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Regio- and Stereospecific Formation of Protected Allylic Alcohols via Zirconium-Mediated S_N2' Substitution of Allylic Chlorides

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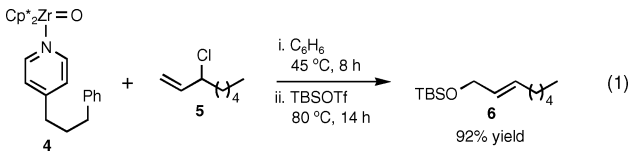
The metal-heteroatom multiple-bonded complexes Cp^*_2(pyr)-Ti═S (**1**, $Cp^* = \eta^5$-C_5Me_5) and Cp_2(THF)Zr═NTBS (**2**, TBS = *tert*-butyldimethylsilyl) react with *E*- and *Z*- allylic chlorides and trimethylsilyl allyl ethers, respectively, to selectively furnish S_N2' substitution products.[1] Monomeric group IV oxometal complexes are rare compared with their sulfur and nitrogen analogues, and as a result their reactions with organic substrates remain much less studied.[2] The availability of effective synthetic access to Cp^*_2(L)-Zr═O (where L = pyridine derivative) provides an opportunity to rectify this situation.[3] In this communication, we report the reactions of oxozirconium complexes with allylic substrates that exhibit regiochemical behavior substantially different from that seen with the M═NR and M═S systems.[1] However, under proper conditions, regio- and stereospecific S_N2' conversion of allylic chlorides into TBS-protected allylic alcohols can be achieved.

Experiments between oxo complex Cp^*_2(4-*tert*-butyl-pyridine)-Zr═O (**3**), previously reported by Parkin and co-workers,[3] and a variety of allylic functionality revealed that, unlike the systems involving **1** and **2**, the regioselectivity of substitution was dramatically affected by the olefin geometry, leaving group and solvent. For example, reaction of **3** with *E*- and *Z*-1-bromo-2-hexene in benzene led to a 2:1 and 1:2 mixture of S_N2'/S_N2 zirconium alkoxide products, respectively, while substitution with *E*-1-iodo-2-hexene proceeded with complete S_N2 selectivity. In contrast to our observations with **2**, allylic ethers were unreactive. Furthermore, changing the solvent from benzene to methylene chloride in the reaction between **3** and *E*-1-bromo-2-hexene led to complete S_N2 substitution.

To eliminate the possibility of complications resulting from heterogeneity (compound **3** was not completely soluble in the solvents tested in the above experiments), we prepared zirconium oxo complex **4**, possessing substantially improved solubility, and examined its reaction with allylic chlorides. We discovered that reaction of 3-chloro-1-octene (**5**) with **4** proceeded under mild and homogeneous reaction conditions with complete S_N2' regioselectivity, and that the initially formed zirconium alkoxide could be efficiently trapped with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) to furnish TBS ether **6** as a single *E*-isomer in 92% yield in a single flask (eq 1).[4]

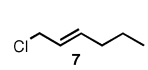
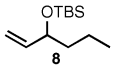
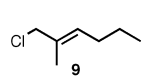
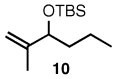
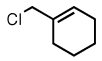
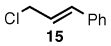
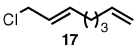
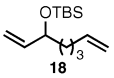
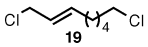
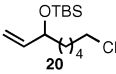
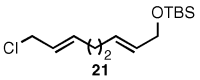
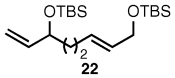
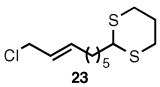
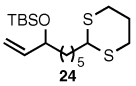
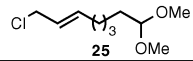
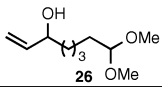


(1)

Since S_N2' derived product **6** would have been expected to be favored over direct S_N2 substitution based on steric effects, we next investigated the reaction of **4** with a variety of primary allylic chloride substrates to determine the scope of the S_N2' regioselectivity. Reaction of **4** with *E*-1-chloro-2-hexene (**7**), followed by addition of TBSOTf, furnished S_N2' derived TBS ether **8** as the sole product in 70% isolated yield (Table 1, entry 1). As we observed in our preliminary experiments with **3**, reaction of the corresponding *Z*-isomer (i.e., *Z*-1-chloro-2-hexene) with **4** led to a 3.6:1 mixture of S_N2'/S_N2 zirconium alkoxide products. However, variously substituted aliphatic (entries 2−4) and aromatic (entry 5) *E*-allylic chlorides reacted with **4**, followed by TBSOTf, to afford the S_N2' products exclusively.

In addition to exhibiting complete S_N2' regioselectivity with *E*-allylic chlorides, the substitution reaction employing **4** also demonstrated excellent functional group tolerance. For example, substitution could be effectively executed in the presence of terminal

Table 1. S_N2' Substitution of (*E*)-Allylic Chlorides with **4**

Entry	Substrate	Conditions[a]	Product	Yield
1	 **7**	A	 **8**	70%
2	 **9**	B	 **10**	87%
3	 **11**	C	 **12**	92%
4	 **13**	C	 **14**	59%
5	 **15**	D	 **16**	76%
6	 **17**	A	 **18**	86%
7	 **19**	A	 **20**	88%
8	 **21**	A	 **22**	89%
9	 **23**	A	 **24**	84%
10	 **25**	E	 **26**	77%

[a] Conditions: All reactions run in C_6H_6 at 0.036 M with 1.3 equiv of **4**, unless otherwise noted; (A) (i) 45 °C, 6 h, (ii) 2.0 equiv of TBSOTf, 80 °C, 24 h; (B) (i) 75 °C, 3 h, (ii) 4.0 equiv of TBSOTf, 105 °C, 14 h; (C) (i) 75 °C, 3 h, 0.014 M, (ii) 4.3 equiv of TBSOTf, 105 °C, 14 h; (D) (i) 45 °C, 8 h, (ii) 2.0 equiv of TBSOTf, 105 °C, 14 h; (E) (i) 45 °C, 6 h, (ii) 2.0 equiv of 4-(trifluoromethyl)phenol, rt, 30 min.

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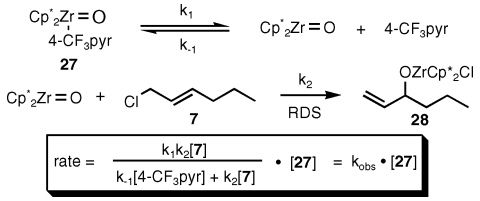
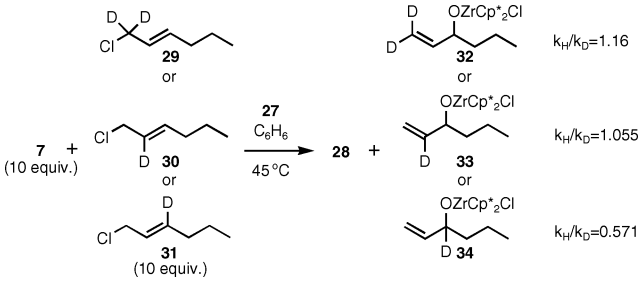
Scheme 1. Proposed Mechanism for Substitution



Scheme 2. Secondary Kinetic Isotope Effect Studies



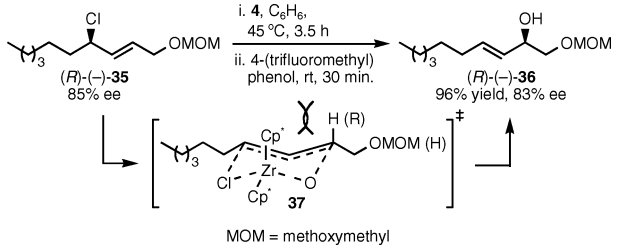
alkene, alkyl chloride, allylic TBS ether, dithiane, and dimethyl acetal functionality (Table 1, entries 6−10).[5]

Motivated to further understand the elementary steps associated with the S_N2' reaction, we next initiated a kinetic study by monitoring the homogeneous reaction of oxo complex **27** with **7** by ^{1}H NMR spectroscopy.[6] In the presence of excess 4-trifluoromethylpyridine (4-CF_3pyr) and **7**, the substitution exhibited pseudo-first-order kinetics with no observable intermediates, indicating the overall reaction is first-order in **27**.[7] In addition, the first-order rate constant for the reaction ($k_{obs} = (1.4 \pm 0.1) \times 10^{-3}$ s^{-1} at 27 °C) was found to be independent of the initial concentration of **27**, while the k_{obs} values obtained in the presence of **7** and various concentrations of 4-CF_3pyr established that the overall reaction is inverse first-order in [4-CF_3pyr].[6] Based on these data, and in analogy to complexes **1** and **2**,[1] we propose that the S_N2' reaction is initiated by rapid and reversible dissociation of the pyridine ligand, followed by rate-limiting C−O bond formation (Scheme 1). Consistent with the rate law predicted by this mechanism, we observed that the substitution reaction exhibited saturation kinetics at high concentrations of **7**.[6] By measuring k_{obs} at different [4-CF_3pyr]/[**7**] ratios, we were able to extract values for $k_1 = (8.40 \pm 0.01) \times 10^{-4}$ (s^{-1}) and $k_{-1}/k_2 = 3.1 \pm 0.1$ at 10 °C.[6]

To provide support for rate-limiting C−O bond formation we also conducted competition experiments between *E*-1-chloro-2-hexene (**7**) and deuterated analogues **29**, **30**, and **31** (Scheme 2). As expected based on hybridization changes,[8] we observed the averaged secondary isotope effects (k_H/k_D) of 1.16, 1.055, and 0.571, respectively, shown in Scheme 2.[6]

Following our kinetic studies, we sought to determine the stereochemical outcome of the S_N2' reaction for a chiral allylic chloride. We subjected allylic chloride (−)-**35** to reaction with **4**, followed by quenching with 4-(trifluoromethyl)phenol, to furnish allylic alcohol (−)-**36** in 96% yield (Scheme 3). Importantly, the substitution proceeded with essentially complete *syn* selectivity.[9] Based on this stereochemical outcome, we propose transition state **37** for C−O bond formation. Cyclic transition states such as **37** have previously been postulated to rationalize *syn* stereochemistry in allylic substitutions,[1,10] as well as for the formation of Cp_2*Zr(I)(OH) via reaction of Cp_2*(pyr)Zr=O with *tert*-butyl iodide.[3c] In

Scheme 3. Substitution of (*R*)-(−)-**35** with **4**



MOM = methoxymethyl

addition, the unfavorable steric interaction depicted between one of the Cp* ligands and axial substituent of a *Z*-allylic chloride (see (R) in **37**) is consistent with our observation that reaction of *Z*-1-chloro-2-hexene with **4** was less regioselective than that of the corresponding *E*-isomer.

In conclusion, we have discovered a new mode of reactivity for zirconium oxo complexes that results in the regio- and stereospecific S_N2' substitution of *E*-allylic chlorides. We have also found that the oxo complexes exhibit excellent substrate scope and functional group compatibility, and that the initially formed zirconium alkoxides could be efficiently trapped with TBSOTf to furnish TBS protected allylic ethers in a single flask. Finally, we have carried out detailed kinetic, isotope labeling and stereochemical experiments that allow us to propose a mechanism for the overall reaction, involving a concerted "closed" transition state for rate-determining C−O bond formation. These results provide insight into the reactivity of zirconium oxo complexes and may aid in the development of alternative transition metal-mediated S_N2' reactions.

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Supporting Information Available: Experimental procedures and spectral data for products (PDF). This material is available free of charge via the Internet at http://pubs/acs/org.

References

(1) (a) Sweeney, Z. K.; Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 7825. (b) Lalic, G.; Blum, S. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 16790.

(2) For the in situ formation and trapping of Cp*$_2$Zr=O and Cp*$_2$Zr=S, see: (a) Carney, M. J.; Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8751. (b) Carney, M. J.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6426. (c) Carney, M. J.; Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *Organometallics* **1992**, *11*, 761.

(3) (a) Howard, W. A.; Waters, M.; Parkin, G. *J. Am. Chem. Soc.* **1993**, *115*, 4917. (b) Howard, W. A.; Parkin, G. *J. Am. Chem. Soc.* **1994**, *116*, 606. (c) Howard, W. A.; Trnka, T. M.; Waters, M.; Parkin, G. *J. Organomet. Chem.* **1997**, *528*, 95. For reactions involving the corresponding titanium analogue, see: (d) Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 5393.

(4) Both **3** and **4** furnished similar S_N2'/S_N2 ratios with all substrates, demonstrating that the S_N2' selectivity for allylic chlorides was not the result of the pyridine substituent or homogenicity.

(5) 4-(Trifluoromethyl)phenol was substituted for TBSOTf in entry 10 due to incompatibility of TBSOTf with the dimethyl acetal moiety.

(6) For details of kinetics and kinetic isotope effect experiments, see the Supporting Information.

(7) **4** was replaced with **27** for the kinetic studies since minor amounts of S_N2 substitution were detected when the reaction between **4** and **7** was run in the presence of excess 4-(3-phenylpropyl)pyridine and **7**. The increased electron-withdrawing nature of 4-(trifluoromethyl)pyridine presumably enhances the rate of ligand dissociation.

(8) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry;* University Science Books: Sausalito, CA, 2006; Chapter 8.

(9) The absolute stereochemistry of (−)-**36** was verified by Kakisawa−Mosher ester analysis. See the Supporting Information for details.

(10) Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813.

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