Radical cyclization

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Résumé **La cyclisation radicalaire**

Cet article est une revue de l'état de l'art des cyclisations radicalaires. Les caractéristiques générales de ces réactions sont données dans la première partie. Cela inclut un historique avec la mise en perspective de deux principaux développements dédiés aux réactions en cascade conduisant à des molécules polycycliques complexes (incluant la synthèse totale de produits naturels) et aux cyclisations asymétriques.

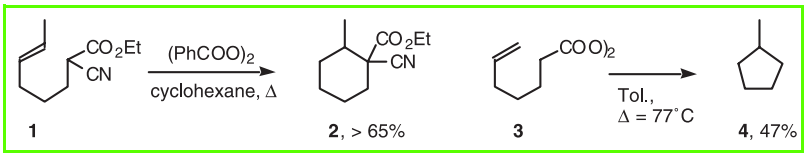
Mots-clés **Radicaux libres, cascades, synthèse asymétrique, synthèse totale.**

Key-words **Free-radicals, cascades, asymmetric synthesis, total synthesis.**

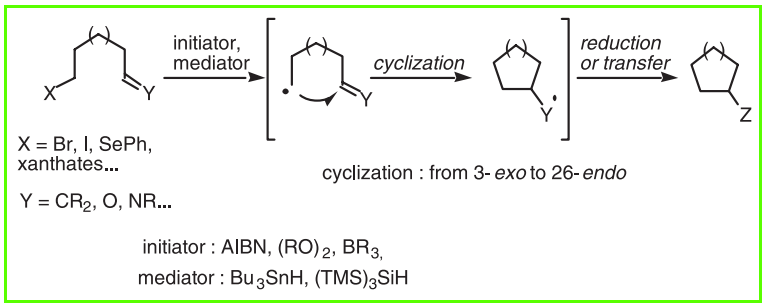
Because of their high versatility, selectivity and compatibility with densely functionalized substrates, radical cyclizations are now frequently introduced in retrosynthetic strategies and have already led to the total synthesis of various and relevant natural products [1]. Two recent contributions fully illustrate this. Thus, Danishefsky used a 5-*exo-trig* cyclization of a vinyl radical onto a highly congested butenolide system as a key step in the total synthesis of (±)-merrilactone [2], and Lee exploited a 6-*endo-trig*, 6-*exo-trig* tandem of radical cyclizations to construct the central core of Lasonolide A [3]. From an historical point of view [4], it is interesting to note that the first examples of radical cyclizations (5-*exo-trig*) have been described by polymer chemists [5], and then by physical chemists in the gas phase [6] or in photochemical studies [7]. The first studies in solution phase which paved the way for further synthetic interests were reported by Julia in 1960 [8] and by Lamb in 1963 [9]. In Julia's seminal work, it was showed that unsaturated cyanoesters like **1** could undergo a 6-*endo-trig* cyclization (adduct **2**) when heated in presence of peroxide in boiling cyclohexane. Further examples of this process were given including notable entries in the formation of polycyclic adducts via a very pioneering version of what we would call now a radical cascade, as well as probably one of the first example of asymmetric radical cyclization involving a (-)-menthyl ester, resulting in an asymmetric induction of 30% [4a]. In parallel to this, Lamb observed that the thermal decomposition of 6-heptenoyl peroxide **3** gave methylcyclopentane **4** as the major adduct, something that was considered quite puzzling at that time since it corresponded to the anti-Kharash adduct (*scheme 1*). The irreversibility of the reaction in their conditions was demonstrated and it was concluded that the 5-*exo* mode of cyclization originated from kinetic control. This also suggested that the cyclization involving the cyanoester was reversible to afford the most stable cyclohexyl radical. All this was confirmed by physical organic studies [4b] and the 5-hexenyl radical cyclization became the cornerstone of radical chemistry. Its kinetics [10], modelisation (Beckwith-Houk model) [11] and stereochemical attributes [12] have been fully addressed.

So how could things further evolve? It was clear that this system could lend itself to variations on different parameters. With the development of the radical chain reaction [13], different sources of alkyl, vinyl [14], aryl or acyl [15] radicals had to be found and halides (bromide or iodide, seldom chloride), seleno or to a lesser extent thio and nitro groups have been extensively employed. The Barton-type deoxygenation reaction, followed by the development of the xanthate chemistry has also opened versatile alternatives for the generation of cyclizing radicals [16]. It should also be mentioned that heteroradicals like alkoxy [17], nitrogen- [18] and sulfur-centered [19] radicals can also be engaged in radical cyclizations. The radical cyclization step can also follow a previous radical step like and addition to an unsaturated partner [20], or a radical translocation step [21]. Traditional initiators are peroxides, azobisisobutyronitrile (AIBN) and congeners. The recently introduced trialkylborane/O_2 system [22] allows to work at low temperature and in aqueous media [23]. Tin hydride mediators have shown a great versatility [24]. However, for very specialized applications, like slow hydride delivery, germanes and silanes have been utilized. Among them, Chatgililoglu's tris(trimethylsilyl)silane occupies a prominent position [25]. It is commercially available, non toxic and has proven to be a valid substitute for tributyltinhydride in the majority of radical chain reactions. This development of substitutes also corresponds to an important need, since the use of tin-based reagents displays several drawbacks like toxicity and the difficult removal of tin residues. Several options have been looked at including for instance special work-up procedures, catalytic processes, and the developments of new reagents or reducing agents whose enumeration would be beyond the scope of this article [26] (*scheme 2*). In the same line, it should be mentioned that radical cyclizations can also be operated as atom transfer reactions [27] and that a variety of metal-catalyzed or mediated processes relying for instance on manganese (III) [28] (Snider type) or samarium (II) have been worked out [29]. Photochemical processes can also be used for green radical chemistry [30].

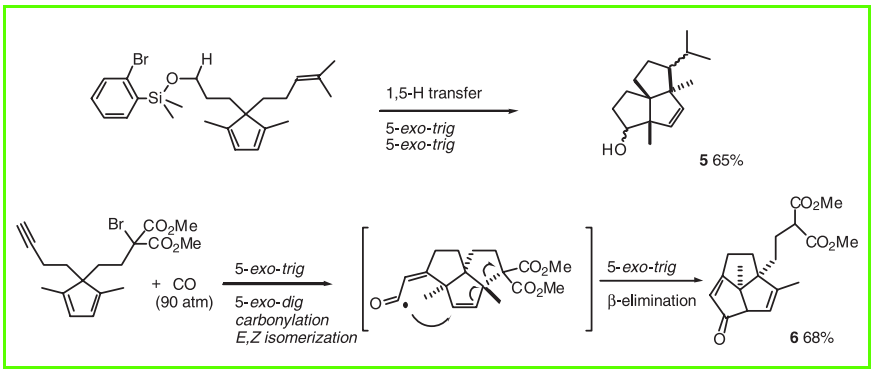
The nature of the radical acceptor is the other key partner. The work of Giese on intermolecular radical



Scheme 1.



Scheme 2.



Scheme 3.

additions (the Giese reaction) has drawn important guidelines on the match/mismatch of radicals with olefinic partners by using the frontier orbital theory. The role of steric effects on the regio- and stereoselectivity was also rationalized [31]. These findings could also be transposed to intramolecular additions. Thus, alkenes, alkynes but also arenes and allenes [32] are common acceptors. But heteropartners like carbonyl derivatives (aldehydes, and ketones) [33], as well as partners based on C-N double bonds (imine, hydrazone, oximes...) and nitriles [34] have yielded versatile synthetic applications.

Another less common, but synthetically useful type of ring closure, is the cyclization by homolytic substitution [35].

Finally an important question raises: what size of cycles can be made? From a rapid glance at the literature, it appears that besides the highly common 5- and also 6-membered rings, small rings (cyclopropanes or cyclobutanes), macrocycles (up to 26-membered ring) [36] and even medium-size rings (cyclooctanes) [37] can be assembled through radical processes. In the latter cases, tricks had to be devised to overcome these difficult modes of cyclization. Thus for cyclopropanes or cyclobutanes, unless a particularly stabilized radical is generated [38], a fast irreversible step has to be consecutive to the cyclization step, serving as a driving force that beats the high reversibility of these cyclizations. This can be for instance a fast oxidation [39] or reduction [40] of the radical intermediate, an intermolecular radical trapping [41] or an intramolecular one like cyclization [42] or translocation step [43], and a β-elimination step [44]. Conformational effects like *gem*-disubstituent effects have also been used [45]. For macrocycles, high-dilution are often required as well as activated radical traps (Michael acceptors) [46]. It is also noteworthy that radical processes are ideal tools for promoting cyclizations like 5-*endo-trig* [47] or 4-*exo-dig* [43] which are forbidden according to Baldwin.

Cascades

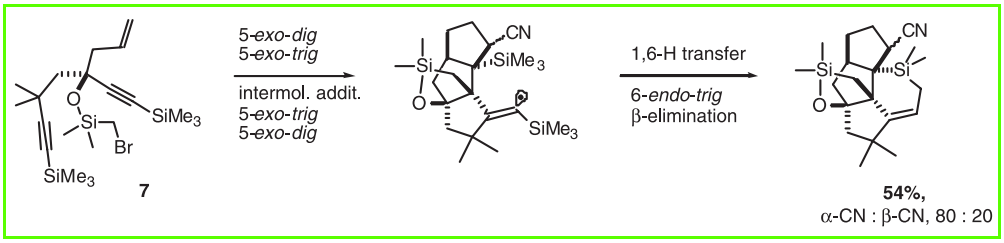
Because a radical cyclization gives birth to a new radical species that can also engage in a new radical cyclization and so on, a great number of synthetic sequences involving radical cyclizations in cascades have been devised. This principle was initially worked out on tandem radical cyclizations relying on a cyclopentene templating ring. Landmarks in this concept include for instance the total synthesis of hirsutene by Curran [48], and a more elaborated version relying on the use of samarium (II) chemistry and leading to an advanced precursor of hypnophilin and coriolin [49]. Among the examples proceeding from a cyclopentadiene precursor, angular triquinane **5** was also reached by Curran based on a key 1,5-H transfer [50] as well as an angularly fused tricyclic ketone **6** prepared by Ryu and Curran through a key isomerization of an α,β-unsaturated acyl radical obtained via a radical carbonylation of a vinyl radical intermediate [51] (*scheme 3*).

Cascades starting from acyclic precursors are particularly ambitious. Since the first examples reported by Beckwith in 1985 [52], many sophisticated polycyclic skeletons including steroids [53], homosteroids [54], diterpenes [55], and also triquinanes [56] have been assembled. Among them, a linear triquinane framework emerged from an acyclic enediyne bromomethyldimethyl silyl (BMDMS) ether **7** by a cascade mixing intra and intermolecular radical additions and also H-transfer and β-elimination [57] (*scheme 4*).

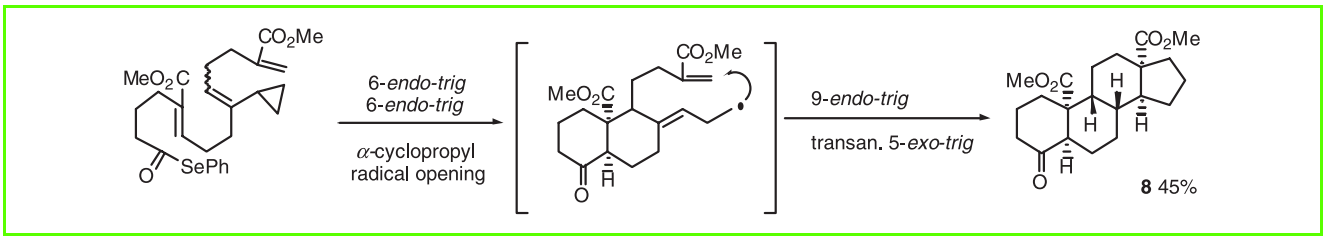
Pattenden recently illustrated the potentiality of the opening of α-cyclopropyl radical associated with a 6-*endo* tandem, 9-*endo* macrocyclization and transannular processes to form efficiently a steroidal skeleton **8** [58] (*scheme 5*).

Transannular radical cascade constitutes an adaptable strategy to both natural protoilludane, as illustrated by the biomimetic total synthesis of *epi*-illudol **9** [59], or the efficient access to linear triquinane framework **10** [60] depending on the propargylic position chosen for the radical generator BMDMS ether (*scheme 6*).

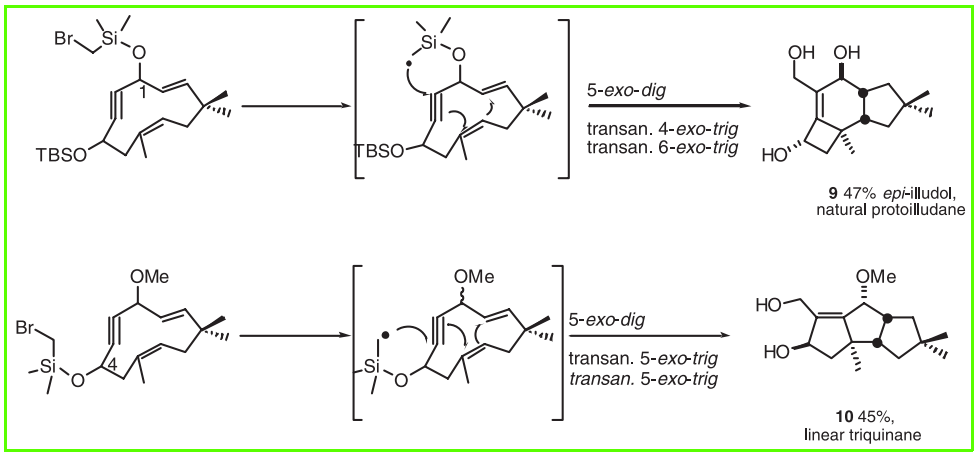
The fascinating structural complexity of natural alkaloids can be solved elegantly by radical cyclizations, as described for example in 2002 by Zard relying on the closure of an amidyl radical **11** to build the tetracyclic skeleton of 13-deoxyserratine [61], and by Murphy proposing a tandem



Scheme 4.



Scheme 5.



Scheme 6.

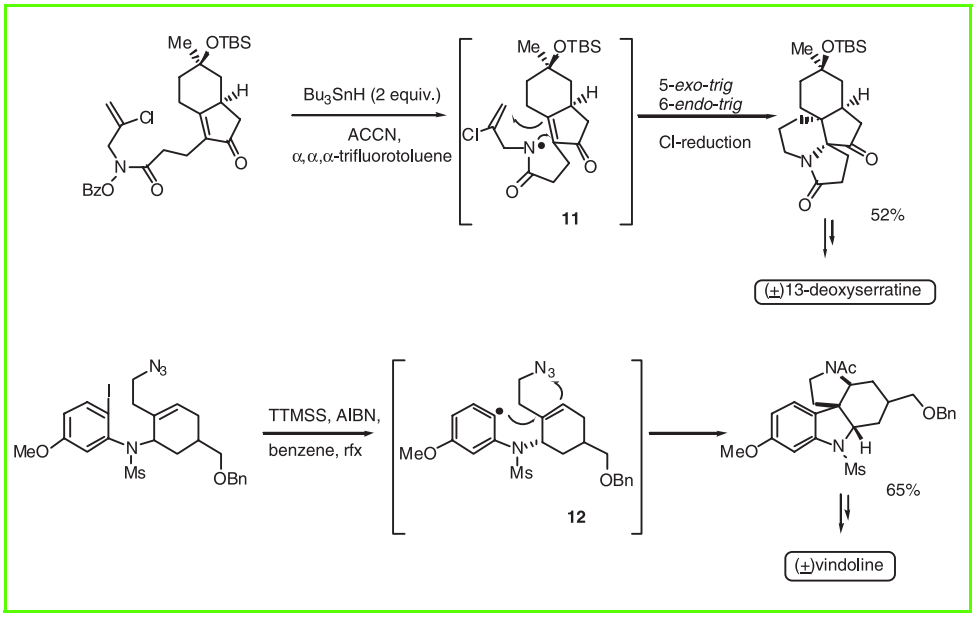
radical cyclization from an iodoaryl azide **12** to assemble the ABCE tetracyclic framework of vindoline [62] (*scheme 7*).
The few examples presented, chosen among so many contributions [63], constitute a thorough overview of the potentialities of the radical cascade in building highly elaborated polycyclic compounds.

Asymmetric radical cyclizations

Aside of diastereoselective reactions which will not be covered here, asymmetry can be introduced in three possible ways: a chiral auxiliary can be put either on the radical or on the double bond undergoing cyclization; chiral information can be transferred to the reagents from a suitable chiral additive.

Chiral auxiliary on the radical

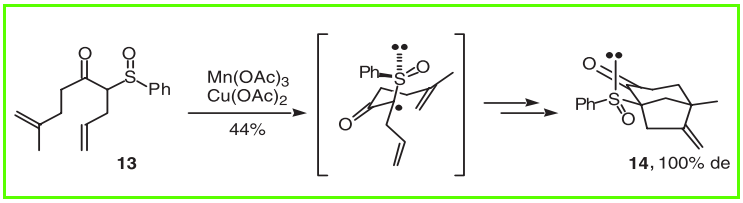
Following the aforementioned seminal work by Julia, other groups addressed the transfer of chirality from a chiral auxiliary attached to the prochiral radical. One of the main players in this field is the Snider group who reported the Mn(III)-based oxidative cyclization of unsaturated β-ketosulfoxides [64]. Thus, precursor **13** led to bicyclic adduct **14** *via* a totally selective radical cascade (*scheme 8*). Yield in **14** is acceptable (44%). A thorough study on the nature of the chiral auxiliary and the length of the tether has shown that yields in cyclized products can be increased with chiral ketoesters, but at the expense of the diastereoselection [65]. Ketoamides give bad yields but good de's.
This findings apply also to cascades (see above). A very nice extension has been reported by Yang, who showed that lanthanide Lewis acids could spectacularly improve the de's obtained with phenylmenthol ester derivatives driving them up to 38:1 ds [66-68].
Renaud was recently able to get excellent diastereoselectivity for the tin-mediated radical cyclization of α-sulfinyl radicals [69], a challenge he [70] and Tsai [71] tackled inconclusively ten years ago.
Another important pioneering contribution has been made by Curran, who was able to perform a 9:1 selective cyclization of α-amide radicals derived from the Oppolzer sultam [72].
Other strategies involve activation of a C-H bond of chiral acetals and give good de's in α-chiral cyclopentanones [73]. Nonetheless, the scope of this reaction is limited by unwanted competitive 1,5-H translocation on most of the auxiliaries.



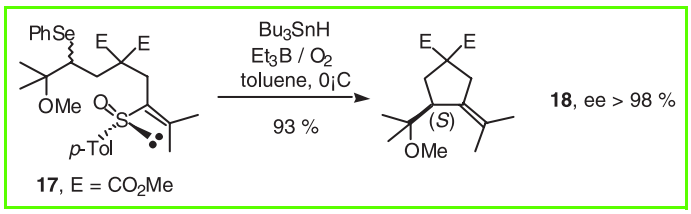
Scheme 7.

Chiral auxiliaries attached to the unsaturated moiety

The obvious alternative to the previous strategy would be to put the auxiliary



Scheme 8.

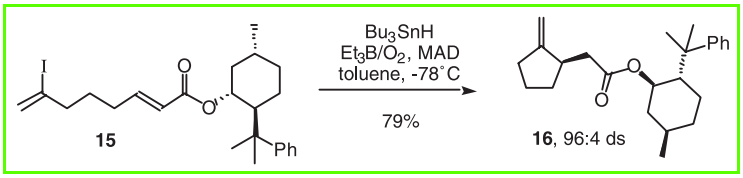


Scheme 10.

onto the double bond undergoing cyclization. A lot of chemists devoted their efforts to that question, which can be divided in two main parts, depending on the position of the chiral group relative to the reacting carbon.

2-1-β-selectivity

Hart was one of the first to address this theme. The cyclization of 8-phenylmenthyl α,β-unsaturated esters was not selective because of the low conformational rigidity of his sytem [74]. An elegant solution to this problem was reported by Nishida, who carried out the cyclization of iodoester **15** in the presence of a bulky Lewis acid [75]. MAD plays the role of a conformational lock. Approach of the radical occurs *anti* to the π-stacked phenyl group and leads to **16** as a nearly unique diastereomer (*scheme 9*).



Scheme 9.

Other examples in that domain include our work on 2-sulfinyl enol ethers [76], or Badone's work with Evans' oxazolidinones [77]. In the latter case, a Lewis acid is required to get acceptable selectivities.

Overall, β-control has proved quite difficult to master in a satisfactory manner, mainly because of the conformational freedom and/or the remoteness of the chiral auxiliary from the prochiral carbon characterizing most of the systems. These two limitations see their influence decrease when looking at chiral auxiliaries attached in the α position.

2-2-α-selectivity

Porter was the first to report a high selectivity in such a case [78]. Macrocyclization of a γ-keto C_2-symmetric acrylamide led to both the 14 and 15-membered rings. The 14-*exo-trig* attack proceeded with no selectivity (β-control), while the 15-*endo-trig* (α-control) was totally diastereoselective. This example illustrates quite nicely the differences between α- and β-control.

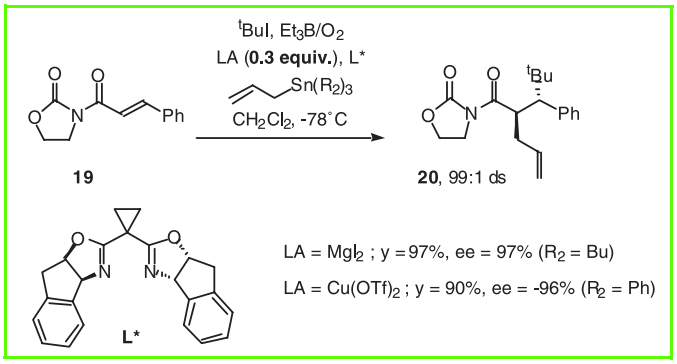
Chiral enamines were also studied for asymmetric 4-*exo-trig* cyclizations, but they lead to moderate selectivities [79]. This disappointing result could arise from the nature of the strained transition state.

We devised a tandem α-cyclization/β-elimination of prochiral radicals onto vinylsulfoxides [80]. In this process, the sulfinyl group acts as a self-immolative chiral auxiliary leading to a totally enantioselective alkenylation of the radical (*scheme 10*).

Good stereocontrol was made possible by an allylic strain-induced freeze of the system's liberty, which is a prerequisite for success. More, addition of oxophile aluminum-based Lewis acids leads to almost complete inversion of the selectivity. The absolute configuration of the product can thus be tuned only by choosing the reaction conditions.

Chiral additives

In contrast to the other options, this route has scarcely been studied. This reflects the difficulty in finding catalytic radical processes. Some enantioselectivity has been reported by Nishida who used stœchiometric amounts of binol aluminated derivatives [81]. Ee's are low. The impressive work by Sibi has so far been limited to intermolecular reactions [82-83]. In the example shown below, oxazolidinone could undergo enantioselective catalytic radical addition to quantitatively give **20** (*scheme 11*). Depending on the choice of the metal, one enantiomer or the other can be prepared from the same ligand. One can just hope such a result can be extended to radical cyclizations, pushing the frontier one step forward.



Scheme 11.

Conclusion

It appears from this overview that the radical process of cyclization is now mature. The variety of precursor patterns giving birth to a myriad of organic substrates, the possibility of running the reactions in cascade as well as the high diastereocontrols that can be reached render the radical cyclizations particularly attractive and versatile for the synthetic community.

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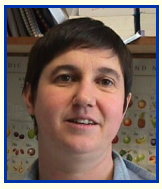

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