Radical reactions in the synthesis of fragrance molecules

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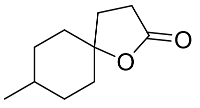
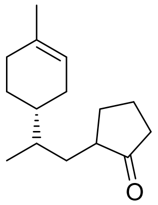
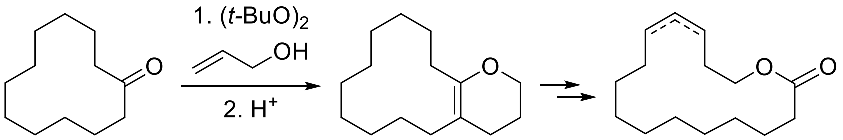
Despite tremendous developments in the field of radical chemistry in the last decades, the use of radical reactions in the industrial synthesis of fragrance ingredients still remains underexploited. Existing processes include the formation of spirolactones, notably coumarin-like ingredient Methyl Laitone, by the radical cross-coupling of 4-methyl cyclohexanol and an acrylate.[1] The α-alkylation of ketones with olefins is a particularly important reaction, as it is involved in the preparation of peach odorant Nectalactone by the radical addition of cyclopentanone to (R)-limonene[2] and in the synthesis of musk ingredient Habanolide, where cyclododecanone is alkylated with allyl alcohol in the first step.[3] These processes all involve the use of di-tert-butyl peroxide as a radical initiator, and elevated temperatures required for its homolytic cleavage.



Methyl Laitone

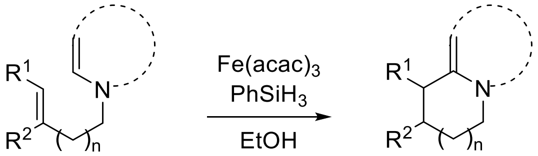


Nectalactone



Habanolide

The increasing number of available and scalable radical methodologies is a great opportunity for quickly accessing molecular structures that were previously out of reach. We will herewith showcase selected examples of the progress achieved so far. In particular, recent advances in the direct generation of radicals from olefins[4] enabled us to prepare new polycyclic derivatives, potentially useful as analogues of known fragrance ingredients.



[1] R. T. Dahill, K. L. Purzycki, E. F. Golle (*Givaudan*), US 4519944, filed May 16th, **1983**.
[2] E. Brenna, C. Fuganti, F. G. Gatti, L. Malpezzi, S. Serra, *Tetrahedron: Asymmetry* **2008**, *19*, 800–807.
[3] R. Hopp, K. Bauer (*Haarmann & Reimer*), DE 21346496, filed July 21st, **1971**.
[4] (a) J. C. Lo, Y. Yabe, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307; (b) S. Bordi, J. T. Starr, *Org. Lett.* **2017**, *19*, 2290–2293.