Application of Group 3 and lanthanide metallocenes as catalysts for selective organic synthesis*

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Abstract: Metallocene complexes of the Group 3 metals and lanthanides have been utilized for cyclization/silylation reactions of polyunsaturated organic substrates. Acyclic dienes, trienes, enynes, and dienynes can be selectively cyclized to provide five- and six-membered rings in high yields.

INTRODUCTION

The worldwide production each year of millions of metric tons of polyethylene and polypropylene represents one of the most important industrial processes for the synthesis of organic materials. Lanthanocenes are among the most active catalysts for the synthesis of these polymers, and as such they constitute an important class of complexes for the formation of carbon–carbon bonds between alkene partners [1]. Inspired by the incredible efficiency of these organometallics in polymer synthesis, we set out to adapt them to the selective construction of small molecules.

There were several challenges and potential difficulties in extrapolating these polymerization processes to the selective synthesis of small organic molecules. For example, to be widely applied the catalysts would have to react with alkenes from several different substitutional classes. However, the Group 3 and lanthanide metallocenes were known to be highly sensitive to steric effects, and in fact even allylic substitution on monosubstituted alkenes often created difficulties in the polymerization process [2]. Outside of the reactive carbon–carbon double bond, ethylene and propylene possess no functional groups. For small molecule synthesis the incorporation of a wide range of functionality would be a necessity, and it was not clear which, if any, of these would be tolerated by the highly reactive, Lewis acid catalyst. Additionally, selectivity issues would have to be addressed. In polyunsaturated systems, chemoselectivity in the insertion of a single alkene or alkyne would be essential. Furthermore, the reaction of prochiral or chiral substrates would require diastereoselective cyclization events. The discussion below outlines some of the progress we have made in employing various metallocenes as catalysts in cyclization/silylation reactions of polyunsaturated organic substrates.

RESULTS AND DISCUSSION

The facility with which organolanthanides and Group 3 organometallics undergo olefin insertion reactions provided a means by which appropriate dienes, trienes, and other polyunsaturated molecules could be used as substrates for cyclization processes. Thus, a precatalyst [Ln = Y or lanthanide, Cp* = C_5Me_5, R' = Me, $CH(TMS)_2$] reacts with a suitable silane via a σ bond metathesis reaction [3], generating the active hydride catalyst and a volatile organosilane byproduct (Fig. 1). Selective insertion of the less hin-
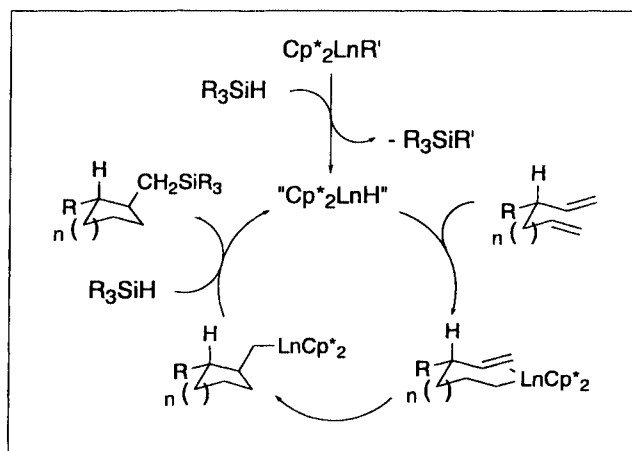
Fig. 1 Catalytic cycle for cyclization/silylation reactions.

dered of the two alkenes into the metal hydrogen bond produces the initial organometallic intermediate. Cyclization through a highly ordered six-membered transition structure leads to a second organometallic intermediate. Silylation via σ bond metathesis terminates the process, thereby completing the catalytic cycle and introducing functionality into the final product. The silanes thus generated are stable compounds and can be carried through several further synthetic transformations. Alternatively, they can be oxidized directly to the corresponding alcohols employing well-established protocols [4]. One highly desirable feature of this catalytic cycle is that it represents an "atom economical" process [5] whereby all of the atoms of the organic substrate and the silane are incorporated into the final product, with no byproducts generated. As a result, workup procedures for the reactions can be greatly simplified.

In practice, the process works extraordinarily well [6]. Thus, the triene in eq. 1 reacts with complete selectivity at each stage of the reaction. The less-hindered allylic side chain is the first site of reaction, generating the initial organometallic. Subsequently, selective olefin insertion at the least substituted of the two remaining, equally disposed alkenes, followed by silylation results in the cyclized silane. Both five- and six-membered rings can be constructed in this manner.


(1)
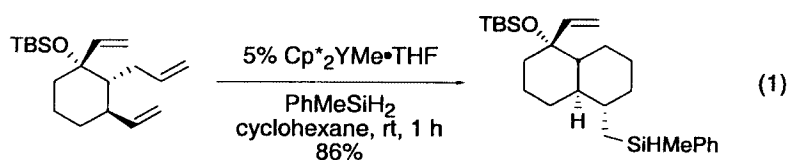
Acyclic trienes can serve as substrates for multiple bond-forming processes resulting in the formation of bicyclic frameworks. In eq. 2, the symmetrical triene is stitched together to create a bicyclo[3.3.0] system [6]. Two carbon–carbon bonds and a carbon–silicon bond are created in this one-pot process, with an overall yield of greater than 70%. Interestingly, in the intramolecular step of the process a 5-*exo* cyclization at the more-hindered alkene takes precedent over 6-exo cyclization at the less hindered counterpart. Subsequent oxidation of the crude silane unveils the synthetic equivalency between the silane and an alcohol. Of note is the fact that the highly strained *trans*-bicyclo[3.3.0] product is created in the reaction, providing one of the few convenient synthetic routes to this structural motif.


(2)
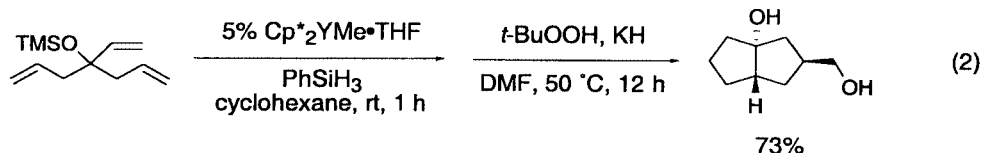
As mentioned in the introduction, Group 3 and lanthanide metallocene catalysts are highly sensitive to steric effects. The polyene systems described above all possess monosubstituted alkenes as their reactive units. In order to expand the range of alkenes that could be employed in these reactions, a new family of precatalysts was developed [7]. The ligand chosen, Cp^{TMS}, provided more space about the metal center for incoming substrates, allowing reaction at the more highly hindered, less-reactive disubstituted alkenes (eq. 3).

$$\text{(3)}$$
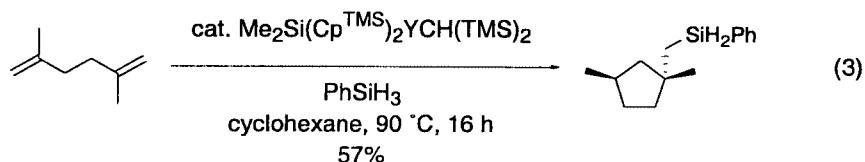
In spite of their Lewis basicity, amine substrates function very well in the cyclization reactions [8]. As shown in eq. 4, isolated dienes are transformed according to the normal reactivity patterns. Dienes in which one of the alkenes is conjugated with an aromatic system, however (eq. 5), react via an "aryl-directed" process whereby the conjugated alkene reacts first, even though it is more sterically encumbered [9]. Another consequence of the "aryl-directed" process is a regioinversion in the first insertion. In the example shown, a tertiary organometallic is generated initially, with subsequent cyclization affording the observed product.

$$\text{(4)}$$

78% yield, 12 :1 ds

$$\text{(5)}$$

68% yield
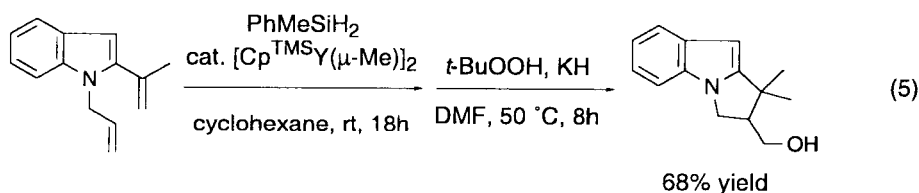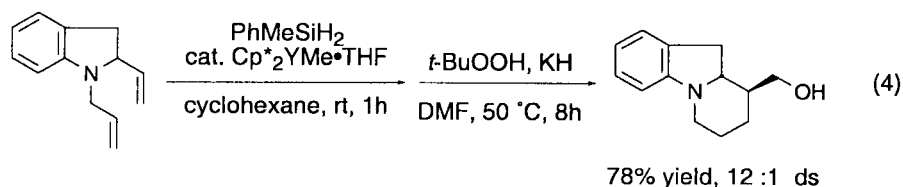
Enynes also undergo the cyclization/silylation reaction [10]. Because alkynes react faster with the organometallic hydrides than alkenes [11], the site of initiation in the process is the carbon–carbon triple bond. To achieve regioselection in the initial insertion, the alkyne must be branched at the propargyl position distal to the alkene (eq. 6).

$$\text{(6)}$$
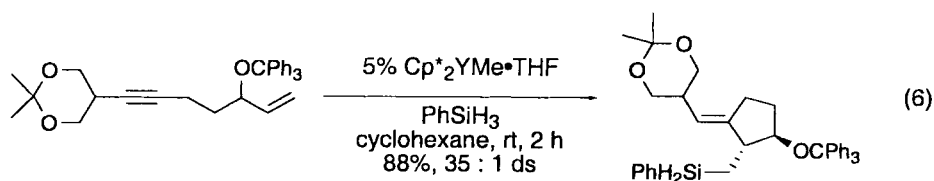
In addition to carbocycles, both monocyclic (eq. 7) and bicyclic (eq. 8) nitrogen heterocycles can be constructed from acyclic enyne substrates in excellent yields and with exceptional stereochemical control [12].

$$\text{(7)}$$

$$\text{(8)}$$
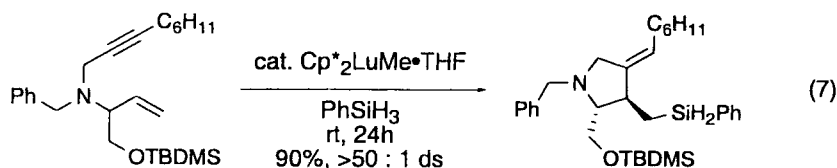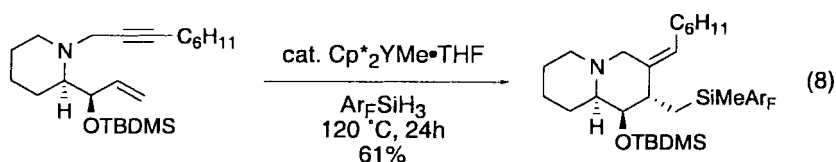
As in the case of olefinic substrates, multiple carbon–carbon bond-forming events can be achieved with alkyne substrates [13]. Thus, acyclic dienynes can be readily cyclized to form bicyclic silanes in high yields with near complete control of stereochemistry (eq. 9).

$$\text{(9)}$$
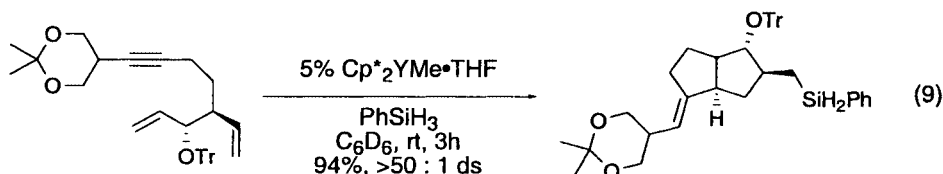
CONCLUSIONS

The application of metallocene polymerization catalysts to small molecule synthesis has been demonstrated. These catalysts show high reactivity and selectivity in cyclization/silylation reactions of dienes, trienes, enynes, and dienynes. The reactions are convenient to carry out under very mild conditions, and the workup is facilitated by the fact that the processes exhibit "atom economy", with no byproducts formed. The silanes thus generated serve as the synthetic equivalent of alcohols. Both carbocycles and heterocycles can be synthesized utilizing the methods developed. Tertiary amines, halides, acetals, dithioacetals, and protected alcohols can all be tolerated in the reactions. Finally, substrates containing alkenes and alkynes are quite readily prepared themselves, and thus a wide variety of structurally diverse products can be rapidly generated.

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