Pure & Appl. Chem., Vol. 66, No. 7, pp. 1557–1564, 1994.
Printed in Great Britain.

Novel Lewis acid catalysis in organic synthesis

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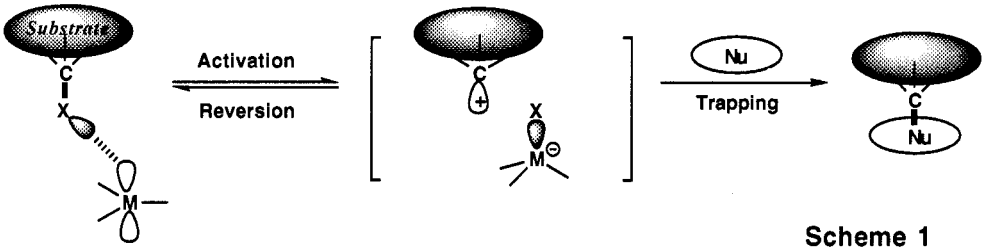
Abstract: Cationic zirconocene or hafnocene complexes serve as a novel class of Lewis acid with unique reactivities, which are to be exploited in organic synthesis. Four categories of reactivities are discussed, that is, (A) C–F bond activation/cleavage, (B) Coordinative activation of ether linkages, (C) Carbonyl activation, and (D) C–O bond cleavage via zirconocene alkoxide.

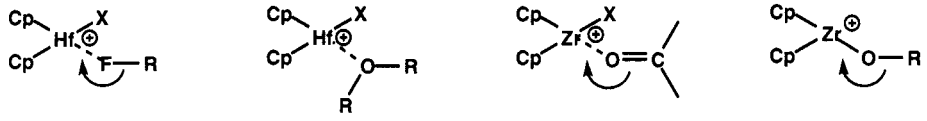
Introduction

Lewis acid-promoted reactions are becoming of increasing importance in current organic synthesis (ref. 1). A general idea for such reactions is shown in Scheme 1. Initial coordination of a Lewis acid occurs to the basic site of the substrate. When the activation level reached high enough, the ionization occurs to generate a cationic species, which is reverted to the starting material or trapped by a nucleophile to give the product. The Lewis acid plays the key role to determine the overall reaction path by controlling the generation and trapping of the cationic species. If the substrate has many basic functionalities, specificity is required for this acid–base interaction in that one particular functionality is to be activated but not the others. The Lewis acid decides also the nature of the cationic species generated, an ion pair or a loosely bound covalent species or somewhere in-between.



Scheme 1

In this context, we have recently been finding that the cationic zirconocene or hafnocene complexes behave as a new class of Lewis acid with unique reactivities, which would be useful in organic synthesis. Four categories (A–D) of the reactivities of such cationic complexes are discussed.



A *C–F bond Cleavage* **B** *Activation of Ether Linkage* **C** *Carbonyl Activation* **D** *C–O Bond Cleavage*

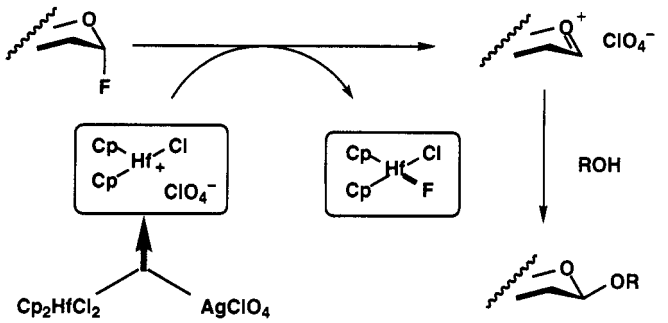
Results and Discussion

(A) The C–F bond activation/cleavage

Some years ago, we found that the combination of hafnocene dichloride and silver perchlorate acts as a powerful activator of glycosyl fluoride (ref. 2). Scheme 2 shows our reasoning for the origin of the

high reactivity: the ligand exchange generates a hafnocene perchlorate complex which, as a highly electrophilic 14 electron species, strongly activates the C–F bond in the glycosyl fluoride to generate an oxonium species as the key species in the glycosidation. Due to the high fluorophilicity of such a group-4 cationic complex, this reaction is endowed with an extremely high reactivity and have been applied to many occasions of *O*-glycoside synthesis. We subsequently found that the double ligand exchange, by using hafnocene dichloride and silver perchlorate in 1:2 ratio (eq. 1), leads to even higher reactivity (ref. 3). The counter anion is important, and perchlorate proved to be the best in terms of the reactivity among the non-coordinating anions tested. Considering the potential hazard associated with this anion, however, triflate could be used as an alternative, although the reactivity is slightly lower.

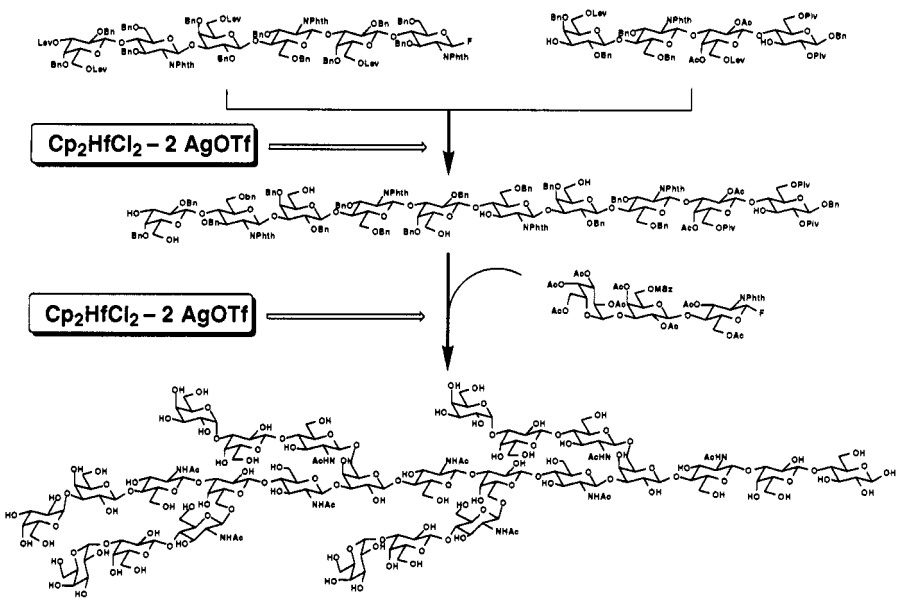
Scheme 2



$$Cp_2HfCl_2 + 2\ AgClO_4 \longrightarrow Cp_2Hf(ClO_4)_2 \qquad (1)$$

The most impressive application of this activation method was recently reported by Prof. Ogawa (ref. 4). A giant molecule composed of 25 saccharides has been synthesized by this method. This example clearly illustrates the specific and high-level activation of the C–F bond achieved by the cationic hafnocene complex even in the presence of many Lewis basic sites (Scheme 3).

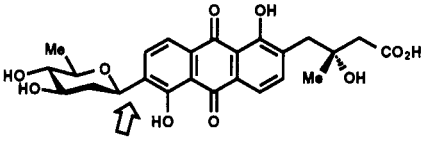
Scheme 3



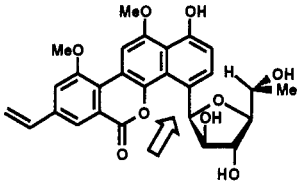
(B) The coordinative activation of ether linkages

Aryl *C*-glycoside antibiotics constitute an emerging class of bioactive natural product (ref. 5). For the selective formation of the key aryl *C*-glycoside bond, we developed a versatile reaction, where the cationic hafnocene complex works nicely (ref. 6). Particularly, we became aware of another useful role

of cationic hafnocene complex, that is, the coordinative activation of ether functions. The features are discussed in the context of the total syntheses of two of the natural products, **1** and **2**.

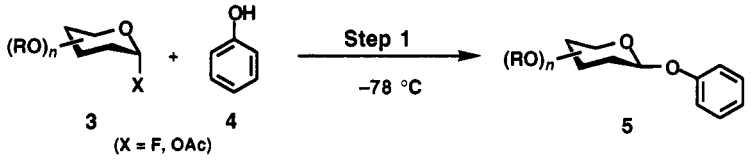


Vineomycinone B_2 (**1**)

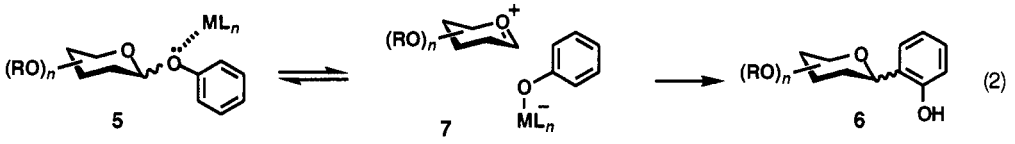


Gilvocarcin V (**2**)

The reaction is what we call the *O*→*C* glycoside rearrangement (Scheme 4). In the presence of a Lewis acid, glycosyl fluoride quickly reacts with phenol at low temperature (typically at –78 °C) to form *O*-glycoside **5**, since phenol is highly reactive in such occasions. By simply raising the temperature, e.g. 0 °C, gradual conversion of the *O*-glycoside **5** to the corresponding *C*-glycoside **6** is observed. This conversion may proceed through an oxonium–phenolate ion pair as **7**, generated by the Lewis-acid complexation to the exocyclic oxygen (eq. 2), and the trapping at an aromatic carbon leads to irreversible *C*-glycoside formation. This latter step is highly dependent on the Lewis acid employed.

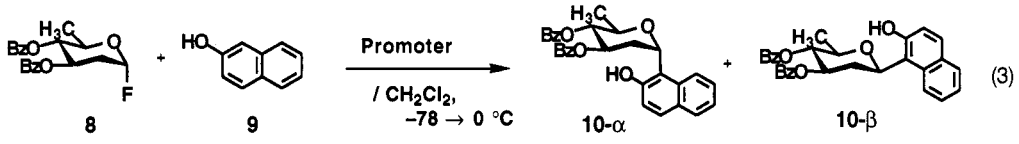


Scheme 4



(2)

The reaction shown in eq. 3 is illustrative of the reaction profile. As the Lewis acid promoter, BF_3•OEt_2 and Cp_2HfCl_2–$AgClO_4$ were employed for comparison. With BF_3•OEt_2, the reaction (–78 → 0 °C) gave **10** in 70% yield along with unconverted *O*-glycoside. In contrast, the reaction with the hafnocene couple completes already below 0 °C to give **10** almost quantitatively, showing the prominent reactivity of the hafnocene combination for promoting the *O*→*C* rearrangement.



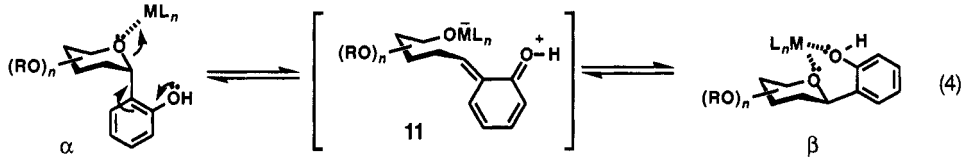
(3)

Promoter	Yield / %	α / β
BF_3•OEt_2	70[a)]	3.4 / 1
Cp_2HfCl_2 – $AgClO_4$	98	1 / >99

a) *O*-Glycoside was obtained in 28 % yield.

Another thing special is the difference in the anomeric composition. With BF_3•OEt_2, the **10**-α is favored, whereas the hafnocene promoter leads to almost perfect β-selectivity. It suggests that there is

an additional step, i.e. the α→β-anomerization, which again is better promoted by the hafnocene complex. Indeed, when **10**-α was treated with the hafnocene reagent, the anomerization occurs to give a mixture rich in the β-anomer. A closer experiment showed that, in the hafnocene case, the kinetically formed *C*-glycoside is already rich in the β-anomer, ca. 9/1 level, which is reinforced by the anomerization process to give the β-anomer as the sole product.

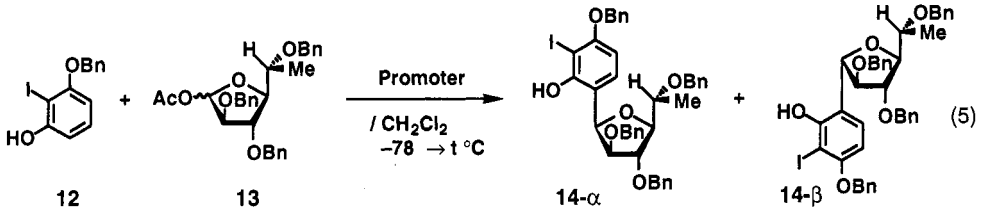


(4)

Mechanistically, the Lewis acid activates the endocylic oxygen to facilitate the generation of a quinone methide species as **11**, and the ring opening–reclosure drives the system to the thermodynamic control (eq. 4). Note that the anomeric effect is not important, and the equatorial disposition of C(1)-aryl substituent is favored, and if such an equilibration path is offered by a suitable Lewis acid complexation, the α→β transition occurs. It should be noted that the chelation effect as shown in eq. 4 may be operative in determining the equilibrium point, although the extent of the contribution is not clear at present. By virtue of this reaction, we completed the total synthesis of vineomycinone B_2 (**1**), which shows not only the synthetic potential of this reaction in aryl *C*-glycoside synthesis but also the versatile roles of cationic hafnocene complex (ref. 7).

Another interesting feature was observed in the total synthesis of the gilvocarcin V (**2**), an antitumor compound with an exceptionally low toxicity. The most challenging issue comes from the *C*-glycoside linkage disposed in a apparently unfavorable manner. Indeed, the natural product undergoes acid-catalyzed anomerization or even ring enlargement to the pyranosides under acidic conditions, most probably through the mechanism via a quinone methide-related species as discussed above.

The reaction of phenol **12** and glycosyl acetate **13** was investigated as the key step in the total synthesis (ref. 8). Initially, we found a slightly α-selective coupling is achievable by using tin tetrachloride at the final temperature of –20 °C (run 1). However, the temperature effect is quite delicate and when the final temperature was 0 °C it became β-rich (run 2). This anomerization was even more impressive in the coexistence of silver perchlorate, which occurred at lower temperatures (runs 3, 4). Gratifyingly, the hafnocene combination turned out to give the desired α-anomer with 8/1 selectivity at –20 °C (run 5). Furthermore, in this particular case, the anomerization was sluggish, and 7/1 level of α-selectivity held even after the warm-up to room temperature (run 6). We have no rationale for this outcome, and the story is not simple and a host of factors are involved including the center metal and the counter anion. For further improvement, see ref. 9.



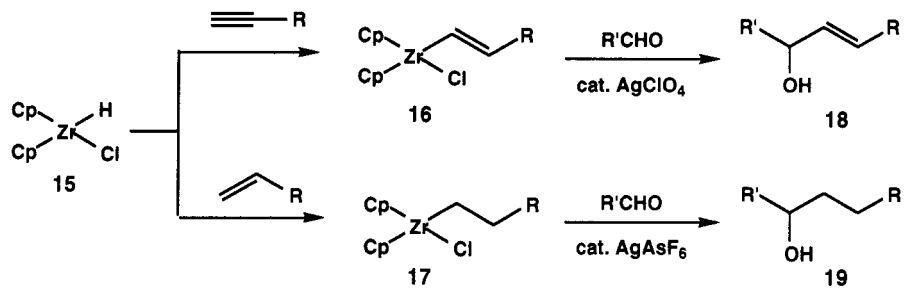
(5)

Run	Promoter	Final Temp. (t °C)	Yield/%	α/β
1	$SnCl_4$	–20	67	2.6 / 1
2	$SnCl_4$	0	75	1 / 2.5
3	$SnCl_4$ – $AgClO_4$	–40	60	5.1 / 1
4	$SnCl_4$ – $AgClO_4$	–20	69	1 / 58
5	Cp_2HfCl_2 – $AgClO_4$	–20	86	8.2 / 1
6	Cp_2HfCl_2 – $AgClO_4$	+25	88	7 / 1

(C) Carbonyl activation

We next addressed the question of whether such cationic complexes serve for the carbonyl activation or not by examining the reactivity of organozirconocene chlorides, readily accessible via hydrozirconation.

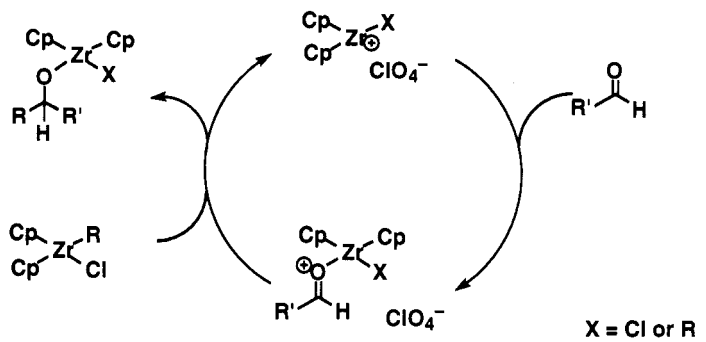
Reaction of alkyne or alkene by Schwartz reagent (**15**) provides alkenyl- or alkylzirconocene chlorides (**16** or **17**) in high yield (ref. 10), which have been often utilized in organic synthesis, primarily as precursor of various organometallic species via transmetallation. These species are, however, unreactive as nucleophiles so that the Grignard-type addition to carbonyl group has been recognized as impractical. The reaction of **17** (R- = C_4H_9-) and an aldehyde (R'- = $C_6H_5(CH_2)_2$-) was indeed slow and the yield was only 23% even after overnight at room temperature. With a notion to generate a cationic species which would hopefully serve as the carbonyl activator, we added 5 mol% of silver perchlorate to find the reaction to proceed in 10 min to give **18** in 90% yield (ref.11). The catalytic activity is quite high and the reaction goes nicely even when the catalyst was reduced to 1 or 0.1 mol%. This alkenylation proved to be widely applicable, some of which will be discussed later. On the other hand, behavior of the corresponding alkyl complexes is less satisfactory so far as silver perchlorate is used as the catalyst. It requires longer reaction time, more of the reagent and more of the catalyst, presumably due to deterioration of the cationic complex by competing β-hydride elimination via agostic interaction. However, it turned out that silver hexafluoroarsenate, which was totally ineffective for the alkenyl case, is an extremely efficient catalyst for the alkyl addition (ref. 12).



(6)

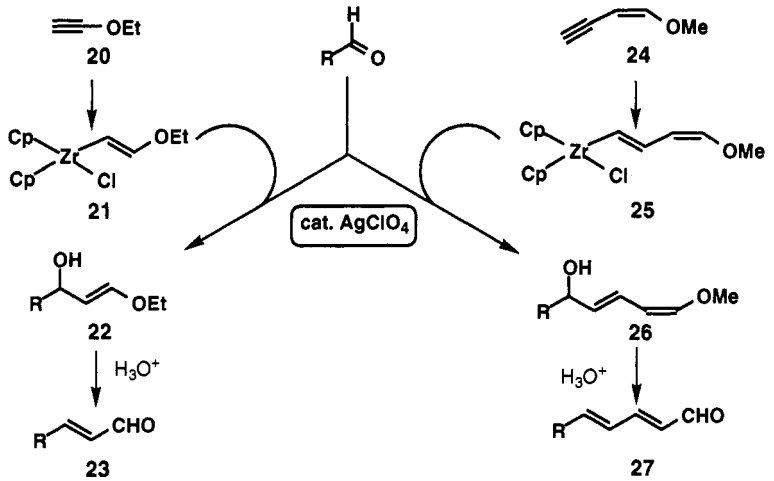
Scheme 5 shows mechanistic proposal, where the cationic species acts as the carbonyl activator. Although it is not clear whether the transfer of the organic moiety is intramolecular or intermolecular, every addition regenerates the cationic species for further activation so that a catalytic silver salt suffices for the whole reaction to proceed.

Scheme 5



Scheme 6 shows a useful application of this alkenylation reaction, that is, the two- and four-carbon homologation of aldehyde (ref. 13). Commercially available ethoxyacetylene (**20**) is subjected to hydrozirconation to generate **21**, which cleanly adds to aldehyde in the presence of silver perchlorate, and subsequent treatment of the adduct with dilute acid yielded enal **23** in high yield with excellent (*E*)-selectivity. The same story is true for the four-carbon homologation which starts with a methoxyeneyne **24**, which is also commercially available, leading to the formation of dienal **27** in high yield and with high (*E,E*)-selectivity. These methods proved to be reiterative to offer an efficient route to polyenal synthesis. We have synthesized up to hexa-enal with all (*E*)-geometries.

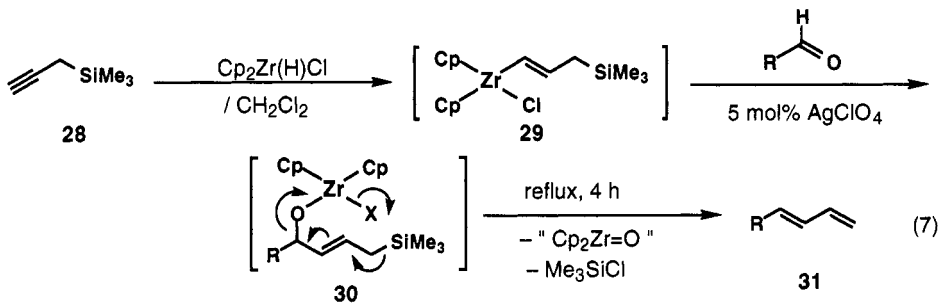
Scheme 6



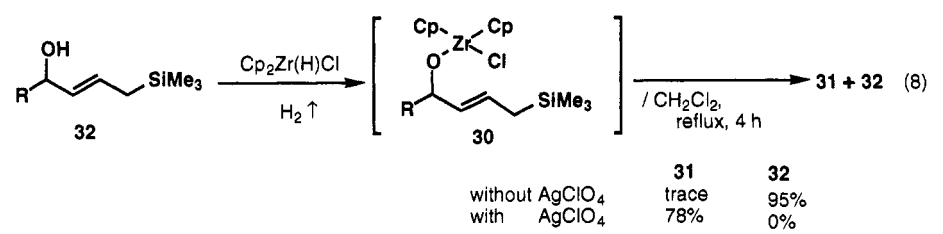
(D) C–O bond cleavage

In the mean time during such an application study, we came to notice another reactivity exhibited by cationic zirconocene species, which is associated with the departure of an oxygen from the organic substrate, a process which calls for the electron deficiency at the center metal.

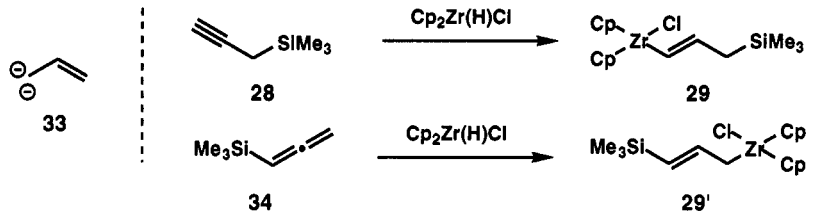
We were interested in the generation and the reactivity of such a (Si, Zr)-bimetallic species as **29** (eq. 7). Indeed, hydrozirconation of propargylsilane (**28**) cleanly generates **29**, which adds to aldehyde in the presence of silver perchlorate. Without isolation, gentle warming of the mixture effects the cascade eliminations, expelling zirconocene oxide and trimethylsilyl chloride, to afford 1,3-diene **31** in high yield.



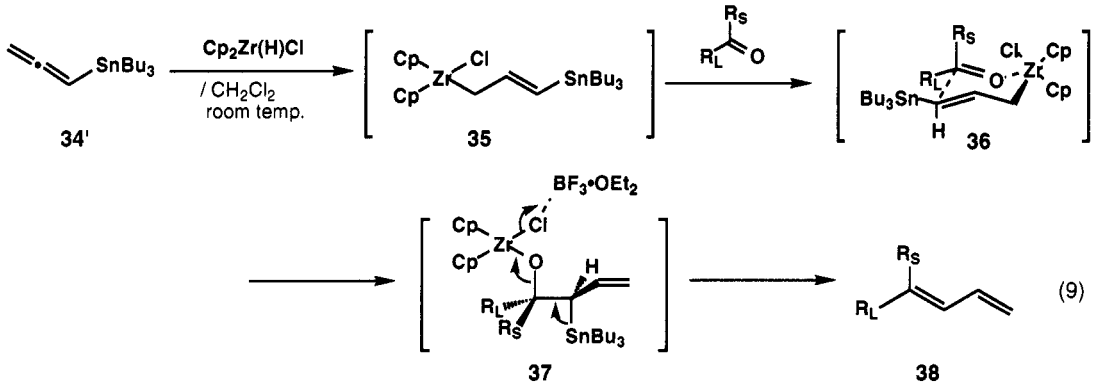
It turned out that the group X is important for the elimination reaction to occur. We prepared the possible intermediate **30** by other means by the reaction of the intermediary alcohol **32** with Schwartz reagent (eq. 8). Hydrogen gas evolution was soon observed, and then the mixture was refluxed as above. The diene was not obtained at all, but the starting alcohol was recovered almost quantitatively. The only difference is presence or absence of the catalytic silver perchlorate, and, indeed its addition to this mixture cleanly effected the elimination reaction to give the 1,3-diene **31** in 78% yield. The silver ion is out of the system at the early stage, and so the presence of the perchlorate ion is essential, which serves to generate the cationic species to trigger the departure of the oxygen for the 1,4-elimination. The perchlorate carrier is most probably trimethylsilyl perchlorate (ref. 14).



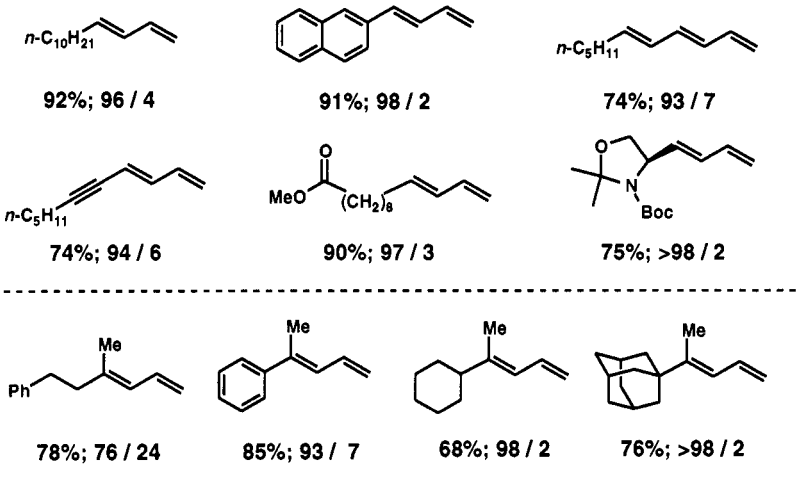
The above 1,3-bimetallic species **29** serves as a 1,1-dianion equivalent **33**, if the net conversion made by this reagent is considered. This includes an alkenyl-Zr moiety and an allyl-Si moiety. We were interested in exchanging the two metals to see how the reactivity changes over. A possible way to generate such a species **29'** is the hydrozirconation of allenylsilane.



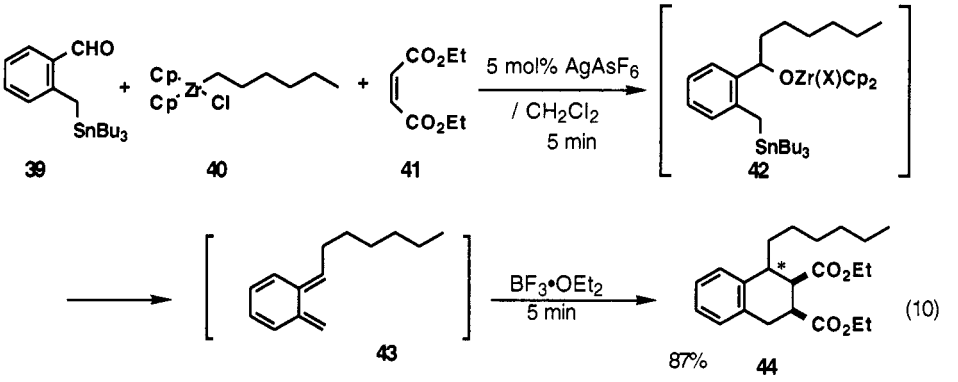
For the ease of preparation, we employed allenyltin **34'** rather than allenylsilane **34** (eq. 9). Hydrozirconation goes nicely to generate the 1,3-bimetallic species **35** with (*E*)-geometry by NMR. This is an allylic zirconium, so it attacks aldehyde without resort to the silver catalysis in S_E2' manner. Direct treatment of the mixture with boron trifluoride etherate leads to the high yield formation of the 1,3-diene in high yield. Our reasoning on the role of boron trifluoride is again to polarize the Zr–Cl bond to trigger the C–O bond cleavage.



This reaction turned out to be quite useful in many ways in terms of the yield, the chemoselectivity, and the high geometrical selectivity. Due to the steric constraint felt at the six-membered transition state, stereo-defined adduct is obtained, which then undergoes stereospecific *anti*-elimination to give (*E*)-dienes in high stereoselectivity. The reaction works nicely with aliphatic, aromatic, α,β-unsaturated or functionalized aldehydes, providing the corresponding 1,3-dienes uniformly in high yields and with high (*E*)-selectivities. Notably the reaction works for ketones, and the (*E*) selectivity is high provided that the size difference in two groups was sufficient (ref. 15).



The above results represent the generation of 1,3-diene structure by 1,4- or 1,2-elimination triggered by cationic zirconocene alkoxide. Such story is also true across an aromatic nucleus, to generate quinodimethane species to achieve the cycloaddition (eq. 10). Aldehyde **39** is treated with hexylzirconocene chloride (**40**) and diethyl maleate (**41**), and nothing happens at this stage. Addition of 5 mol% of silver hexafluoroarsenate cleanly promotes the addition reaction to generate **42** in high yield in 5 min. Direct treatment of this mixture with boron trifluoride etherate brings about the Lewis acid-promoted version of "Sano reaction" (ref. 16) to generate a quinodimethane species **43**, which is immediately trapped by the coexisting olefin **41** to give [4 + 2] cycloadduct **44** as a single isomer whose stereostructure is to bo be determined (ref. 12). This last example illustrates as interesting possibility in Lewis acid-catalyzed reactions: two "orthogonal" Lewis acids activate different functionalities to allow sequential multi-component reaction in one flask.



39 40 41 42 43 44 (10)

Acknowledgments: I deeply appreciate all coworkers whose names appear in the reference. Financial support from the Ministry of Education, Science, and Culture of Japan is deeply acknowledged.

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