

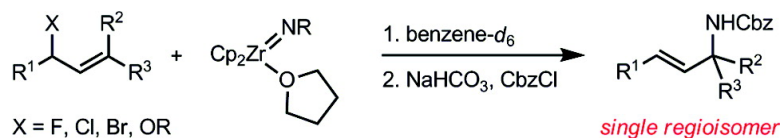
Article

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Scope and Mechanism of Formal S_N2' Substitution Reactions of a Monomeric Imidozirconium Complex with Allylic Electrophiles

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Abstract: The zirconium imido complex Cp₂(THF)Zr=NSi(*t*-Bu)Me₂ (**1**) reacts with allylic ethers, chlorides, and bromides to give exclusively the products of the S_N2' reaction; i.e., attack at the allylic position remote from the leaving group with migration of the double bond. The primary amine products can be isolated in excellent yields, after in situ Cbz protection, in the presence of variety of functional groups. Good diastereoselectivity and complete stereoselectivity allowed the formation of enantioenriched allylic amines from enantioenriched allylic ethers. Regiospecific substitution with **1** has also been achieved with allylic fluorides, which are notoriously poor substrates in other substitution reactions. On the basis of rate and kinetic isotope effect studies, we propose a general mechanism for the allylic substitution reactions with **1** which involves dissociation of THF and binding of the substrate, followed by the substitution step. In a DFT study of the substitution reaction, we identified a six-membered closed transition state for the substitution step and other relevant stationary points along the reaction coordinate. This study shows that the substitution reaction can be described as a concerted asynchronous [3,3]-sigmatropic rearrangement. This detailed knowledge of the reaction mechanism provides a rationale for the origins of the observed regio-, diastereo-, and stereoselectivity and of the unusual reactivity profile observed in the reaction.

Introduction

In the past 20 years, metal-promoted S_N2' reactions with carbon nucleophiles have become valuable tools in organic synthesis.¹ Several protocols for stoichiometric² and catalytic³ copper-mediated allylic substitutions with carbon nucleophiles have been developed that allow complete control over the regio- and stereoselectivity of these reactions. In comparison, general S_N2' substitution reactions with heteroatom nucleophiles are less well-known.

Isolated examples of S_N2' reactions of allylic halides and esters with amines, alkoxides, and thiols have been known for some time.⁴ However, selective formation of the rearranged (S_N2') products has been achieved only when the competing S_N2 reaction is sterically disfavored.^{5,6} More recently, attempts were made to develop metal-catalyzed substitution reactions. In the presence of a number of transition metal complexes, regioconvergent substitution of some allylic electrophiles has

been accomplished with both oxygen and nitrogen nucleophiles.⁷ In these reactions, both regioisomers of an electrophile can provide the same regioisomer of the product, and a proper choice of catalyst can ensure a selective formation of either more or less substituted allylic ethers and amines from a variety of electrophiles. Another approach has involved the isomerization of allylic alcohols by oxo complexes of rhenium,⁸ vanadium,⁹ chromium¹⁰ and other transition metals. In these reactions, the product distribution is determined by the thermodynamic stability of the two regioisomers and, in certain cases, high selectivity can be achieved.¹¹ Despite these developments, the regiospecificity observed in the reaction of Cp*₂(py)Ti=S (**2**, Cp* = η⁵-C₅Me₅) with allylic chlorides,¹² which provides rearranged products regardless of the substitution pattern of the electrophile, is still rare in substitution reactions with heteroatom nucleophiles. We attributed this unusual regiospecificity to the closed transition state presented in Figure 1.

Recently, as a result of our long-term exploration of early transition metal complexes containing multiple-bonded heteroa-

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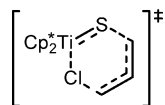
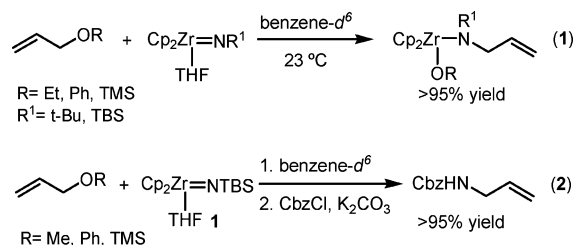


Figure 1. Postulated closed transition state in substitution reactions with **2**.

tom ligands,¹³ we discovered a new formal S_N2' reaction of zirconium imido complexes that allows regio- and stereospecific transformation of allylic ethers into Cbz-protected allylic amines.¹⁴ In this work, we describe the full scope of this transformation, including reactions with allylic halides and acetals. We also present the results of a detailed experimental and theoretical analysis of the reaction mechanism which provides insight into the origin of the unusual chemo-, regio-, and stereoselectivity of the reaction.

Results and Discussion

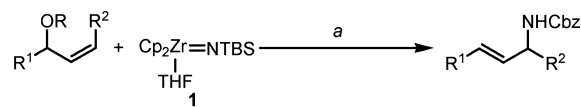
Reactions with Allylic Ethers. Our preliminary experiments established that, unlike titanocene sulfido complex **2**,¹² the *tert*-butylimidozirconocene complex $Cp_2(THF)Zr=Nt-Bu$ reacts with alkyl, aryl, and trimethylsilyl (TMS) allyl ethers at room temperature, to yield substitution products in greater than 95% yield (eq 1). These results were surprising, considering the limited number of reported substitution reactions with allylic ethers,¹⁵ and prompted us to further explore the scope of this transformation.



To facilitate isolation of the amine products, broaden the scope of the reaction, and increase the utility of the amine products, we decided to focus on the formation of the conveniently protected primary amines. With this goal in mind, we turned our attention to the known but virtually unexplored zirconocene imido complex **1**¹⁶ (TBS = *tert*-butyldimethylsilyl), which would afford TBS-protected primary amine products. In reactions with alkyl, aryl, and trimethylsilyl (TMS) allyl ethers, substitution products were obtained in similarly high yields, but with higher reaction rates. More importantly, the initial substitution products were successfully transformed into Cbz-protected allylamine, after in situ hydrolysis and Cbz protection of the free amines. With a convenient procedure for the isolation of Cbz-protected amine products in hand, we explored the reaction with other allylic ethers.

The reactions with several α -substituted TMS ethers provided the S_N2' products in good yields (Table 1, Entries 2–3). The size of the α -substituent had a significant effect on the observed diastereoselectivity and required temperature (Entry 2 vs Entry

Table 1. Allylic Substitution of Allylic Ethers



Entry	Substrate	T (°C) ^b	Yield (%) ^c
1		23	96
2		23	92 ^d
3		45	89 ^e
4		70	94
5		70	90
6		70	92
7		70	89
8		70	92
9		70	77
10		23	99
11		23	92

^a (1) C_6D_6 , 23 °C 2) CbzCl, K_2CO_3 , 23 °C. ^b Reactions performed at 23 °C were complete in 12 h. Reactions performed at 70 °C were complete in 16 h. ^c Reported are the isolated yields of the purified products. ^d 3:1 dr. ^e >10:1dr.

3, Table 1). The *tert*-butyl substituent proved prohibitively large, and no product was observed after 12 h at 75 °C. In reactions with both ethyl- and isopropyl-substituted ethers, only one regioisomer was detected in the ¹H NMR spectrum of the crude reaction mixture with the isopropyl ether affording significantly higher diastereoselectivity. In order to assess the inherent regioselectivity of the nucleophile, we explored the reactivity of substrates that would favor S_N2' substitution.

We found that a variety of ethers of *Z*-substituted primary allylic alcohols reacts with **1** at elevated temperatures. The most reactive substrates were the electron-rich (trimethylsilyl)methyl ethers, which provided the products of S_N2' substitution in up to 94% yield (Table 1, Entries 4–9). Interestingly, less electron-rich ethers of the same alcohols, such as methyl and phenyl ethers, reacted only at higher temperature and provided products in significantly lower yield. Similarly, *E* isomers of the same ethers were not reactive and provided the desired products in less than 20% yield.¹⁷

Although substitution at the 3-position of the substrates presented in Table 1 might be expected to favor the S_N2 pathway, the more substituted product of S_N2' substitution was still the only product observed in the ¹H NMR spectra of the crude reaction mixtures. The reactions with the substrates presented in Table 1 also illustrate an unprecedented chemoselectivity for the reactions of zirconium imido complexes. The substitution reaction is not affected by the presence of a variety of functional groups, including terminal alkenyl, phenoxy, and 1,3-dithianyl (Table 1, Entries 5–7). Even in the presence of an electrophilic primary chloro group, the S_N2' product was isolated in 92% yield (Table 1, Entry 8).

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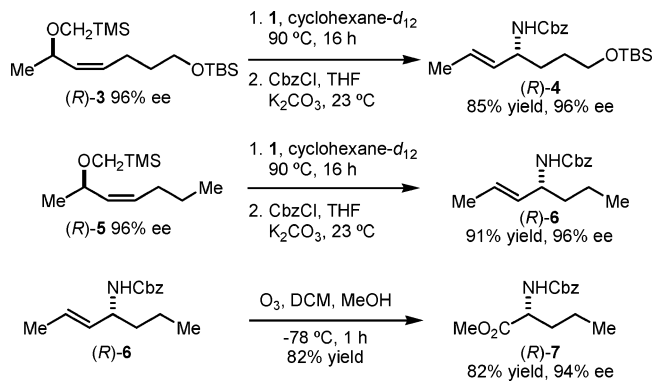
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Scheme 1



Other types of allylic ethers, such as epoxides and acetals (Table 1, Entries 10 and 11), also readily participate in the substitution reaction. As with other substrates, in each of these reactions, a single regioisomer and a single diastereoisomer of the product was formed. Allylic epoxides are relatively common electrophiles in allylic substitution reactions; however, there are only a few examples of S_N2' reactions with allylic acetals.¹⁸

Another important feature of the substitution reactions with **1** is the complete chirality transfer observed in the reactions with enantioenriched 1,3-disubstituted allylic ethers. The reaction of (*R*)-**3** with **1** resulted in the regio- and stereospecific formation of (*R*)-**4** in 85% yield (Scheme 1). Similarly, the reaction with (*R*)-**5** produced only rearranged product (*R*)-**6** as a single diastereoisomer. These experiments demonstrated the use of the formal S_N2' substitution reaction in a highly stereoselective synthesis of enantioenriched allylic amines and also allowed us to determine the stereochemistry of the reaction. The substitution product **6** was converted to a commercially available methyl ester of *N*-Cbz-norvaline (**7**) which allowed us to determine the absolute stereochemistry of the product. Comparison of the absolute configurations of the starting material and product revealed that the substitution proceeds with syn stereochemistry.

Reactions with Allylic Halides. In S_N2' reactions, the most commonly used electrophiles are allylic halides (chlorides and bromides) and some of the more electrophilic alcohol derivatives such as allylic esters, carbamates and sulfonates. From our preliminary experiments, we knew that allylic halides provide substitution products and we were hoping that the increased electrophilicity of these compounds relative to that of allylic ethers would circumvent some of the limitations we previously encountered in formal S_N2' reactions of **1**. In agreement with results obtained with allylic ethers, a single regioisomer was obtained in each of the reactions of **1** with several allylic chlorides and bromides (Table 2). In all cases, only the product of the S_N2' reaction was formed. Because of the greater reactivity of the allylic halides, these reactions were complete within 1 h hour at room temperature. Furthermore, while *E*-substituted allylic ethers were unreactive even under forcing conditions, *E*-substituted allylic halides provided the S_N2' product in high yield.

In contrast to the oxo¹⁹ zirconium and sulfido titanium¹² complexes previously described, **1** does not react with alkyl or

Table 2. Allylic Substitution of Allylic Halides

Entry	Substrate	Yield (%) ^b
1		96 ^c
2		92
3		89
4		94
5		90
6		92

^a (1) C_6D_6 , 23 °C; (2) CbzCl, $NaHCO_3$, 23 °C, 2 h. ^b Reported are the isolated yields of the purified products. ^c 2:1 mixture of diastereoisomers.

even benzyl halides. Exposure of **1** to benzyl chloride or 1-chlorohexane over several hours at room-temperature did not lead to the formation of any observable products, and heating led to decomposition of the starting materials. This difference in reactivity is most likely a result of the bulky TBS substituent on the imido ligand, which prevents a direct S_N2 substitution reaction. This observation is also consistent with the absence of the S_N2 products in substitution reactions of **1**.

Organic fluorides are exceedingly unreactive in substitution reactions relative to other organohalides. Consequently, substitution reactions with allylic fluorides have not been described in literature. The low polarizability of fluorine and the weak σ -basicity of its lone pairs result in a low propensity of transition metals to interact with organofluorine compounds,²⁰ hampering the task of developing metal-catalyzed transformation of organofluorine compounds.²¹ Considering the high affinity of zirconium (IV) for the fluoride anion,²² and the closed transition state we proposed, we reasoned that **1** may successfully participate in a substitution reaction with allylic fluorides.²³ In an initial experiment we observed that **1** reacted quantitatively with allyl fluoride even at -20 °C.

Encouraged by this result, we decided to explore the reactivity of other allylic fluorides, but were surprised to discover that a general procedure for the synthesis of allylic fluorides has not been previously reported. However, a published method for the synthesis of alkyl fluorides using anhydrous TBAF was identified, and this was adapted for the synthesis of allylic fluorides.²⁴ After considerable effort, we also discovered that allylic fluorides could be obtained in sufficiently pure form by vacuum transfer with benzene- d_6 from a crude reaction mixture in DMSO. Following this procedure, we were able to prepare (*E*)-1-fluoro-2-hexene (**8**) and (*Z*)-1-fluoro-2-hexene (**9**) in excellent yields from the corresponding chlorides. Both **8** and **9** readily

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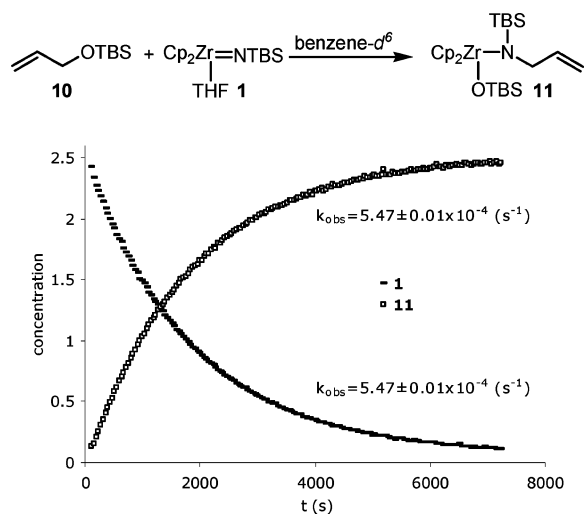


Figure 2. Normalized integrations of the ^1H NMR peaks for the starting material **1** and the substitution product **11** over time.

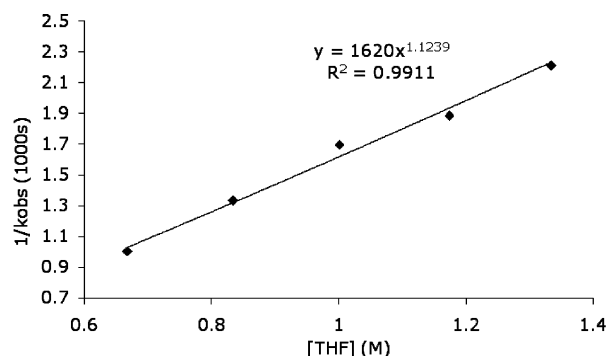


Figure 3. Dependence of the reciprocal of the observed rate constant on the concentration of THF toluene- d_8 .

participated in the reaction with **1** to afford the expected substitution product in high yield. These allylic fluorides not only participated in reaction with **1**, but also were more reactive than the corresponding chlorides and bromides. This unusual reactivity profile is yet another indication that the mechanism of the reaction merits a closer examination.

Reaction Mechanism—Experimental Approach. During the development of the apparent $\text{S}_{\text{N}}2'$ reaction with **1**, we made several observations that could not be easily explained by assuming that the reaction proceeds by a simple direct substitution: (1) the extraordinary regio- and stereoselectivity of the reactions; (2) the higher reactivity of allylic fluorides relative to other halides; (3) the higher reactivity of electron-rich TMS ethers relative to other ethers; (4) the lack of reactivity of simple alkyl and benzyl halides; and (5) the difference in reactivity of E and Z substituted electrophiles. Hoping to gain an understanding of the mechanistic origin for these observations and a better insight into the chemistry of zirconium imido complexes in general, we decided to study the reaction of allyl *tert*-butyldimethylsilyl (TBS) ether **10** with **1**.

The reaction of TBS allyl ether **10** with **1** was monitored by ^1H NMR spectroscopy. The reaction exhibits first-order behavior with no observable intermediates in the presence of excess THF and substrate. Furthermore, the rate of product formation was identical to the rate of starting material disappearance. The first-order rate constant for the reaction ($k_{\text{obs}} = 5.47 \pm 0.01 \times 10^{-4}$

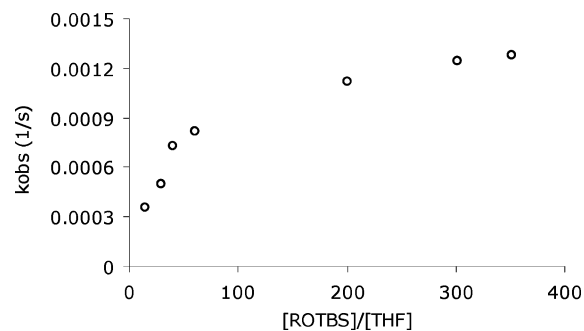
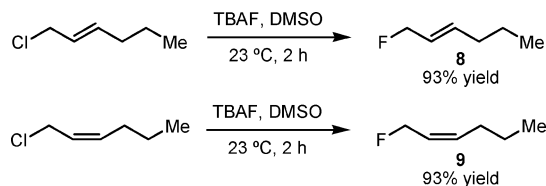
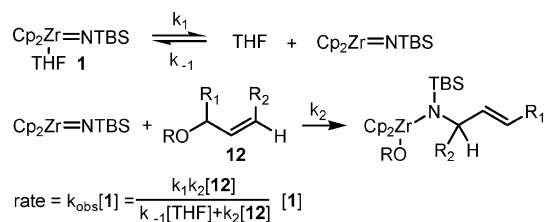


Figure 4. Saturation kinetics observed at the high ratio of substrate and THF concentrations.

Scheme 2



Scheme 3



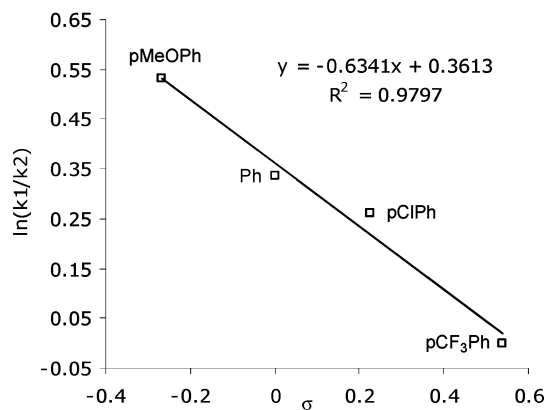
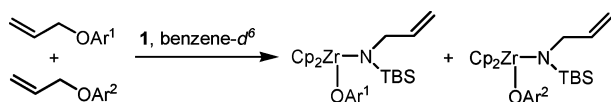
s^{-1} , at 21.5 °C) is independent of the initial concentration of **1**, confirming that the overall reaction is first order in **1**.

Previous mechanistic investigation of the related reaction of zirconium imido complexes with epoxides²⁵ and substitution reactions with titanium sulfido¹² complexes indicated that the first step involves reversible dissociation of one of the ligands (THF in the case of the imido complexes and pyridine in reactions of sulfido complexes). From the $1/k_{\text{obs}}$ vs [THF] plot (Figure 3) obtained using the pseudo-first-order rate constants measured in the presence of various concentrations of THF, we established that the overall reaction is inverse first order in THF, indicating a reversible dissociation of THF. On the basis of these results and the mechanisms of related reactions of zirconium imido complexes,²⁵ we propose that the substitution reaction involves reversible dissociation of THF, followed by coordination of the substrate and the rate-limiting substitution step (Scheme 3).

The rate law for the proposed mechanism predicts that at a high ratio of allylic substrate to THF concentration, k_{obs} should become independent of the concentrations of THF and the substrate. By measuring k_{obs} at different ratios of concentrations of THF- d_8 and allylic ether **10** (Figure 4) in toluene- d_8 solution, we did indeed observe the predicted saturation. From the same data, we were able to extract values for $k_1 = 1.4 \pm 0.1 \times 10^{-3}$ (s^{-1}) and $k_2/k_{-1} = 2.2 \pm 0.2 \times 10^{-2}$ at -7.5 °C.

Also consistent with the proposed mechanism and C–N bond formation in the rate-determining step is the inverse secondary kinetic isotope effect, calculated from the measured pseudo-

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Scheme 4. Results of a Hammett Study

first-order rate constants for the reactions with TBS allyl ether and (*E*)-1-(*tert*-butyldimethylsiloxy)-3-deuterioprop-2-ene ($k_H/k_D = 0.88 \pm 0.01$ at 20.6 °C).

Some insight into the substitution step of the reaction can be obtained from the syn stereoselectivity and the high regioselectivity observed in the substitution reaction. In the literature, syn stereochemistry of allylic substitutions has been interpreted as a strong indication of a cyclic transition state.²⁶ The most well-documented and studied example is the copper-promoted substitution of allylic electrophiles, in which the stereochemistry of the substitution has been directly linked to the ability of the leaving group to interact with copper.² The exclusive formation of the S_N2' product has also been used as a strong indication of the closed transition state in a related allylic substitution reaction.¹² Furthermore, the Lewis acidity of the metal center in **1** also favors interaction with the leaving group that would lead to a closed transition state. Similarly, the relatively modest nucleophilicity of **1**, which is evident from the inability of **1** to react with electrophiles as reactive as benzyl chloride, supports the notion of a closed transition state which is available only in reactions with allylic substrates.

To probe the direct interaction between the leaving group and the zirconium center necessary for the closed transition state of the substitution step, we performed a Hammett study (Scheme 4). The competition experiments were done using an excess (10 equiv) of the equimolar mixture of para-substituted allyl ethers and the relative rates of the reactions were extracted from the product distribution at the end of the reactions. The negative ρ value is consistent with a closed transition state and the need for an electron-donating leaving group to coordinate strongly to zirconium, a property that would not be expected for the direct S_N2 mechanism.

Reaction Mechanism—Theoretical Approach. In order to gain more insight into the nature of the substitution step, we performed a DFT study of a model reaction between methyl allyl ether and a TMS-substituted zirconium imido complex. All calculations were performed in Gaussian03²⁷ at the B3LYP^{28/}

LanL2DZ²⁹ level of theory. The energies are reported as electronic energies plus unscaled zero-point energy corrections. All stationary points were confirmed by frequency calculations and transition states were characterized by exactly one imaginary vibrational frequency. IRC calculations proved that the calculated transition state structures connected those of the products and reactants.

In agreement with the kinetics experiments, the calculations predict that the THF-adduct starting material **SM** is favored over the substrate-bound complex **SC-OMe** by 1.2 kcal/mol (Figure 5). We were also able to identify a six-membered closed transition state **TS-OMe** for the substitution step that was calculated to be 22 kcal/mol higher in energy than the initial ground state. In this transition state structure **TS-OMe**, the carbon–oxygen bond is elongated by 25% relative to the same bond in **SC-OMe** (1.855 vs 1.493 Å), while the carbon–nitrogen bond is elongated by 46% relative to same bond in **P-OMe** (2.213 vs 1.511 Å). Similarly, bond lengths in the allyl fragment in the transition state are closer to the bond lengths in **SC-OMe** than to those in the product. These differences in the relative bond lengths in the ground states and the transition state indicate a relatively early transition state, which is consistent with an exothermic reaction. Overall, these results suggest that the substitution reaction is best described as a concerted, asynchronous [3,3]-sigmatropic rearrangement with an early transition state.

This reaction is mechanistically closely related to [3,3]-sigmatropic rearrangements of imidates³⁰ and phosphorimidates,³¹ which have been the most reliable and selective methods for transformation of allylic alcohols into rearranged allylic amines. The major difference is that one of the covalent bonds in the closed transition state is replaced by a dative bond between the metal and the leaving group. This general strategy has been applied in the rearrangement of allylic alcohols catalyzed by metal oxo complexes^{8–10} and, more recently, in the reaction of allylic alcohols catalyzed by titanium imido complexes.³²

To explore the origins of the observed differences in reactivity of *E*- and *Z*-substituted allylic ethers, we modeled the reactions of both *E* and *Z* isomers of 1-methoxy-2-butene (Figure 6). As expected, no significant difference in the stability of the zirconium-bound substrates (less than 0.5 kcal/mol) was predicted. However, the activation energy corresponding to **TS-**

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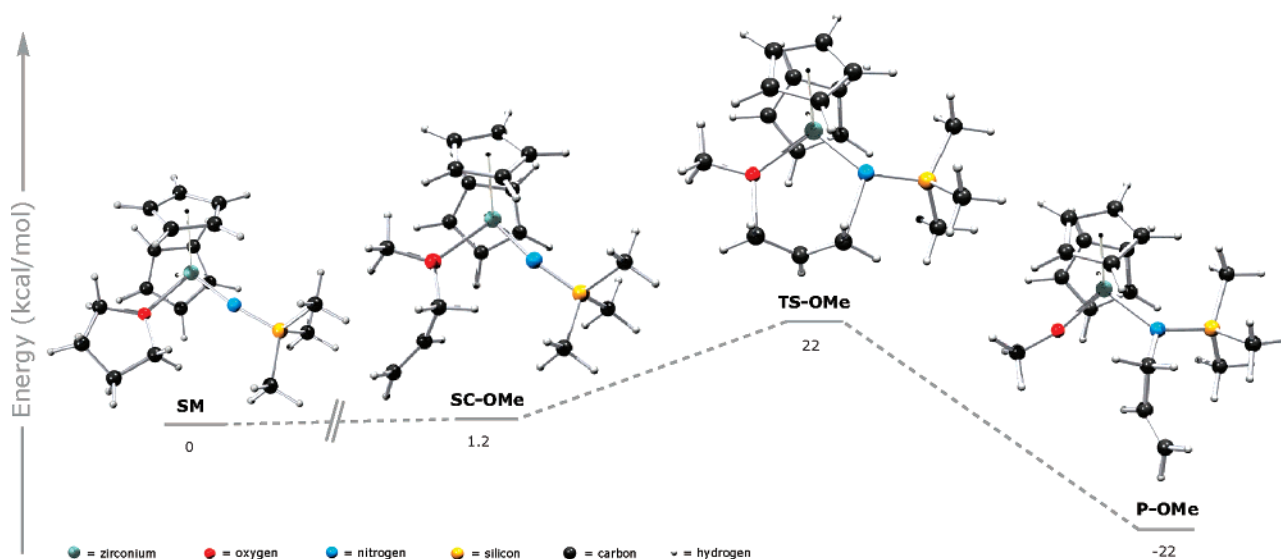


Figure 5. Calculated structures and relative energies for reaction of **1** with methyl allyl ether.

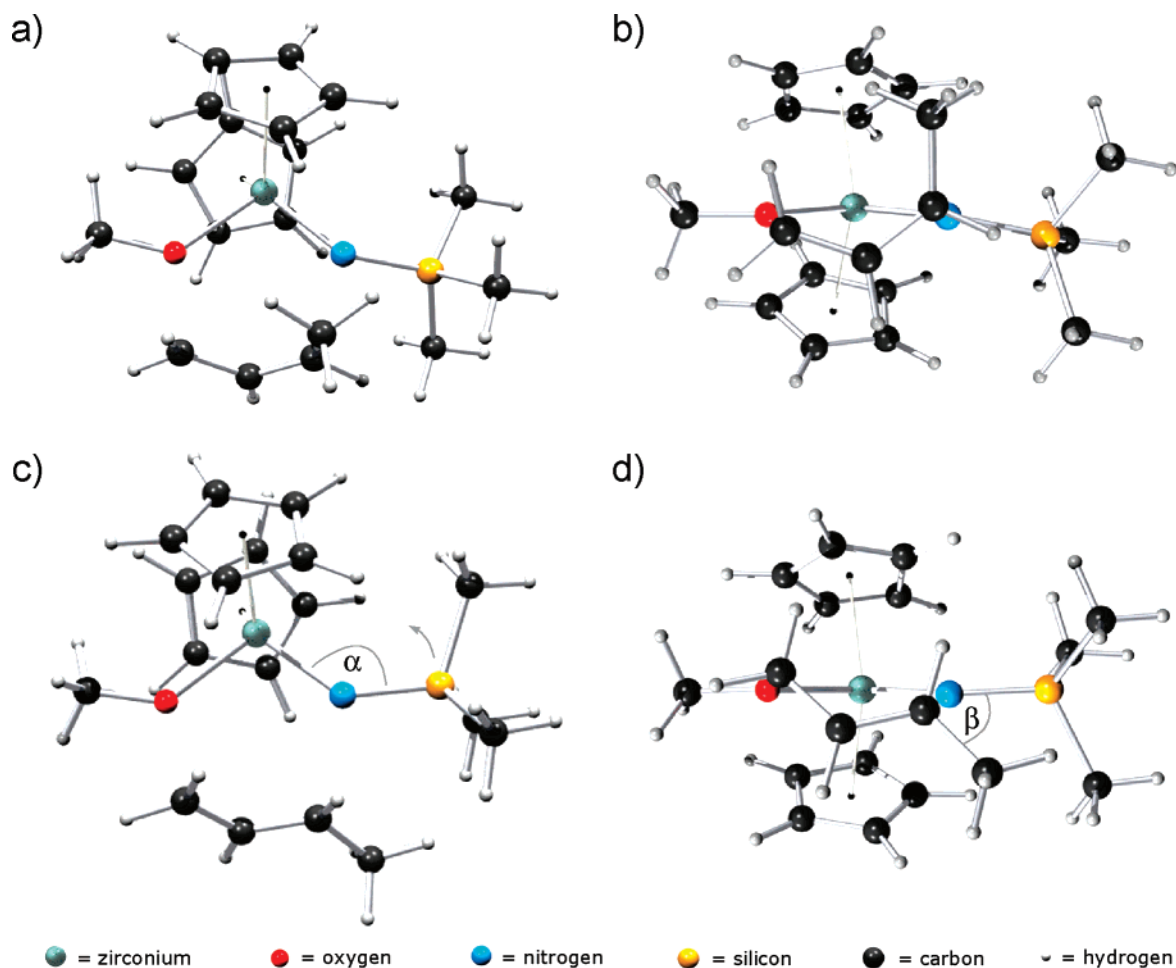


Figure 6. (a) Calculated transition state for the substitution of (*Z*)-1-methoxy-2-butene (top view); (b) side view of the same transition state; (c) calculated transition state for the substitution of (*E*)-1-methoxy-2-butene (top view); (d) side view of the same transition state.

E-OMe is calculated to be significantly higher than the activation energy for **TS-Z-OMe** (29 kcal/mol vs 25 kcal/mol), in agreement with our experimental results. Comparison of transition structures **TS-Z-OMe** and **TS-E-OMe** to transition structure **TS-OMe** suggests a rationale for the difference in the calculated activation energies for the two isomers. Somewhat

surprisingly, the methyl group in the *Z*-substituted ether can be accommodated in the pseudoaxial position without a significant change in the overall geometry of the transition state and the corresponding activation energy (see Figure 6a).

The same transition structure geometry for the *E*-substituted ether leads to an eclipsing interaction between the methyl group

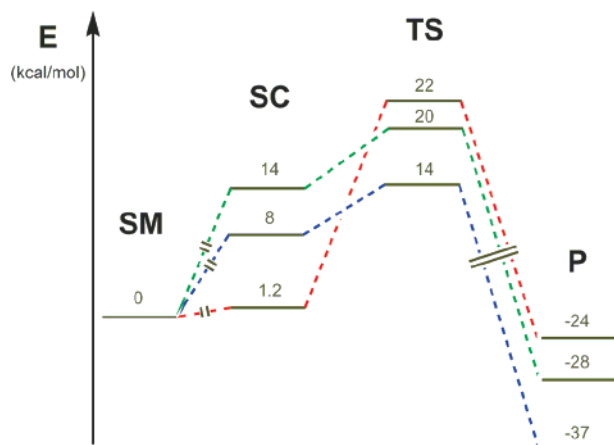


Figure 7. Calculated relative energies for the substitution of methyl allyl ether (red), allyl fluoride (blue), and allyl chloride (green). The energies of starting materials arbitrarily scaled to 0.

and the TMS group (Figure 6). As a result, the TMS group is bent away from the substrate ($\alpha = 137^\circ$ vs 145° in **TS-Z-OMe**, Figure 6c) to avoid interacting with the methyl group, and the allyl moiety is twisted so that the dihedral angle β is 43° (Figure 6). As a reference, the corresponding dihedral angles in **TS-OMe** and **TS-Z-OMe** are 18° and 14° , respectively. It appears that these forced changes in geometry of transition state **TS-Z-OMe** are responsible for the higher activation energy for reactions of E-substituted electrophiles.

In an effort to understand the relative reactivity of allyl ethers and allyl halides, we also examined the reactions of allyl fluoride and allyl chloride. The displacement of THF by allyl fluoride and allyl chloride was predicted to be less favorable than displacement by allylic ethers, as could be expected based on the lower Lewis basicity of halides (see Figure 7). However, it is surprising that coordination of the fluoride is predicted to be significantly more favorable than coordination of the chloride ($\Delta E = 6$ kcal/mol). According to our calculations, the reactions of both allyl fluoride and allyl chloride are overall more thermodynamically favorable relative to the reaction of allyl ether (15 kcal/mol for the fluoride and 4 kcal/mol for the chloride). In addition, the activation barrier for the rearrangement of allyl fluoride is calculated to be 8 kcal/mol lower than the corresponding barrier for the reaction of allyl methyl ether and 6 kcal/mol lower than that for allyl chloride. The difference in calculated activation energies for substitution of ethers, chlorides and fluorides can be explained by partial formation of a bond between zirconium and the leaving group. This interaction is expected to contribute to the stability of the corresponding transition states and as a result the relative energies of these transition states are correlated with the bond dissociation energies of the corresponding zirconium-leaving group bond,

Table 3. Substitution of Allylic Fluorides

Entry	Substrate	T (°C)	Yield ^b (%)
1		-20	99
2		23	88
3		23	91

^a (1) C_6D_6 , $23^\circ C$; (2) $CbzCl$, $NaHCO_3$, $23^\circ C$. ^b Reported are the isolated yields of the purified products.

which is consistent with the relative exothermicity of these reactions. Another significant difference is that both the fluoride and the chloride have significantly earlier transition states than the one calculated for allylic ethers. The carbon–nitrogen distance in **TS-F** is 0.4 \AA longer than the corresponding length in **TS-OMe** and 0.1 \AA shorter than that in **TS-Cl**.

Conclusions

We have described a new reaction of zirconium imido complexes that allows regio- and stereospecific transformation of allylic ethers and halides directly into rearranged Cbz-protected allylic amines. Among the substrates that were successfully used, particularly interesting are allylic fluorides, which rarely participate in substitution reactions. Through a detailed experimental and theoretical study of the reaction mechanism, we have discovered that the apparent S_N2' reaction is best described as a concerted, asynchronous [3,3]-sigmatropic rearrangement. This mechanism provides a rationale for the observed regio-, stereo-, and diastereoselectivity observed in the reaction, and also accounts for the differences in reactivity between various electrophiles. Furthermore, a detailed understanding of this mechanism, which closely resembles the mechanism of the [3,3]-sigmatropic rearrangements of allylic imidates and phosphorimidates, could guide the further development of a practical method for the S_N2' substitution reactions of allylic ethers and halides. Overall, the results presented provide additional insight into the reactivity of zirconium imido complexes and may facilitate further advances in formal S_N2' substitution reactions.

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Supporting Information Available: Complete reference 27, experimental procedures and spectral data for products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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