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Investigation of montmorillonite clay-mediated reactions of aldehydes

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**INVESTIGATION OF MONTMORILLONITE
CLAY-MEDIATED REACTIONS OF ALDEHYDES**

A Thesis
Presented in
Partial Fulfillment of the
Requirements for the Degree of
Master of Science

December, 2009

BY
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ABSTRACT

Montmorillonite clays are employed as effective and environmentally benign heterogeneous catalysts for several reactions of aldehydes: (1) the hetero-Diels-Alder reaction of aromatic aldehydes with 2,3-dimethyl-1,3-butadiene to give dihydropyran products; (2) the cyclotrimerization of aliphatic aldehydes; (3) the oxidation of aliphatic aldehydes to the corresponding carboxylic acids; (4) the addition of allyltrimethylsilane to electron deficient benzaldehydes to give homoallylic silyl ethers. The hetero-Diels-Alder and allyl silylation reactions are effected in the presence of heat-activated Montmorillonite K10 clay, at room temperature or below, in the presence of minimal solvent. A temperature dependent equilibrium is observed for the cyclotrimerization of aliphatic aldehydes in the presence of untreated Montmorillonite K10, while aerobic oxidation to the carboxylic acids is observed in the presence of Montmorillonite KSF.

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CHAPTER 1. Introduction

In the process of developing synthetic routes to physiologically beneficial compounds, industrial and academic research laboratories also generate a significant amount of chemical waste that is hazardous to the environment. Since the Pollution Prevention act was passed in 1990, chemists have attempted to minimize waste by designing new, more environmentally friendly methods for organic synthesis. This movement, often referred to as "green chemistry," has resulted in the development of an array of new technologies for use in the modern synthesis laboratory.¹

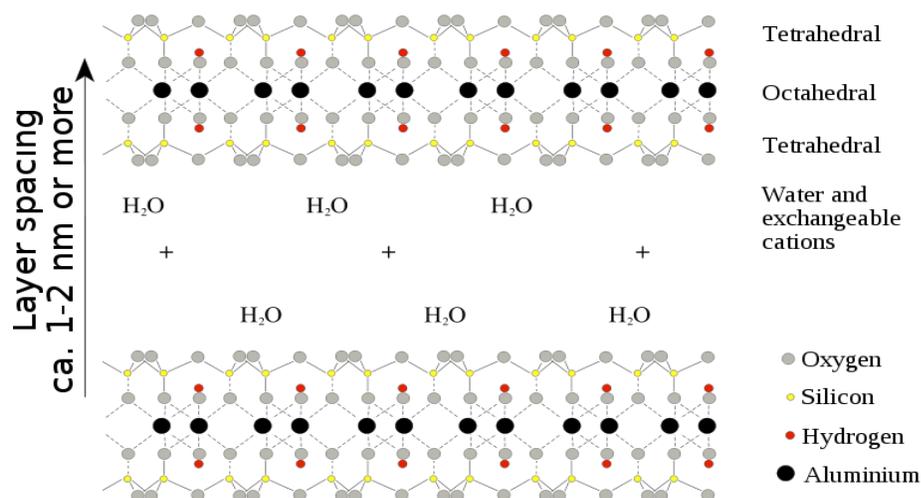
Green chemistry “attempts to reduce the environmental impact of the chemical enterprise by developing a technology base that is inherently non-toxic to living things and the environment.” More specifically, green chemistry employs a set of twelve principles meant to reduce or eliminate the use or generation of hazardous substances in chemical processes or applications. Ideally, green chemistry should incorporate: (1) waste prevention; (2) atom economy; (3) less hazardous chemical syntheses; (4) design of safer chemicals; (5) safer solvents and auxiliaries; (6) energy efficiency; (7) use of renewable feedstock; (8) reduction of derivatives; (9) catalysis; (10) design for degradation; (11) real time analysis for pollution prevention; and (12) inherently safer chemistry for accident prevention.¹ Application of naturally benign substances, like clays, as catalysts for chemical reactions constitutes an exciting component of green chemistry and is promising for the industrial synthesis of physiologically active compounds.

Naturally occurring Brønsted and Lewis acidic aluminosilicate minerals, clays are ideally suited for achieving many of the ecological objectives of green chemistry when used as catalysts for organic reactions. A catalyst is a chemical species that induces a chemical reaction (a chemical transformation) to occur at a reasonable rate, without itself being consumed in the process. Clays are safe, reusable, inexpensive, and can prevent waste and promote atom economy.²

In the most general sense, clays are a type of fine-grained earth, primarily composed of alumina and silicate minerals.³ Montmorillonite clays are thought to have formed from volcanic ash during the Jurassic and later periods, and were named for the location of their discovery, Montmorillon, France, in the 1800s. These clays are now mined from regions all over the world, including Europe, Africa, Asia, South and North America, with U.S. mines in Florida, Georgia, Illinois and Texas. Montmorillonite clays have a wide variety of applications, including being employed as catalysts for chemical reactions.⁴

As silicate minerals, clays possess imbalanced negative charges and layered structures such that polar molecules can be “trapped” and suitably oriented, favoring specific reactions. In addition, modification of the original composition of clays and use under particular conditions offer several possibilities for synthetic applications. Most of clays consist of layers of connected tetrahedral silicate ions, SiO_4^{4-} . In order for these negatively compiled silicates complexes to be stabilized inside the crystal structure of clays, oxygen atoms are shared with adjacent tetrahedrons and extra positively charged ions are included inducing a variety of arrangements. Tetrahedral sheet (T) and octahedral sheet (O) are common structures in silicate minerals. In some of the structural units, Al^{3+} or Fe^{3+} may replace silicon ions Si^{4+} causing increase of negative charge in the layers. Al^{3+} may also coordinate with OH^- group in octahedral sheet structure. Alternative dispositions of these two types of sheets-tetrahedral and octahedral sheets- form different classes of mica clays including Montmorillonite clays. These Montmorillonite clays represent the main constituents of Bentonites and fuller’s earth, in which a TOT arrangement predominates (Figure 1). Exchangeable alkaline and alkaline earth cations such as Na^+ , Mg^{2+} , and Ca^{2+} as well as NH_4^+ and water are attracted to the spaces between layers.³

Figure 1. Structure of Montmorillonite clay³

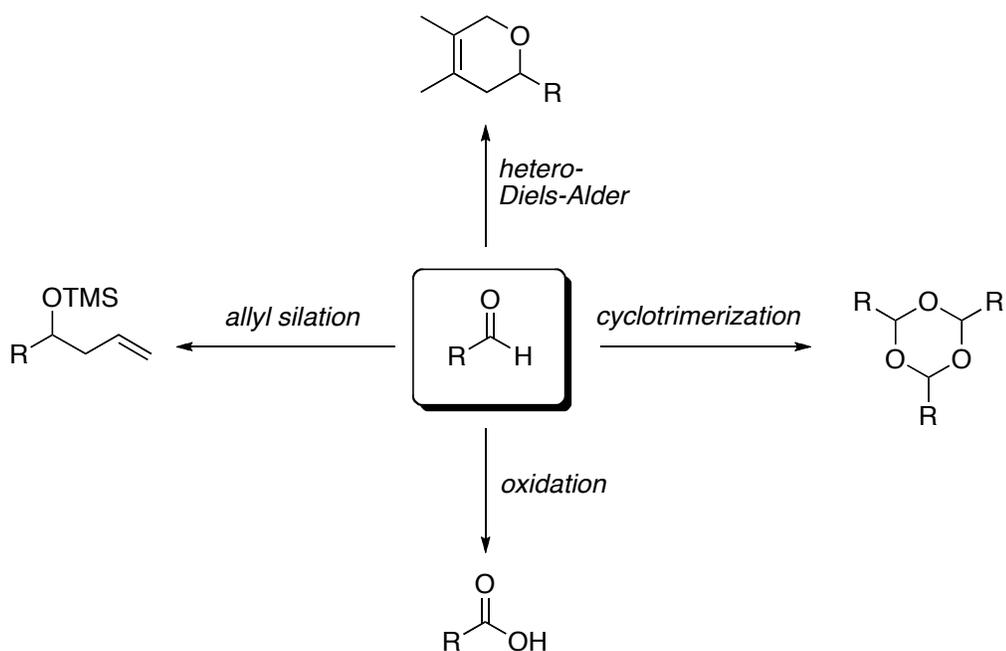


Montmorillonite clays have been used as catalysts in organic synthesis because of their high capacity for cation exchange and favorable swelling properties. As smectite aluminosilicate minerals, Montmorillonite clays can be modified by insertion of large cations to produce novel clays such as clayfen with Fe²⁺, claycop with Cu²⁺, and clayzinc with Zn²⁺.² K10 and KSF are two major Montmorillonite clays. Montmorillonite K10 has a much larger surface area (~250 m²/g) than KFS (~10m²/g). Their acidities are comparable to that of concentrated sulfuric acid.²

Lewis and Brønsted acidic characteristics have been observed when using Montmorillonite clays as heterogeneous catalysts. The Lewis acidities are associated with the edge sites of the lamellae containing the three-fold coordinated Al³⁺, and Fe³⁺ ions, whereas the Brønsted sites are mainly found in the interlamellar regions since the external OH⁻ groups can easily liberate their protons.² The acidity of the clays depends highly on the quantity of trapped water molecules in the inter-layers. Thus, heating results in a decrease in Brønsted acidity while and an increase in Lewis acidity. In addition, oxidative properties are observed with some clays containing metallic reductive ions like Fe³⁺ and Cu²⁺ ions.²

As green methodology becomes more sought-after in organic synthesis, environmentally benign clays are becoming attractive alternatives to more toxic Lewis acid catalysts for a host of reactions.² The focus of this research is on the further development of Montmorillonite clays as catalysts for organic reactions that are useful in synthesis. Herein, we report our investigations of four clay-mediated reactions of aldehydes: hetero-Diels-Alder cycloaddition; cyclotrimerization; oxidation; and allyl silylation (Scheme 1). Optimal experimental conditions for and scope of each reaction are presented in the following chapters.

Scheme 1. Four clay-mediated reactions of aldehydes

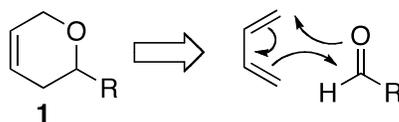


CHAPTER 2. Montmorillonite Clay-catalyzed Hetero-Diels-Alder Reaction of Aromatic Aldehydes

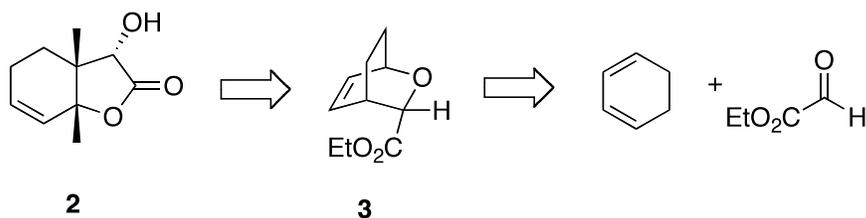
2.1 Background

Construction of the dihydropyran ring system (**1**) via hetero-Diels-Alder reactions that employ aldehydes as dienophiles (Scheme 2a) is well preceded and has been featured in the synthesis of a multitude of natural products.⁵⁻⁶ For example, in their construction of the sesquiterpene lactone (**2**), a useful synthon in natural products synthesis, Johannsen and coworkers employed a copper(II) bisoxazoline-catalyzed hetero-Diels-Alder reaction to generate key intermediate (**3**) from cyclohexadiene and ethyl glyoxylate (Scheme 2b).⁷

Scheme 2. Hetero-Diels-Alder synthesis of dihydropyrans



(a) General synthesis of the dihydropyran ring system via hetero-Diels-Alder reaction

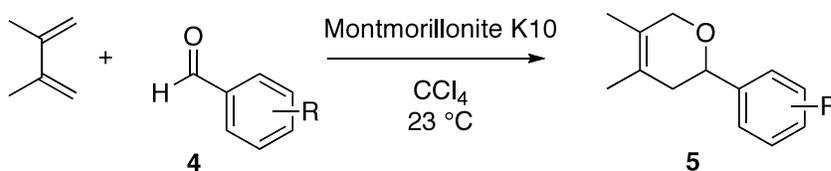


(b) Hetero-Diels-Alder reaction in the synthesis of sesquiterpene lactone **2**

There are numerous reports in the literature on the hetero-Diels-Alder reaction of aldehydes with activated dienes (such as Danishefsky's diene and the like) or with nonactivated simple dienes under forced conditions.⁸ The reactions of aldehydes with simple, nonactivated dienes under mild

conditions, however, are much less prevalent in the literature. In our labs we have shown that activated Montmorillonite K10 clay is an effective catalyst for the synthesis of heterocyclic compounds like benzopyrans⁹ and chromenes.¹⁰ We were thus encouraged to investigate the synthesis of heterocyclic dihydropyrans through the clay-catalyzed hetero-Diels-Alder reaction of aromatic aldehydes with 2,3-dimethyl-1,3-butadiene (Scheme 3).¹¹

Scheme 3. Montmorillonite K10 clay-catalyzed hetero-Diels-Alder reaction

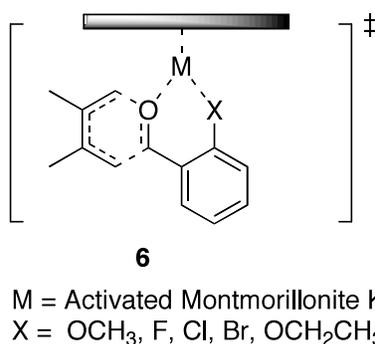


2.2 Results and Discussion

Preliminary experiments, which were conducted with benzaldehyde and 2,3-dimethyl-1,3-butadiene in carbon tetrachloride with Montmorillonite K10 clay (1 equiv by weight relative to the aldehyde), were minimally encouraging. Only about 10% conversion to the desired Diels-Alder adduct (**5**) was observed by GCMS analysis, along with unreacted benzaldehyde and dimerized diene. We found that preheating the clay to 110 °C for one hour prior to conducting the reaction made for a more active Lewis acid catalyst and resulted in improved conversion of reactants to the desired Diels-Alder adduct, though dimerization was still a competing side-reaction. Heating the clay at a higher temperature (200 °C, 1 h) provided an even more active catalyst, presumably due to collapse of the clay's interlayer structure as water is extruded, with subsequent decrease in Brønsted acidity and increase in Lewis acidity.¹² We found that this more activated clay promoted much better conversion to the desired product and successfully suppressed dimerization of the diene.

We next surveyed a variety of substituted benzaldehydes to determine reaction scope (Table 1). Interestingly, the best percent conversions were observed for benzaldehyde derivatives with electronegative substituents in the *ortho* position, in particular *o*-anisaldehyde, which we surmise allows for transition-state stabilization involving possible chelation of the clay's metal ions with the aldehyde oxygen (Figure 2).

Figure 2. Suggested mechanism of Montmorillonite K10 clay-catalyzed hetero-Diels-Alder reaction



Apparently, the stabilizing interaction of the aldehyde's *ortho*-substituent with the clay compensates for electronic deactivation, especially with substrates like (**4b**), for which hetero-Diels-Alder reactions have until now been absent from the literature.¹¹ Minimal Diels-Alder reaction observed with *o*-tolualdehyde (**4i**), for which chelation is not possible, further supports our proposal for possible transition-state stabilization via coordination of the clay with the aldehyde oxygen and electron rich *ortho*-substituents.

In order to further optimize the desired reaction, we investigated the effect of the relative amount of clay used on the hetero-Diels-Alder reaction of *o*-anisaldehyde (**4b**) with 2,3-dimethy-1,3-butadiene. Reactions were run with increasing amounts of clay, and a sharp increase in percent conversion to (**5b**) was observed with 1.4 - 2.0 mass equivalents of clay relative to aldehyde (Table 2

and Figure 3). Thus, the reaction appeared to work best with clay that was activated at 200 °C for one hour and used in two-fold mass excess relative to the aldehyde.

Table 1. Scope of the Montmorillonite K10-catalyzed hetero-Diels-Alder reaction

Entry	Aldehyde	Time (h)	Product	% Conversion ^a
1	benzaldehyde (4a)	1	5a	52
2	<i>o</i> -anisaldehyde (4b)	1	5b	81
3	<i>o</i> -ethoxybenzaldehyde (4c)	1	5c	25
4	<i>o</i> -fluorobenzaldehyde (4d)	1	5d	49
5	<i>o</i> -chlorobenzaldehyde (4e)	1	5e	34
6	<i>o</i> -bromobenzaldehyde (4f)	1	5f	68
7	<i>o</i> -cyanobenzaldehyde (4g)	24	5g	22
8	<i>o</i> -nitrobenzaldehyde (4h)	1	5h	75
9	<i>o</i> -tolualdehyde (4i)	1	5i	7
10	<i>p</i> -anisaldehyde (4j)	1	5j	<1
11	<i>p</i> -chlorobenzaldehyde (4k)	24	5k	56
12	<i>p</i> -nitrobenzaldehyde (4l)	24	5l	56

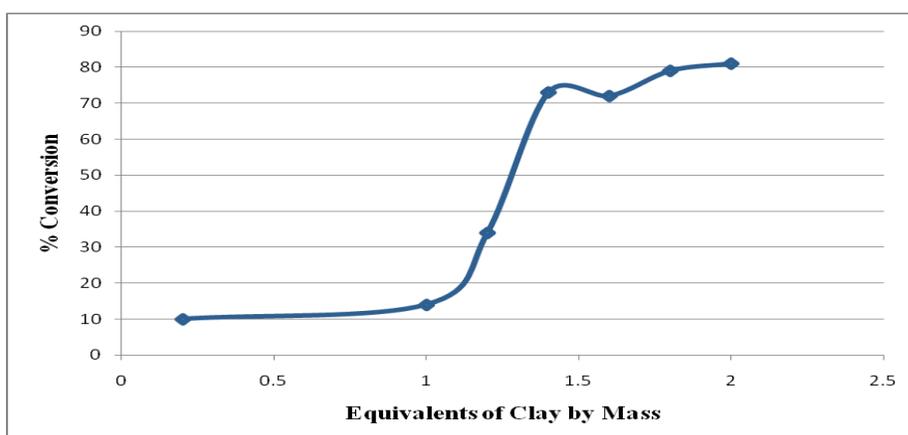
^aMeasured by GC-MS

Table 2. Clay titration with *o*-anisaldehyde in hetero-Diels-Alder reaction

Entry	Amount of clay ^a	% Conversion ^b
1	0.2	10
2	1.0	14
3	1.2	34
4	1.4	73
5	1.6	72
6	1.8	79
7	2.0	81

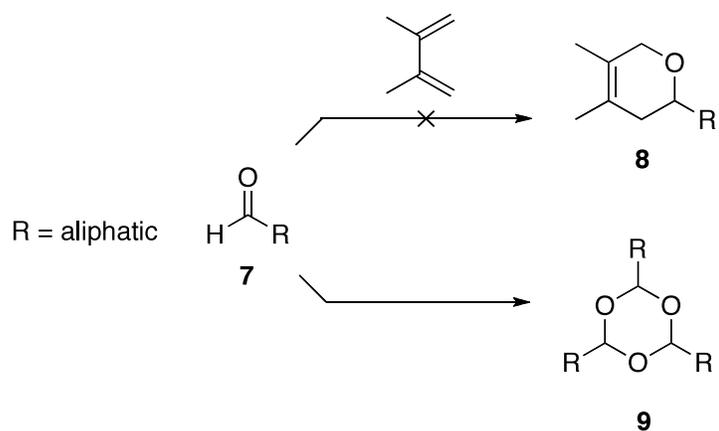
^aBy mass relative to the aldehyde; ^bMeasured by GC-MS

Figure 3. Clay titration with *o*-anisaldehyde in hetero-Diels-Alder reaction



Attempts to carry out similar reactions with less activated dienes, such as isoprene, were only minimally successful, giving some of the desired Diels-Alder adducts but larger amounts of products of higher molecular weights. Use of aliphatic aldehydes, such as propanal and butanal (**7**, Scheme 4) as the dienophile component resulted not in formation of the Diels-Alder adducts (**8**), but gave predominantly the corresponding trioxane products (**9**). This reaction was investigated in detail and results are presented and discussed in the following chapter.

Scheme 4. Clay-catalyzed trimerization of aliphatic aldehydes

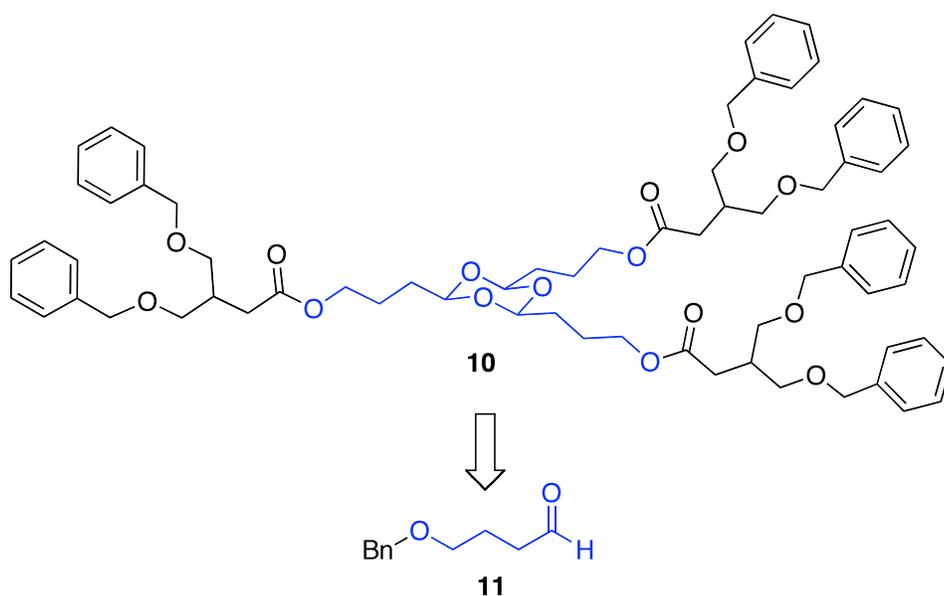


CHAPTER 3. Clay-Catalyzed Cyclotrimerization and Oxidation of Aliphatic Aldehydes

3.1 Background

As described in the preceding chapter, our efforts to effect the Montmorillonite K10 clay-catalyzed hetero-Diels-Alder reaction of aliphatic aldehydes with 2,3-dimethyl-1,3-butadiene were unsuccessful, primarily due to a competing side reaction: cyclotrimerization to give the corresponding 1,3,5-trioxanes (**9**, Scheme 4).¹¹ 1,3,5-Trioxanes have been implicated in a host of practical applications: as flavoring agents;¹³ as carriers for scents and deodorants;¹⁴ as stabilizers in color photography;¹⁵ as insecticides;¹⁶ and as synthetic precursors to complex dendritic molecules, such as the dendrimer (**10**) shown in Figure 4.¹⁷ A variety of catalysts have been found to promote the cyclotrimerization of aldehydes, including Bronsted¹⁸⁻²⁰ and Lewis acids,²¹⁻²⁴ but the synthesis of trioxanes has not been reported in the presence of untreated Montmorillonite clay. We were therefore encouraged to further investigate this reaction.

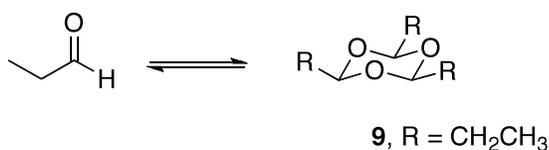
Figure 4. An interesting trioxane dendritic precursor



3.2 Results and Discussion

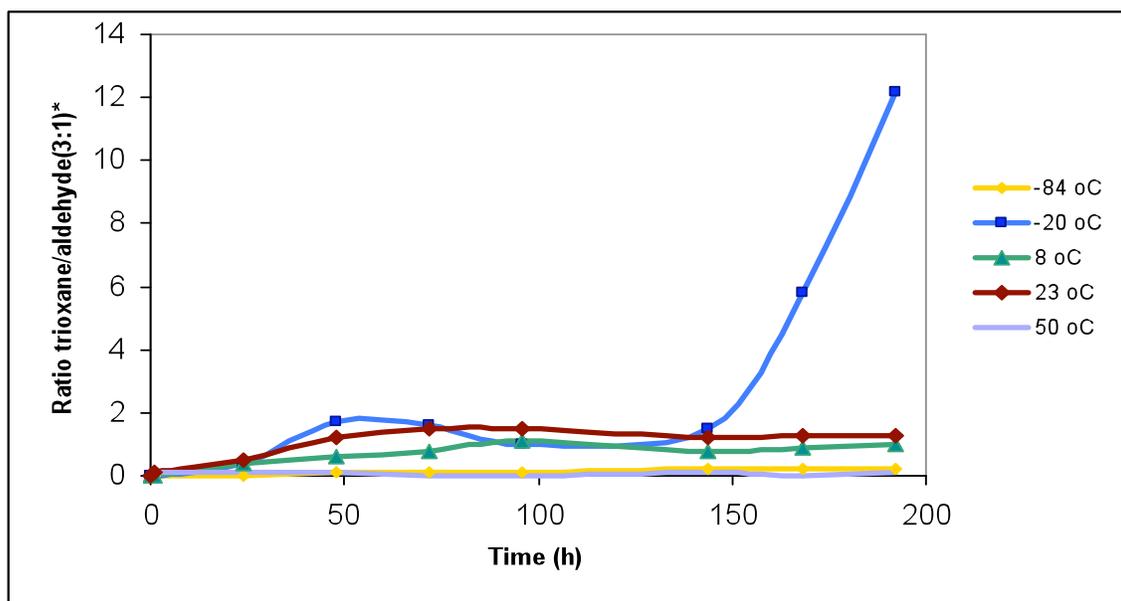
Under conditions that were optimal for the hetero-Diels-Alder reaction (heat-activated Montmorillonite K10 clay, 1h, 23 °C in CCl₄) we observed only minimal formation of trioxane.¹¹ Thus, we set out to optimize conditions for the cyclotrimerization of propanal as a model system (Scheme 5), by varying the following experimental parameters: solvent, stoichiometry, temperature, time, and type of clay.

Scheme 5. Cyclotrimerization of propanal



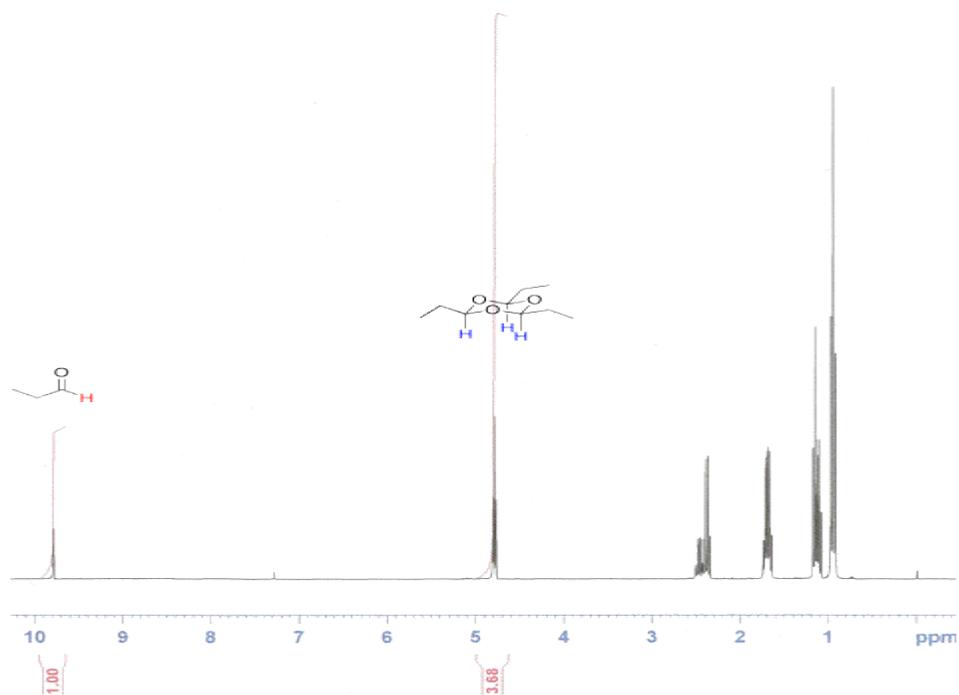
In keeping with the tenets of green chemistry, we were delighted to find that solvent was completely unnecessary for cyclotrimerization. Similarly, varying the amount of clay (10-100 % by mass relative to aldehyde) had minimal impact on the conversion of propanal to **9**. Further, the use of unactivated (“wet”) clay was observed to be much more effective at promoting trimerization than the heat-activated clay. The effects of temperature and time were investigated simultaneously, using neat, wet clay (Figure 5). The relative ratio of trioxane product to aldehyde was assessed by ¹H NMR analysis; specifically, by comparison of the integration values for the aldehydic proton with the ketal protons (Figure 6). Our results indicated that the trimerization reaction was very slow, reaching equilibrium only after about 192 h. Interestingly, the K10 clay-mediated equilibrium appeared to favor the trioxane product only at low temperature (-20 °C). Small amounts of byproducts, presumably from aldol condensations, were also observed at -20 °C.

Figure 5. Temperature-/time-dependence of the cyclotrimerization of propanal



* Ratio of Trioxane-to-aldehyde determined by integration of the ^1H NMR spectrum (Figure 6)

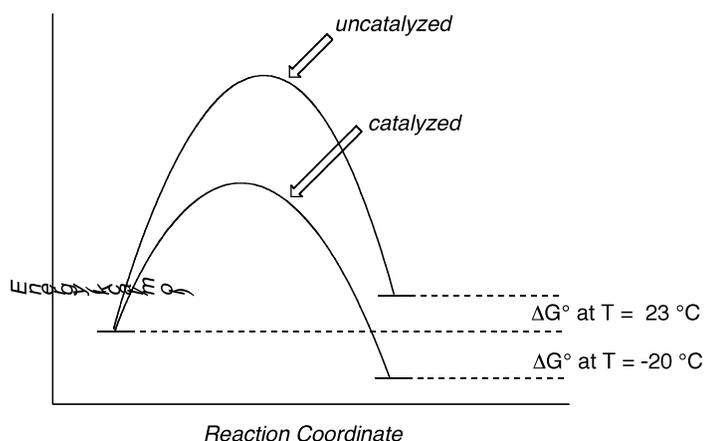
Figure 6: Representative ^1H -NMR spectrum for the trimerization reaction



A rudimentary analysis of the thermodynamics and kinetics of this reaction (Figure 7 and equation 1) suggests that it is neither thermodynamically nor kinetically favored in the absence of a catalyst. The activation energy may be lowered in the presence of a catalyst, which makes the reaction kinetically feasible. However, the reaction only becomes thermodynamically feasible (or spontaneous, with $\Delta G^\circ < 0$) at low temperature (-20 °C was optimal). Lowering the temperature serves to compensate for the negative change in entropy (ΔS°) for the formation of a cyclic trimer from three individual aldehyde molecules:

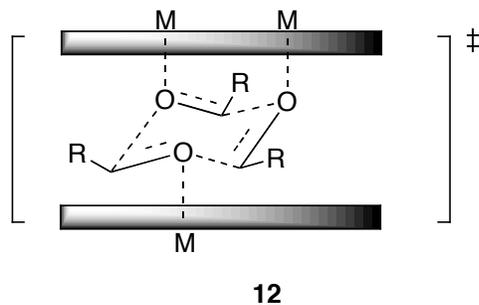
$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ < 0 \text{ only if } T \text{ is low} \quad (1)$$

Figure 7. Energy diagram for the trimerization reaction



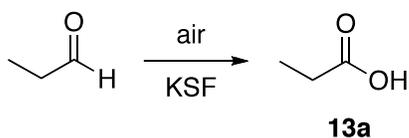
Thus, the synergistic effect between the clay and low temperature allowed for some control over the reaction. A concerted mechanism, with closed transition state, is proposed (12, Figure 8); the electrophilic character of the aldehyde is increased by coordination of carbonyl oxygen with the clay's metal ions, while the layered structure of the clay allows for clustering and favorable orientation of the substrates.

Figure 8. Proposed mechanism for the Montmorillonite K10-catalyzed trimerization of aldehydes



Although interesting from a theoretical perspective, we found this reversible reaction to be rather capricious in the presence of Montmorillonite K10, minimizing its potential usefulness in synthesis. Thus, we next investigated the use of Montmorillonite KSF clay in place of the K10, anticipating that the smaller surface area of KSF compared to that of K10 might afford better control of the forward reaction. However, in the presence of Montmorillonite KSF *we observed a different reaction all together*: oxidation of propanal to propanoic acid (**13a**, Scheme 6).

Scheme 6. Montmorillonite KSF mediated air oxidation of aliphatic aldehydes

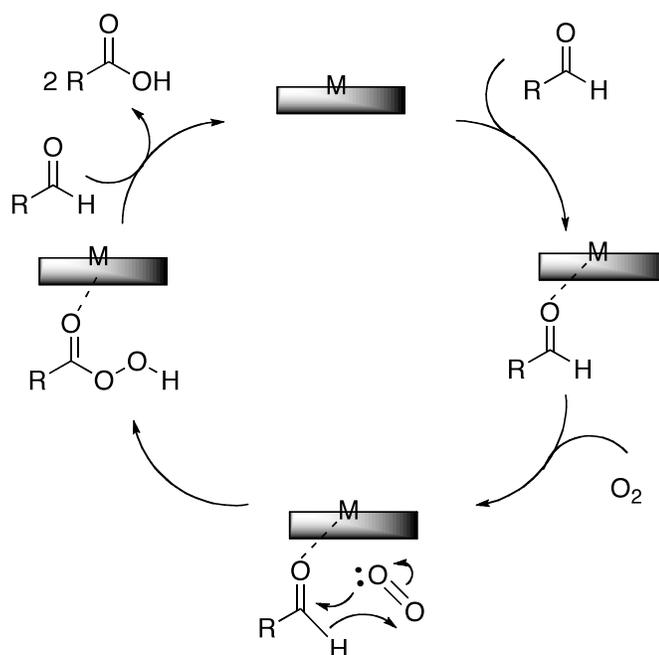


Oxidation proceeded slowly at ambient temperature or above, but was irreversible, resulting in good yield of the acid in approximately 168 h. In order to confirm that atmospheric oxygen was acting as the oxidizing agent for this reaction, a control experiment was conducted at room temperature under a nitrogen environment. Indeed, in the absence of atmospheric oxygen, no reaction was observed after 168 h.

The oxidation of aldehydes by atmospheric oxygen is well known, and while the mechanism is not entirely understood, it is believed that the direct oxidation product is the peroxy acid (RCO₃H),

which disproportionates in the presence of another molecule of aldehyde to give two molecules of the carboxylic acid.²⁵ We propose a mechanism (Scheme 7) consistent with this, in which the clay facilitates the process by (a) activating the aldehyde towards attack by molecular oxygen, and (b) providing a surface on which the reaction may occur.

Scheme 7. Suggested mechanism of the clay-catalyzed oxidation of aldehydes



The scope of the oxidation reaction is fairly general with aliphatic substrates (Table 3). Conjugated or aromatic aldehydes, however, were not observed to undergo oxidation in the presence of Montmorillonite KSF.

Table 3. Scope of the Montmorillonite KSF-catalyzed oxidation reaction

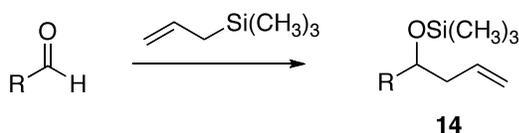
Entry	Aldehyde	Carboxylic Acid	% Yield
1	Propanal	Propanoic acid (13a)	59
2	Butanal	Butanoic acid (13b)	81
3	Pentanal	Pentanoic acid (13c)	95
4	Hexanal	Hexanoic acid (13d)	90
5	Cyclohexanecarboxaldehyde	Cyclohexanecarboxylic acid (13e)	57
6	Isobutyraldehyde	Isobutyric acid (13f)	58

CHAPTER 4. Montmorillonite K10 Clay-catalyzed Synthesis of Homoallylic Silyl Ethers

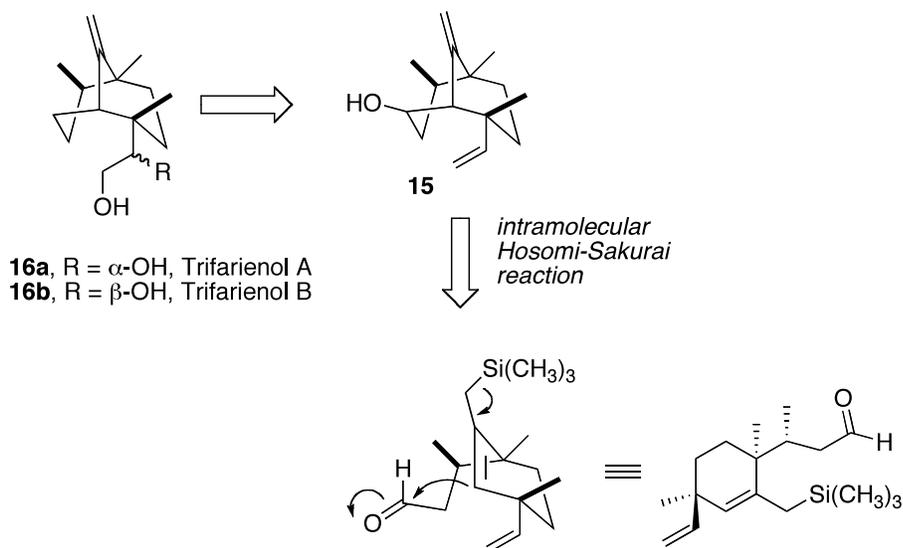
4.1 Background

The Hosomi-Sakurai²⁶⁻²⁷ reaction of allylsilanes with aldehydes to give homoallylic silyl ethers (**14**) is among the most widely utilized carbon-carbon bond-forming reactions in natural products synthesis (Figure 9a).²⁸⁻³⁷ For example, an intramolecular Hosomi-Sakurai reaction was recently employed as one of the key steps in the synthesis of **15**, a synthetic precursor to the structurally interesting trifarane-type sesquiterpenes, trifarienols A and B (**16a**, **16b**, Figure 9b).³⁸

Figure 9. The Hosomi-Sakurai reaction



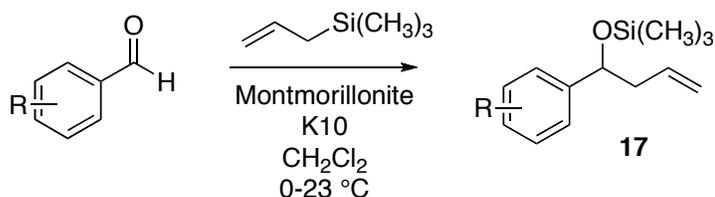
(a) General Hosomi-Sakurai reaction



(b) Hosomi-Sakurai reaction in the synthesis of Trifarienols A and B

The products that result from the Hosomi-Sakurai reaction of aldehydes with allyl trimethyl silane, homoallylic alcohols or silyl ethers (**14**), are useful platforms for further synthetic elaboration, especially in the event that the allylation reaction proceeds stereoselectively.³⁹⁻⁴⁶ Although powerful Lewis acids, like SnCl₄, TiCl₄, BF₃•OEt₂, AlCl₃, and Sc(OTf)₃, have been shown to successfully catalyze the Hosomi-Sakurai reaction, the negative impact of these reagents on the environment encouraged us to investigate the clay-catalyzed version of this reaction. Indeed, we found that activated Montmorillonite K10 clay was an extremely efficient catalyst for the addition of allyltrimethylsilane to electron deficient benzaldehydes to give homoallylic silyl ethers (**17**) in good to excellent yields (Scheme 8).⁴⁷ In the best-case scenarios, the reaction proceeded rapidly at room temperature or below in the presence of minimal solvent, and in quantitative yield with near-perfect atom economy.

Scheme 8. Montmorillonite K10 clay-catalyzed Hosomi-Sakurai reaction of benzaldehydes



4.2 Results and Discussions

Our previous investigations (Chapter 2) have shown that Montmorillonite K10 clay is effective at activating aromatic aldehydes toward nucleophilic attack, particularly when the clay was first activated by heating (200 °C, 1h).^{11,12} We set out to investigate the clay-catalyzed addition of allyltrimethylsilane to aromatic aldehydes and found that treatment of 3-nitrobenzaldehyde with allyltrimethylsilane in the presence of activated Montmorillonite K10 (neat) led to a highly exothermic reaction. Extraction of the product mixture with dichloromethane and analysis by ¹H

NMR and GC-MS showed evidence of the desired homoallylic silyl ether product (**17a**), along with some unreacted starting materials and a mixture of other unidentified products. We proceeded to effect better control of the reaction by taking up a mixture of the clay and aldehyde in a minimal amount of dichloromethane and cooling the mixture to 0 °C prior to careful addition of the allyltrimethylsilane. The reaction mixture was stirred at 0 °C for five minutes, and then allowed to warm to ambient temperature over the course of one hour. Filtration of the reaction solution and concentration under vacuum gave a near quantitative yield of the desired product (**17a**), with no further purification necessary. Next, we assayed a variety of aromatic aldehydes and observed similar results with other electron deficient compounds (Table 4, entries 1-8). No reaction was observed with the more electron rich *p*-anisaldehyde, presumably due to its decreased electrophilicity. The reaction with *o*-anisaldehyde, however, proceeded to some extent but did not go to completion. As we reported for the clay-catalyzed hetero-Diels-Alder reaction (Chapter 2), apparently favorable chelation of the clay's metal ions with the oxygen atoms of *o*-anisaldehyde may compensate for its diminished electrophilicity.¹¹

Table 4. Montmorillonite K10 clay-catalyzed Hosomi-Sakurai reaction of aromatic aldehydes

Entry	Aldehyde	Product	Yield (%) ^a
1	<i>m</i> -nitrobenzaldehyde	17a	99
2	<i>o</i> -nitrobenzaldehyde	17b	84
3	<i>p</i> -nitrobenzaldehyde	17c	99
4	<i>m</i> -fluorobenzaldehyde	17d	97
5	<i>p</i> -chlorobenzaldehyde	17e	99
6	2,6-dichlorobenzaldehyde	17f	99
7	<i>m</i> -cyanobenzaldehyde	17g	99
8	benzaldehyde	17h	75 ^b
9	<i>p</i> -anisaldehyde	17i	0 ^c
10	<i>o</i> -anisaldehyde ^c	17j	70 ^b

^aisolated yield; ^bGC yield; ^cbased on recovered starting materials

Control experiments with 3-nitrobenzaldehyde showed that varying the amount of clay, from 100% to 25% by mass relative to the mass of the aldehyde had minimal effect on the yield of

product. However, no reaction between *m*-nitrobenzaldehyde and allyl trimethylsilane was observed in the absence of clay or in the presence of unactivated clay.

Although the reaction proceeded fairly with some aliphatic aldehydes (Table 5, entries 1-4), it was neither as clean nor as high yielding as with the aromatic systems, presumably due to competitive cyclotrimerization (Chapter 3).¹¹ No reaction was observed with α - β -unsaturated aldehydes (Table 5, entries 5-7). While treatment of some aliphatic ketones (Table 5, entries 8-9) with allyltrimethylsilane in the presence of activated K10 gave good yields of the corresponding 3° homoallylic silyl ethers, no reaction was observed with cyclopentanone or with aromatic ketones (Table 5, entries 10-12).

Table 5. Montmorillonite K10 clay-catalyzed Hosomi-Sakurai reaction of aliphatic and α , β -unsaturated aldehydes, and ketones

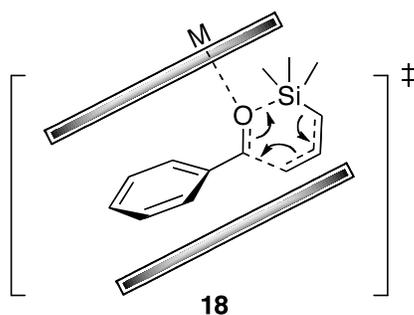
Entry	Carbonyl Compound	Yield (%) ^a
1	Propanal	16
2	Butanal	47
3	Isobutyraldehyde	61
4	Cyclohexancarboxaldehyde	25
5	3-Methyl-2-butenal	0 ^b
6	Crotonaldehyde	0 ^b
7	<i>trans</i> -Cinnamaldehyde	0 ^b
8	Acetone	70
9	2-Butanone	90
10	Cyclopentanone	0 ^b
11	Acetophenone	0 ^b
12	Benzophenone	0 ^b

^aGC yield; ^bbased on recovered starting material

In contrast to the computational and experimental evidence reported for the mechanism of the homogeneous Lewis acid-catalyzed Hosomi-Sakurai reaction,⁴⁸ our results suggest a closed transition state model, concerted mechanism for the clay-mediated process (**18**, Figure10). Thus, not only does the reaction generate a new C-C bond, but it also has the advantage of providing the products in their protected form, as the trimethylsilyl ethers. Deprotection, if desired, can be effected

quantitatively by adding a slight excess of methanol to the reaction mixture and stirring for 20 min prior to filtering.

Figure 10. Suggested mechanism for the clay-catalyzed Hosomi-Sakurai reaction



This methodology constitutes a milder, environmentally friendlier, and more cost effective alternative to the use of transition metal halides or oxides for the catalysis of the Hosomi-Sakurai reaction.

CHAPTER 5. Summary and Conclusions

As concern for the environment continues to shape the way chemists think about the construction of physiologically active compounds, the development of synthetic methodologies that promote greener reactions is essential. Environmentally benign clays are ideally suited for the “greening” of modern synthetic chemistry—they are naturally abundant, inexpensive, nontoxic, chemically versatile, and recyclable. The work reported here has proven important in our ongoing efforts to demonstrate the utility of Montmorillonite clays in organic synthesis, and may prove useful for others as well. We have demonstrated the application of heat-activated Montmorillonite clay as an effective and mild Lewis acid catalyst for the hetero-Diels-Alder reaction of 2-3-dimethyl-1,3-butadiene with some aromatic aldehydes, and the Hosomi-Sakurai reaction of aldehydes and select ketones with allyltrimethylsilane. These are two of the most frequently used carbon-carbon bond forming reactions in the synthesis of natural products, and our methodology constitutes significant improvement over the existing technologies for effecting these reactions. We have also shown that untreated Montmorillonite KSF clay is an efficient and exceedingly mild catalyst for the aerobic oxidation of aliphatic aldehydes to the corresponding carboxylic acids. Although the clay-catalyzed cyclotrimerization reaction of aliphatic aldehydes was found not to be synthetically useful, the observed equilibrium between the free aldehyde and trioxane represents an interesting example of an entropy-driven reaction—spontaneous at low temperature and non-spontaneous at higher temperatures.

CHAPTER 6. Experimental

Solvents and reagents were purchased from Sigma Aldrich and used without further purification, except where specified. Proton nuclear magnetic resonance (^1H) spectra and carbon-13 (^{13}C) spectra were recorded at 400 MHz and 100 MHz, respectively. The proton signal of residual, non-deuterated solvent ($\delta 7.26$ ppm for CHCl_3) was used as an internal reference for ^1H spectra. For ^{13}C spectra, chemical shifts are reported relative to the $\delta 77.23$ ppm resonance of CDCl_3 . Coupling constants are GCMS analysis was performed on a Hewlett Packard 5890 Series II gas chromatograph with a 5971 Series mass selective detector.

6.1 The Montmorillonite K10 clay-catalyzed hetero-Diels-Alder reaction with *o*-anisaldehyde

3,6-dihydro-4,5-dimethyl-(2-methoxyphenyl)-2H-pyran (5b). Montmorillonite K10 clay (50 mg) was measured into a vial and heated in an oven at approximately $200\text{ }^\circ\text{C}$ for 1 h. The activated clay was transferred to a desiccator and allowed to cool to room temperature. To the clay was added 0.1 mL CCl_4 , followed by 0.11 mmol of *o*-anisaldehyde. The mixture was allowed to sit for about 5 min. Then, 2,3-dimethyl-1,3-butadiene (0.10 mmol) was added via pipette. The reaction mixture was allowed to sit at room temperature for 1 h, then filtered, washing with CH_2Cl_2 , to remove the clay. Solvent was removed under vacuum to give the crude product as a pale yellow oil. The crude product was purified by column chromatography over silica gel, eluting with 1:1 hexane-ethyl acetate, and characterized by IR, ^1H NMR, ^{13}C NMR and GCMS: IR(CDCl_3) 2918, 2835, 1589, 1493, 1462, 1371, 1287, 1242, 1100, 1050, 1032, 753 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.63 (d, $J = 7.6$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 6.92 (d, $J = 8.1$ Hz, 1H), 5.04 (dd, $J = 3.8, 8.2$ Hz, 1H), 4.27 (m, 2H), 3.87 (s, 3H), 2.30 (m, 2H), 1.79 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.8, 136.5, 128.1, 126.1, 124.3, 120.9, 110.1, 70.9, 70.5, 55.2, 37.6, 18.4, 13.9

ppm; GC-MS (70 eV), $t_r = 11.612$ min, m/z 218 M^+ (44%); 135, $[M-83]^+$ (100%); 82, $[M-136]^+$ (79%); 67, $[M-151]^+$ (87%).

6.2 The Montmorillonite K10 clay-catalyzed cyclotrimerization reaction (9)

Freshly distilled propanal (1mmol) was mixed with Montmorillonite K10 clay (50% by mass relative to aldehyde) in a glass vial, capped and allowed to sit in a freezer at -20 °C for 8 days. The mixture was taken up in 2 ml of $CDCl_3$ and filtered through a small plug of cotton and sand directly into an NMR tube for analysis. The ratio of trioxane-to-aldehyde was assessed by integration of the 1H NMR spectra of the crude product mixture.

6.3 The Montmorillonite KSF clay-catalyzed oxidation reaction of aliphatic aldehydes

The aldehyde (200 mg) was thoroughly mixed with Montmorillonite KSF clay in a scintillation vial. The mixture was allowed to sit at room temperature for 168 h, and then taken up in 3 mL CH_2Cl_2 , filtered and washed with 3-5 mL methanol. The filtrate was concentrated under vacuum to give corresponding carboxylic acid (crude yields presented in Table 3). IR, 1H - and ^{13}C NMR data for compounds **13a-f** are presented:

Propanoic acid (13a): IR ($CDCl_3$) 2968, 2940, 2880, 1734, 1653, 1463, 1412, 1381, 1340, 1154, 1095, 950, 668 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 11.73 (s, 1H), 2.40 (m, 2H), 1.17 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 27.2, 8.9.

Butanoic acid (13b): IR ($CDCl_3$) 2963, 2936, 2875, 1711, 1465, 1412, 1381, 1150, 1105, 966, 775 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 11.70 (s, 1H), 2.35 (t, $J = 7.4$ Hz, 2H), 1.68 (m, 2H), 1.00 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 36.0, 18.7, 13.3.

Pentanoic acid (13c): IR (CDCl₃) 2960, 2935, 2874, 1711, 1467, 1413, 1381, 1279, 1216, 1108, 940, 751 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 11.77 (s, 1H), 2.36 (t, J=7.4 Hz, 2H), 1.62 (m, 2H), 1.37 (m, 2 H), 0.9 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 180.0, 34.0, 27.8, 22.6, 14.0.

Hexanoic acid (13d): IR (CDCl₃) 2957, 2933, 2870, 2861, 2700, 1711, 1467, 1450, 1414, 1379, 1292, 1245, 1213, 1146, 1111, 934 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 11.80 (s, 1H), 2.35 (m, 2H), 1.65 (m, 2H), 1.30 (m, 4H), 0.9 (t, J = 6.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 180.3, 34.0, 31.7, 24.6, 22.0, 14.0.

Isobutyric acid (13e): IR 2966, 2876, 1703, 1682, 1471, 1390, 1368, 1253, 1221, 1120, 1025, 994, 752, 739, 702, 665 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 11.76 (s, 1H), 2.6 (m, 1H), 1.22 (d, J = 7.0 , 6H); ¹³C NMR (75MHz, CDCl₃) δ 183.4, 32.8, 18.8.

Cyclohexanecarboxylic acid (13f): IR (CDCl₃) 2934, 2856, 1701, 1452, 1420, 1312, 1256, 1213, 1182, 1136, 922, 895 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 11.81 (s, 1H), 2.35 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.65 (m, 1H), 1.46 (m,1H), 1.3 (m, 1H), 1.2 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 182.3, 43.0, 28.8, 25.7, 25.45.

6.4 The Montmorillonite K10 clay-catalyzed Hosomi-Sakurai reaction of benzaldehydes

Montmorillonite K10 clay (200 mg) was added to a glass scintillation vial and heated in an oven at 200 °C for 1 h. The clay was cooled to ambient temperature in a desiccator, then treated with aldehyde (200 mg) and 2 mL dichloromethane. The mixture was cooled to 0 °C in an ice water bath and stirred gently with a magnetic stir bar. To the cooled mixture was added allyltrimethylsilane (1.5 molar equivalents relative to aldehyde) and the resulting mixture stirred at 0 °C for 5 min. The ice water bath was removed and the reaction mixture was allowed to warm to ambient temperature over the course of 1 h. The reaction mixture was vacuum filtered, washing

with an additional 1 mL of dichloromethane, and concentrated under vacuum (isolated yields are presented in Table 4). IR, ^1H -, ^{13}C NMR, and GCMS data for compounds **13a-g** are presented:

1-nitro-3-[1-[(trimethylsilyl)oxy]-3-buten-1-yl]benzene (17a): IR (CDCl_3) 3077, 2958, 2902, 1641, 1432, 1479, 1437, 1351, 1310, 1252 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.19 (s, 1H), 8.10 (ddd, $J = 1.13, 2.26, 8.1$ Hz, 1H), 7.66 (d, $J = 7.72$ Hz, 1H), 7.49 (t, $J = 7.91$ Hz, 1H), 5.75 (m, 1H), 5.02 (m, 2H), 4.81 (dd, $J = 5.56, 6.88$ Hz, 1H), 2.45 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.21, 147.12, 133.96, 131.99, 129.06, 122.12, 120.89, 117.88, 73.75, 44.88, 0.05; GC-MS (70 eV), $t_{\text{R}} = 18.158$ min, m/z 265 (<1 %); 250 $[\text{M}-15]^+$ (2 %); 224 $[\text{M}-41]^+$ (50 %); 73 $[\text{M}-192]^+$ (100 %).

1-nitro-2-[1-[(trimethylsilyl)oxy]-3-buten-1-yl]benzene (17b): IR (CDCl_3) 3077, 2958, 1701, 1641, 1610, 1577, 1527, 1445, 1346, 1298. 1252 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.89 (m, 2H), 7.63 (m, 1H), 7.40 (m, 1H), 5.86 (m, 1H), 5.38 (dd, $J = 4.05, 7.63$ Hz), 5.07 (m, 2H), 2.52 (m, 1H), 2.41 (m, 1H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.17, 140.64, 139.31, 134.46, 133.12, 128.63, 127.72, 123.98, 117.59, 69.63, 44.24, 0.27; GC-MS (70 eV), $t_{\text{R}} = 11.843$ min, m/z 265 M^+ (<1%); 224 $[\text{M}-41]^+$ (60 %); 73 $[\text{M}-192]^+$ (100 %).

1-nitro-4-[1-[(trimethylsilyl)oxy]-3-buten-1-yl]benzene (17c): IR (CDCl_3) 3079, 2958, 2903, 1641, 1607, 1522, 1492, 1432, 1416, 1350, 1316, 1292, 1253 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.19 (d, $J = 8.29$ Hz, 2H), 7.49 (d, $J = 8.29$ Hz, 2H), 5.74 (m, 1H), 5.03 (m, 2H), 4.80 (dd, $J = 5.65, 6.78$ Hz, 1H) 2.45 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 152.37, 147.06, 133.93, 126.63, 123.43, 117.85, 73.85, 44.79, 0.02; GC-MS (70 eV), $t_{\text{R}} = 20.424$ min, m/z 265 M^+ (< 1 %); 224 $[\text{M}-41]^+$ (70 %); 73 $[\text{M}-192]^+$ (100 %).

1-fluoro-3-[1-[(trimethylsilyl)oxy]-3-buten-1-yl]benzene (17d): IR (CDCl_3) 3078, 2957, 2903, 1704, 1642, 1616, 1593, 1489, 1450, 1359, 1252 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.30 (m, 1H), 7.10 (m, 2H), 6.95 (m, 1H), 5.80 (m, 1H), 5.06 (m, 2H), 4.72 (dd, $J = 5.46, 7.16$ Hz, 1H), 2.48 (m,

2H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.73, 146.57, 134.77, 130.20, 121.4, 118.94, 113.97, 112.61, 72.56, 43.82, 0.06; GC-MS (70 eV), $t_{\text{R}} = 8.711$ min, m/z 238 M^+ (<1 %); 223 $[\text{M}-15]^+$ (5 %); 197 $[\text{M}-41]^+$ (100 %); 73 $[\text{M}-165]^+$ (95 %).

1-chloro-4-[1-[(trimethylsilyl)oxy]-3-buten-1-yl]benzene (17e): IR (CDCl_3) 3078, 2958, 2903, 1641, 1598, 1491, 1432, 1409, 1360, 1295, 1262, 1252 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.30 (m, 4H), 5.77 (m, 1H), 5.05 (m, 2H), 4.68 (dd, $J = 5.46, 7.35$ Hz, 1H), 2.43 (m, 2H), 0.07 s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.41, 134.77, 132.62, 128.06, 127.28, 117.20, 74.17, 45.04, 0.10; GC-MS (70 eV), $t_{\text{R}} = 11.263$ min, m/z 254/256 $\text{M}^+/\text{M}+2$ (<1 %); 213/215 $[\text{M}-41]^+$ (98%); 73 $[\text{M}-181]^+$ (100 %).

1,3-dichloro-2-[1 [(trimethylsilyl)oxy]-3-buten-1-yl]benzene (17f): IR (CDCl_3) 3078, 2958, 1642, 1581, 1562, 1437, 1251 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.29 (m, 2H), 7.11 (m, 1H), 5.81 (m, 1H), 5.50 (m, 1H), 5.05 (dd, $J = 6.40, 8.10$ Hz, 1H), 2.86 (m, 1H), 2.68 (m, 1H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.92, 134.73, 129.38, 128.93, 128.60, 117.16, 71.45, 40.00, 0.12; GC-MS (70 eV), $t_{\text{R}} = 13.209$ min, m/z 288/290/292 $\text{M}^+/\text{M}+2/\text{M}+4$ (<1 %); 247/249/251 $[\text{M}-41]^+$ (93 %); 73 $[\text{M}-215]^+$ (100 %).

3-[1-[(trimethylsilyl)oxy]-3-buten-1-yl]benzotrile (17g): IR (CDCl_3) 3078, 2958, 2902, 2230, 1641, 1602, 1584, 1482, 1434, 1359, 1285, 1252 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.62 (m, 1H), 7.53 (m, 2H), 7.42 (m, 1H), 5.73 (m, 1H), 5.01 (m, 2H), 4.72 (dd, $J = 5.65, 6.78$ Hz, 1H), 2.41 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 146.41, 134.01, 130.76, 130.33, 129.55, 119.00, 117.79, 112.16, 73.73, 44.89, 0.04; GC-MS (70 eV), $t_{\text{R}} = 14.267$, m/z 245 M^+ (<1 %); 230 $[\text{M}-15]^+$ (10 %); 204 $[\text{M}-41]^+$ (98 %); 73 $[\text{M}-172]^+$ (100 %).

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