

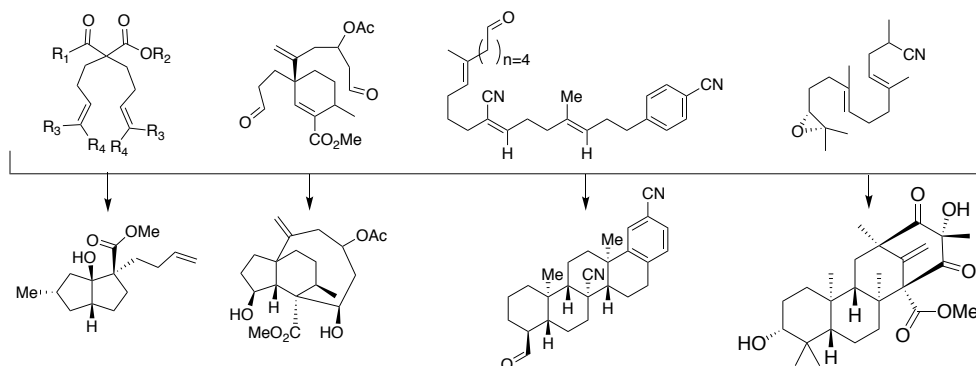
# ASYMMETRIC REDUCTIVE RADICAL CASCADE CYCLIZATIONS

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## INTRODUCTION

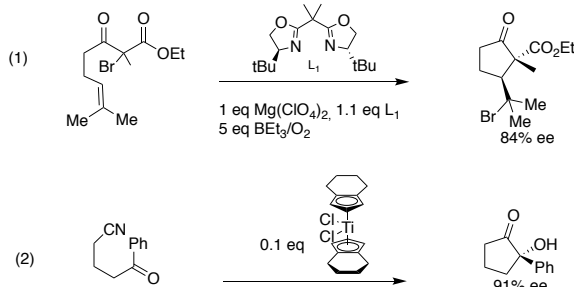
Traditionally thought of as extremely reactive but unselective, radical-mediated reactions have been shown to be highly chemo- and regioselective in the alkylation and cyclization of alkenes and alkynes. Seminal studies by Porter and Sibi showed that introducing chiral Lewis acids to radical-mediated reactions not only increased the system's reactivity and yield, but also increased stereocontrol.<sup>1</sup> Following this work, many have developed enantioselective radical cyclizations mediated by chiral Lewis acids,  $\text{SmI}_2$ , transition metals and organocatalysts. A few of these examples include radical cascade cyclizations that generated polycyclic products.<sup>2</sup> In this context, reductive single electron transfer (SET) cascade cyclization has proven to be a useful synthetic tool for the atom-, energy- and waste-economical production of sterically cumbersome polycyclic compounds, whose efficient and enantioselective synthesis is still a frontier problem (**Fig. 1**).<sup>3,4</sup>



**Figure 1.** Examples of stereoselective radical cascade cyclizations.

## ENANTIOSELECTIVE CYCLIZATION: PRECEDENT

There are reports describing the enantioselective cyclization of acyclic substrates via coordination to chiral Lewis acids such as trialkylaluminum, zinc triflate and magnesium perchlorate (**Fig. 2, eq. 1**).<sup>5</sup> While the yields and enantioselectivities of these reactions can be high, stoichiometric amounts of the Lewis acid are often required. There are a few examples of reductive cyclizations mediated by transition-metal catalysts such as titanium (**Fig. 2, eq. 1**). Good yields and enantiocontrol are reported, but methodologies for cascade cyclizations have yet to be further developed.

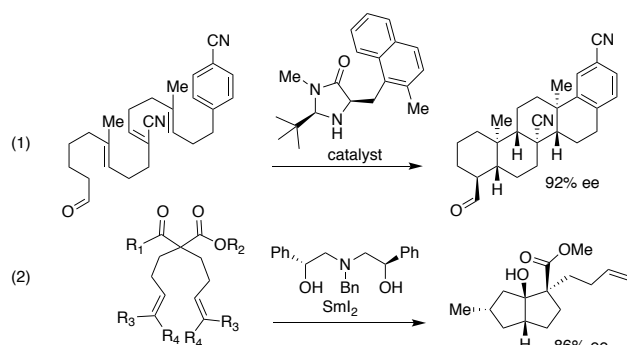


**Figure 2.** 1) Chiral Lewis Acid cyclization.

2) Chiral Transition Metal cyclization.

## ENANTIOSELECTIVE CASCADE CYCLIZATION: RECENT DEVELOPMENTS

While enantioselective cyclizations are well preceded in the literature, there are very few

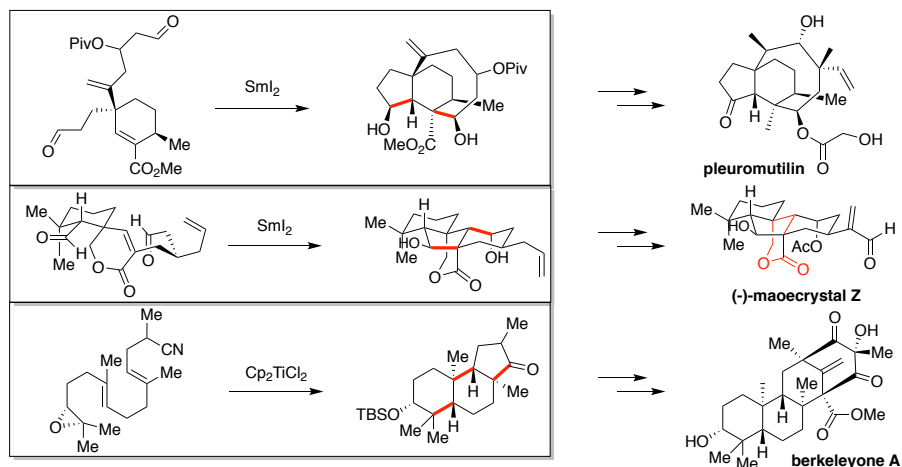


**Figure 3.** 1) SOMO catalysis for enantioselective cascade cyclization. 2) Chiral ligand used with Sml<sub>2</sub>.

examples enantioselective cascade cyclization. MacMillan and coworkers demonstrated these cyclizations via SOMO catalysis.<sup>6</sup> The chiral catalyst can produce several polycyclic compounds from achiral, acyclic starting materials in good enantiocontrol. Most notably, Procter has developed a chiral tripodant aminodiol ligand capable of enantioselective radical cascade cyclization and desymmetrization of unsaturated ketoesters.<sup>7</sup>

## APPLICATION IN TOTAL SYNTHESIS

The synthetic utility of these cascade reactions is revealed in the asymmetric total syntheses of (+)-pleuromutilin, (-)-maoecrystal, and meroterpene berkeleyone A (**Fig. 3**). No enantioselective cascade cyclization method has, to date, been used in asymmetric total syntheses of natural products.



**Figure 3.** Examples of diastereoselective radical cascade cyclizations in total synthesis.

## CONCLUSION

Asymmetric reductive cascade cyclization is a powerful method for the production of complex polycyclic scaffolds in a highly atom-, energy-, and waste- economical fashion.

## REFERENCES

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