 90:10). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.71 (s, 1H), 7.43–7.23 (m, 8H), 7.12–7.10 (m, 2H), 5.13 (s, 2H), 2.65 (t, $J$=7.9 Hz, 2H), 2.45–2.25 (m, 2H), 2.06 (s, 3H), 1.67 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 171.4, 169.8, 152.1, 150.7, 137.4, 129.5, 128.4, 128.0, 125.9, 121.5, 79.9, 76.3, 33.8, 29.0, 22.8, 21.8. HRMS (LSIMS) calcd for $C_{21}H_{23}NO_5Na$ [M+Na$^+$] 392.1474, found 392.1459.

### 4.2. Preparation of sulfonyl oxime (1b)

*4.2.1. N-((2-(Trimethylsilyl)ethoxy)methoxy)formimidoyl chloride (**13**).* In a dry two-neck round-bottom flask equipped with a condenser was dissolved oxime **12** (37 mg, 0.21 mmol) in anhydrous DMF (3 mL). NCS (42 mg, 0.31 mmol) was then added and the resulting mixture was heated to 45 °C. After total consumption of the starting material, the yellow mixture was partitioned between water (10 mL) and diethylether (10 mL) and the layers were separated. The aqueous layer was extracted with diethylether (3×10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (Petroleum ether/EtOAc 100:0→95:05) to afford **13** as a yellow oil (31 mg, 70%). $R_f$=0.72 (Petroleum ether/EtOAc 75:25). IR (neat, NaCl) $\nu_{max}$ (cm$^{-1}$) 3083, 2954, 2896, 1725, 1595, 1249. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ (ppm) 6.99 (s, 1H), 5.13 (s, 2H), 3.66 (t, $J$=8.6 Hz, 2H), 0.89 (t, $J$=8.6 Hz, 2H), −0.03 (s, 9H). $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 125.2, 97.2, 66.0, 17.5, −1.8. HRMS (ESI) calcd for $C_7H_{16}ClNO_2SiNa$ [M+Na$^+$] 403.2060, found 403.2061.

*4.2.2. 9,9-Dimethyl-1-phenyl-4,6-dioxa-1-thia-3-aza-9-siladec-2-ene (**14**).* In a flame-dried 25 mL two-neck flask equipped with a magnetic stirrer, PhSH (0.16 mL, 1.56 mmol) was added to a slurry mixture of NaH (37 mg, 1.56 mmol) in dry THF (5 mL) at 0 °C. After 1 h, oxime **13** (189 mg, 0.9 mmol) was added dropwise to the heterogeneous reaction mixture. After total consumption of the starting oxime, saturated aqueous solution of $NaHCO_3$ (10 mL) was carefully added and the mixture was extracted with dichloromethane (3×10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil, which was then subjected to silica gel chromatography (Petroleum ether/EtOAc 100:0→95:5) to yield **14** as a colorless oil (198 mg, 78%). $R_f$=0.65 (Petroleum ether/EtOAc 90:10). IR (neat, NaCl) $\nu_{max}$ (cm$^{-1}$) 2953, 2879, 1568, 1486, 1247, 1107, 1004. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.38–7.19 (m, 6H), 5.14 (s, 2H), 3.70 (t, $J$=8.2 Hz, 2H), 0.91 (t, $J$=8.2 Hz, 2H), −0.03 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 146.4, 131.8, 131.1, 128.9, 128.1, 96.8, 66.6, 17.4, −1.8. HRMS (ESI) calcd for $C_{13}H_{21}NO_2SSiNa$ [M+Na$^+$] 306.0963, found 306.0954.

*4.2.3. Phenylsulfonylmethanal O-(2-(trimethylsilyl)ethoxy) methyl oxime (**1b**).* In a dry two-neck round-bottom flask equipped with a condenser was dissolved oxime **14** (80 mg, 0.28 mmol) in dry dichloromethane (5 mL). $NaHCO_3$ (59 mg, 0.70 mmol), and *m*-CPBA (195 mg, 1.12 mmol) were carefully added to the vigorously stirred solution. The resulting heterogeneous mixture was then heated to reflux overnight. The final white and heterogeneous mixture was partitioned between NaOH 10% and dichloromethane. After the mixture had became clear, it was poured into a funnel and the layers were separated. The aqueous layer was washed with dichloromethane (3×10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (Petroleum ether/EtOAc 95:5→90:10) to afford **1b** as a colorless oil (78 mg, 88%). $R_f$=0.34 (Petroleum ether/EtOAc 90:10). IR (neat, NaCl) $\nu_{max}$ (cm$^{-1}$) 3614, 3060, 2962, 1699, 1446, 1306. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 8.10 (s, 1H), 7.94–7.52 (m, 5H), 5.17 (s, 2H), 3.60 (t, $J$=7.9 Hz, 2H), 0.85 (t, $J$=7.9 Hz, 2H), −0.05 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 149.7, 137.6, 134.4, 129.3, 128.1, 99.1, 67.3, 17.8, −1.5. HRMS (ESI) calcd for $C_{13}H_{21}NO_4SSiNa$ [M+Na$^+$] 338.0865, found 338.0852.

### 4.3. General procedure for the three-component carbo-oximation with sulfonyl oxime (1b) (Table 2). Three-component adducts (19a–n)

In a dry two-neck round-bottom flask equipped with a condenser and a magnetic stirrer were successively added oxime **1b** (1 or 2 equiv, See Table 2), iodoester **8** (1 equiv) and the desired alkene partner (4–5 equiv) in benzene (0.4 M). Argon was then bubbled directly into the flask for 30 min $(Bu_3Sn)_2$ (1.5 equiv) was then injected and the flask was heated to 60 °C. DTBHN was added after 5 min, then every 90 min if required (TLC). After total consumption of the starting iodide, the resulting mixture was concentrated in vacuo and purified by silica gel chromatography (Petroleum ether/EtOAc) to afford the desired product.

*4.3.1. Phenyl 2,2-dimethyl-10-((trimethylsilyl)methyl)-5,7-dioxa-8-aza-2-silatridec-8-en-13-oate (**19a**).* Prepared according to general procedure described above. Purification over silica gel (Petroleum ether/EtOAc 98:2→90:10) afforded **19a** as a colorless oil (82%). $R_f$=0.83 (Petroleum ether/EtOAc 75:25). IR (neat, NaCl) $\nu_{max}$ (cm$^{-1}$) 2976, 2957, 2855, 2711, 1732, 1690, 1513, 1278, 939. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 7.36 (t, $J$=8.1 Hz, 2H), 7.26–7.17 (m, 2H), 7.10–7.03 (m, 2H), 5.10 (AB syst., $J_{ab}$=8.2 Hz, 2H), 3.69 (m, 2H), 2.64–2.47 (m, 3H), 2.05–1.85 (m, 2H), 0.97 (t, $J$=8.4 Hz, 2H), 0.78 (d, $J$=7.4 Hz, 2H), 0.12 (s, 9H), 0.09 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 171.5, 155.7, 150.6, 129.2, 125.6, 121.4, 96.5, 65.8, 35.8, 31.8,

31.0, 21.1, 18.0, −0.9, −1.4. HRMS (ESI) calcd for $C_{21}H_{37}NO_4SiNa$ [M+Na$^+$] 446.2158, found 446.2159.

### 4.4. General procedure for the hydrolysis of the SEM-oxime. Aldehyde (23a–e)

In a dry 10 mL round-bottom flask was dissolved the oxime **19** (0.1–0.2 mmol) in anhydrous dichloromethane (1.0 M). The colorless solution was cooled to 0–5 °C in an ice bath, then TFA (TFA/$CH_2Cl_2$ 1:4) was added dropwise under vigorous stirring. The ice-bath was removed and the course of the reaction was monitored by TLC. After total consumption of the starting oxime (1.5–2 h), the slightly colored solution was directly concentrated under vacuum to afford an oily residue, which was rapidly purified by flash chromatography over deactivated ($Et_3N$) silica gel (60 Å). The column was rapidly eluted with a mixture of Petroleum ether/EtOAc (96:4→92:8) to isolate the expected aldehydes **23a–e**.

*4.4.1. Phenyl 4-formyl-5-(trimethylsilyl)pentanoate (**23a**).* Prepared according to the general procedure described above from oxime **19a** (162 mg, 0.38 mmol). Purification over silica gel (Petroleum ether/EtOAc 98:2→90:10) afforded the desired compound as a colorless oil (56 mg, 53%). $R_f$=0.67 (Petroleum ether/EtOAc 90:10). IR (neat, NaCl) $\nu_{max}$ (cm$^{-1}$) 3423, 2953, 2715, 1759, 1723, 1594, 1493, 1416, 1250, 1196, 841. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 9.57 (d, $J$=2.6 Hz, 1H), 7.38 (t, $J$=7.4 Hz, 2H), 7.23 (t, $J$=7.4 Hz, 1H), 7.09–7.05 (m, 2H), 2.67–2.44 (m, 3H), 2.12–1.88 (m, 2H), 0.94 (dd, $J$=7.1, 14.8 Hz, 1H), 0.63 (dd, $J$=7.2, 14.9 Hz, 1H), 0.07 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 203.7, 171.4, 150.5, 129.4, 125.8, 121.4, 47.3, 31.6, 26.3, 16.1, −0.8. HRMS (ESI) calcd for $C_{15}H_{22}O_3SiNa$ [M+Na$^+$] 301.1241, found 301.1230.

### 4.5. General procedure the free-radical-3CR/oxime hydrolysis/Sakurai reaction/lactonization cascade. Lactones (24a–d)

In a dry two-neck round-bottom flask equipped with a condenser and a magnetic stirrer were successively added oxime **1b** (2 mmol), iodoester **8** (1 mmol) and the alkene **3** (5 mmol) in 1,2-dichloroethane (2 mL). The reaction mass was degassed with argon gas for about 30 min $(Bu_3Sn)_2$ (1.5 mmol) was then introduced and the flask was heated to 60 °C. The radical initiator DTBHN (*t*-BuON=NO*t*-Bu) was then added two times in portions of 0.1 mmol each at an interval of 2 h. After total consumption of the starting material, the resulting mixture was cooled to room temperature and trifluoroacetic acid was added (such as TFA/DCE=1:4% vol). The reaction was monitored by TLC and after completion of the hydrolysis, the reaction mixture was concentrated under vacuum for at least 4 h to yield a dark-brown oil. This mixture was purified through a short path of deactivated silica gel doped with KF (5% wt) with Petroleum ether/EtOAc (90:10 to 80:20) and the resulting oil was subjected to further reaction. To a solution of the preceding aldehyde (1 equiv) and allyltrimethylsilane (2 equiv) in dry dichloromethane (1 M) at 0 °C was added dropwise $TiCl_4$ (1 M solution in $CH_2Cl_2$, 1.2 equiv) The colorless solution became gradually red. The ice bath was removed and the course of the reaction was monitored by T.L.C. After all the aldehyde has been consumed, water (10 mL) was added to the reaction mixture and the resulting yellow heterogeneous mixture was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. Purification over silica gel (Petroleum ether/EtOAc) furnished the desired lactones **24**.

*4.5.1. 6-Allyl-5-((trimethylsilyl)methyl)tetrahydro-2H-pyran-2-one (**24a**).* Prepared according to the general procedure described above. Purification over silica gel (Petroleum ether/EtOAc 90:10→70:30). $R_f$=0.42 (Petroleum ether/EtOAc 75:25). IR (neat, NaCl) $\nu_{max}$ (cm$^{-1}$) 3453, 3041, 2912, 2859, 1742, 1622, 1459, 1201, 1043. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 5.87–5.73 (m, 1H), 5.19–5.06 (m, 2H), 4.06–3.94 (m, 1H), 2.58–2.25 (m, 4H), 1.89–1.65 (m, 3H), 0.73–0.51 (m, 2H), 0.04 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 178.9, 178.7, 134.6, 117.8, 117.7, 67.5, 66.0, 40.0, 39.9, 39.1, 31.4, 31.3, 29.7, 28.4, 18.3, 16.4, −0.7, −0.8. HRMS (ESI) calcd for $C_{12}H_{22}O_2SiNa$ [M+Na$^+$] 249.1286, found 249.1290.

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### Supplementary data

Experimental procedures for compounds not described in the experimental part can be found. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.051.

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