Articles

Tandem Transformations Involving Allylic Silanes. 2. Highly Diastereoselective Substitutions Involving [(Trialkylsilyl)methyl]cyclohexene Derivatives with Aldehydes. Synthetic Studies on the Problem of Lewis Acid-Promoted Protodesilylation and Enolization

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Diels−Alder cycloaddition of 2-[(trialkylsilyl)methyl]-1,3-butadienes with a variety of dienophiles and substitution reactions between these allylsilane-containing adducts and aldehyde or acid chloride electrophiles have been combined into "tandem sequential reactions." These tandem sequences proceed with equal or greater yield (50−80%) than the reactions performed separately with no decrease in regio- or stereoselectivity. The sequence produces cyclic compounds with three or four stereogenic centers with good to excellent diastereoselectivity from three simple, noncyclic, and achiral reaction partners. Unprecedented levels of diastereoselectivity (de >93%) have been achieved in allylic substitution reactions involving substituted [(trialkylsilyl)methyl]cyclohexene derivatives with aldehyde electrophiles. During the course of these studies, protodesilylation of allylsilanes has been investigated in detail, and a cocatalyst system of $TiCl_4$ and Me_2AlCl has been developed that has eliminated silicon loss in the substitution reactions studied. Lewis acid-promoted enolization of ester and ketone substrates with chiral centers adjacent to the carbonyl moiety has been studied also. It has been shown that this event in our studies occurs primarily during catalyst quench. This isomerization is prevented by quenching the catalyst with a Lewis base, such as methanol or triethylamine, prior to aqueous workup.

Introduction

The preparation of complex molecules from simple, cheap, and readily available ones is a strong starting point to making a synthesis practical. Further, when such starting materials are incorporated into an approach that brings about a rapid increase in molecular complexity, the approach is also regarded as efficient.[1] Tandem reactions represent a powerful approach to addressing overall synthetic efficiency.[2] One-pot synthetic sequences reduce the time, waste, and cost associated with synthetic chemistry.

In a recent report, we disclosed our first results in the area of "tandem reaction sequences" that combine transformations of different fundamental mechanism using allylsilane substrates.[3] Such sequences require the addition of a second (or third) compound after the first reaction has been judged complete. Further, the first reaction is required to provide the functionality necessary to allow the second reaction to take place.[2e] Many tandem reactions in the literature are of the same mechanism. Examples include sequential Michael additions,[4] pericyclic rearrangements,[5] and transition-metal-catalyzed coupling procedures[6−8] to name just a few. The present study is directed at expanding the scope of "key-step" tandem reactions that can be used in synthesis. Combining fundamentally different reactions can gener-

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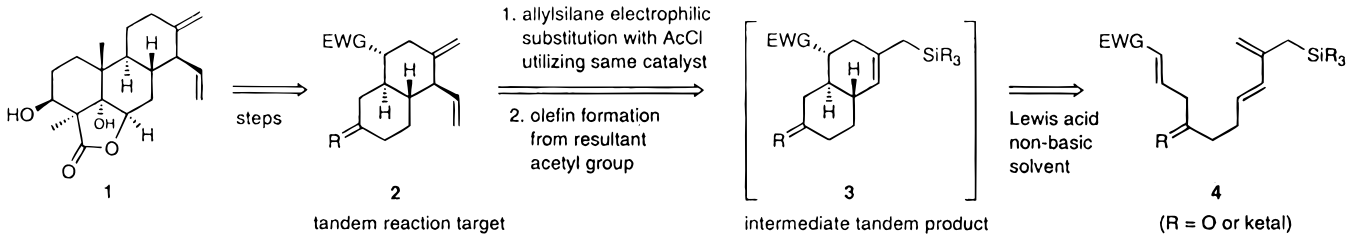
Scheme 1



ate products with unique structure and functionality patterns from a tandem procedure that are not readily obtainable from sequences involving reactions of the same mechanism.[3,4,9] Therefore, these reactions are intended to complement tandem reactions of the same mechanism.

The tandem reaction strategy described in this report focuses on functional groups that are capable of supporting a wide range of chemical transformations. Reaction conditions are then developed to allow such transformations to be conducted on a substrate in a predictable sequence. Allylsilanes are well suited for this purpose for a number of reasons.[10] They have been used widely in reactions of radical,[11] cationic,[12] and anionic mechanism.[13] Silanes are among the most stable compounds that contain a carbon−metal bond, especially allylmetal moieties.[14] Therefore, silane moieties can be incorporated into the structure of starting materials and carried through a number of steps before they are activated selectively.[15] *This is critical to the success of this chemistry.* It is a long-term goal of our program to investigate the combination of any of the above-mentioned mechanisms into sequential transformations to produce complex compounds from relatively simple precursors in one operation.

In the short term, we have developed a tandem pericyclic/ionic reaction sequence involving 2-[(trialkylsilyl)methyl]-1,3-butadienes and a variety of dienophile and electrophile partners, all of which can be reacted selectively in a stepwise fashion using the same or different Lewis acid catalyst. The retrosynthetic sequence in Scheme 1 demonstrates how this methodology could be used to prepare the core of sonomolide A (**1**), a compound of interest to us. Recently isolated and characterized, sonomolide A has demonstrated pronounced antifungal activity.[16]

This report also discusses deleterious side reactions that occur with allylsilanes in allylic substitution reactions promoted by $TiCl_4$. Despite the aforementioned stability of the carbon−silicon bond and the tunable reactivity of allylsilanes, Brønsted acid will protonate the olefin, and this is accompanied by loss of silicon.[17] Protodesilylation can also occur as a side reaction in Lewis acid-catalyzed substitutions with carbon electrophiles.[18] In the course of our studies, we encountered this problem and developed a catalyst system that minimizes this side reaction.

Lewis acid-promoted enolization of ketones and esters is an unfortunate process that can lead to epimerization of these sites. This results in a significant reduction of diastereomeric purity for compounds possessing multiple chiral centers. Further, if the solution containing the compound is optically enhanced, loss in enantiomeric purity can also result. This issue is also addressed in this study.

Results and Discussion

Diels−Alder Reaction. The first step in the general sequence investigated was a [4 + 2] cycloaddition be-

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Scheme 2

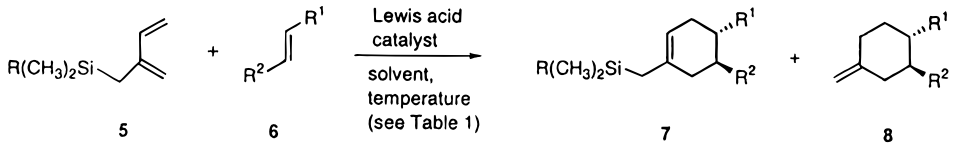

Table 1. Reaction Conditions for Diels–Alder Cycloaddition between 2-[(Trialkylsilyl)methyl]-1,3-butadienes 5 and Various Dienophiles 6 (See Scheme 2 for Structures)

entry	diene	dienophile	R	R^1	R^2	catalyst[a]	T (°C)	solvent	product no.	yield[b]
1	**5a**	**6a**	$-CH_3$	$-CO_2CH_3$	H	$AlCl_3$	40	CH_2Cl_2	**7a**	38[c]
2	**5a**	**6a**	$-CH_3$	$-CO_2CH_3$	H	Me_2AlCl	40	CH_2Cl_2	**7a**	88
3	**5a**	**6a**	$-CH_3$	$-CO_2CH_3$	H	$EtAlCl_2$	40	CH_2Cl_2	**7a**	52
4	**5a**	**6a**	$-CH_3$	$-CO_2CH_3$	H	$BF_3{\cdot}OEt_2$	40	CH_2Cl_2	**7a**	15
5	**5a**	**6a**	$-CH_3$	$-CO_2CH_3$	H	$TiCl_4$	40	CH_2Cl_2	**7a**	38[d]
6	**5b**	**6a**	$-Ph$	$-CO_2CH_3$	H	Me_2AlCl	40	CH_2Cl_2	**7b**	84
7	**5b**	**6b**	$-Ph$	$-COCH_3$	H	Me_2AlCl	rt	CH_2Cl_2	**7c**	97
8	**5b**	**6c**	$-Ph$	$-COCH_2CH_3$	$-CH_3$	Me_2AlCl	rt	CH_2Cl_2	**7d**	95
9	**5b**	**6d**	$-Ph$	$-CO_2CH_3$	$-CO_2CH_3$	no catalyst	100	toluene	**7e**	84
10	**5b**	**6d**	$-Ph$	$-CO_2CH_3$	$-CO_2CH_3$	Me_2AlCl[e]	40	CH_2Cl_2	**7e**	90
11	**5b**	**6e**[f]	$-Ph$	$-(C(O)CH_2CH_2CH_2)-$		Me_2AlCl	40	CH_2Cl_2	**7f**	59
12	**5b**	**6f**[g]	$-Ph$	$-(C(O)OC(O))-$		no catalyst	rt	CH_2Cl_2	**7g**	89

[a] 0.2 equiv of catalyst was used relative to **5** unless stated otherwise. [b] All reported yields are based on purified material following silica gel chromatography. [c] Thirty-five percent of the protodesilylated side product **8** was also formed. [d] Thirty-six percent of the protodesilylated side product **8** was also formed. [e] One equiv of Lewis acid was required. [f] Dienophile **6e** was 2-cyclohexen-1-one. [g] Dienophile **6f** was maleic anhydride.

tween 2-[(trialkylsilyl)methyl]-1,3-butadienes and a variety of dienophiles (see Scheme 2 and Table 1). Such reactions have been carried out using 2-[(trimethylsilyl)-methyl]-1,3-butadiene (**5a**)[3] with α,β-unsaturated carbonyl and ester substrates, both with and without catalysis.[19] Diene **5a** and methyl acrylate were used to optimize the reaction conditions. Of all the catalysts tried, Me_2AlCl provided the best yield (Table 1, entry 2). The principal reason for lower yield with other catalysts is protodesilylation of **7a** producing **8**. It was discovered subsequently that adducts derived from 2-[(dimethylphenylsilyl)methyl]-1,3-butadiene (**5b**)[3] were less susceptible to protodesilylation, so all subsequent reactions were done with this diene. Addition of **5b** to a variety of dienophiles under Me_2AlCl catalysis provided all adducts in very good yield (Table 1, entries 6, 7, 8 and 10). The *para* adduct was isolated in all cases with unsymmetrical dienophiles when the reaction was performed using Lewis acid catalysis.

These selective and high-yielding results are critical for the success of the tandem sequence. It is imperative that the first reaction goes to completion and that it proceeds regioselectively and stereoselectively where applicable. The number of potential isomers produced in subsequent step(s) doubles for each additional adduct or suitably reactive byproduct generated in the first step. Obviously, this would have a negative effect on yield, but product isolation from a complex mixture of isomers could make such a tandem approach impractical.

When the reaction indicated in entry 8 (Table 1) (i.e., product **7d**) was worked up using the standard conditions of saturated $NaHCO_3$ quench followed by ether extraction, a 2.4:1 *trans*:*cis* ratio of adducts was observed. The ^1H NMR spectrum of the reaction mixture at the completion of the Diels–Alder reaction revealed all *trans* isomer prior to workup. This indicated that isomerization occurred as a result of the heterogeneous conditions of the aqueous quench. To avoid this, a nonaqueous quench was performed by adding neutral alumina directly to the reaction mixture followed by solvent removal *in vacuo*. The crude product/alumina mixture was then loaded to the top of a prepacked silica gel column and eluted off, providing the adduct, now with only a trace of the *cis* isomer (21:1, *trans*:*cis*). This epimerization is discussed further in the next section.

Electrophilic Substitution Reactions. Cycloadducts **7** were then reacted in a series of electrophilic substitutions with a variety of aldehydes and acid chlorides. In doing so, a number of Lewis acids and reaction conditions have been probed to optimize these substitutions.

i. Additions to Aldehydes. The first allylic substitution reactions were attempted with adduct **7a** and propionaldehyde (**9a**) to optimize reaction conditions, i.e., Lewis acid, solvent, and temperature (see Scheme 3 and Table 2). Although Me_2AlCl catalysis worked very nicely for the Diels–Alder study, it failed to promote the substitution reaction, and starting materials were recovered quantitatively. Stronger Lewis acids such as $AlCl_3$ and $TiCl_4$ promoted conversion of **7a** and **9a** to **10a** and **11a** (see method A, Table 2). However, this was accompanied by substantial protodesilylation of **7a** leading to the formation of **8a**. It was shown subsequently that

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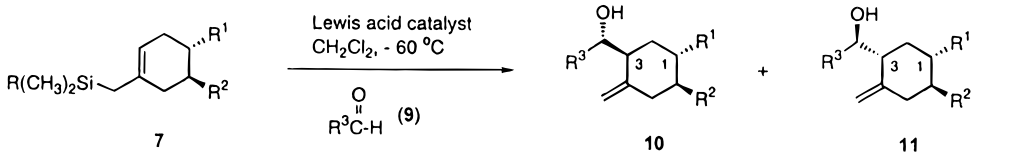
Scheme 3



a: $R^1 = -CO_2CH_3$, $R^2 = -H$, $R^3 = -CH_2CH_3$
b: $R^1 = -CO_2CH_3$, $R^2 = -H$, $R^3 = -CH(CH_3)_2$
c: $R^1 = -CO_2CH_3$, $R^2 = -H$, $R^3 = -CH_2CH_2Ph$
d: $R^1 = -C(O)CH_3$, $R^2 = H$, $R^3 = -CH_2CH_3$
e: $R^1 = -C(O)CH_3$, $R^2 = -H$, $R^3 = -CH_2CH_2Ph$
f: $R^1 = -C(O)CH_3$, $R^2 = -H$, $R^3 = -CH(CH_3)_2$
g: $R^1 = -C(O)CH_2CH_3$, $R^2 = -CH_3$, $R^3 = -CH_2CH_3$
h: $R^1 = -C(O)CH_2CH_3$, $R^2 = -CH_3$, $R^3 = -CH(CH_3)_2$

Table 2. Substitution Reaction Conditions with Cyclic Allylsilane Diels–Alder Adducts 7 and Aldehyde Electrophiles 9 (See Scheme 3 for Structures)

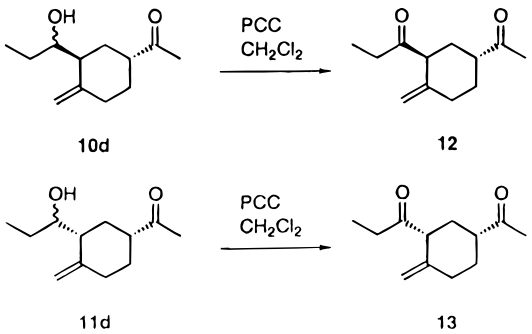
entry	starting adduct	aldehyde	R	R^1	R^2	R^3	catalyst[a]	product numbers	yield[d] (%)/ **10:11**
1	**7a**	**9a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	$AlCl_3$	**10a and 11a**	40[e]/4:1
2	**7a**	**9a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	Me_2AlCl	**10a and 11a**	no reaction
3	**7a**	**9a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	$BF_3{\cdot}OEt_2$	**10a and 11a**	trace
4	**7a**	**9a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	$TiCl_4$[b]	**10a and 11a**	60*e*/4.4:1
5	**7b**	**9a**	−Ph	$-CO_2CH_3$	H	$-CH_2CH_3$	$TiCl_4$[b]	**10a and 11a**	61[e]/4.3:1
6	**7b**	**9a**	−Ph	$-CO_2CH_3$	H	$-CH_2CH_3$	$Me_2AlCl/TiCl_4$[c]	**10a and 11a**	65/4.9:1
7	**7b**	**9b**	−Ph	$-CO_2CH_3$	H	$-CH(CH_{3)2}$	$TiCl_4$[b]	**10b and 11 b**	60[e]/1.1:1
8	**7b**	**9b**	−Ph	$-CO_2CH_3$	H	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	**10b and 11 b**	70/1.3:1
9	**7b**	**9b**	−Ph	$-CO_2CH_3$	H	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	**10b and 11 b**	82[f]/2:1
10	**7b**	**9c**	−Ph	$-CO_2CH_3$	H	$-CH_2CH_2Ph$	$TiCl_4$[b]	**10c and 11 c**	54[e]/5.8:1
11	**7b**	**9c**	−Ph	$-CO_2CH_3$	H	$-CH_2CH_2Ph$	$Me_2AlCl/TiCl_4$[c]	**10c and 11 c**	76/7.4:1
12	**7c**	**9a**	−Ph	$-COCH_3$	H	$-CH_2CH_3$	$TiCl_4$[b]	**10d and 11 d**	55[e]/3:1
13	**7c**	**9a**	−Ph	$-COCH_3$	H	$-CH_2CH_3$	$Me_2AlCl/TiCl_4$[c]	**10d and 11 d**	72/3.6:1
14	**7c**	**9c**	−Ph	$-COCH_3$	H	$-CH_2CH_2Ph$	$TiCl_4$[b]	**10e and 11 e**	53[e]/4.4:1
15	**7c**	**9c**	−Ph	$-COCH_3$	H	$-CH_2CH_2Ph$	$Me_2AlCl/TiCl_4$[c]	**10e and 11 e**	62/4.4:1
16	**7c**	**9b**	−Ph	$-COCH_3$	H	$-CH(CH_3)_2$	$TiCl_4$[b]	**10f and 11 f**	54[e]/2.3:1
17	**7c**	**9b**	−Ph	$-COCH_3$	H	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	**10f and 11 f**	69/1.8:1
18	**7d**	**9a**	−Ph	$-COCH_2CH_3$	CH_3	$-CH_2CH_3$	$Me_2AlCl/TiCl_4$[c]	**10g and 11g**	65/4.6:1
19	**7d**	**9b**	−Ph	$-COCH_2CH_3$	CH_3	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	**10h**	53/*trans* only
20	**7e**	**9a**	−Ph	$-CO_2CH_3$	$-CO_2CH_3$	$-CH_2CH_3$	$Me_2AlCl/TiCl_4$[c]	NR[g]	
21	**7f**	**9a**	−Ph	−(C(O)CH2CH2CH2)−		$-CH_2CH_3$	$Me_2AlCl/TiCl_4$[c]	NR	
22	**7g**	**9a**	−Ph	−(C(O)OC(O))−		$-CH_2CH_3$	$Me_2AlCl/TiCl_4$[c]	NR	

[a] One equiv of active catalyst was used in these reactions. [b] Method A: a solution of allylsilane **7** and aldehyde **9** in CH_2Cl_2 was cooled to −60 °C and $TiCl_4$ added dropwise. [c] Method B: a solution of dimethylaluminum chloride (0.2 equiv) and $TiCl_4$ (1.0 equiv) in CH_2Cl_2 was cooled to −60 °C and then added to a second flask containing **7**, **9**, and 0.2 equiv of Me_2AlCl, also at −60 °C. [d] All reported yields are based on purified material following silica gel chromatography. [e] Up to 20% of the desilylated compound **8** was obtained in addition to the substitution products **10** and **11**. [f] 2.0 equiv of the aldehyde was used. [g] No substitution product was produced in this reaction, and most of the starting allylsilane was recovered.

when this reaction was performed using $TiCl_4$ catalysis in the presence of Me_2AlCl (see method B, Table 2), protodesilylation was eliminated and yield was enhanced considerably (compare entries 5 vs 6, 7 vs 8, 10 vs 11, 12 vs 13, and 14 vs 15 in Table 2). This effect is discussed below. All substitutions involving aldehyde electrophiles proceeded with allyl inversion. Of the four possible diastereomers (eight for addition to **7d**) that can arise from this substitution, only two were observed, i.e., **10** and **11** (one in the case of **10h**).

Structural Elucidation of Substitution Products with Aldehyde Substrates. It has been confirmed that the substituents at C1 and C3 of **10d** and **11d** are *cis* and *trans* as indicated. Independent oxidation of these two compounds with PCC provided different products, i.e., **12** and **13** (Scheme 4). This proved that the two isomers are *cis* and *trans*. However, at the time, it provided no information to distinguish between them or any indication as to the relative stereochemistry at the carbinol center.

Scheme 4



The structure of the major isomer from the reaction of **7b** and isobutyraldehyde, i.e., **10f**, has been unambiguously established by single-crystal X-ray analysis (Figure 1). The structure demonstrates that the alcohol-containing side chain occupies the axial position and is *trans* to the acetyl moiety that is equatorial. This conformation, albeit in the solid state, proved to be important in relating the connectivity of this structure to the structure of the

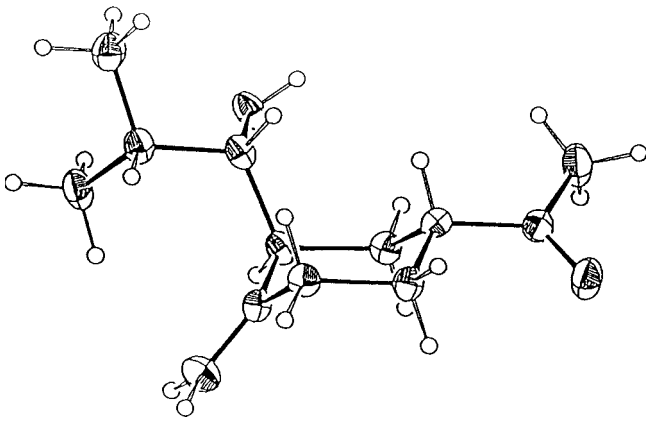


Figure 1. Single crystal X-ray structure of **10f**.

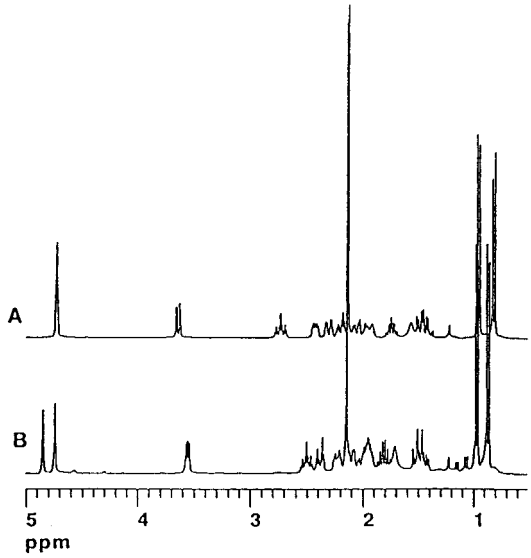


Figure 2. ^{1}H NMR spectra of *trans* adduct **10f** (A) and *cis* adduct **11f** (B).

minor isomer **11f** and other products in this sequence by NMR spectroscopy.

Examination of the ^{1}H NMR spectra of products **10** and **11** reveal that the signal for each exocyclic proton is a singlet for both isomers. Further, the signals for these protons overlap for one of the isomers, while they are separated by at least 0.2 ppm in the case of the second isomer. *These values are characteristic and diagnostic for all adducts in this study.* The ^{1}H NMR spectrum of **10f** (confirmed by X-ray analysis) and the minor isomer **11f** are shown in Figure 2. From Figure 2A, we extrapolated the structure of the major isomer for all electrophilic substitution reactions, i.e., they are all *trans* products resulting from an axial transition state.

The chemical shift values of the vinyl protons can be understood by examining the conformation of the major and minor products (Figure 3). The *trans* adducts **10** place the alcohol sidechain axial, which reduces the $A^{1,3}$-strain between this group and the exocyclic methylene (see Figure 1). The result is that both H^a and H^b are in remotely similar environments resulting in closer chemical shifts for these protons. The *cis* adducts **11** place both groups equatorial, which results in an interaction between the alcohol side chain and H^b. Therefore, the

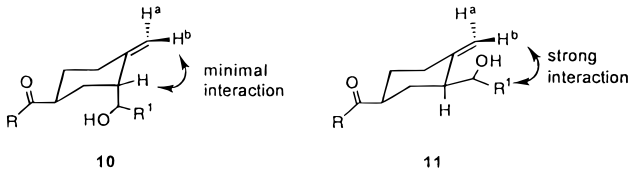


Figure 3. Proposed conformations of substitution products to account for differences between the ^{1}H NMR chemical shifts of the exocyclic methylene protons.

signals for these two protons might be expected to be separated by a larger chemical shift than those of **10**. The ^{1}H NMR spectra of **10f** and **11f** clearly illustrate this difference. Similar structural assignments have been suggested for cyclohexane compounds possessing an exocyclic methylene adjacent to a (1-oxoalkane) side chain.[20]

Stereoselectivity in Substitution Reaction with Aldehyde Substrates. That **7d** was epimerized by Me_2-AlCl in the Diels−Alder study raised the possibility that $TiCl_4$ might be causing some epimerization of the products from the substitution reaction. This would occur by enolization of the position on the ring next to the ketone or ester functionalities. Thus, "observed stereoselectivity" in the substitution reaction would be lowered. To test this possibility, *trans* isomer **10a** was treated with 1 equiv of $TiCl_4$ in CH_2Cl_2 and worked up as if it were a regular substitution reaction using saturated $NaHCO_3$ to quench the catalyst (Scheme 5).

The ^{1}H NMR spectrum of this mixture revealed that 20% of **10a** had been converted to **11a**. The structure of **11a** drawn in Scheme 5 is the enantiomer of that drawn for **11a** in Scheme 3, and they represent the same compound in this study (i.e., the study is on racemic material). Coincidentally, this was the same ratio obtained when the substitution reaction was performed and worked up in the usual way. This result provided two separate pieces of information. First, it confirmed the possibility that at least some of **11** could have been formed by Lewis acid-catalyzed isomerization of **10**. Second, it confirmed the structure of the minor isomer in this study. Conversion of **10a** to **11a**, rather than some other diastereomer, can only happen if the carbinol center, in addition to C3, has the same relative stereochemistry in the major and minor isomers.

With this result in hand, a substitution reaction was performed with **14** (Scheme 6). This compound was similar to **7c** except that it lacks the ketone moiety on the two-carbon side chain. Any isomerization occurring as a direct result of the carbonyl moiety would not have been possible with any substitution product derived from **14**. The ethyl group would serve the same role as the acetyl group as the conformational anchor of the cyclohexene ring. Thus, any axial/equatorial selectivity seen in a substitution reaction should be similar to that seen for the ketone parent, providing coordination to that carbonyl group was not involved in any observed stereoselectivity.

Substitution under identical conditions as for **7c** with propionaldehyde electrophile (saturated $NaHCO_3$ workup) yielded the axial addition product **15** almost exclusively (93% diastereomeric excess (de)). The same addition with **7c** provided a ratio of 3.6:1 of **10d**:**11d** (56% de). Although it cannot be said with certainty that the initial selectivity observed in substitutions involving **7** were all equal to that observed with **14**, it indicates that

(20) Pillot, J.-P.; Déléris, G.; Dunoguès, J.; Calas, R. *J. Org. Chem.* **1979**, *44*, 3397−3400.

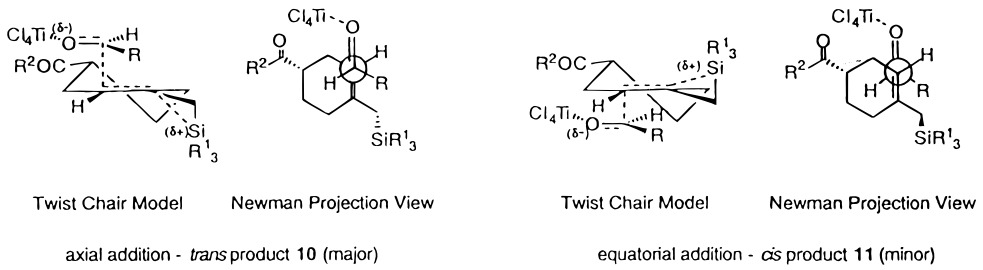
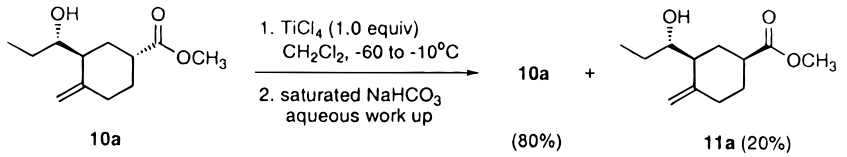
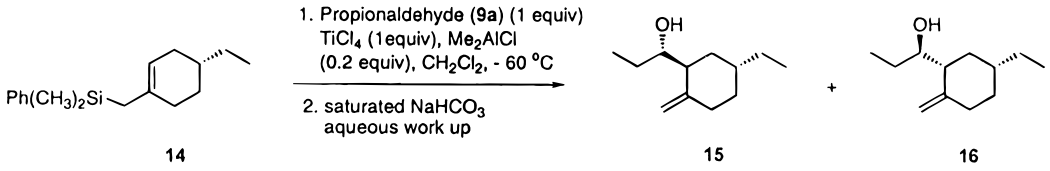


Figure 4. Proposed transition state structures leading to the products of axial, i.e., trans, and equatorial, i.e., *cis* addition.

Scheme 5

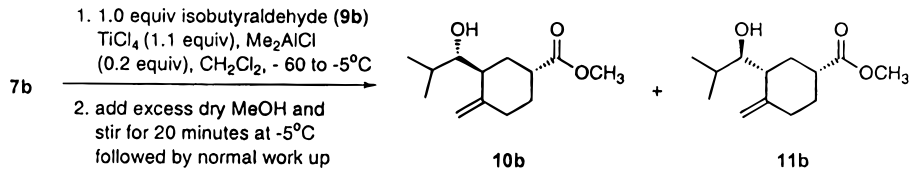


Scheme 6



Ratio of **15** : **16**; 27 : 1 (60% Yield)

Scheme 7



Ratio of **10b** : **11b**; 28 : 1 (41% yield)

such substitutions warrant further investigation. Compounds **10** may have been the principal initial products formed in the substitution step, and subsequent isomerization lowered the observed selectivity.

In order to confirm that enolization of the substitution products (**10**) was indeed linked to observed stereoselectivity, it had to be determined if enolization occurred during the reaction at all or if it happened exclusively upon quench. In light of the epimerization observed with **7d** in the Diels−Alder study, attention was focused on the nature of the quench of the substitution reaction. The substitution reaction involving **7b** and isobutyraldehyde (**9b**) using either method A or B produced a ratio of axial to equatorial substitution products (i.e., **10b**:**11b**) of approximately 1:1 following workup and purification. This reaction was chosen for these experiments because any change in diastereoselectivity in this reaction would be readily apparent as there was no appreciable selectivity displayed previously. Despite the success in controlling enolization using neutral alumina in the Diels−Alder reaction (**7d**), quenching $TiCl_4$ with triethylamine or methanol was viewed to be easier to carry out and more likely to become a general protocol if successful.

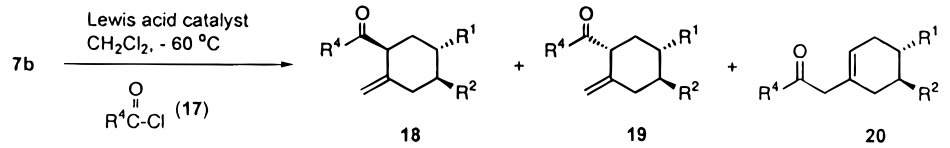
The substitution reaction was performed following method B, and when the reaction was judged to be complete by TLC analysis, 5 equiv of dry methanol was added at −5 °C and the mixture stirred for 20 min (see Scheme 7). Then, the mixture was diluted with ether and washed with saturated $NaHCO_3$ in the usual way.

The ^1H NMR spectrum of the crude mixture revealed that the equatorial substitution product **11b** was barely detectable (93% de). The ratio of axial to equatorial products was now 28:1 in stark contrast to the 1:1 mixture obtained previously. A similar result was observed when **7b** was reacted with propionaldehyde (**9a**) (Table 2, entries 5 and 6). In the absence of the methanol quench, the observed selectivity for **10a**:**11a** was approximately 4.5:1 (63% de). This ratio with the methanol quench improved to 9:1 (80% de).

These results confirm suspicions that enolization occurs to a large extent during aqueous workup. Although these experiments do not discount that enolization occurs during the substitution reaction itself, they indicate that it is a minor event if it does occur at all. Further, the active form of the titanium catalyst that promotes this isomerization is presumably $TiCl_3OR$. The excess methanol is thought to form $Ti(OCH_3)_4$, which is then too weak of a Lewis acid to promote enolization.

It is highly likely that the majority of electrophilic substitution reactions performed in this study using aldehyde electrophiles are highly stereoselective for the axial product. To our knowledge, the results reported here are the most highly selective electrophilic substitutions reported using cyclic allylsilanes of this type. Further, these results are important for any researcher working in the area of Lewis acid-promoted transformations that employ such sensitive substrates—particularly

Scheme 8



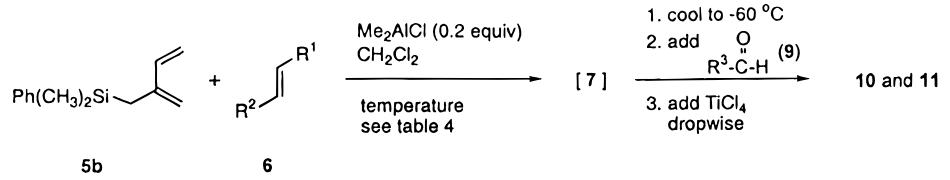
a: $R^1 = -COCH_3$, $R^2 = -H$, $R^4 = -CH_3$
b: $R^1 = -COCH_3$, $R^2 = -H$, $R^4 = -CH{=}CH\text{-}Ph$ (*E*)
c: $R^1 = -CO_2CH_3$, $R^2 = -H$, $R^4 = -CH{=}CH\text{-}Ph$ (*E*)
d: $R^1 = -CO_2CH_3$, $R^2 = H$, $R^4 = -Ph$
e: $R^1 = -C(O)CH_2CH_3$, $R^2 = -CH_3$, $R^3 = -Ph$

Table 3. Substitution Reaction Conditions with Cyclic Allylsilane Diels–Alder Adducts 7 and Acid Chloride Electrophiles 17 (See Scheme 8 for Structures)

entry	adduct	acid chloride	R^1	R^2	R^4	catalyst[a]	product no.	yield[g] (%) 18:19:20
1	**7c**	**17a**	$-COCH_3$	H	$-CH_3$	Me_2AlCl[b]	**18a, 19a, and 20a**	no reaction
2	**7c**	**17a**	$-COCH_3$	H	$-CH_3$	$Me_2AlCl/TiCl_4$[c]	**18a, 19a, and 20a**	24[h]/1.5:1:0
3	**7c**	**17a**	$-COCH_3$	H	$-CH_3$	$Me_2AlCl/AlCl_3$[d]	**18a, 19a, and 20a**	78/2.3:1.6:1
4	**7c**	**17a**	$-COCH_3$	H	$-CH_3$	$Me_2AlCl/AlCl_3$[e]	**18a, 19a, and 20a**	67/4.0:3.0:1
5	**7c**	**17a**	$-COCH_3$	H	$-CH_3$	$AlCl_3$[f]	**18a, 19a, and 20a**	85/2:1:7.6
6	**7c**	**17b**	$-COCH_3$	H	$-CH{=}CH-Ph$ (*E*)	$Me_2AlCl/AlCl_3$[d]	**18b, 19b, and 20b**	78/1.6:0.8:1
7	**7b**	**17b**	$-CO_2CH_3$	H	$-CH{=}CH-Ph$ (*E*)	$Me_2AlCl/AlCl_3$[d]	**18c, 19c, and 20c**	96/10.5:10:1
8	**7b**	**17b**	$-CO_2CH_3$	H	$-CH{=}CH-Ph$ (*E*)	$AlCl_3$[f]	**18c, 19c, and 20c**	87/2:1.7:1
9	**7b**	**17c**	$-CO_2CH_3$	H	$-Ph$	$Me_2AlCl/AlCl_3$[d]	**18d, 19d, and 20d**	68/1:1:1
10	**7d**	**17c**	$-COCH_2CH_3$	$-CH_3$	$-Ph$	Me_2AlCl / $AlCl_3$[d]	**18e, 19e, and 20e**	78/1:1.3:0

[a] In all cases, the silane was the limiting reagent and 1.5 equiv of the acid chloride was used. [b] Two equiv of catalyst was used. [c] Two equiv of $TiCl_4$ was used with 0.2 equiv of Me_2AlCl. [d] Two equiv of $AlCl_3$ were used with 0.2 equiv of Me_2AlCl. [e] Two equiv of $AlCl_3$ was used with 1.2 equiv of Me_2AlCl. [f] Two equiv of catalyst was used. [g] All reported yields are based on purified material following silica gel chromatography. [h] In addition to these products, 10% of **18** and **19** isomerized from the exocyclic methylene to the conjugated enone.

Scheme 9



5b 6

those in the area of asymmetric synthesis (e.g., Diels–Alder cycloaddition).

Transition States for Substitution Reaction. Transition states that would lead to the axial (i.e., **10**) and equatorial (i.e., **11**) substitution products obtained in this study are shown in Figure 4.[21] Although other transition states are possible, we do not believe that they are operative. We propose that the transition states leading the major (axial) product and the minor (equatorial) product, if in fact it is operative at all, both proceed via the antiperiplanar arrangements indicated. This places the bulky R-groups away from the ring in either case.[22] Further, we believe that reaction takes place mainly via the axial route shown (*vide supra*). If we assume that the bulky R-group never sits on top of the cyclohexene ring in any favorable transition state, favorable synclinal transition states would result in opposing stereochemistry at the carbinol site in both the major and minor isomers.

ii. Additions to Acid Chlorides. Electrophilic substitution with **7** and a range of acid chlorides (**17**) provided adducts **18**–**20** in good yield (see Scheme 8 and Table 3). The best results here were achieved using $AlCl_3$ catalysis (2.0 equiv) with 0.20 equiv of Me_2AlCl cocatalyst. In almost all cases, the ratio of *cis*:*trans* substitution adducts (**18**:**19**) was approximately 1:1. Similar stereoselectivity was observed by Pillot and co-workers in analogous substitutions with acid chlorides.[20] We believe that isomerization of these adducts, now containing two enolizable sites, is responsible to a large degree for the poor observed stereoselectivity. Elucidation of the structure of the products in this section was done in a manner similar to that discussed for the aldehyde substitution products (*vide supra*). The chemical shifts of exocyclic protons in the ^1H NMR spectra once again serve as a diagnostic marker for *cis* and *trans* substitution products.

Tandem Diels–Alder/Electrophilic Substitution Reactions. i. Step Two:Aldehyde Additions. For the majority of tandem reactions, the Diels–Alder reaction was performed using the optimal conditions of 0.2 equiv of Me_2AlCl in CH_2Cl_2 at either rt or at reflux (see Scheme 9 and Table 4). When cycloaddition was judged complete by TLC, the solution was cooled to −60 °C, and 1.0 equiv of the aldehyde was added followed by dropwise addition

(21) For early discussions concerning the origin of axial vs equatorial selectivity in additions to cyclohexene derivatives, see: (a) Allinger, N. L.; Riew, C. K. *Tetrahedron Lett.* **1966**, 1269–1272. (b) House, H. O.; Terfertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935–942. (c) Chamberlain, P.; Witham, G. H. *J. Chem. Soc, Perkin Trans. 2* **1972**, 130–135.

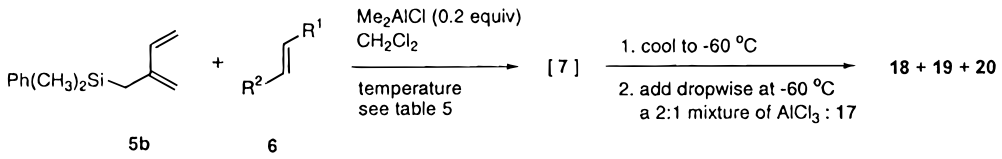
(22) For discussion concerning synclinal and antiperiplanar transition states in allylsilane substitution reactions, see: (a) Hayashi, H.; Ito, H.; Kumada, M. *Tetrahedron Lett.* **1982**, *23*, 4605–4606. (b) Hayashi, H.; Konishi, M.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 281–282. (c) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655–1660. (d) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, *59*, 5130–5132. (e) Denmark, S. E.; Hosoi, S. *J. Org. Chem.* **1994**, *59*, 5133–5135.

Table 4. Tandem Diels–Alder Cycloaddition/Aldehyde Substitution Sequence (See Scheme 9 for Structures)

entry	dienophile[a]	R^1	R^2	Diels–Alder T (°C)	second step	aldehyde	R^3	product no.	yield[b]/ **10**:**11**
1	**6a**	$-CO_2CH_3$	H	40		**9a**	$-CH_2CH_3$	**10a and 11a**	73/4.3:1
2	**6a**	$-CO_2CH_3$	H	40		**9b**	$-CH(CH_3)_2$	**10b and 11b**	41/2:1
3	**6a**	$-CO_2CH_3$	H	40		**9b**	$-CH(CH_3)_2$	**10b and 11b**	66[c]/2:1
4	**6a**	$-CO_2CH_3$	H	40		**9c**	$-CH_2CH_2Ph$	**10c and 11c**	59[d]/7:1
5	**6a**	$-CO_2CH_3$	H	40		**9c**	$-CH_2CH_2Ph$	**10c and 11c**	66/7:1
6	**6b**	$-COCH_3$	H	rt		**9a**	$-CH_2CH_3$	**10d and 11d**	75/3:1
7	**6b**	$-COCH_3$	H	rt		**9c**	$-CH_2CH_2Ph$	**10e and 11e**	56/4.2:1
8	**6b**	$-COCH_3$	H	rt		**9b**	$-CH(CH_3)_2$	**10f and 11f**	51/2.1:1
9	**6b**	$-COCH_3$	H	rt		**9b**	$-CH(CH_3)_2$	**10f and 11f**	57%[c]/3.1:1
10	**6c**	$-COCH_2CH_3$	$-CH_3$	rt		**9a**	$-CH_2CH_3$	**10g**	65/3:1
11	**6c**	$-COCH_2CH_3$	$-CH_3$	rt		**9b**	$-CH(CH_3)_2$	**10h and 11h**	53/*trans* only

[a] Diene **5b** was used for all tandem reactions. [b] All reported yields are based on purified material following silica gel chromatography. [c] Two equiv of the aldehyde was used in the second step in the sequence. [d] One equiv of $TiCl_4$ was used in the first step with no Me_2AlCl followed by addition of the aldehyde upon complete formation of **7b**.

Scheme 10



5b 6

Table 5. Tandem Diels–Alder Cycloaddition/Acid Chloride Substitution Sequence (See Scheme 10 for Structures)

entry	dienophile[a]	R^1	R^2	Diels–Alder T (°C)	second step	acid chloride	R^4	product no.	yield[b]/ **18**:**19**:**20**
1	**6b**	$-COCH_3$	$-H$	40		**17a**	$-CH_3$	**18a, 19a, and 20a**	71/1.9:1.5:1
2	**6b**	$-COCH_3$	$-H$	40		**17b**	$-CH{=}CHPh$ (*E*)	**18b, 19b, and 20b**	70%/ 1.1:0.6:1
3	**6a**	$-CO_2CH_3$	$-H$	rt		**17b**	$-CH{=}CHPh$ (*E*)	**18c, 19c, and 20c**	73/20:17:1
4	**6a**	$-CO_2CH_3$	$-H$	rt		**17c**	$-Ph$	**18d, 19d, and 20d**	54/1.1:1.1:1
5	**6c**	$-COCH_2CH_3$	$-CH_3$	rt		**17v**	$-Ph$	**18e, 19e, and 20e**	79/ 1:1.1:0

[a] Diene **5b** was used for all tandem reactions. [b] All reported yields are based on purified material following silica gel chromatography.

of $TiCl_4$ (1.1 equiv). In each case, the yield of the tandem sequence was higher than the overall yield of the pericyclic and ionic reactions performed independently. Clearly, the reduction in product handling is playing a major role in this improvement in synthetic efficiency. Within experimental limits, the ratios of *cis* and *trans* products from the independent substitution reactions and tandem sequences are the same. Of course, this would be expected on the basis of the epimerization studies outlined above.

ii. Step Two:Acid Chloride Additions. In light of the fact that Me_2AlCl was used in the Diels–Alder reaction, all tandem runs therefore used the cocatalyst system (see Scheme 10 and Table 5). When the cycloaddition was complete, the mixture was cooled and the electrophile solution added. This mixture was prepared by combining $AlCl_3$ (2.0 equiv) with Me_2AlCl (0.3 or 1.2 equiv) in CH_2Cl_2 at rt, stirring for 20 min, and then adding the requisite acid chloride. This slurry was cooled to −65 °C, stirred until homogeneity was reached, and then transferred to the flask containing the cycloaddition intermediate **7**. Unlike the tandem runs with aldehyde electrophiles, there was not a profound increase in yield over the product of the two steps performed independently. The protodesilylated cycloadduct **8** will react also with the acylium ion, thus contributing to overall yield. In the aldehyde case, once protodesilylation occurred, the olefin is no longer nucleophilic enough to promote substitution. Therefore, there is no reason to expect a major difference in yield for substitutions with acid chloride electrophiles. That being said, all tandem yields are quite comparable to those obtained by performing the operations separately, indicating that this is still a highly efficient one-pot sequence.

Protodesilylation Studies. The principal cause of reduced yields in both the Diels–Alder and substitution reactions with aldehydes is protodesilylation of the allylsilane moiety of cycloadducts **7** (see Tables 1 and 2). The presence of Me_2AlCl in either the Diels–Alder or substitution reaction mixtures dramatically increases the yield of these transformations. This can be seen when the yields of the tandem procedure employing aldehyde electrophiles are compared with the results of the substitution reaction itself. In most cases, the overall yield of the tandem procedure was superior to the yield of the corresponding substitution reaction with **7** and the same electrophiles. This is seen upon inspection of Table 2, entries 5, 10, and 12 vs Table 4, entries 1, 5, and 6, respectively. If the Diels–Alder reactions are quantitative with 1:1 stoichiometry of the diene and dienophile as indicated by the high yields shown in Table 1, the only possible difference between the tandem run following the cycloaddition and the independent substitution reaction is the presence of Me_2AlCl. To verify any involvement of this catalyst in yield enhancement, 0.2 equiv of Me_2AlCl was added to substitution reaction mixtures and then they were allowed to proceed as usual. In most cases, the yield increased significantly (see Table 2, entries 8, 11, 13, 15, and 17).

Allylsilanes are protodesilylated by Brønsted acid as either a planned procedure[17] or as an undesired side reaction.[18] It is possible that Me_2AlCl is serving as a proton scavenger in the present study and is essentially cleaning the $TiCl_4$ *in situ* as has been suggested previ-

ously.[23,24] Although this appears to be a reasonable explanation for the substitution results, it is unlikely that the trace amount of acid present in the reaction mixtures in this study (presumably from $TiCl_4$) could be responsible for the amount of protodesilylation observed in the Diels−Alder reaction (Table 1, entry 5). However, several equivalents of HCl would be produced upon aqueous catalyst quench with saturated $NaHCO_3$. Perhaps the biphasic nature of the quench prevents the acid from being consumed by the base before it effects protodesilylation of the allylsilane moiety in **7**.

A series of experiments was conducted to try to pinpoint when protodesilylation was occurring to better understand the process. One tandem sequence was performed using $TiCl_4$ to compare with the standard conditions that use Me_2AlCl during the cycloaddition followed by $TiCl_4$ for the substitution. The yield with Me_2AlCl was approximately 7% better than without it (Table 4, entries 4 and 5), which is a significant difference, but not a large one. This result is in stark contrast to the 38% yield obtained for the Diels−Alder result catalyzed with $TiCl_4$ (Table 1, entry 5). It was not clear how the two-step tandem yield with $TiCl_4$ (59%) could be so much higher than the Diels−Alder result by itself. To this end, the course of the $TiCl_4$-catalyzed Diels−Alder reaction leading to the formation of **7b** was followed by ^1H NMR spectroscopy, and the spectra are shown in Figure 5.

With 20 mol % $TiCl_4$, the cycloaddition required several hours to complete, and only a trace amount of **8b** was visible at the end (Figure 5D, $T = 18$ h). A similar result was found when 1.0 equiv of $TiCl_4$ was used. In this case, the reaction was complete in 13 min. However, when the catalytic reaction was worked up in the usual way ($NaHCO_3$ quench and ether extraction), the ^1H NMR spectrum of the crude material revealed that 52% of **7b** had protodesilylated (Figure 5E). These results cast serious doubt that protodesilylation occurs during the cycloaddition, but rather occurs on aqueous workup, even though the work-up conditions are basic.

In the tandem experiments using aldehyde electrophiles, allylsilanes **7** were both formed and reacted *in situ*, thus minimizing protodesilylation, which illustrates one clear advantage of this tandem strategy. This was confirmed in a separate ^1H NMR experiment. Using 1.0 equiv of $TiCl_4$, **7b** was both formed and subsequently reacted with propionaldehyde in a single NMR tube, providing the tandem products **10c** and **11c** with minimal formation of **8c**. This is consistent with the results discussed above for the tandem reaction using $TiCl_4$ catalysis alone that provided results similar to those obtained when the cocatalyst Me_2AlCl was used (entries 4 and 5 in Table 4).

In another protodesilylation study, the effect of Me_2AlCl in a substitution reaction with acetyl chloride was studied (see Scheme 8 and Table 3, entries 3−5). When the reaction was catalyzed with $AlCl_3$ alone, the ratio of products resulting from inversion:retention, i.e., **18c** + **19c**:**20c**, was 1:2.5. Pretreating the $AlCl_3$/acid chloride mixture with 0.2 equiv of Me_2AlCl prior to silane addition

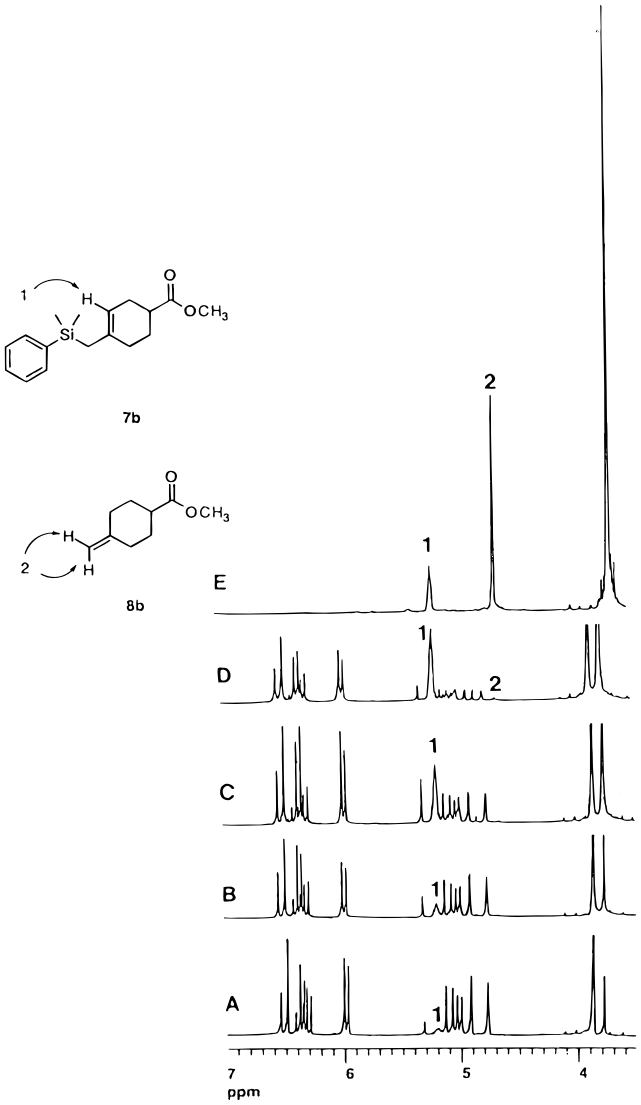


Figure 5. ^1H NMR spectra from 3.5 to 7.0 PPM of the Diels−Alder cycloaddition between **5b** and **6a** (1.5:1) using 20 mol % $TiCl_4$ in CD_2Cl_2. Spectra were taken at 3 min (A), 10 min (B), 60 min (C), 18 h (D), and following quench with saturated $NaHCO_3$ and aqueous workup (i.e., crude; E). The peak denoted as "1" is the signal for the vinyl proton on **7b**, while the peak denoted as "2" is the signal for the equivalent exocyclic methylene protons of the protodesilylated product **8b**. Peaks centered at 5.98, 6.35, and 6.52 are vinyl signals from **6a**, while those at 4.78, 4.92, 5.04, and 6.35 (overlapping with those of **6a**) are vinyl signals from **5b**.

inverted this ratio to 4:1. When 1.2 equiv of Me_2AlCl was employed, the ratio widened to 7:1.

These results suggest that substitution occurs by two different pathways of similar mechanism. Brønsted acid present in the reaction flask could have protodesilylated **7c**, providing **8c**, and formation of **20** arises by Friedel−Crafts acylation on the trisubstituted olefin.[25] The regioselectivity of the substitution with **8c** is determined by the stability of the tertiary cation intermediate formed on the way to **20c**, the apparent product of retention. In the absence of Brønsted acid, which has been removed by the Me_2AlCl prior to silane addition, "normal" allylsilane attack on the electrophile occurs providing the

(23) The role of the proton scavenger in such reactions was initially proposed by Snider; see: (a) Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealfon, S. *J. Am. Chem. Soc.* **1979**, *101*, 5285−5293. (b) Snider, B. B.; Rodini, D. J. *Tetrahedron Lett.* **1980**, *21*, 1815−1818.

(24) Monti, H.; Audran, G.; Monti, J.-P.; Leandri, G. *J. Org. Chem.* **1996**, *61*, 6021−6023.

(25) A similar rationale for analogous substitutions involving allylsilanes and acid chlorides has been proposed by other groups; see: (a) Polla, M.; Frejd, T. *Acta Chem. Scand.* **1993**, *47*, 716- 720. (b) Also see ref 20.

product of inversion (i.e., **18c** and **19c**). The presence of acid is no doubt highly variable in Friedel−Crafts reactions because it can enter the reaction flask from a number of sources including the catalyst (i.e., $AlCl_3$) and the acid chloride reagent that inevitably contains some amount of the carboxylic acid. The amount of acid present dictated which of these pathways dominates.

The cocatalyst system developed herein provides a *convenient and reliable method* for controlling the mechanism of allylsilane substitution with acid chloride electrophiles. Pillot had reported that when the acid chloride/$AlCl_3$ complex was added to the allylsilane, rather than the reverse, the product of allyl inversion was isolated as the major product and in good yield.[20] In our hands, we could not reproduce this effect by altering the order of addition of reaction components. With our substrates, the yield and ratio of products of inversion and retention did not vary greatly regardless of the order of addition. However, use of the cocatalyst system has provided nearly complete control over this reaction.

Conclusions and Future Considerations

Results presented in this report indicate that pericyclic [4 + 2] cycloaddition and ionic allylsilane substitution reactions can be combined effectively in a sequential fashion. Further, these sequences are highly efficient when compared to the same reactions performed independently in terms of yield. That is, yield is at least as good in the tandem sequences as it is the for the overall yield of the reactions performed independently. Further, this is accompanied by no significant changes in regio- or stereoselectivity. The products obtained in this study also illustrate a rapid buildup of molecular complexity from very simple starting materials.

A cocatalyst system employing Me_2AlCl and $TiCl_4$ has been developed that exhibits dramatic effects on yields in substitution reactions employing allylsilane nucleophiles and aldehyde electrophiles. The proposed role of Me_2AlCl is that of a proton scavenger that is "cleaning" the stronger $TiCl_4$ catalyst that is necessary to promote the electrophilic substitutions with aldehyde electrophiles.[23]

The presence of Me_2AlCl in the reaction medium of Friedel−Crafts acylation reactions employing allylsilanes has demonstrated remarkable effects on regioselectivity. The cocatalyst is presumably consuming Brønsted acid that otherwise would be involved in protodesilylating the starting silane, thus altering the reaction pathway. Further, we believe that more experimentation with this cocatalyst system will result in reliable regioselectivity in these acylation reactions.

The selectivity demonstrated in the substitution reactions involving aldehyde electrophiles is, to the best of our knowledge, the most selective of any substitution reaction employing such cyclic allylsilane nucleophiles. It has also been demonstrated that this result is only observable when care is taken to decompose the highly reactive titanium species present following substitution to prevent isomerization during aqueous workup. This was accomplished by the addition of anhydrous methanol prior to aqueous workup. These results demonstrate that cyclic allylsilane substrates of this type, which, by-in-large, have been ignored synthetically, could be used in a reliable fashion to set the stereochemistry of contiguous centers off the carbocycle.

These results give a strong indication that this tandem sequence can be carried out asymmetrically in the Diels−Alder step using either chiral catalysts or a chiral auxiliary on the dienophile to provide useful optically enhanced (pure) building blocks.[26] In fact, some excellent enantiomeric excesses have been achieved already using **5a** with a chiral copper catalyst.[26c]

In addition to continuing to explore the all-carbon system in these tandem studies using allylsilanes, we are currently exploring a number of projects stemming from these initial studies. Diels−Alder reactions employing glyoxylic acid derivatives[27,28] as dienophiles followed by electrophilic substitution with aldehyde electrophiles has already yielded promising results in the pursuit of substituted pyran-based targets. The use of aza dienes[29] to produce pyridine- and piperidine-based molecules are similarly being pursued. These results will be reported in due course.

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of dry argon unless otherwise indicated. Solvents were distilled prior to use: Et_2O was distilled from sodium benzophenone; CH_2Cl_2 was distilled from CaH_2. All $TiCl_4$ used in these studies was drawn from a sample that had been distilled and stored in an air-free storage flask equipped with a glass 14/20 joint (sealed with fluorine-based grease) through which needles were inserted while the flask was under a positive pressure of dry argon that was supplied through a side arm equipped with a Teflon needle valve. A distilled sample of $TiCl_4$ was used over a maximum period of 3 weeks, at which time it was redistilled. Melting points are uncorrected. Unless otherwise indicated, ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$. Chemical shifts are listed relative to $CHCl_3$ (δ 7.24) for ^1H NMR and (δ 77.00) for ^{13}C NMR.

Preparations and spectral data not included here have been published previously.[3] However, the general procedures for all procedures have been included here along with the spectral data for previously unreported structures.

Methyl 4-[(Trimethylsilyl)methyl]-3-cyclohexenecarboxylate (7a). The following general procedure was used for all cycloadditions unless noted otherwise. To a flame-dried flask equipped with a stir bar was added 3 mL of dry CH_2Cl_2, 42 mg of **5a** (0.30 mmol), and 48 mg of methyl acrylate (**6a**) (0.56 mmol). This was followed by dropwise addition of dimethylaluminum chloride (60 μL of a 1 M solution, 0.06 mmol). The mixture was heated to reflux for 3 h, cooled to rt, and quenched with saturated $NaHCO_3$. The layers were

(26) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (b) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (c) Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616−9617.

(27) For Diels−Alder reactions using aldehyde dienophiles, see: (a) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087−3128. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(28) (a) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, 4607−4610. (b) Schmidt, R. R.; Abele, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 302−304. (c) Schmidt, R. R.; Wagner, A. *Tetrahedron Lett.* **1983**, *24*, 4661−4664. (d) Jurczak, J.; Golebiowski, A.; Rahm, A. *Tetrahedron Lett.* **1986**, *27*, 853−856. (e) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1985**, *26*, 5175−5178. (f) Hosomi, A.; Otaka, K.; Sakurai, H. *Tetrahedron Lett.* **1986**, *27*, 2881−2884.

(29) (a) Fitton, A. O.; Frost, J. R.; Houghton, P. G.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1450−1463. (b) Moore, H. W.; Hughes, G. M. *Tetrahedron Lett.* **1982**, *23*, 4003- 4006. (c) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983**, *48*, 2499−2502. (d) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781−793. (e) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869−2939. (f) Ohshiro, Y.; Komatsu, M.; Uesaka, M.; Agawa, T. *Heterocycles* **1984**, *22*, 549−559. (g) Boger, D. L.; Honda, T.; Dang, Q. *J. Am. Chem. Soc.* **1994**, *116*, 5619−5630. (h) González, C.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1995**, *60*, 6318−6326. (i) Pérez, D.; Burés, G.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1996**, *61*, 1650−1654.

separated, and the aqueous layer was twice extracted with ether. The pooled organic fraction was washed with water and dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (2% ether in hexanes), providing 60 mg of **7a** as a clear colorless liquid (88% yield). All spectra correspond to that previously reported.[19]

Dimethyl 4-[(Dimethylphenylsilyl)methyl]-4-cyclohexene-1,2-dicarboxylate (7e). Following the general cycloaddition procedure, 75 mg of **5b** (0.37 mmol), 36 mg of dimethyl fumarate (**6d**) (0.25 mmol), and 23 mg of dimethylaluminum chloride (250 μL of a 1 M solution, 0.25 mmol) provided, following flash chromatography (20% ether in hexanes), 77 mg of allylsilane **7e** as a clear colorless liquid (89% yield): IR (thin film) 3070, 3000, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.43 (m, 2 H), 7.37−7.30 (m, 3 H), 5.15 (s, 1 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 2.83−2.66 (m, 2 H), 2.41−2.29 (m, 1 H), 2.21−1.91 (m, 3 H), 1.64 (s, 2 H), 0.28 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—sevens up (+), odds down (−)) δ 175.5 (+), 175.2 (+), 138.6 (+), 133.5 (−), 133.1 (+), 129.0 (−), 127.7 (−), 117.2 (−), 51.8 (−), 41.8 (−), 41.1 (−), 33.3 (+), 28.1 (+), 26.4 (+), −2.9 (−), −3.0 (−); HRMS calcd for $C_{19}H_{26}O_4Si$ 346.1601, found 346.1598.

***cis*-4-[(Dimethylphenylsilyl)methyl]-4-cyclohexene-1,2-dicarboxylic anhydride (7g).** To a flame-dried flask equipped with a stir bar was added 5.0 mL dry CH_2Cl_2, 100 mg of **5b** (0.49 mmol), and 66 mg of maleic anhydride (**6e**) (0.67 mmol). The reaction mixture was heated to reflux for 5 h and cooled to rt. Following solvent removal *in vacuo*, the product was purified by flash chromatography (60% ether in hexanes), providing 132 mg of **7f** as a clear colorless liquid (89% yield): IR (thin film) 3070, 3048, 1843, 1778 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.44 (m, 2 H), 7.38−7.31 (m, 3 H), 5.40 (m, 1 H), 3.21 (m, 2 H), 2.50 (dd, J = 14.7, 6.6 Hz, 1H), 2.32−1.97 (m, 3 H), 1.89 (d, J = 13.2 Hz, 1 H), 1.72 (d, J = 13.2 Hz, 1 H), 0.28 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.43, 174.22, 137.99, 136.39, 133.42, 129.12, 127.77, 117.89, 39.98, 39.36, 29.48, 28.06, 24.05, −2.95, −3.24; HRMS calcd for $C_{17}H_{20}O_3Si$ 300.1182, found 300.1188.

General Procedure for Electrophilic Substitution with Aldehydes and Diels−Alder Adducts 7. To avoid a very lengthy section here, one experimental procedure for each set of electrophilic substitution conditions is discussed in detail along with the appropriate spectral data for those compounds. Every substitution indicated on Table 2 was done using either method A or B on the same scale. Also included is the general procedure for the tandem Diels−Alder/electrophilic substitution sequence using aldehyde electrophiles.

Method A: Methyl 3-(1-Hydroxypropyl)-4-methylenecyclohexanecarboxylate (10a and 11a). To a flame-dried flask equipped with a stir bar was added 3.0 mL of dry CH_2Cl_2, 100 mg of **7b** (0.35 mmol), and 24 mg of propionaldehyde (**9a**) (0.39 mmol). After the solution was cooled to −60 °C, 66 mg of $TiCl_4$ (0.35 mmol) was added dropwise, producing an orange solution. After being stirred for 1 h, the mixture was allowed to warm to −10 °C, at which point the reaction was quenched with saturated $NaHCO_3$. The layers were then separated, and the aqueous layer was twice extracted with ether. The pooled organic layers were then dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (45% ether in hexanes), providing 45 mg of combined products (**10a:11a**, 4.3:1, 61% yield).

Method B: Methyl 3-(1-Hydroxy-2-methylpropyl)-4-methylenecyclohexane carboxylate (10b and 11b). To a flame-dried flask equipped with a stir bar was added 0.75 mL of dry CH_2Cl_2, 50 mg of **7b** (0.17 mmol), and 14 mg of isobutyraldehyde (**9b**) (0.19 mmol). After the mixture was cooled to −60 °C, 3.2 mg of dimethylaluminum chloride (35 μL of a 1.0 M solution, .035 mmol) was added dropwise. In a separate flame-dried flask equipped with a stir bar was added 0.5 mL of dry CH_2Cl_2, 3.2 mg of dimethylaluminum chloride (35 μL of a 1 M solution, 0.35 mmol), and 36 mg of $TiCl_4$ (0.19 mmol). This yellow solution was stirred for 20 min at rt, cooled to −60 °C, and added by cannula to the allylsilane solution, generating an orange solution. After being stirred for 1 h, this mixture was allowed to warm to −10 °C, at which point the reaction was quenched with saturated $NaHCO_3$. The layers were then separated, and the aqueous layer was twice extracted with ether. The pooled organic layers were then dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (35% ether in hexanes), providing 27 mg of combined products (**10b:11b**, 1.3:1, 70% yield).

General Procedure for Tandem Reaction Using an Aldehyde in the Second Step. The following procedure was used for all tandem reactions involving diene **5b**, dienophiles **6**, and aldehydes **9**.

Methyl 3-(1-Hydroxy-3-phenylpropyl)-4-methylenecyclohexanecarboxylate (10c and 11c). To a flame-dried flask equipped with a stir bar was added 3.0 mL of dry CH_2Cl_2, 100 mg of **5b** (0.49 mmol), and 43 mg of methyl acrylate (**6a**) (0.49 mmol) followed by dropwise addition of 9.3 mg of dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol). The mixture was heated to reflux for 4 h, at which time the cycloaddition was judged complete and the solution was cooled to −60 °C. Seventy-two mg of hydrocinnamaldehyde (**9c**) (0.54 mmol) was added, followed by 102 mg of $TiCl_4$ (0.54 mmol), producing a red mixture.

After being stirred for 1 h, the mixture was allowed to warm to −10 °C, at which point the reaction was quenched with saturated $NaHCO_3$. The layers were then separated, and the aqueous layer was twice extracted with ether. The pooled organic layers were then dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (35% ether in hexanes), providing 93 mg of combined products (**10c:11c**, 7:1, 66% yield).

***trans*-1-(5-Acetyl-2-methylenecyclohexyl-2-oxopropane (12).** To a flame-dried flask equipped with a stir bar was added 1.5 mL of dry CH_2Cl_2, 23 mg of **10d** (0.12 mmol), and 76 mg of pyridinium chlorochromate (PCC) (0.35 mmol). This dark mixture was stirred at room temperature for 30 h and quenched with saturated NH_4Cl. The layers were separated and the aqueous layer twice extracted with ether. The pooled organic phase was dried over anhydrous $MgSO_4$, and solvent was removed *in vacuo*. Flash chromatography (30% ether in hexanes) provided 12 mg of **12** as a clear oil (51% yield): IR (thin film) 3080, 1716, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.79 (s, 1 H), 4.35 (s, 1 H), 3.13 (dd, J = 11.8, 3.7 Hz, 1 H), 2.67−2.34 (m, 4 H), 2.17−2.05 (m, 1 H), 2.13 (s, 3 H), 2.01−1.91 (m, 2 H), 1.78 (q, J = 11.8 Hz, 1 H), 1.48 (qd, J = 11.8, 3.7 Hz, 1 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 212.01 (+), 210.33 (+), 146.47 (+), 108.84 (+), 54.75 (−), 49.97 (−), 35.71 (+), 35.16 (+), 30.80 (+), 29.56 (+), 27.77 (−), 7.57 (−); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1312.

***cis*-1-(5-Acetyl-2-methylenecyclohexyl-2-oxopropane (13).** Following the protocol for the preparation of **12**, 25 mg of **11d** (0.13 mmol) and 82 mg of PCC (0.38 mmol) in 1.5 mL of CH_2Cl_2 gave following flash chromatography (20% ether in hexanes) 9 mg of **13** as a clear oil (36% yield): IR (thin film) 3075, 1713, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.94 (m, 1 H), 4.90 (m, 1 H), 3.35 (m, 1 H), 2.87 (tt, J = 11.8, 3.7 Hz, 1 H), 2.61−2.38 (m, 2 H), 2.34−2.24 (m, 1 H), 2.15 (s, 3 H), 2.05−1.89 (m, 2 H), 1.51−1.15 (m, 3 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 211.62 (+), 211.31 (+), 145.27 (+), 113.22 (+), 54.94 (−), 46.45 (−), 33.40 (+), 32.03 (+), 29.27 (+), 29.14 (+), 28.43 (−), 7.84 (−); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1313.

4-Ethyl-1-[(dimethylphenylsilyl)methyl]-1-cyclohexene (14). To a flask equipped with a stir bar was added 1 mL of dry ethanol, 539 mg of **5b** (1.98 mmol), and 369 mg of *p*-toluenesulfonylhydrazide (1.98 mmol). The mixture was heated to reflux for 2 h and allowed to gradually cool to rt, at which time the formation of white crystals was observed. The slurry was cooled further in an ice bath, and the crystals were collected by vacuum filtration. These crystals were dried under high vacuum and used directly in the reduction. To a flame-dried flask was added 6 mL of dry THF and 300 mg of the crude hydrazone (0.68 mmol). The solution was cooled to 0 °C and 52 mg of $LiAlH_4$ (1.36 mmol) added slowly. The

mixture was heated to reflux for 12 h. After the mixture was cooled to rt, 25 mg of water was added followed by 40 μL of a 1 M NaOH solution. The solution was stirred for 30 min and then dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (straight hexanes), providing 20 mg of **14** (11% yield) as a clear, colorless oil: IR (thin film) 3069 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53−7.46 (m, 2 H), 7.37−7.30 (m, 3 H), 5.18 (m, 1 H), 2.11−1.99 (m, 1 H), 1.94−1.51 (m, 4 H), 1.63 (s, 2 H), 1.35−1.02 (m, 4 H), 0.87 (t, *J* =7.4 Hz, 3 H), 0.27 (s, 3 H), 0.26 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.59, 134.58, 133.58, 128.78, 127.62, 119.27, 35.13, 31.90, 31.19, 29.14, 29.08, 26.69, 11.54, −2.74; HRMS calcd for $C_{17}H_{26}Si$ 258.1805, found 258.1803.

1-(5-Ethyl-2-methylenecyclohexyl)-1-propanol (15 and 16). Following the protocol for the preparation of **10b** and **11b** (i.e., method B), 42 mg of **14** (0.16 mmol), 10 mg of propionaldehyde (**9a**) (0.18 mmol), 34 mg of $TiCl_4$ (0.18 mmol), and 47 mg of dimethylaluminum chloride (50 μL of a 1 M solution, 0.05 mmol) in 2 mL of dry CH_2Cl_2 gave, after flash chromatography (5% ether in hexanes), 17 mg of combined products (**15**:**16**, 27:1, 60% yield). Compounds **15** and **16** were inseparable, and the ratio of each was determined by ^1H NMR spectroscopy on both the crude mixture and purified sample using the well-dissolved vinyl proton signals (see text for discussion). The spectral data for **15**, the major isomer, are included here: IR (thin film) 3362, 3070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.68−4.63 (m, 2 H), 3.69 (td, *J* = 9.6, 3.0 Hz, 1 H), 2.22−1.00 (m, 13 H), 0.94 (t, *J* = 7.4 Hz, 3 H), 0.89 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 150.29 (+), 109.28 (+), 71.62 (−), 50.03 (−), 34.63 (+), 34.19 (+), 33.55 (−), 32.19 (+), 29.48 (+), 28.16 (+), 11.57 (−), 9.89 (−); HRMS calcd for $C_{12}H_{22}O$ 182.1672, found 182.1665.

General Procedure for Electrophilic Substitution with Acid Chlorides and Diels−Alder Adducts 7 Using $AlCl_3$ Catalysis. Substitution reactions using this catalyst system, as indicated in Table 3, were carried out using the following general procedure.

1,3-Diacetyl-4-methylenecyclohexane (18a and 19a) plus Regioisomer 20a. To a flame-dried flask equipped with a stir bar was added 2.0 mL of dry CH_2Cl_2, and 48 mg of $AlCl_3$ (0.36 mmol). The mixture was cooled to −65 °C, and 22 mg of acetyl chloride (**17a**) (0.27 mmol) was added. After the mixture was stirred for 10 min, 50 mg of **7c** was added dropwise, and the solution was allowed to warm gradually to −10 °C. The reaction was then diluted with ether and quenched with saturated $NaHCO_3$. The layers were separated, and the aqueous phase was extracted twice with ether. The combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (20% ether in hexanes), providing 27.5 mg of combined products (**18a**:**19a**:**20a**, 2:1:7.6, 85% yield). Compound **18a** was cleanly separable from **19a** and **20a**, which could only be isolated together as a mixture. Ratios were determined by ^1H NMR spectroscopy on both the crude mixture and purified sample of **19a** and **20a** using the well-resolved vinyl proton signals (see text for discussion).

18a: a clear, colorless oil; IR (thin film) 3075, 1713, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.95 (s, 1 H), 4.92 (s, 1 H), 3.33 (m, 1 H), 2.81 (tt, *J* =11.8, 3.7 Hz, 1 H), 2.34−2.25 (m, 2 H), 2.13 (s, 3 H), 2.12 (s, 3 H), 2.03−1.89 (m, 2 H), 1.50−1.20 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 211.12 (+), 208.91 (+), 145.08 (+), 113.43 (+), 55.86 (−), 46.35 (−), 31.97 (+), 29.25 (+), 28.83 (+), 28.33 (−), 27.86 (−); HRMS calcd for $C_{11}H_{16}O_2$ 180.1151, found 180.1152.

Compounds **19a** and **20a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.52 (br s), 4.81 (s), 4.42 (s), 3.09 (dd, *J* = 11.8, 3.7 Hz), 3.00 (s), 2.59−2.37 (m), 2.18 (s), 2.13 (s), 2.12 (s), 2.08 (s), 2.01−1.89 (m), 181−1.67 (m), 1.63−1.38 (m).

General Procedure for Electrophilic Substitution with Acid Chlorides and Diels−Alder Adducts 7 using $AlCl_3$/Me_2AlCl Catalysis. Substitution reactions using this catalyst system, as indicated in Table 3, were carried out using the following general procedure.

1-Acetyl-4-methylene-3-((*E*)-3-phenyl-1-oxo-2-propenyl)-cyclohexane (18b and 19b) plus Regioisomer 20b. To a flame-dried flask equipped with a stir bar was added 1.5 mL of dry CH_2Cl_2, 50 mg of **7c** (0.18 mmol), and 4 mg of dimethylaluminum chloride (54 μL of a 1 M solution, 0.054 mmol). In a separate flame-dried flask equipped with a stir bar were added 48 mg of $AlCl_3$ (0.50 mmol), 0.75 mL of dry CH_2Cl_2, and 2 mg of dimethylaluminum chloride (25 μL of a 1 M solution, 0.025 mmol). This yellow slurry was stirred for 20 min at rt, 46 mg of cinnamoyl chloride (**17b**) (0.28 mmol) was added, and both solutions were cooled to −60 °C. The acid chloride solution was added by cannula to the allylsilane solution generating a yellow mixture that was allowed to warm gradually to −10 °C. Following dilution with ether, the mixture was quenched with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was twice extracted with ether. The organic layers were combined and dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (11% ether in hexanes), providing 53 mg of combined products (**18b**:**19b**:**20b**, 1.6:0.8:1, 78% yield). Compound **18b** was cleanly separable from **19b** and **20b**, which could only be isolated together as a mixture. Ratios were determined by ^1H NMR spectroscopy on both the crude mixture and purified sample of **19b** and **20b** using the well-resolved vinyl proton signals (see text for discussion).

18b: white crystals; mp 105.9−107.3 °C; IR (thin film): 3078, 3062, 1710, 1683 cm^{-1}; H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, *J* = 16.2 Hz, 1 H), 7.56−7.48 (m, 2 H), 7.39−7.33 (m, 3H), 6.99 (d, *J* = 16.2 Hz, 1 H), 5.03−4.99 (m, 2 H), 3.60−3.55 (m, 1 H), 2.94 (tt, *J* = 11.8, 3.7 Hz, 1 H), 2.46−2.36 (m, 1 H), 2.32 (dt, *J* = 14.0, 3.7 Hz, 1 H), 2.17 (s, 3 H), 2.15−1.92 (m, 2H), 1.67−1.53 (m, 1 H), 1.40 (qd, *J* = 11.8, 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.30, 199.11, 145.27, 142.80, 134.44, 130.48, 128.85, 128.40, 122.89, 113.40, 54.49, 46.42, 32.16, 29.37, 29.22, 28.40. Anal. Calcd for $C_{18}H_{20}O_3$: C, 80.56; H, 7.51. Found: C, 80.21; H, 7.54.

Compounds **19b** and **20b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61(d, *J* = 13.2 Hz), 7.56−7.49 (m), 7.40−7.34 (m), 6.84 (d, *J* = 15.5 Hz), 6.76 (d, *J* = 16.2 Hz), 5.61 (br s), 4.85 (s), 4.51 (s), 3.37 (dd, *J* = 11.8, 3.8 Hz), 3.26 (m), 2.63−2.44 (m), 2.16 (s), 2.15 (s), 2.26−1.43 (m).

General Procedure for Tandem Reactions Using an Acid Chloride in the Second Step: Methyl 4-Methylene-3-((*E*)-3-phenyl-1-oxo-2-propenyl)cyclohexanecarboxylate (18c and 19c) plus Regioisomer 20c. To a flame-dried flask equipped with a stir bar was added 2.0 mL of dry CH_2Cl_2, 100 mg of 2-[(dimethylphenylsilyl)methyl]-1,3-butadiene (**5b**) (0.49 mmol), and 42 mg of methyl acrylate (**6a**) (0.49 mmol). This was followed by dropwise addition of 14 mg of dimethylaluminum chloride (150 μL of a 1 M solution, 0.15 mmol). The mixture was stirred at rt for 4 h, at which time the cycloaddition was judged complete and the solution was cooled to −65 °C. In a separate flame-dried flask equipped with a stir bar was added 131 mg of $AlCl_3$ (0.98 mmol), 1.5 mL of dry CH_2Cl_2, and 5 mg of dimethylaluminum chloride (47 μL of a 1 M solution, 0.047 mmol). This yellow slurry was stirred for 20 min at rt, and 123 mg of cinnamoyl chloride (**17b**) (0.74 mmol) was added. After the solution was cooled to 65 °C, the acid chloride solution was added by cannula, generating a yellow mixture that was allowed to warm gradually to −10 °C. At that point, the mixture was diluted with ether and quenched with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was twice extracted with ether. The combined organic phase was then washed with water and dried over anhydrous $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (11% ether in hexanes), providing 102 mg of combined product (**18c**:**19c**:**20c**, 20:17:1, 73% yield).

18c: white needles recrystallized from hexanes; mp 89.2−90.3 °C; IR (thin film) 3060, 3028, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, *J* =16.2 Hz, 1 H), 7.56−7.47 (m, 2 H), 7.40−7.31 (m, 3 H), 6.97 (d, *J* =16.2 Hz, 1 H), 5.00 (s, 1 H), 4.96 (s, 1 H), 3.65 (s, 3 H), 3.56 (m, 1 H), 2.88 (tt, *J* =11.8, 3.7 Hz, 1 H), 2.44 (m, 1 H), 2.37−2.24 (m, 1 H), 2.15−1.95 (m, 2 H), 1.80-1.67 (m, 1 H), 1.63−1.47 (m, 1 H); ^{13}C NMR ($CDCl_3$,

75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 198.91 (+), 175.80 (+), 145.32 (+), 142.69 (−), 134.48 (+), 130.42 (−), 128.83 (−), 128.36 (−), 123.15 (−), 113.07 (+), 54.18 (−), 51.58 (−), 38.57 (−), 32.11 (+), 30.06 (+), 29.90 (+). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.95; H, 7.11.

19c: colorless oil; IR (thin film) 3081, 3027, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 77.60 (d, J = 16.2 Hz, 1 H), 7.56−7.49 (m, 2 H), 7.40−7.33 (m, 3 H), 6.83 (d, J = 16.2 Hz, 1 H), 4.85 (s, 1 H), 4.50 (s, 1 H), 3.66 (s, 3 H), 3.35 (m, 1 H), 2.63-2.42 (m, 2 H), 2.34−1.51 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 199.83 (+), 175.08 (+), 146.03 (+), 142.44 (−), 134.44 (+), 130.46 (−), 128.87 (−), 128.36 (−), 125.38 (−), 109.91 (+), 53.73 (−), 51.71 (−), 42.14 (−), 35.37 (+), 31.45 (+), 30.17(+); HRMS calcd for $C_{18}H_{20}O_3$ 284.1413, found 284.1427.

Methyl 4-Methylene-3-(1-oxo-1-phenyl)cyclohexanecarboxylate (18d and 19d) plus Regioisomer 20d. Following the general tandem procedure with acid chloride electrophiles, 150 mg of 2-[(dimethylphenylsilyl)methyl]-1,3-butadiene (**5b**) (0.74 mmol), 64 mg of methyl acrylate (**6a**) (0.74 mmol), 21 mg of dimethylaluminum chloride (220 μL of a 1 M solution, 0.22 mmol), 156 mg of benzoyl chloride (**17c**) (1.11 mmol), and 197 mg of $AlCl_3$ (1.48 mmol) in 6 mL of dry CH_2Cl_2 gave, after flash chromatography (10% ether in hexanes), 102 mg of combined products (**18d**:**19d**:**20d**, 1.1:1.1:1, 54%). Compound **18d** was cleanly separable from **19d** and **20d**, which could only be isolated together as a mixture. Ratios were determined by ^1H NMR spectroscopy on both the crude mixture and purified sample of **19d** and **20d** using the well-resolved vinyl proton signals (see text for discussion).

18d: clear, colorless oil; IR (thin film) 3072, 1738, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96−7.90 (m, 2 H), 7.56−7.38 (m, 3 H), 4.88 (br s, 1 H), 4.72 (br s, 1 H), 4.32 (t, J = 5.2 Hz, 1 H), 3.65 (s, 3 H), 3.01 (m, 1 H), 2.40−2.27 (m, 3 H), 2.04−1.91 (m, 2 H), 1.78−1.64 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.04, 175.77, 145.93, 136.50, 132.90, 128.54, 128.48, 112.22, 51.65, 48.76, 38.49, 32.18, 31.14, 30.01; HRMS calcd for $C_{16}H_{19}O_3$ ($M^+ + 1$) 259.1335, found 259.1346.

Compounds **19d** and **20d**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93 (m), 7.59−7.49 (m), 7.46−7.38 (m), 5.55 (m), 4.81 (s), 4.33 (s), 3.92 (dd, J = 12.5, 3.0 Hz), 3.66 (s), 3.64 (s), 3.59 (br s), 2.66−2.44 (m), 2.27 (m), 2.23−1.95 (m), 1.78−1.54 (m).

4-Methyl-6-methylene-1-(1-oxo-1-phenyl)-3-(1-oxopropyl)cyclohexane (18e and 19e) plus Regioisomer 20e. Following the general tandem procedure with acid chloride electrophiles, 100 mg of 2-[(dimethylphenylsilyl)methyl]-1,3-butadiene (**5b**) (0.49 mmol), 48 mg of 4-hexen-3-one (**6c**) (0.49 mmol), 103 mg of benzoyl chloride (**17c**) (0.74 mmol), 131 mg of $AlCl_3$ (0.98 mmol), and 14 mg of dimethylaluminum chloride (150 μL of a 1 M solution, 0.15 mmol) in 4 mL of dry CH_2Cl_2 gave, after flash chromatography (10% ether in hexanes), 104 mg of combined products (**18e**:**19e**:**20e**, 1.0:1.1:0, 79% yield).

18e: white crystals recrystallized from pentane; mp 58.0−58.9 °C; IR (thin film) 3072, 1707, 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91 (d, J = 7.4 Hz, 2 H), 7.55−7.47 (m, 1 H), 7.40 (t, J = 7.4 Hz, 2 H), 4.90 (s, 1 H), 4.86 (s, 1 H), 4.31 (m, 1 H), 2.88 (td, J = 9.6, 3.7 Hz, 1 H), 2.60−2.32 (m, 2 H), 2.18 (m, 2 H), 1.96 (t, J = 12.5 Hz, 1 H), 1.89−1.64 (m, 2 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.85 (d, J = 5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 215.09 (+), 201.01 (+), 144.88 (+), 136.32 (+), 132.84 (−), 128.46 (−), 128.41 (−), 113.12 (+), 52.02 (−), 49.26 (−), 39.94 (+), 36.81 (+), 35.21 (−), 31.38 (+), 20.03 (−), 7.49 (−). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.84; H, 8.19.

19e: white needles recrystallized from hexanes; mp 111.9−112.7 °C; IR (thin film): 3083, 1708, 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J =7.4 Hz, 2 H), 7.56−7.49 (m, 1 H), 7.41 (t, J =7.4 Hz, 2 H), 4.80 (s, 1 H), 4.30 (s, 1 H), 3.93−3.86 (m, 1 H), 2.58−2.32 (m, 4 H), 2.03−1.85 (m, 4 H), 1.03 (t, J =7.4 Hz, 3 H), 0.88 (d, J =5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 231.38 (+), 200.69 (+), 147.05 (+), 136.74 (+), 133.10 (−), 128.53 (−), 128.45 (−), 110.43 (+), 57.22 (−), 50.42 (−), 44.33 (+), 35.84 (−), 34.89 (+), 32.34 (+), 20.10 (−), 14.08 (−). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.87; H, 8.14.

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Supporting Information Available: ^1H or ^{13}C NMR spectra for all compounds prepared in this study and X-ray crystallographic data for **10f** (44 pages). This information is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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