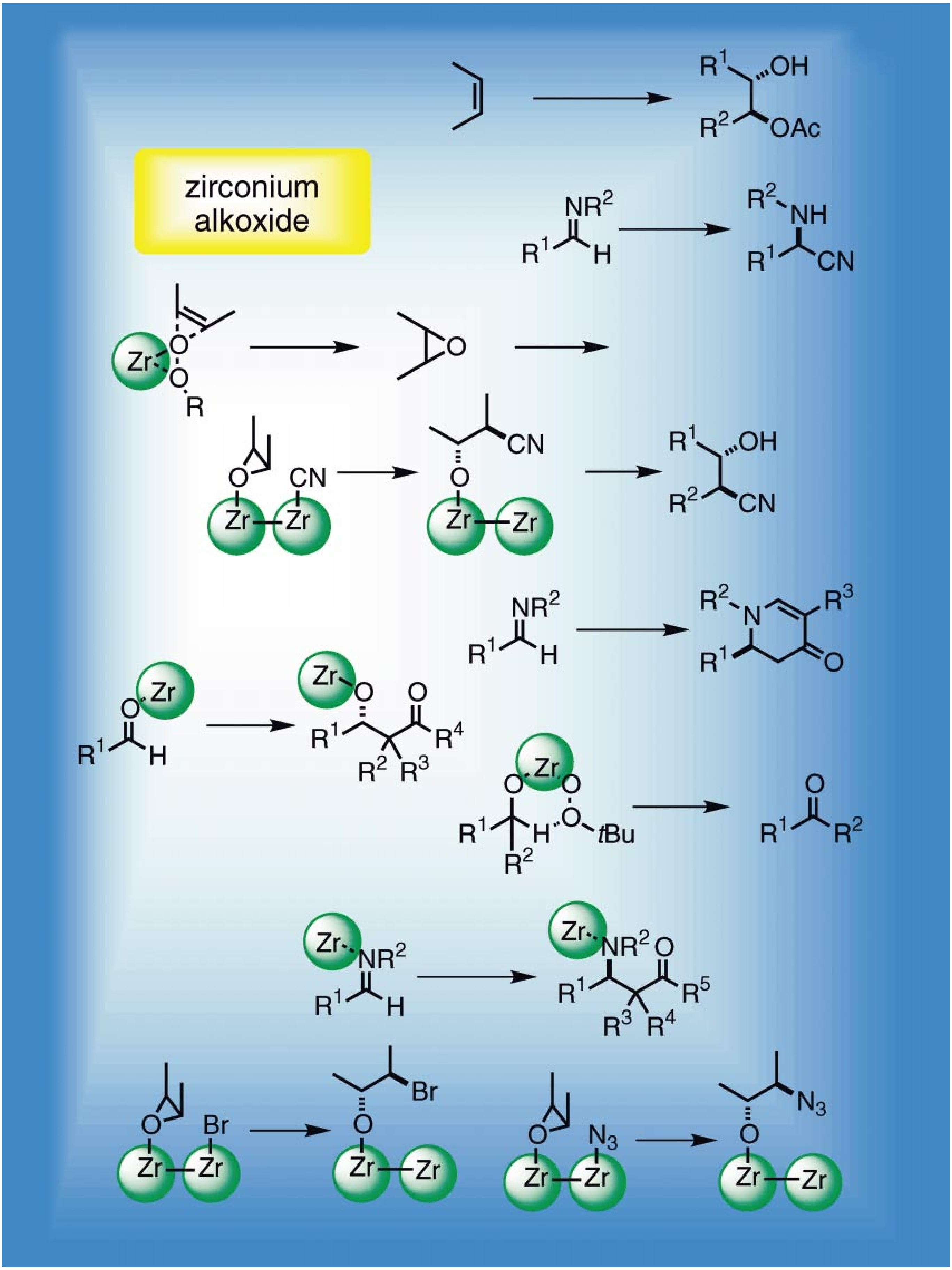

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Zirconium Alkoxides in Catalysis

Shingo Yamasaki, Motomu Kanai, and Masakatsu Shibasaki*[a]

Abstract: This paper presents recent advances in the reactions catalyzed by zirconium alkoxide. Catalytic asymmetric reactions with chiral zirconium catalysts and redox reactions are first discussed. The diverse characteristics of zirconium alkoxides as Lewis acids, Brönsted bases, and nucleophiles, are key for promoting these unique reactions. Our recent development of novel reactions, one-pot synthesis of *trans*-1,2-diol derivatives and *trans*-β-cyanohydrins from olefins, is also described. These reactions cannot be produced using other metals.

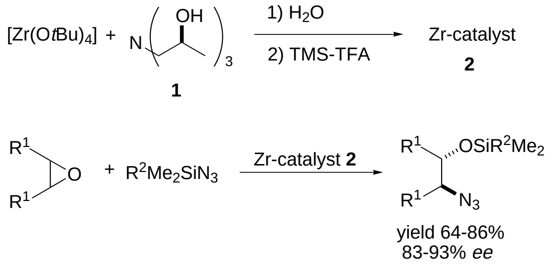
Keywords: asymmetric catalysis • Lewis acids • one-pot reaction • redox chemistry • zirconium alkoxide

Introduction

Over the past two decades, Group 4 elements have become increasingly important in organic synthesis.[1] They offer considerable advantages, such as low or no toxicity and low cost. When the discovery of hydrozirconation was reported in 1969, zirconium reagents in the form of zirconocene complexes first attracted the attention of synthetic chemists.[2] Since then many synthetically useful zirconocene-catalyzed reactions, such as enyne cyclization, carbomagnesation, and olefin polymerization, have been developed.[3] At the initial stage, however, zirconium alkoxides were not as thoroughly investigated. Zirconium alkoxides possess interesting characteristics, such as moderate Brönsted basicity,[4] Lewis acidity, high nucleophilicity of the alkyl group on zirconium (e.g., $RZr(OR')_3$), and a high ligand exchange rate.[1] Due to these diverse characteristics of zirconium alkoxides, various mechanistically different catalytic reactions have recently been realized. In the first half of the 1990s, zirconium alkoxides were applied to many reactions as alternatives to titanium alkoxides. These investigations revealed that zirconium alkoxides were superior to titanium alkoxides in some reactions, such as oxidation of benzylic, allylic, primary, and secondary alcohols,[5] the Meerwein–Ponndorf–Verley reduction[6] and other redox reactions,[7, 8] allylation of aldehydes,[8d, 9] the Diels–Alder reaction,[10] polymerization of olefins,[11] and others.[8d, 12] Recently, special properties of zirconium alkoxides led to the development of novel reactions that could not be produced by using other metals. Herein, we describe these prominent achievements with new concepts in the catalysis of zirconium alkoxide.

Discussion

Enantioselective catalysis is currently one of the most important areas in synthetic organic chemistry. Chiral modification of the zirconium catalyst **2** was reported by Nugent in the desymmetrization of *meso* epoxides in 1992.[13] The chiral zirconium catalyst was prepared from $Zr(OtBu)_4$, chiral trialkanolamine **1**, water, and trimethylsilyl trifluoroacetate, which promoted the enantioselective addition of azide to *meso* epoxides, affording the corresponding azido silyl ethers in good yield and enantioselectivity (Scheme 1). The catalyst structure was proposed to be a dimeric species based on elemental analysis, measurement of molecular weight of the catalyst, and other experimental results. Based on the catalyst structure and kinetic studies, a reaction mechanism was proposed in which zirconium activates the epoxides as a Lewis acid and the azide nucleophile through transmetallation and generation of zirconium azide (Scheme 2). Therefore, the bimetallic zirconium catalyst **3** was proposed to promote a rapid and effective catalysis of the asymmetric epoxide-opening reaction with azide. Catalytic enantioselective epox-



Scheme 1. Epoxide desymmetrization with azide.

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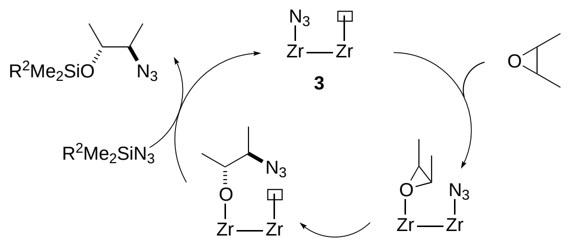
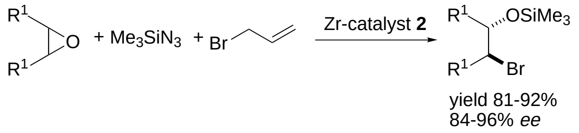


Scheme 2. Mechanism of Zr-catalyzed epoxide desymmetrization.

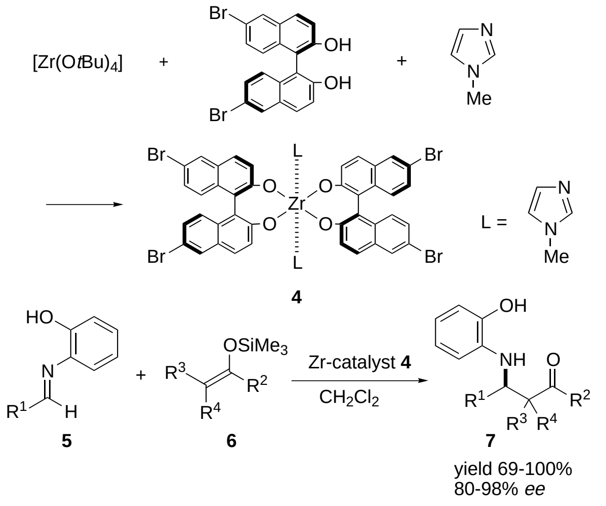
ide-opening by azide could not be accomplished by means of other metal complexes until 1995.[14]

Nugent recently applied this catalyst system to the desymmetrization of *meso* epoxides with halides, based on a mechanistic insight.[15] The use of the allyl halide and trimethylsilyl azide gave the corresponding halohydrins from epoxides in high yield and enantioselectivity (Scheme 3). The zirconium azide in **3** could be converted to the zirconium halide through the nucleophilic substitution of the azide by allyl halide.



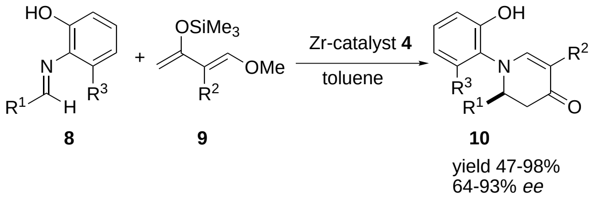
Scheme 3. Synthesis of protected β-bromohydrins by desymmetrization of *meso* epoxides with zirconium catalyst.

In 1997, a novel chiral zirconium catalyst was reported by Kobayashi for the catalytic enantioselective Mannich-type reaction.[16] The catalyst **4** was prepared from $[Zr(OtBu)_4]$, 6,6′-dibromobinaphthol (6-BrBINOL), and *N*-methylimidazole (NMI); the structure was revealed by ^1H and ^{13}C NMR spectroscopy as the C_2-symmetric complex constructed from a 1:2:2 ratio of zirconium, 6-BrBINOL, and NMI (Scheme 4). In the presence of the catalyst, treatment of aldimines **5** with ketene silyl acetals **6** afforded the corresponding adducts **7** in high yield and enantiometic excess. Deactivation of the Lewis acid catalyst by the Lewis basic product, amine **7**, or substrate, imines **5**, was not observed. In fact, before the discovery of this catalyst system, more than stoichiomeric amounts of the Lewis acids were necessary for the Mannich-type reaction because the catalysts were trapped by the nitrogen atom. In spite of the high ligand exchange rate of zirconium alkoxide, the phenolic function of the substrates **5** did not exchange with BINOL, possibly due to the p*K*a difference. Rather, it seems to prevent the decomposition by the silylation of BINOL (see below).



Scheme 4. Catalytic asymmetric Mannich-type reaction using a zirconium catalyst.

Kobayashi applied the same catalyst to the first enantioselective aza-Diels–Alder reaction of aldimines **8** and Danishefsky's diene **9** to give a wide variety of the chiral piperidine derivatives **10** (Scheme 5).[17] In this reaction, other Group 4 metals, titanium and hafnium, were investigated. The chiral hafnium catalyst produced as high yields and enantiomeric excesses as the zirconium catalyst, whereas a titanium catalyst produced a lower yield and enantiomeric excess. These results indicate that zirconium, as well as hafnium, are excellent catalysts in this reaction system. The enantioselective aza-Diels–Alder reaction was also catalyzed by the similar zirconium binaphthol complex **11** prepared from the 1:1 ratio of $[Zr(OtBu)_4]$ and 3,3′-disubstituted BINOL (Figure 1).[17b] Even by using the same absolute configuration of BINOL, the asymmetric induction in this case was opposite to that observed in the previous case.



Scheme 5. Catalytic asymmetric aza-Diels–Alder reaction using a zirconium catalyst.

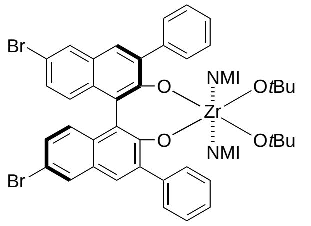


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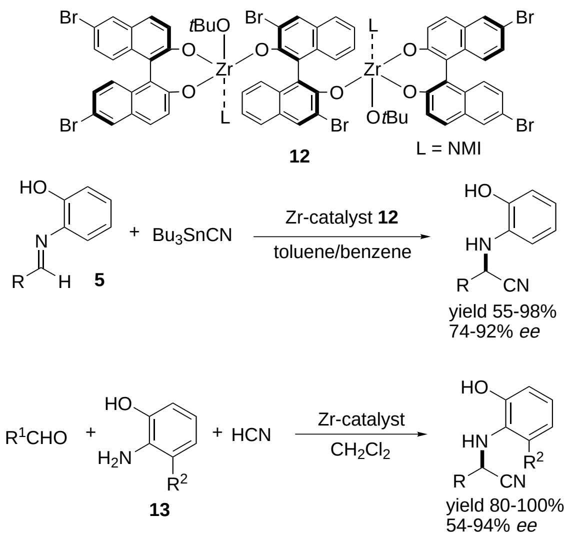
Figure 1. Another type of zirconium catalyst for asymmetric aza-Diels–Alder reaction.

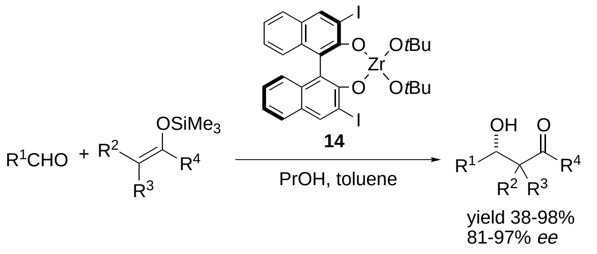
Another type of zirconium binaphthol complex catalyzes highly enantioselective Strecker reactions of aldimines **5** with broad generality.[18] This type of catalyst was prepared from $[Zr(OtBu)_4]$, (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-6-BrBINOL), (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3-Br-BINOL), and NMI. Based on NMR spectroscopic studies, the catalyst structure was proposed to be **12** (Scheme 6). This



Scheme 6. Catalytic asymmetric Strecker-type reactions using a zirconium catalyst.

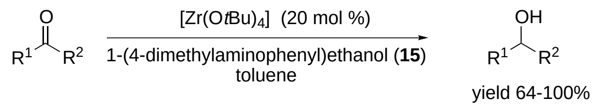
complex can also catalyze the three-component asymmetric Strecker process with aldehydes, the amine **13**, and hydrogen cyanide (HCN). As expected from the high ligand exchange rate of zirconium alkoxides, the zirconium tertiary butoxide moiety in the catalyst **12** was converted to zirconium cyanide, which was assumed to be the actual catalyst.

Recently zirconium complex **14** prepared from [Zr(O*t*Bu)$_4$] and 3,3′-iodo-1,1′-bi-2-naphthol (3-I-BINOL) catalyzed the asymmetric aldol reactions of enol silyl ethers with aldehydes (Mukaiyama aldol reaction).[16f, 19] The zirconium catalyst activates aldehydes and promotes the aldol reaction to afford the corresponding aldol products in high *anti* selectivity and enantiomeric excess in the presence of propanol (Scheme 7). Use of the protic additive (propanol) facilitates the catalyst turnover. In the absence of propanol, mono trimethylsilyl BINOL was observed, indicating decomposition of the catalyst.



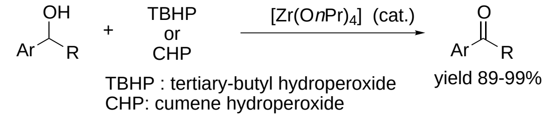
Scheme 7. Catalytic asymmetric aldol reaction using a zirconium catalyst.

The catalysis of zirconium alkoxide is not limited to the reactions catalyzed only by Lewis acids. It can be applied to other mechanistically different reactions such as redox reactions. The heterogeneous system of the Meerwein—Ponndorf–Verley reduction, promoted by hydrous zirconium oxide[20] and zirconium 2-propoxide on silica gel,[21] has been successfully applied. On the other hand, the effective homogeneous system was also reported by Krohn in 1995.[5] Under optimized conditions, 1-(4-dimethylaminophenyl)ethanol (**15**) was used as the reducing alcohol and [Zr(O*t*Bu)$_4$] as the catalyst. Aldehydes and ketones were reduced under mild conditions to the corresponding alcohols in high yield (Scheme 8). This variation of the Meerwein–Ponndorf–Verley reduction was kinetically controlled and highly stereoselective, in contrast to the conventional Meerwein–Ponndorf–Verley reduction which is thermodynamically controlled. In this case, [Zr(O*t*Bu)$_4$] can be used in a catalytic amount without a serious decrease in the reaction rate compared to [Al(O*t*Bu)$_3$], which is a representative stoichiometric promoter of the Meerwein–Ponndorf–Verley reduction. It was assumed that the high reactivity of [Zr(O*t*Bu)$_4$] was due to its monomeric structure.[22] The turnover of the zirconium catalyst might be due to a much faster exchange rate of the alkoxide ligand. Later, this reaction was extended to the catalytic asymmetric reaction, although preparatively useful enantiomeric excess was not obtained.[6c]



Scheme 8. Meerwein–Ponndorf–Verley reduction catalyzed by zirconium alkoxide.

Oxidations catalyzed by zirconium alkoxides were also developed. Zirconium alkoxides could also catalyze various types of oxidation such as Oppenauer oxidations,[7b] oxidations of amine to nitro compounds,[7c] sulfoxidations,[7d,e] and others.[7a] Among them, oxidation of alcohols to the corresponding aldehydes or ketones provides a synthetically useful method.[5, 23] Benzylic alcohols were readily oxidized to the corresponding aldehydes and ketones by using [Zr(O*n*Pr)$_4$] and hydroperoxide (Scheme 9).[5a] In this reaction, [Zr(O*n*Pr)$_4$] was far superior to [Ti(O*i*Pr)$_4$]. The electron-rich alcohol was dehydrogenated much more rapidly than the electron-deficient alcohol; this suggests a mechanism that includes hydride transfer accompanying the development of a partial positive charge on the benzylic carbon atom. Therefore, a six-membered transition state **16** was proposed (Figure 2). In the transition state, zirconium metal would have three roles: 1) coordination of the substrate alcohol and the hydride acceptor TBHP, 2) activation of O–O bond of TBHP, and 3) activation of the C–H bond of the substrate. The properties of zirconium, both as a Lewis acid and an electron donor, are required to minimize the activation energy of the hydride transfer.



TBHP : tertiary-butyl hydroperoxide
CHP: cumene hydroperoxide

Scheme 9. Oxidation of benzylic alcohol catalyzed by zirconium alkoxide.

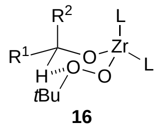


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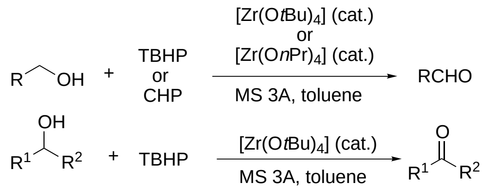
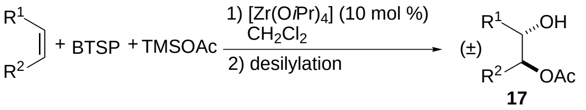
Figure 2. Proposed transition state of TBHP oxidation catalyzed by zirconium alkoxide.

Nonactivated alcohol was also dehydrogenated by using the more active [Zr(O*t*Bu)$_4$] as a catalyst, hydroperoxide as an oxidant, and molecular sieves as the dehydrating agent (Scheme 10).[5b] Secondary alcohols were dehydrogenated faster than primary alcohols. Primary allylic alcohol gave only epoxidation products similar to those obtained by the Sharpless epoxidation; however, the secondary allylic alcohol yielded the dehydrogenation product in high yield.



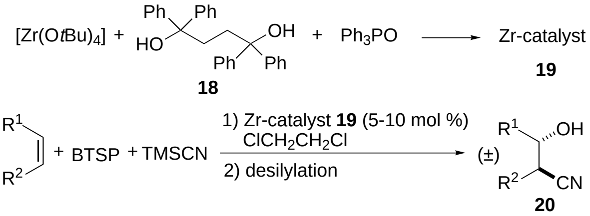
Scheme 10. Oxidation of primary and secondary alcohols catalyzed by zirconium alkoxide.

These multicharacteristics of zirconium alkoxides are artfully combined in our one-pot process of *trans*-*β*-1,2-diol synthesis and *trans*-*β*-cyanohydrin synthesis. To improve the efficiency of organic synthesis, including minimizing the energy costs and chemical waste, a tandem reaction would be a powerful tool in which some mechanistically different reactions were performed in one pot. Considering the ability of zirconium alkoxide to promote various reactions mentioned above, zirconium alkoxide should be one of the candidates that catalyze each step of the sequential reactions. Therefore, we are interested in developing zirconium-alkoxide-catalyzed tandem reactions. In 2000, we reported the one-pot synthesis of *trans*-1,2-diol derivatives directly from olefins.[24] In this reaction, various olefins were converted to the corresponding *trans*-*β*-acetoxy alcohols **17** in high yield and good selectivity in the presence of 10 mol% [Zr(O*i*Pr)$_4$] as a catalyst, bis(trimethylsilyl) peroxide (BTSP) as an oxidant, and TMSOAc as a nucleophile (Scheme 11). Epoxides were intermediates of this tandem conversion, which was confirmed by the ^{1}H NMR spectra of the reaction mixture, as well as by the fact that the epoxide reacted smoothly to give the acetoxy alcohol in the presence of the catalyst. These results suggest that zirconium alkoxide could promote both the epoxidation of olefins and the opening of the resultant epoxides. Moreover, it is noteworthy that no titanium alkoxides could catalyze this reaction.

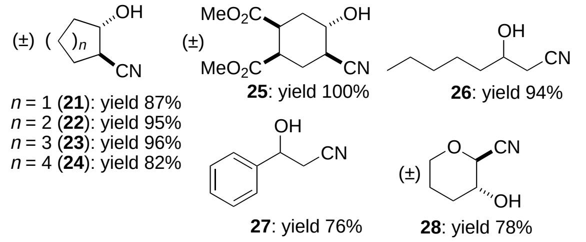


Scheme 11. Direct synthesis of *trans*-*β*-acetoxy alcohols from olefins catalyzed by a zirconium catalyst.

We planned to extend this chemistry to a more valuable carbon–carbon bond-forming reaction, using TMSCN as the nucleophile.[25] In contrast to the acetoxy alcohol synthesis, the *β*-cyanohydrin formation was sluggish. The addition of the bulky diol ligand to the zirconium and the use of triphenylphosphine oxide significantly facilitated the reaction to a synthetically useful range. A variety of olefins were converted to the corresponding *trans*-*β*-cyanohydrins **20** in one pot in the presence of the catalyst **19** prepared from [Zr(O*t*Bu)$_4$], 1,1,4,4-tetraphenyl-1,4-butanediol **18**, and Ph$_3$PO, BTSP as an oxidant, and TMSCN as a nucleophile (Scheme 12). The reaction proceeded in high yield and selectivity. Some selected examples are listed in Scheme 13. A much less reactive cyclooctene was converted to the cyanohydrin **24** in good yield. Cyclohexene bearing the ester substituents gave the single isomer **25** in quantitative yield, and terminal olefins gave the secondary alcohols **26** and **27** as the sole regioisomer. In the absence of Ph$_3$PO, however, the styrene was converted to the primary alcohol as the main product, indicating the importance of Ph$_3$PO for the regiochemical course as well. These results suggested that the epoxidation occurs favorably on the sterically less crowded side and the cyanide attacks mainly at the less hindered carbon in the presence of Ph$_3$PO.



Scheme 12. Direct synthesis of *trans*-*β*-cyanohydrins from olefins catalyzed by zirconium alkoxide.



Scheme 13. Selected examples of one-pot syntheses of *β* cyanohydrins from olefins catalyzed by a zirconium catalyst.

This reaction also proceeded via the epoxide intermediate, and the catalyst promoted both the epoxidation of olefin and the epoxide-opening reaction. Interestingly, TMSCN was necessary for generating the catalytic species to promote the epoxidation step, indicating that the real active species has a Zr-CN moiety. Finally, the kinetic studies demonstrated that the reaction rate of the epoxidation step had a first-order dependency on the catalyst concentration and the rate of the epoxide-opening step had a second-order dependency. The results of the kinetic studies indicated that the catalyst(s) should change the mode of action in one pot, promoting the epoxidation step in the single metal-centered mechanism and the epoxide-opening step in the bimetallic mechanism. These results, together with those of previous studies of titanium-catalyzed epoxidation, ytterbium-catalyzed epoxide-opening reaction with cyanide, zirconium-catalyzed epoxide-opening reaction with azide, and the other zirconium-alkoxide-catalyzed reactions mentioned above, led us to propose a working model for this novel reaction (Scheme 14). This reaction

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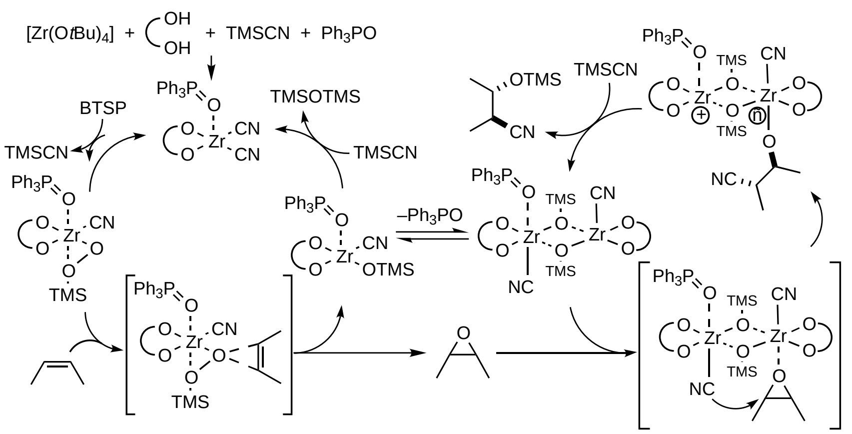
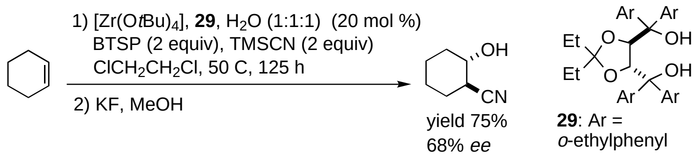


Scheme 14. Working model for the zirconium-catalyzed one-pot synthesis of β-cyanohydrins from olefins.

mechanism is consistent with the reaction rate dependency on the catalyst observed in the kinetic studies. Therefore, the zirconium catalyst works as an oxidant, a Lewis acid, and a nucleophile. These multiple actions of the zirconium catalyst are key for the success of this one-pot process. This synthetically useful reaction was applied to the catalytic asymmetric reaction with the TADDOL derivative **29** as the chiral ligand (Scheme 15). Although further improvement of enantioselectivity is necessary, this result demonstrated the possibility of the catalytic asymmetric process of this reaction. We are currently attempting an efficient catalytic asymmetric synthesis of biologically active compounds.



Scheme 15. Catalytic asymmetric one-pot synthesis of β-cyanohydrins from olefins catalyzed by a chiral zirconium catalyst.

Future Outlook

Zirconium alkoxide has multiple functions and can catalyze the many mechanistically different reactions as mentioned above. These multiple functions lead to the possibility of a new catalytic enantioselective one-pot synthesis of β-cyanohydrins. The use of these characteristic properties of zirconium alkoxides should realize many other environmentally benign catalytic enantioselective syntheses of target compounds; this is one of the major goals of synthetic organic chemistry. We hope that this new concept of the tandem reactions will facilitate the design of new catalysts and general methodology for novel reactions.

Acknowledgements

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