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# Tandem anionic Michael addition/radical cyclizations: a new and efficient strategy for the synthesis of functionalized cyclopentanes†

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**The combination of anionic Michael addition of lithium ester enolates with radical 5-*exo* cyclizations through SET oxidation gives highly functionalized cyclopentanes.**

Radical reactions have developed into a valuable tool in organic synthesis. Especially radical cyclizations are widely used since one of their advantages is the versatility to design tandem processes.[1] However, this advantage is offset by tedious precursor preparation. Radical addition/cyclization sequences are conceptually attractive since the gain in complexity from simple precursors is high. However, this strategy suffers from drawbacks: 1) radical additions (Giese reactions) obey complex kinetics, requiring an excess of one precursor (often a α,β-unsaturated carbonyl compound).[2] This excess, however, may interfere with the following reaction steps in the tandem processes thus limiting overall efficiency. 2) The radical acceptor should be unsubstituted in the β-position to achieve useful addition rates.[2,3]

A promising alternative to radical addition/cyclization cascades should be one in which the addition step is performed on the anionic oxidation stage allowing better reactivity/selectivity control. An attractive approach is the anionic Michael addition[4] proceeding with stoichiometric amounts of reagents, but the resulting enolate is normally not able to undergo anionic cyclization to unpolar functionalities.[5] However, by oxidizing the adduct enolate, radical cyclizations may be induced.[6]

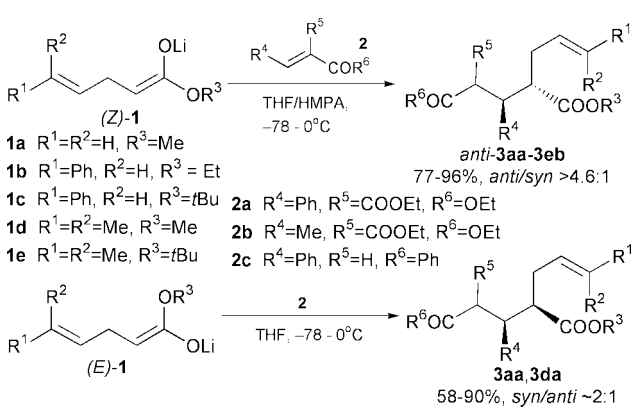
Here, efficient tandem Michael addition/radical cyclizations[7] are reported. Cyclopentane derivatives with up to five stereocenters can be created from simple precursors.

An initial study of the Michael addition revealed that (*Z*)-enolates **1a**–**e** generated by deprotonation of the ester with LDA–THF–HMPA underwent a useful *anti*-selective addition to Michael acceptors **2a**–**c** providing good yields of **3** [Scheme 1, dr > 6.6 : 1 except for **1e**/**2b** (4.6 : 1), see Table 2 in the ESI†]. Enolates (*E*)-**1a**,**d** (generated with LDA–THF) gave *syn*-**3** with a very moderate selectivity. Additions of **1** to **2a**,**b** provided **3** directly while those of **1** to **2c** formed the aldol adduct at −78 °C that rearranged to **3** on warming to 0 °C.[4a,b]

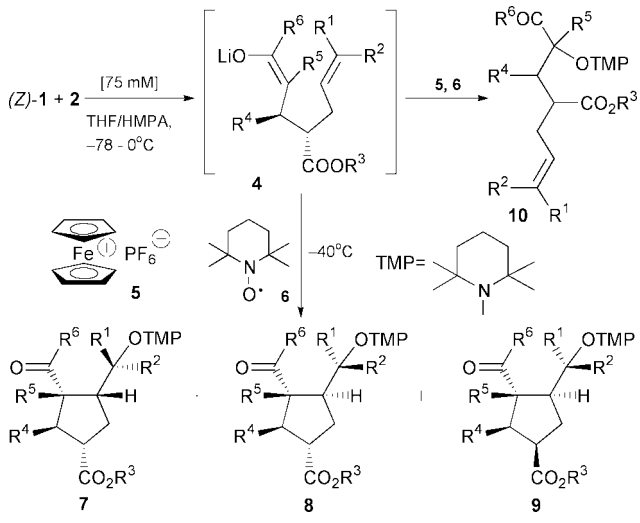
With these results in hand, the Michael addition/radical cyclizations were studied (Scheme 2, Table 1). Addition of **2a** or **2c** to (*Z*)-**1** in THF–HMPA at −78 °C followed by warming to 0 °C generated the enolates **4** that were treated with a thoroughly homogenized solid mixture of SET oxidant ferrocenium hexafluorophosphate **5**–TEMPO **6** as oxygenation/termination reagent at −40 °C (Scheme 2, Table 1). For 5-unsubstituted **1a** and **2a**,**c** oxygenated cyclopentane derivatives **7aa**‡ and **7ac** were formed with good to excellent diastereoselectivity (entries 1,2). 5-Monosubstituted **1b** gave an inseparable 1.6 : 1 diastereomeric mixture of **7ba**‡ and **8ba** in 87% yield with good control of the exocyclic stereocenter (entry 3). More bulky ester **1c** improved the cyclization diastereoselectivity **7ca**/**8ca** only slightly, but induced excellent diastereoselectivity at the exocyclic stereocenter (entry 4). Even a fifth stereocenter can be controlled with reasonable efficiency. Applying **1c** and **2c** provided 61% (75% based on **1c**) of a partly separable 13.5:3.3:1 mixture of **7cc**/**8cc**/**9cc** (entry 5). The *cis*/*trans*-cyclization diastereoselectivity for *anti*-**4** amounted to 4.1 : 1. Michael addition/radical cyclization of **1d**/**2a** gave a 2 : 1 diastereomeric mixture of **7da** and **8da** in good yield (entry 6).

The protected alcohol function in **7** can be regenerated by reductive N–O bond cleavage[6,8] as exemplified for **7aa** providing **11aa** in 63% yield (Scheme 3).

The sequences are not limited to TEMPO trapping of the cyclized radical (Scheme 4). If Michael donors **1d**,**e** were coupled with **2a,b** followed by addition of 2.5–3 equiv. of **5**, isopropenylcyclopentanes **12** were formed as the major products together with minor amounts of **13**–**18**. The sequence of methyl ester **1d**/**2a** in the absence of additives gave **12da** in 51% yield as a 3:1 diastereomeric mixture accompanied by **14da**–**16da**. Alcohol α-**15da** lactonized to **17da** during purification. The more bulky ester **1e** and addition of 3 equiv. of KO*t*Bu




**Scheme 1**




**Scheme 2**

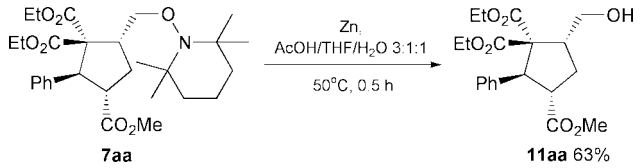
† Electronic supplementary information (ESI) available: further experimental and spectral data. See http://www.rsc.org/suppdata/cc/b1/b104415j/

 DOI: 10.1039/b104415j

**Table 1** Tandem Michael addition/radical cyclizations of **1**/**2**

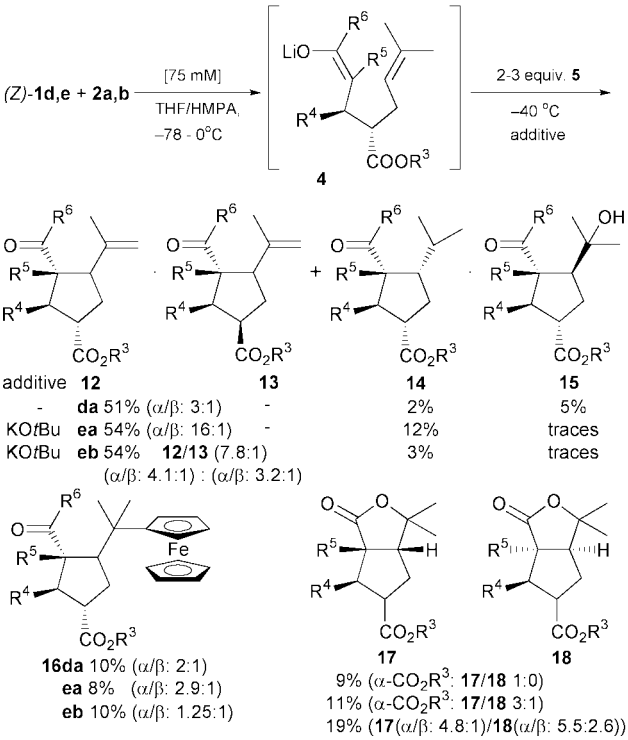
| Entry | 1 | 2 | Yield (%) 7+8+9 | dr: 7 : 8 : 9 7(βR¹:αR¹)[a] | 8(αR¹:βR)[a] | 9 | 10 (%) |
|---|---|---|---|---|---|---|---|
| 1 | **a** | **a** | 71 | 100(−) | 0 | 0 | — |
| 2 | **a** | **c** | 53[b] | 7.5(−) | 1(−) | 0 | 25[c] |
| 3 | **b** | **a** | 87 | 1.6(6:1) | 1(>20:1) | 0 | — |
| 4 | **c** | **a** | 86 | 2.3(22:1) | 1(>20:1) | 0 | — |
| 5 | **c** | **c** | 61(75)[d] | 13.5(5.4:1) | 3.3(2:1) | 1 | — |
| 6 | **d** | **a** | 82 | 1.8(−) | 1(−) | 0 | — |

[a] Configuration at exocyclic stereocenter. [b] A cyclized dimer was also formed in 4.7% yield. [c] Mixture of four diastereomers (not assigned). [d] Yield in parentheses represents yield based on recovered **1c**.



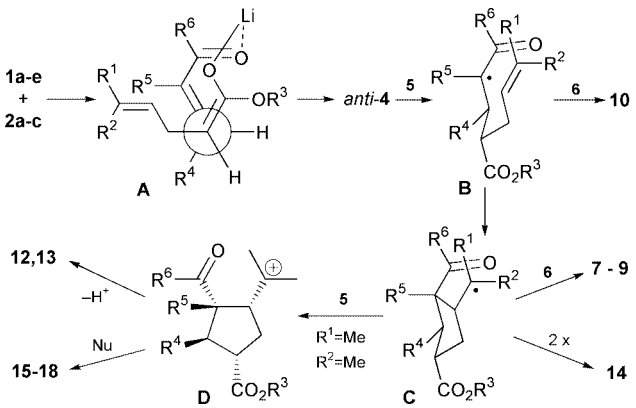

**Scheme 3**

improved the product distribution and the diastereoselectivity of the sequence to **12ea**. Some **14ea**, **16ea**, **17ea** and **18ea**, but almost no **15ea**, were formed. From ethylidenemalonate **2b** and **1e**, all four diastereomers of **12eb**/**13eb** were isolated in 54% yield in a 26:6:3:1 ratio due to the lower *anti*-selectivity of the Michael addition (4.6:1). Although not that interesting from the synthetic point of view, this example strengthened the configuration assignment to all products and indicated that *syn*-**4** may cyclize as efficiently as *anti*-**4**.




**Scheme 4**

The tandem processes can be rationalized by assuming a chelation controlled Michael addition step *via* **A** to *anti*-**4**[9] (Scheme 5). SET oxidation of **4** by **5** occurs predictably to radicals **B**. The cyclization diastereoselectivity to **C** can be explained by a preferred Beckwith–Houk chair transition state **B**[10] depending on the substitution pattern of the alkene in **1** followed by combination with TEMPO **6** to the major diastereomer **7**. TEMPO trapping of radical **B** does not play a significant role except for the **1a**/**2c** combination. Tertiary radicals **C** are predominately oxidized to carbenium ions **D**




**Scheme 5**

giving **12**(**13**) and **15**–**18** *via* deprotonation and nucleophilic trapping, respectively, while **14** and **16** may be formed from **C** *via* disproportionation or ligand transfer with ferrocenium/ferrocene, respectively.

In summary, it was shown that Michael addition/radical cyclization cascades are a convenient strategy to overcome limitations of purely radical or anionic addition/cyclization sequences. The results may have many implications for the design of heterointermediate strategies since other enolate generating reactions such as conjugate additions or anionic rearrangements can be envisaged to be coupled with radical reactions thus expanding the opportunities of organic synthesis.

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## Notes and references

‡ Configuration determination by X-ray crystal structure analysis.

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