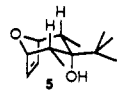
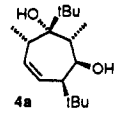
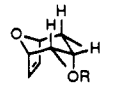
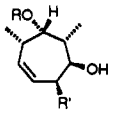
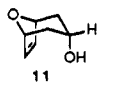
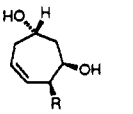
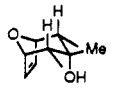
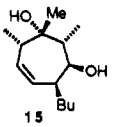
Table I. Organolithium Opening of Oxabicyclo[3.2.1]octenes

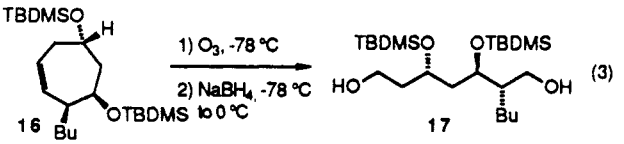
entry	oxabicyclo[3.2.1]-octenes	product	yield,[a] %
1			85
			
2	(a) **6**, R = H (b) **6**; R = H (c) **9**; R = TBDMS	**7**, R = H, R′ = Bu **8**; R = H, R′ = Me **10**; R = TBDMS, R′ = Bu	92 72[b] 79
			
3	(a) (b)	**12**; R = *t*-Bu **13**; R = *n*-Bu	82 88
4			74

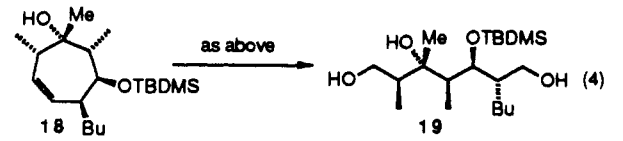
[a] Isolated yields of analytically pure material. [b] 1:1 ether/TMEDA were required as solvent before reaction occurred.

give ring-opened products.[12d]

Several examples are shown in Table I that demonstrate the utility of this reaction. Tertiary and primary lithium reagents react with equal facility with several of the substrates, implying that there is little or no steric effect associated with the opening. Methyllithium failed to react with several of the substrates under similar conditions. However, upon adding TMEDA, ring opening occurred smoothly. The basicity or electron-transfer ability of the starting lithium reagent vs the product derived from addition of RLi across the olefin may be very important in explaining the lack of reactivity of the less basic methyllithium in the absence of TMEDA. Carbonyl addition does precede ring opening as shown by treating the ketone at low temperature (−78 to 0 °C) with 1 equiv of *t*-BuLi to give the tertiary alcohol **5**. Treatment of **5** under the standard conditions (3 equiv of RLi, 1:1 ether/pentane, 0 °C) provided **4a** in very good yield. Reduction of the carbonyl group in compounds **3** and **1** was effected by using L-Selectride,[13] which gave the axial alcohols **6** and **11** to avoid the double addition process. Each of these compounds underwent facile opening with an organolithium to provide **7**, **8**, **12**, and **13**. Protection of the alcohol in **6** as its silyl ether followed by opening gave **10** in which the two secondary alcohols have been differentiated. We also took advantage of the higher reactivity of the carbonyl group vs the bicyclic opening for the addition of two different "R" groups. Methyllithium reacted with ketone **3** to provide tertiary alcohol **14**. When **14** was treated with 3 equiv of *n*-BuLi at 0 °C in ether we isolated diol **15**. Compounds **12** and **13** contain a 1,2,4 stereochemical array while **4a,b**, **7**, **8**, **10**, and **15** contain five contiguous stereocenters. *Thus, in two (or three) steps, furan is converted into a cycloheptene with control at three to five stereocenters.*

We have subjected two of the protected cycloheptenes to ozonolysis and reduction to show the utility of this methodology for the synthesis of acyclic chains bearing multiple stereocenters.[2] Treatment of **16** and **18**[14] with ozone followed by treatment of the ozonide with sodium borohydride furnished diols **17** and **19** in 92 and 78% yields, respectively, eqs 3 and 4. The use of the oxabicyclic framework to control the stereochemistry of the tertiary alcohol in the eventual acyclic chain is noteworthy.





These results demonstrate the viability of a strategy based on the double ring opening of oxabicyclic compounds for rapid entry into polysubstituted 1,7-hexanediol fragments. Studies are in progress on the application of this sequence to the synthesis of natural products.

Acknowledgment. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, the Bickell Foundation, and BioMega Inc.

Supplementary Material Available: Preparation and spectral data for all new compounds including X-ray parameters for compound **4a** (20 pages); observed and calculated structure factors for **4a** (6 pages). Ordering information is given on any current masthead page.

(13) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(14) Compounds **15** and **16** were prepared by silylation of the secondary alcohols using TBDMSCl, imidazole, DMF; see: Corey, E. J.; Venkateswarlu, Y. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Zr(O-*t*-Bu)$_4$, an Efficient and Convenient Basic Reagent in Organic Synthesis. Utilization in Cross and Intramolecular Aldol Reactions

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Received July 11, 1990

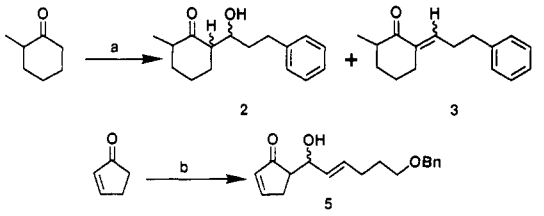
Summary: Zr(O-*t*-Bu)$_4$ has been found to be a mild basic reagent that can be utilized in cross aldol reactions and intramolecular aldol reactions, in which the use of usual metal enolates such as Li enolate and Cp_2ZrCl enolate give unsatisfactory results (2-cyclopentenone → **5**, **7** → **8**, and **13** → **14**).

Among the amphoteric group 4 metal alkoxides, zirconium and hafnium alkoxides exhibit basic rather than acidic character. However, in general, their basicity has been regarded as too weak for use in organic synthesis. Indeed, in spite of a few facile uses of $Zr(O\text{-}n\text{-}Pr)_4$ in intramolecular Michael reactions,[1] additional applications have not been made to date. The limitation in employing $Zr(O\text{-}n\text{-}Pr)_4$ as a basic reagent appears to result from its tendency to form a stable trimer in which the coordination number of the zirconium atom is six.[2] Furthermore, zirconium alkoxides, which consist of secondary and normal alkoxy groups, tend to cause Meerwein–Ponndorf–Verley type reductions.[3] We thought that these disadvantages would be overcome by the use of $Zr(O\text{-}t\text{-}Bu)_4$[4] instead of $Zr(O\text{-}n\text{-}Pr)_4$. On account of its steric bulk, $Zr(O\text{-}t\text{-}Bu)_4$ exists as a tetrahedral monomer,[5] and it was expected that treatment of $Zr(O\text{-}t\text{-}Bu)_4$ with a carbonyl compound would result in the facile formation of a zirconium enolate and *tert*-butyl alcohol. Moreover, since the pKa value of *tert*-butyl alcohol (ca. 19) is somewhat greater than that of 1-propanol (ca. 18), $Zr(O\text{-}t\text{-}Bu)_4$ should be more basic than $Zr(O\text{-}n\text{-}Pr)_4$. In addition, the absence of a transferable hydride prevents the occurrence of a MPV reduction. We report herein the first successful application of $Zr(O\text{-}t\text{-}Bu)_4$ as a basic reagent which can generate zirconium enolates directly.

We began by examining the cross aldol reactions shown in Scheme I, in order to investigate the basicity of $Zr(O\text{-}t\text{-}Bu)_4$. That is, treatment of 2-methylcyclohexanone (2.0 mmol) with 1.3 molar equiv of $Zr(O\text{-}t\text{-}Bu)_4$ in THF at −30 °C for 30 min, followed by stirring for 1 h with 3-phenylpropanal (**1**) (1.0 mmol), gave a mixture of the kinetically favorable cross aldol adducts **2** in 77% yield (based on **1**) and a trace of the enone **3**.[6] Furthermore, treatment of 2-cyclopentenone (0.44 mmol) with 1.5 molar equiv of $Zr(O\text{-}t\text{-}Bu)_4$ in THF at −40 °C for 30 min followed by stirring for 15 min with (*E*)-6-(benzyloxy)-2-hexen-1-al (**4**)[7] (0.29 mmol) afforded the cross aldol adduct **5** in 64% yield (100% based on recovered **4**). Under these conditions, in contrast to the LDA assisted reaction (52% yield, 60% based on recovered **4**), neither self-condensation products nor Michael products were obtained.[8] Moreover, under the same reaction conditions we found that esters, epoxides and alkyl halides were inert to $Zr(O\text{-}t\text{-}Bu)_4$. From these results, $Zr(O\text{-}t\text{-}Bu)_4$ proved to be an accessible, mild, basic reagent which generates zirconium enolates with high regio- and chemoselectivity (Scheme I). When 2-cyclopentenone and **1** were treated with $Zr(O\text{-}n\text{-}Pr)_4$ at −30 °C, no reaction was observed even after 2 days.

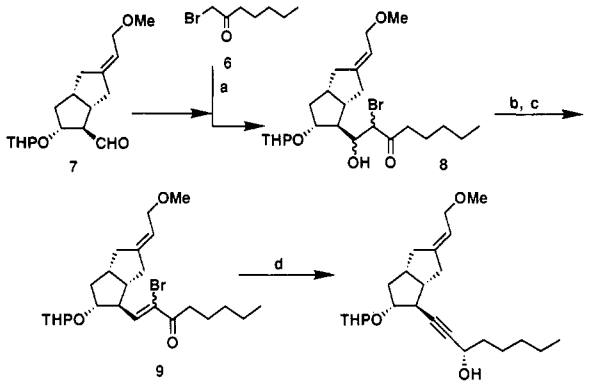
Next we focused our attention on reactions in which lithium and other metal enolates gave unsatisfactory results.[9] The introduction of a carbon–carbon triple bond at the C-13 position in prostacyclin derivatives is an important way to enhance their biological activity and metabolic stability.[10] The hitherto known synthetic methods starting with aldehydes involve dehydrobromination of the intermediate α-bromo enones.[11] We planned to examine the production of α-bromo enones by the $Zr(O\text{-}t\text{-}Bu)_4$-assisted cross aldol reaction. Treatment of the α-bromo ketone **6**[12] (0.25 mmol) with $Zr(O\text{-}t\text{-}Bu)_4$ (0.25 mmol) in THF (−30 °C, 0.5 h), followed by the addition of the aldehyde **7**[11] (0.1 mmol) (−30 °C, 20 min), afforded a mixture of the α-bromo β-hydroxy ketones **8**, which was converted to the α-bromo enone **9** in 56% overall yield from **7** (Scheme II). Contrary to this result, attempts to

Scheme I[a]



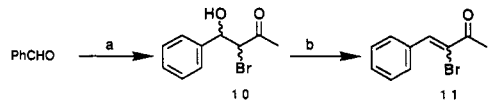
[a] (a) $Zr(O\text{-}t\text{-}Bu)_4$ (1.3 molar equiv), THF, −30 °C, 30 min then 3-phenylpropanal (**1**), −30 °C, 1 h; (b) $Zr(O\text{-}t\text{-}Bu)_4$ (1.5 molar equiv), THF, −40 °C, 30 min then (*E*)-6-(benzyloxy)-2-hexen-1-al (**4**), −40 °C, 15 min.

Scheme II[a]



[a] (a) $Zr(O\text{-}t\text{-}Bu)_4$ (2.5 molar equiv), THF, −30 °C, 30 min then **7**, −30 °C, 20 min; (b) MsCl, Et_3N, CH_2Cl_2, −40 °C; (c) DBU, 0 °C, 12 h; (d) ref 11.

Scheme III[a]



[a] (a) $Zr(O\text{-}t\text{-}Bu)_4$ (1.2 molar equiv to bromoacetone), THF, −30 °C, then bromoacetone, −30 °C, 12 h; (b) MsCl, Et_3N, CH_2Cl_2, −78 °C to −30 °C.

(1) (a) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. (b) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767. (c) Attah-Poku, S. K.; Yadav, F. C. V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418.

(2) Bradley, D. C.; Mehrotra, R. C.; Wardlaw, W. *J. Chem. Soc.* **1952**, 2027.

(3) Seebach, D.; Weidmann, B.; Widler, L. *Modern Synthetic Methods*; John Wiley & Sons: New York, 1983; pp 298–303.

(4) (a) Bradley, D. C.; Wardlaw, W. *J. Chem. Soc.* **1951**, 280. (b) Mehrotra, R. C. *J. Am. Chem. Soc.* **1954**, *76*, 2266.

(5) Bradley, D. C.; Mehrotra, R. C.; Wardlaw, W. *J. Chem. Soc.* **1952**, 4204.

(6) In the case of cyclopentanone, none of the cross aldol products was formed, only the dimerization products of cyclopentanone.

(7) The aldehyde **4** was prepared from known (*E*)-6-(benzyloxy)-2-hexen-1-ol by PCC oxidation: Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

(8) The LDA–Cp_2ZrCl_2 assisted reaction afforded a trace of **5**.

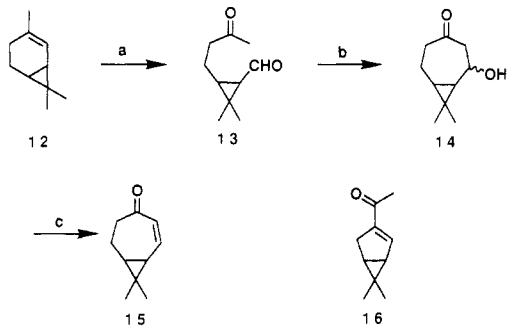
(9) We have already found an interesting result other than carbon–carbon bond forming reactions. Namely, treatment of **i** with 3 molar equiv of $Zr(O\text{-}t\text{-}Bu)_4$ in toluene (−78 °C, 0.5 h) followed by the addition of benzeneselenenyl bromide (1.5 equiv) (−78 °C, 0.4 h) afforded **ii** in 55% yield (72% based on recovered **i**). On the other hand, the LDA-assisted reaction and the LDA–Cp_2ZrCl_2-assisted reaction gave **ii** in 50% (ca. 50% based on recovered **i**) and 80% (80% based on recovered **i**) yields, respectively. Sasai, H.; Ohne, K.; Shibasaki, M. unpublished results.

(10) Skuballa, W.; Schillinger, E.; Sturzebecher, C.-St.; Vorbrüggen, H. *J. Med. Chem.* **1986**, *29*, 313.

(11) Takahashi, A.; Shibasaki, M. *J. Org. Chem.* **1988**, *53*, 1227.

(12) Cardwell, H. M. E.; Kilner, A. E. H. *J. Chem. Soc.* **1951**, 2430.

Scheme IV[a]



[a] (a) Reference 17; (b) $Zr(O\text{-}t\text{-}Bu)_4$ (2.0 molar equiv), THF, -30 °C to room temperature, 6 h; (c) AcONa, Ac_2O, AcOH, 90 °C, 4 h.

construct the α-bromo enone **9** from the α-bromo ketone **6** and the aldehyde **7** using LDA, $Sn(OTf)_2$[13] or *n*-Bu_2BOTf[14] were unsatisfactory.[15] Thus, we have accomplished a cross aldol reaction using the α-bromo ketone **6** for the first time. Furthermore, the α-bromo enone **11** was also obtained, from bromoacetone. That is, treatment of a mixture of benzaldehyde (2.0 mmol) and $Zr(O\text{-}t\text{-}Bu)_4$ (1.2 mmol) in THF (-30 °C) with bromoacetone (1.0 mmol) gave a mixture of the α-bromo β-hydroxy ketones **10**,[15,16] which was transformed to **11** in 56% overall yield from bromoacetone (Scheme III).

A further excellent example that shows the utility of $Zr(O\text{-}t\text{-}Bu)_4$ is a synthesis of (-)-8,8-dimethylbicyclo[5.1.0]oct-2-en-4-one (**15**),[17] which is a useful intermediate for many natural products syntheses.[18] The enone **15** has previously been synthesized from (-)-2-carene (**12**) by the Mukaiyama reaction in order to avoid the formation of the thermodynamically favorable five-membered-ring product **16**.[17] We found that **15**[19] could be readily prepared from **13**[17] via the intramolecular aldol adduct **14**, which was produced in 78% yield by treatment of **13** with 2 molar equiv of $Zr(O\text{-}t\text{-}Bu)_4$ in THF.[20] Dehydration of **14** was carried out using NaOAc and Ac_2O in AcOH at 90 °C to give the desired enone **15** in 79% yield. Other metal enolates (Li, Cp_2ZrCl,[21] $ZnCl$[22]) generated by LDA or metal exchange from the corresponding lithium enolate gave **14** in less than 10% yield together with a mixture of the intermolecular aldol products and the starting material **13**. Another approach using $Sn(OTf)_2$[13] and *n*-Bu_2BOTf[14] gave **14** in trace and 13% yields, respectively (Scheme IV). The facile formation of **14** is attributed to the following features. Owing to the bulkiness of both the tri-*tert*-butoxyzirconium cation and the counter *tert*-butoxy anion, the sterically favorable kinetic enolate should be generated. Also the aldol reaction appears to proceed via an acyclic transition state, thus avoiding the retro-aldol reaction.

In conclusion, we have succeeded in demonstrating the mild basic nature of $Zr(O\text{-}t\text{-}Bu)_4$ and its utility in organic synthesis. We expect $Zr(O\text{-}t\text{-}Bu)_4$ will serve as a new reagent for the synthesis of complex molecules. Utilization of its basicity in other types of reactions and the introduction of chirality to zirconium alkoxides are now in progress.

Acknowledgment. This study was financially supported by Grant-in-Aid for Scientific Research on Priority Areas (Multiplex Organic Systems) from the Ministry of Education, Science and Culture, Japan.

Supplementary Material Available: Experimental procedures and spectral data for **9**, **14**, and **15** (3 pages). Ordering information is given on any current masthead page.

(13) (a) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. (b) Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595.

(14) (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. See also ref 13b and the references cited therein.

(15) The LDA-Cp_2ZrCl_2-assisted reaction afforded none of the desired products.

(16) The $Sn(OTf)_2$-mediated reaction also afforded **10**, which was converted into the α,β-epoxy ketone derivative in 72% overall yield. Mukaiyama, T.; Haga, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1601.

(17) Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B., III *J. Org. Chem.* **1982**, *47*, 3960.

(18) (a) Smith, A. B., III; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Am. Chem. Soc.* **1986**, *108*, 3040. (b) Smith, A. B., III; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Org. Chem.* **1985**, *50*, 3239. (c) Taylor, M. D.; Smith, A. B., III *Tetrahedron Lett.* **1983**, *24*, 1867.

(19) For convenience, commercially available (+)-2-carene was used.

(20) A coordinating solvent like THF is essential. When this reaction was carried out in dichloromethane, toluene, or hexane, a complex mixture was produced.

(21) (a) Panek, J. S.; Bula, O. A. *Tetrahedron Lett.* **1988**, *29*, 1661. (b) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876. (c) *Tetrahedron Lett.* **1980**, *21*, 3975.

(22) (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. See also ref 13b.

N-(Silylmethyl)-Substituted Ketene *N,S*-Acetals as a Synthetic Equivalent of Novel 1,3-Dipolar Reagent, Alkylideneazomethine Ylids: Synthesis and [3 + 2] Cycloadditions[1]

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Received June 8, 1990

Summary: A variety of *N*-(silylmethyl)-substituted ketene *N,S*-acetals, readily prepared by the reaction of ketene dithioacetals with ((trimethylsilyl)methyl)amine, followed by N-alkylation, react smoothly with activated alkenes, carbonyl compounds, and thioketones, to afford α-alkylidenepyrrolidines, oxazolidines, and thiazolidines, via a 1,3-elimination of (methylthio)trimethylsilane. These reagents are synthetic equivalents of alkylideneazomethine ylids.

Azomethine ylids and related 1,3-dipolar reagents are important and interesting chemical species from both synthetic and theoretical points of view. These species are generally unstable and inaccessible if the dipolar centers are not stabilized by electron-withdrawing or conjugating groups.[2] Previously we reported a new method for pre-

† Nagasaki University.

(1) Studies on organosilicon chemistry. 107.

(2) (a) Kellogg, R. M. *Tetrahedron* **1976**, *32*, 2165. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (c) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vols. 1 and 2.

0022-3263/90/1955-5308$02.50/0