

Zr- and Hf-centred Lewis acid in organic synthesis

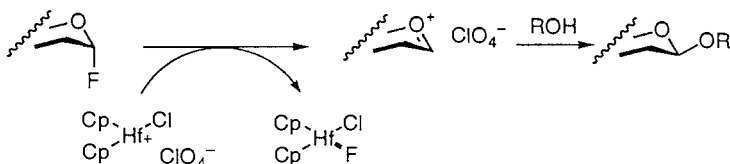
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1. Introduction

The nature of a given Lewis acid, ML_n , can be modified by changing the metal (M), the ligand (L, chiral or non-chiral) as well as the charge (neutral or cationic), thereby endowing it with useful properties in organic synthesis. Early transition metals are attracting current attention to exploit their hard Lewis acidic characters. Although titanium has been studied most, recent attention is also centred at its group-4 congeners, i.e. zirconium and hafnium. Although they have been extensively used in the polymerization field,¹⁻³ the use in organic synthesis is still rather limited either as a tailor-made catalyst or as a transient species in the course of the reaction.⁴ This chapter describes some unique reactivities of cationic zirconocene or hafnocene complexes, thereby dealing with four modes of functional group activation: (1) C-F bond in glycosyl fluoride, (2) ethers, (3) carbonyl groups, (4) C-C multiple bonds.

2. Activation of C-F bond

Combination of Cp_2HfCl_2 and $AgClO_4$ acts as a powerful activator of glycosyl fluoride, providing a glycosylation method used for the synthesis of complex oligosaccharides or other glycoconjugates (Scheme 10.1).⁵⁻⁸ The high fluorophilicity of hafnocene perchlorate complex, cationic, or loosely bound covalent species, is invoked to the origin of high activation of C-F bond to generate an oxonium species. Double ligand exchange by Cp_2HfCl_2 and $AgClO_4$ in 1:2



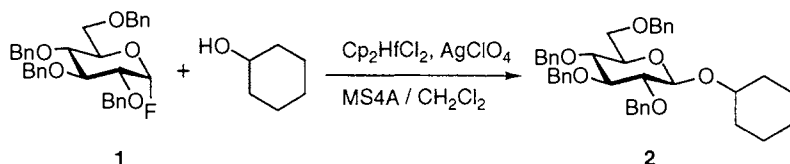
Scheme 10.1

ratio leads to even higher reactivity. Triflate is used as an alternative counter anion considering the potential hazard associated with perchlorate.

Protocol 1.

Metalloocene-promoted *O*-glycosylation (Scheme 10.2)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 10.2

Equipment

- Two-necked, round-bottomed flask (30 mL) containing a magnetic stirring bar, with a side arm bearing a three-way stopcock, and a rubber septum
- Vacuum/inert gas source (gas source may be an argon balloon)
- Dry ice–methanol cooling bath
- All-glass syringe

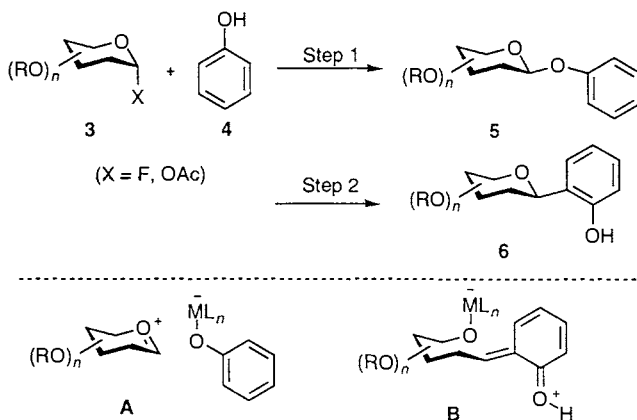
Materials

- AgClO₄ (FW 207), 47.0 mg, 0.227 mmol
 - Cp₂HfCl₂ (FW 379), 43.0 mg, 0.113 mmol
 - dry, distilled CH₂Cl₂
 - Powdered molecular sieves 4A, c. 100 mg
 - Cyclohexanol (FW 100), 22.6 mg, 0.226 mmol
 - Glycosyl fluoride **1** (FW 543), 61.2 mg, 0.113 mmol
- oxidizer, corrosive, explosive
irritant, moisture sensitive**
- irritant, hygroscopic**

1. Assemble the two-necked flask with a stopcock, a stirring bar, and a rubber septum. Flame dry the flask under vacuum, and, after cooling to ambient temperature, purge with argon through the three-way stopcock. Add Cp₂HfCl₂ and AgClO₄ to the flask.
2. Add dry CH₂Cl₂ (0.5 mL) via a syringe, and stir the mixture for 10 min to make a slurry.
3. Add a solution of cyclohexanol in CH₂Cl₂ (0.5 mL). After cooling to –50°C, add glycosyl fluoride **1** in CH₂Cl₂ (1 mL) via a syringe, and stir the mixture for 1 h.
4. Quench the reaction with saturated aqueous NaHCO₃ solution, and filter the mixture through a Celite pad. Extract the products with EtOAc, and wash the combined organic extracts successively with saturated aqueous NaHCO₃ solution and brine. After drying over Na₂SO₄, and evaporate the solvents *in vacuo*.
5. Purify the resulting oil on preparative TLC (hexane–EtOAc, 4:1) to yield *O*-glycoside **2** (65.2 mg, 93%). The product shows characteristic spectroscopic data.

3. Activation of ethers

Cationic hafnocene species are also capable of activating the ether linkages as seen in the unique results in *C*-glycoside synthesis.⁹ In the *C*-glycosylation of phenol via *in situ*-formed *O*-glycoside promoted by a Lewis acid (**3** + **4** → [**5**] → **6**: *O* → *C* glycoside rearrangement), the Cp₂HfCl₂–AgClO₄ combination is particularly effective in terms of the reactivity in converting **5** into **6** as well as the stereoselectivity. Both of these features have their origin in the effective activation of an ether oxygen by a cationic hafnocene species as illustrated in **A** and **B**^{10–13} (Scheme 10.3).



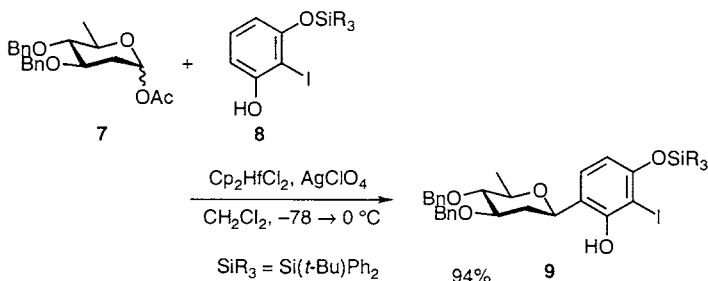
Scheme 10.3

Wipf *et al.*^{14–16} reported the activation of epoxide by a cationic zirconocene species to trigger 1,2-rearrangement.

Protocol 2.

O → *C*-glycoside rearrangement of olivosyl acetate **7** and phenol **8** (Scheme 10.4)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 10.4

Protocol 2. Continued**Equipment**

- Two-necked, round-bottomed flask (100 mL) fitted with a magnetic stirring bar, a three-way stopcock, and a rubber septum
- Dry ice–methanol cooling bath
- Vacuum/inert gas source (gas source may be an argon balloon)
- All-glass syringe

Materials

- AgClO₄ (FW 207.3), 893 mg, 4.31 mmol
- Cp₂HfCl₂ (FW 380), 820 mg, 2.16 mmol
- Dry, distilled CH₂Cl₂
- Powdered molecular sieves 4A, ca. 1.2 g
- Phenol **8** (FW 474), 936 mg, 1.97 mmol
- D-oliviosyl acetate **7** (FW 370), 666 mg, 1.80 mmol

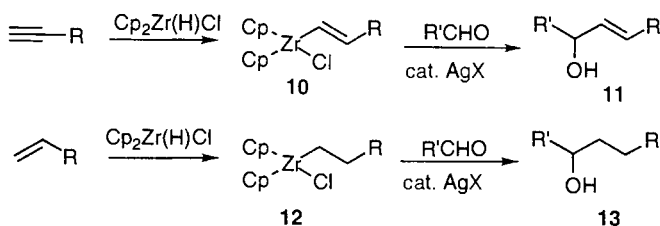
**oxidizer, corrosive, explosive
irritant, moisture sensitive**

1. Assemble the 100 mL round-bottomed flask with a stopcock, a stirring bar, and a rubber septum. Flame dry the vessel containing powdered molecular sieves under vacuum. After cooling, purge with argon. Place Cp₂HfCl₂ and AgClO₄ in the flask.
2. Introduce dry CH₂Cl₂ (5 mL) via a syringe through the rubber septum, and form a slurry by stirring for 15 min.
3. After cooling the mixture to –78°C, add a solution of phenol **8** in CH₂Cl₂ (15 mL) and D-oliviosyl acetate **7** in CH₂Cl₂ (10 mL) via a syringe to this suspension.
4. Let the mixture to warm to 0°C during 40 min, and stir it for 15 min.
5. Quench the reaction with pH 7 phosphate buffer, and acidify it with 2 M HCl. Filter the mixture through a Celite pad, and extract the products with EtOAc. Wash the combined organic extracts with brine. After drying over Na₂SO₄ and filtration, concentrate the solution *in vacuo*.
6. Purify the resulting oil on silica-gel flash column (Hexane–acetone, 85:15) to yield C-glycoside **9** (1.32 g, 93.5%). The product shows characteristic spectroscopic data.

4. Carbonyl activation

Carbonyl groups are also activated by cationic zirconocene species. Alkenyl- or alkyl-zirconocene chlorides, **10** or **12** (Scheme 10.5), readily accessible via hydrozirconation of alkyne or alkene,^{17,18} are unreactive nucleophiles, and their Grignard-type carbonyl addition is slow. However, a catalytic amount of AgClO₄ or AgAsF₆ greatly accelerates the reaction, which is ascribed to the carbonyl activation by the cationic species.¹⁹ Recently, Hf(OTf)₄ was prepared and used as a catalyst for Friedel–Crafts reaction, and for Fries

rearrangement, which are also ascribed to the carbonyl activation by the hafnium reagent^{20,21}

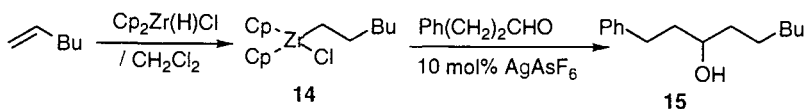


Scheme 10.5

Protocol 3.

AgAsF_6 catalysed addition of alkenylzirconocene chloride to aldehyde (Scheme 10.6)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 10.6

Equipment

- Two-necked, round-bottomed flask (30 mL) fitted with a magnetic stirring bar, a three-way stopcock, and a rubber septum
- Nitrogen gas line
- Vacuum/inert gas source (gas source may be an argon balloon)
- Dry ice-methanol cooling bath
- All-glass syringe

Materials

- $\text{Cp}_2\text{Zr(H)Cl}$ (FW 258), 270 mg, 1.05 mmol
 - AgAsF_6 (FW 296), 20.1 mg, 0.0677 mmol
 - Dry, distilled CH_2Cl_2
 - 1-hexyne (FW 84.2), 93.1 mg, 1.11 mmol
 - 3-phenylpropanal (FW 134), 83.1 mg, 0.619 mmol
- moisture sensitive, light sensitive**
highly toxic, cancer suspect agent

flammable liquid irritant

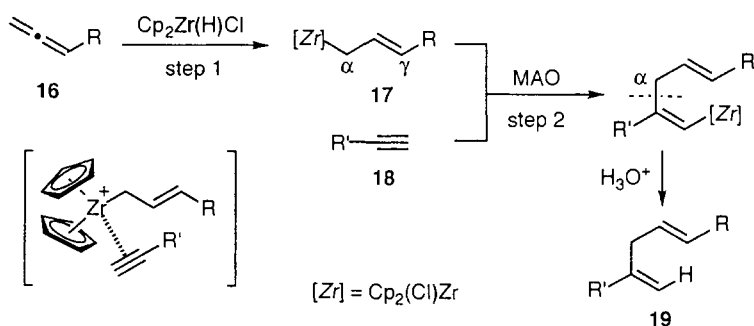
- Assemble the 30 mL round-bottomed flask with a stopcock, a stirring bar, and a rubber septum, and flame dry the flask under vacuum. After cooling to room temperature, fill the apparatus with nitrogen.
- Place Schwartz reagent in the flask, and then rapidly place the rubber septum on the neck of the flask.
- Add a solution of the 1-hexyne in CH_2Cl_2 (3 mL) via a syringe to the flask at -78°C , and then allow the mixture to warm to 25°C , and stir the mixture for 10 min.

Protocol 3. Continued

4. Add a solution of 3-phenylpropanal in CH_2Cl_2 (3 mL) to the mixture.
5. After 5 min, add AgAsF_6 to the mixture, where a deep brown suspension will form.
6. After 10 min, pour the mixture into saturated aqueous NaHCO_3 solution, extract the products with EtOAc. Wash the combined extracts with brine and dry over Na_2SO_4 .
7. Purify the resulting oil on preparative TLC (Hexane–EtOAc, 4:1) to yield **15** as colourless oil (129 mg, 94.5%). The product shows characteristic spectroscopic data.

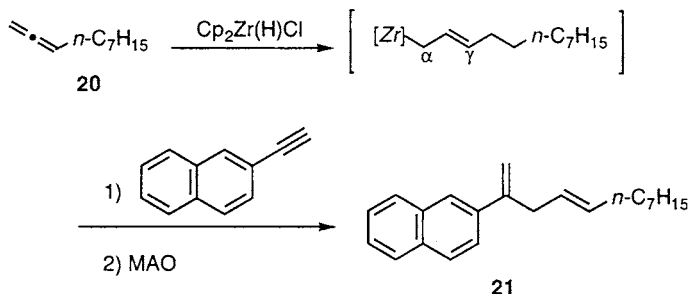
5. Reductive coupling of allenes and alkynes

It is well documented that cationic zirconocene species plays a key role in Kaminsky polymerization, a recent descendant of the Ziegler–Natta process.^{1–3} This process served as a hint to a regio- and stereocontrolled reductive coupling of allenes and alkynes (Scheme 10.7); allylzirconium species **17**, generated by the hydrozirconation of allene **16**, undergoes carbometallation of alkyne **18** promoted by methylaluminoxane (MAO). The overall reaction gives the ‘ α -internal’ coupling product **19** in high selectivity.²²

**Scheme 10.7**

Protocol 4.**MAO-catalysed allylzirconation of 1-alkynes (Scheme 10.8)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

**Scheme 10.8****Equipment**

- Two-necked, round-bottomed flask (30 mL) fitted with a magnetic stirring bar, a three-way stopcock, and a rubber septum
- Nitrogen gas line
- Vacuum/inert gas source (gas source may be an argon balloon)
- Dry ice-methanol cooling bath
- All-glass syringe

Materials

- $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (FW 258), 190 mg, 0.736 mmol
- Methylaluminoxane (MAO) (0.93 M solution in toluene), 0.12 mL
- Dry, distilled CH_2Cl_2
- Allene **20** (FW 138), 86.3 mg, 0.625 mmol
- 2-Ethynynaphthalene (FW 152), 55.4 mg, 0.364 mmol

moisture sensitive, light sensitive**pyrophoric, corrosive**

1. Assemble the two-necked flask with a stopcock, stirring bar, and a rubber septum, and flame dry the flask under vacuum. After cooling to room temperature, purge the flask with nitrogen.
2. Transfer Schwartz reagent from Schlenk flask into the flask which is connected to the nitrogen line, and then rapidly equip the neck of the flask with a rubber septum.
3. Add CH_2Cl_2 (0.7 mL) to the flask to form a slurry at -78°C . Add a solution of allene **20** in CH_2Cl_2 (2.5 mL), warm the mixture to 25°C over 20 min and stir for a further 0.5 h.
4. Chill the resulting red solution to -78°C , and add ethynynaphthalene in CH_2Cl_2 (2.5 mL) via a syringe followed by MAO solution. Warm the mixture to -20°C over 15 min, and stir for 20 min at -20°C . Stop the reaction by carefully adding saturated aqueous K_2CO_3 solution. Stir the mixture for 5 min, and add anhydrous Na_2SO_4 .

Protocol 4. Continued

5. After filtration through a Celite pad and evaporation, purify the resulting oil on preparative TLC (hexane) to give diene **21** (105 mg, 99%). The product shows characteristic spectroscopic data.
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