

RADICALS IN TOTAL SYNTHESIS: C-C BOND FORMATION

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November 25th, 2013

Synthetic plans towards complex organic molecules are typically centered around key bond formation reactions that build requisite oxidation patterns and correct topologies. Radicals, although initially considered too reactive and unpredictable to be useful in the synthesis, has gained widespread applications in total synthesis, often seen in the construction of challenging C-C bonds. It's highly reactive and largely a neutral species, which enables novel bond disconnections in retrosynthetic analysis, compared with traditional "polarity-based" reactions. The use of radical has greatly advanced people's thinking of building up molecules and facilitated the synthesis of many natural products. Future development of this methodology will undoubtedly push the art of synthesis a lot forward.

Radicals are normally easy to generate and the coupling partners are usually double bonds or triple bonds.¹ The facile generation and introduction of the reaction partners allows the radical method to be easily adapted into one's synthetic plan. The total synthesis of Merrilactone A could be a great example (Figure 1). The synthetic challenge involves the fused ABC tricycles bearing an all-carbon quaternary center C9. Up to date, six total syntheses have been reported and five of them all feature a late stage radical-mediated formation of C1-C9 bond.² Interestingly, these five radical reactions are all different in terms of radical precursors or coupling partners, which demonstrate they are widely applicable and can be specially tailored into chemists' needs.

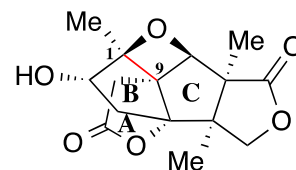
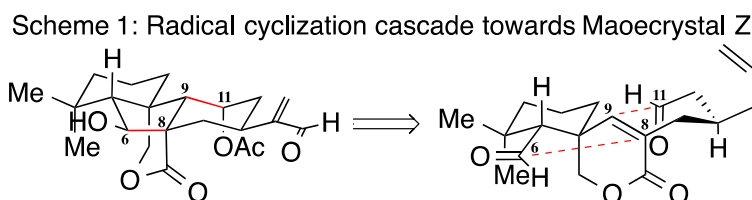


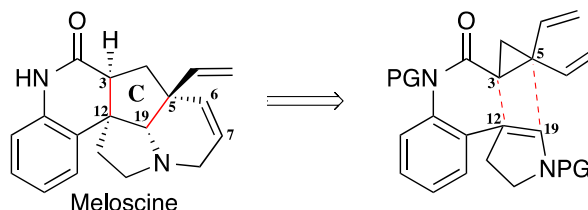
Figure 1: Merrilactone A

Radicals' characteristics of neutral addition enable direct "umpolung" and invoke novel bond disconnections, as illustrated by Reisman's synthesis of Maoecrystal Z (Scheme 1).³ The 5+6+6 tricyclic system is generated in one step through a radical cyclization cascade, starting with a ketyl radical from C11 aldehyde, adding into the double bond and the resulting C8 radical combining with another equivalence of SmI_2 to form an enolate, which after aldol reaction furnish the C6-C8 bond. Vast molecular complexity is generated in one step, with two steric demanding C-C bonds formation, again showing the power of radical reactions.



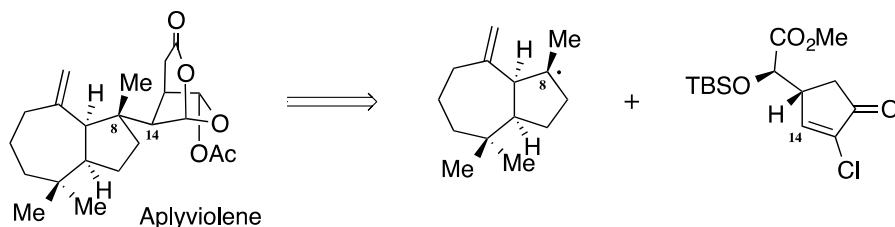
This is further manifested in the total synthesis of Meloscine,⁴ where the ring systems are very complex and the oxidation pattern is not present for easy chemical modification and elaboration. By using a cascade radical annulation strategy, Curran was able to construct the key C ring in one single step, shortening the whole synthesis into 14 steps (Scheme 2). The bond disconnection is straightforward, and no “waste step” is needed.

Scheme 2: Radical annulation reaction towards Meloscine



Intermolecular radical addition has also emerged as a useful tool and could tremendously improve the efficiency of a synthetic route. The key step towards the total synthesis of Aplyviolene involves the construction of C8-C14 bond, which bridges two ring systems and bears one stereogenic quaternary center.⁵ This transformation is achieved by an intermolecular radical addition strategy in high yields and diastereoselectivity.

Scheme 3: Intermolecular radical addition towards Aplyviolene



SUMMARY

Radical reactions hold tremendous power for shaping the art of synthesis. Nevertheless, although great progress has been made, a general strategy for highly enantioselective radical addition reactions needs to be developed.

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