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Intramolecular Hydrogen Transfer Reactions Catalyzed by Pentamethylcyclopentadienyl Rhodium and Cobalt Olefin Complexes: Mechanistic Studies

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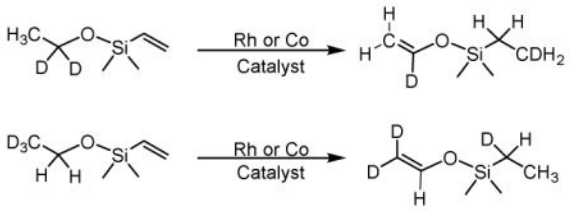
Abstract

The mechanism of intramolecular transfer dehydrogenation catalyzed by [$Cp^*M(VTMS)_2$] (**1**, M=Rh, **2**, M=Co, Cp* = C_5Me_5, VTMS = vinyltrimethylsilane) complexes has been studied using vinyl silane protected alcohols as substrates. Deuterium-labeled substrates have been synthesized and the regioselectivity of H/D transfers investigated using ^1H and ^2H NMR spectroscopy. The labeling studies establish a regioselective pathway consisting of alkene directed α C–H activation, 2,1 alkene insertion, and finally β-hydride elimination to give silyl enol ether products.

Graphical abstract

The mechanism of intramolecular transfer dehydrogenation catalyzed by [Cp*M(VTMS)$_2$] (M=Rh, Co, Cp* = C_5Me_5) complexes has been studied using vinyl silane protected alcohols as substrates. Using deuterium-labeled substrates, the regioselectivity of H/D transfers was investigated using NMR spectroscopy. These studies establish a regioselective pathway involving alkene directed α-C–H activation, 2,1 alkene insertion, and finally β-hydride elimination to give silyl enol ether products



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This article celebrates Malcolm Chisholm's 70th birthday and his numerous path breaking contributions to inorganic chemistry

Introduction

C–H activation/functionalization reactions using transition metal catalysts have received much attention in recent years, resulting in a burgeoning field of new synthetic methods.[1] Initial efforts investigated stoichiometric C–H activation reactions mediated by a transition metal. This early work has blossomed into new catalytic processes for the formation C–C, C–O, C–N, and C–X, bonds.[2] Such processes are finding multiple applications in the synthesis of natural products, pharmaceuticals, and agrochemicals.[3,4]

An alternate, less common strategy to employ C-H activation chemistry in synthesis is to convert saturated linkages to alkenes, R-CH_2-CH_2-R′ to R-CH=CH-R′.[5] Development of new routes to alkenes is attractive since alkenes represent a privileged class of substrates, readily converted into a myriad of other functional groups. Electrophilic additions, oxidations, and olefin metatheses represent just a few examples of the versatile transformations possible using alkenes. As with C–H to C–Y conversions, a dehydrogenation route to alkenes is attractive in that the method can potentially eliminate the need for pre-installed functional groups and the use of harsh reagents (e.g., strong base or acid).

While hydrocarbon cracking using a zeolite catalyst is a common industrial method for the production of short chain ($<C_6$) alkenes, high temperatures are required for this “acceptorless” dehydrogenation and are not compatible with synthetic applications.[6] The hydrogen transfer methodology is most commonly employed to carry out dehydrogenations in solution under mild conditions. Transfer dehydrogenation of alkanes utilizing various olefins as acceptors has seen extensive development.[7] Iridium pincer complexes have emerged as the most robust and widely used catalysts in this regard. Catalysts are typically screened using t-butyl ethylene as the acceptor for the dehydrogenation of cyclooctane to cyclooctene, $\Delta G = -6$ kcal/mol(Scheme 1). Iridium pincer catalysts have achieved turnover numbers of up to 6000 for this transformation.[7,8]

Despite the numerous studies of transfer dehydrogenation of simple alkanes, this method has seen little application for the preparation of functionalized olefins. [9,10] However, a recent report has expanded this work to simple heterocycles. Huang and coworkers have developed a new iridium pincer complex capable of dehydrogenating heterocycles using t-butylethylene as the hydrogen acceptor. Additionally, two significant advances in the dehydrogenation of functionalized substrates utilizing Pd salts as catalysts have been reported. Yu and coworkers have shown in a series of stoichiometric and catalytic studies that the use of an appropriate directing group and benzoquinone as acceptor can promote a C–H activation/β-hydride elimination sequence for the directed installation of an alkene (Scheme 2). [11] Separately Stahl has shown in the absence of a traditional directing group, C–H activation followed by β-hydride elimination can be an effective strategy for constructing alkenes (Scheme 3). [12,13] In a series of elegant studies the authors demonstrated Pd^{II} salts coupled with O_2 as the oxidant (acceptor) to be an effective system for the aerobic dehydrogenation of cyclic ketones to generate α,β unsaturated ketones and phenols. [14]

Our work in this area has stemmed from early investigations using [$Cp^*M(VTMS)_2$] (**1**, M=Rh, **2**, M=Co) (VTMS = vinyltrimethylsilane) complexes as catalysts for H/D exchange reactions in aromatic solvents and for hydroacylation of olefins. [15,16] The use of the labile bulky alkene, trimethylvinylsilane, allowed facile access to the reactive 16-electron fragment, $Cp^*M(VTMS)$, for C–H activation in these reactions. These complexes have been successfully applied to intramolecular transfer dehydrogenation reactions using protected alcohols and cyclic amines (Schemes 4 and 5). In this approach to transfer dehydrogenation, vinyl silane protecting groups are readily installed on the desired substrates and used as hydrogen acceptors. A series of studies in this area has resulted in new base-free, and mild routes to silyl enol ethers [17], 1,2-diheteroatom substituted olefins [18,19], and cyclic enamines. [20] Similar chemistry has been previously reported by Bradley using $Cp^*M(C_6H_6)$, M = Co.[21]

As part of these studies, we proposed a preliminary mechanism for intramolecular transfer dehydrogenation using the $Cp^*Rh(VTMS)_2$ complex as shown in Figure 1. [18] The catalytic cycle was entered by displacement of the labile VTMS ligand by excess substrate to yield **3**. Alkene loss generates a 16-electron complex **4** that undergoes activation of the proximal C–H bond via oxidative addition to give **5**. Then a series of migratory insertion, β-hydride elimination, and reductive elimination reactions (via **6** and **7**) generate the Rh-bound product **8**. Finally, displacement of product by another equivalent of substrate closes the catalytic cycle. An analogous mechanism was proposed for the transfer dehydrogenation of protected amines to generate enamines using $Cp^*Co(VTMS)_2$ complexes. In this report we describe experiments aimed at elucidating the full mechanistic details of these transformations using a series of isotopically labeled substrates.

Results and Discussion

Regioselectivity Studies

To evaluate the regioselectivity of hydrogen transfer in conversion of **9** to **10** (Scheme 6) two deuterium-labeled substrates were synthesized and submitted to the optimized reaction conditions. Vinyl silane-protected alcohols labeled with deuterium at the α(**11**) and β(**13**) positions of the ethoxy group were used and the regioselectivity determined by ^1H and ^2H NMR spectroscopy (Scheme 7, *a* and *b*).

After subjecting **11** to the optimized reaction conditions using either rhodium complex **1** or cobalt complex **2**, **12** was observed as the major d_2 product (Scheme 7, a). Similarly, the isotopologue **13** led to **14** as the major d_3 product (Scheme 7, b). Inspection of the ^1H NMR spectra of **12** and **14** support the labeling patterns shown (Figure S1). The integrals of the terminal vinyl signals and the methylene signal of **12** indicate little or no deuterium incorporation (but see below). Furthermore, the methylene resonance is now a broad triplet (J=7.5 Hz), due to coupling to CH_2D, and the methyl group appears as a triplet of triplets (J=7.8 Hz and 2 Hz) resulting from vicinal coupling to the methylene unit and geminal coupling to one deuterium. Likewise, the spectrum of **14** shows no evidence for significant incorporation of deuterium into either the methine group or the β-methyl group, which appears as a broad doublet (J = 7.5 Hz) due to coupling with a single vicinal H. The methylene group is now an unresolved multiplet integrating for ca. 1H. As captured in

Scheme 7, *a* and *b*, the primary modes of migration are from the α-methylene site of **11** to the β-methyl site in **12** and from the β-methyl site in **13** to the β-methylene site in **14**.

The labeling experiments implicate a regioselective mechanism for hydrogen transfer that follows one of the two pathways (A or B) outlined in Scheme 8. Initial C–H activation can occur via alkene coordination and oxidative addition of either the α or β C–H bond. In pathway A activation of the α C–H bond followed by 2,1 alkene insertion leads to a 5-membered metallacyclic intermediate, **15**. β-Hydride elimination and C–H reductive elimination generates the observed product. In pathway B, activation of the β C–H bond followed 1,2 alkene insertion leads to a 7-membered metallacyclic intermediate, **16**, which can proceed to product by β-elimination and reductive elimination. Below, we outline additional labeling experiments that are consistent with pathway A.

Isotope Scrambling

α-deuterium labeled substrate—Monitoring the reaction (a) in Scheme 7 at early conversions reveals extensive H/D scrambling in the starting material, **11**. Results in the case of the cobalt complex **2** are summarized in Scheme 9. Even at short reaction times (15min) H/D scrambling has occurred to produce a ca. 1:1 ratio of **11** and scrambled product **11s**.

Similar reactivity is observed with catalyst **1** (Rh) under optimized reaction conditions (140°C), albeit at a reduced rate (see Figure 2). After 0.5h, H/D scrambling is observed in the starting material at the site α to oxygen, evident by the appearance of a multiplet at 3.6 ppm in the ^{1}H NMR spectrum. The signal at 3.6 ppm continues to grow and reaches a maximum at ca. 1.5h. At 2.5 h the 3.6ppm signal begins to diminish as hydrogen transfer product, **12**, begins to accumulate as clearly seen by the appearance of the vinyl resonance at 6.3ppm. After 18h, all of **11** and **11s** have been converted to **12**. The scrambling results for both the cobalt and rhodium systems show that this process occurs faster than formation of silyl enol ether product, **12**. These results clearly suggest that pathway A (Scheme 8) operates and that once intermediate **15** forms it returns to starting material **11** faster than formation of **12**. [21]

β-deuterium labeled substrate—Importantly, in contrast to the α-deuterium labeled substrate **11**, H/D scrambling was not observed in starting material **13** under reaction conditions, as shown in scheme 10.

As with **12** (scheme 8), two analogous pathways could result in regioselective formation of the observed product, illustrated in scheme 11 for substrate **13**.

If pathway B were viable, oxidative addition β to oxygen would lead to metallacycle **18**, which would be expected to yield H/D scrambled product **13s** as shown. The conspicuous absence of this product strongly suggests that the mechanism does not proceed via this path. These experiments are consistent with pathway A outlined above (Schemes 8 and 11), comprising initial oxidative addition α to oxygen, followed by 2,1-insertion producing a 5-membered metallacyclic intermediate.

A scrambling process can, however be observed by ^{2}H NMR analysis following formation of **14**. Upon prolonged heating (~18 hours) with catalyst **1** or **2**, ^{2}H signals begin to appear in the Si–methyl positions, while ^{1}H signals grow into the β-vinyl positions (Scheme 12).

This product must ultimately stem from a silyl enol directed C–H activation mechanism as shown in Scheme 13, in which the product alkene directs oxidative addition to the C–H bonds α to Si producing intermediate **19**. Collapse of this product can result in ^{2}H incorporation into the Si-methyl group giving **14s**.

1,2 Diheteroatom substrates—In an earlier report using a similar hydrogen transfer scheme we observed the formation of 1,2 diheteroatom-substituted olefins, a particularly difficult class of substrates to synthesize via direct methods. [19] Our mechanistic investigations next looked at this class of substrates by focusing on similar H/D labeling experiments used above. At the outset we envisioned the same two possible mechanisms (Scheme 14, pathways A and B) for the hydrogen transfer reaction with 1,2 diheteroatom substrates. However, in contrast to **9**, in this class of substrate *both* pathways involve C–H activation α to a heteroatom. Thus these substrates provide an opportunity to investigate the importance of alkene chelation in regioselective transfer hydrogenation. Deuterium isotope labeling of the α C–H bonds provided a useful probe for distinguishing between these mechanistic pathways.

Submitting deuterium-labeled substrate **20** to reaction conditions too mild for hydrogen transfer to occur (Rh catalyst **1**, 70 °C) resulted in significant H/D scrambling exclusively between the labeled C–D bond β to Si and the terminal vinyl positions as depicted in Scheme 15. After 140 minutes scrambling can be observed by the appearance of new ^{1}H NMR resonances at 3.64 ppm (OCH_2 and OCHD) accompanied by a change in the coupling patterns of the vinyl signals.

When **20** was exposed to hydrogen transfer conditions (100 °C, 4.5 h) 93% conversion to the silyl enol ether was observed (Scheme 16). Two stereoisomers were observed in the ^{1}H NMR spectrum consistent with the *trans* and *cis* alkene products in an 8:1 ratio, respectively. Both the *trans* and *cis* enol ether products as well as the remaining starting material have undergone H/D exchange at the alpha C–H bond, results similar to that observed at 70 °C (Scheme 12).

The ^{1}H NMR spectra of **21/22** (d_2 and unlabeled) are shown in Figure 3 and clearly illustrate deuterium incorporation within the methyl group. The coupling pattern of the CH_2 protons in *d_2*- **21**, centered at 0.58 ppm, has changed (compared to that of unl**a**beled **21** and **22**) to a broadened triplet due to co**u**pling to the terminal CH_2D group. The methyl **r**esonance, which is centered at 0.94 ppm, shows **a** coupling pattern which consists primarily of **a** triplet of triplets (vicinal coupling to CH_2($^{2}J_{HH}$ = 8 Hz) and a geminal coupling (^{1}JHD = 1.8 Hz) to one deuterium atom). Transfer dehydrogenatio**n** performed with Co catalyst **2** provided identical results. While there is minor overlap betwee**n** the *trans* and *cis* products the spectra sho**w** no evidence of deuterium incorporation into the alpha position of the silyl ethyl chain.

These experiments support a hydrogen transfer mechanism involving C–H activation at the position α to the siloxy group via pathway A, Scheme 13. Given that the C-H bonds α and β to the siloxy group have relatively similar bond strengths, the regioselective activation of the α C-H bond must be the result of alkene chelation directing activation of this bond and formation of a five-membered chelate. The H/D scrambling noted in **20** prior to product formation establishes that once the five-membered metallacycle is formed it returns to **21** faster than forming product, similar to the mechanism of **11** discussed above.

Summary/Conclusion

After a series of deuterium labeling studies we have established a general mechanism for hydrogen transfer with catalysts **1** and **2**. These results implicate a highly regioselective pathway outlined in Figure 4 below. Following the dissociation of VTMS groups by substrate to give **23**, an alkene directed, reversible α C–H activation occurs to produce intermediate **24**. This step is followed by 2,1 alkene insertion to generate a 5-membered metallacycle **25**. β-Hydride elimination to give **26** and C–H bond-forming reductive elimination leads to the product-bound complex **27**. The H/D scrambling observed after product formation proceeds through a similar intermediate **28** in a similarly regioselective manner, again illustrating the reversibility of these steps. The overall transformation is thermodynamically favored via the formation of an enol or enamine product.

Studies with 1,2 diheteroatom substrates have shown the high regioselectivity observed in hydrogen transfer reactions with **1** and **2** is a result of both the alkene directing group and high preference for formation of a 5-membered metallacycle. Despite the similar bond dissociation energies of the α, β C–H bonds accessible in this system, both **1** and **2** prefer the pathway proceeding through α C–H activation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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21. Minor amounts of deuterium incorporation at the α-methylene group are observed in the interconversion of **11** and **11s** (with **1** and **2**). (This minor pathway is not detectable in the 1-H NMR analysis as it results in only a small indetectable reduction of the 2H integral of methylene group). This labeling result is consistent with a higher energy process in which intermediate **24** (see Figure 4) undergoes reversible 1,2 insertion to form a six-membered metallacycle rather than the favored 5-membered metallacycle via 2,1-insertion. While a minor fraction of product could form via this 6-membered metallacycle, this cannot be determined from these labeling experiments.

Appendix A. Supplementary Data

Experimental details and supplementary data associated with this article can be found in the online version, at xxxx.

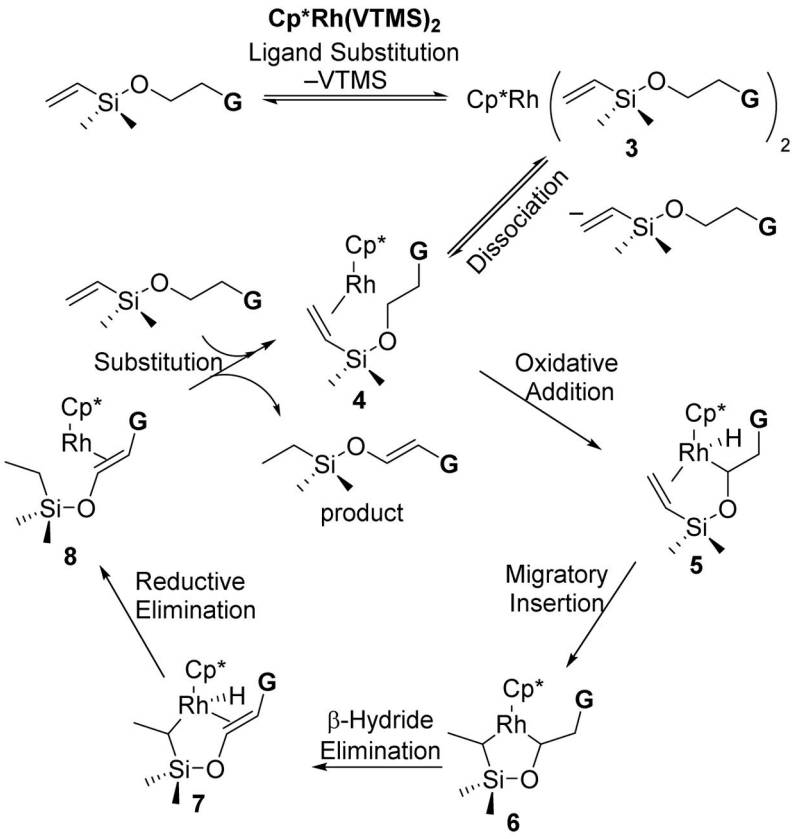


Figure 1.
Proposed mechanism for the intramolecular hydrogen transfer reactions

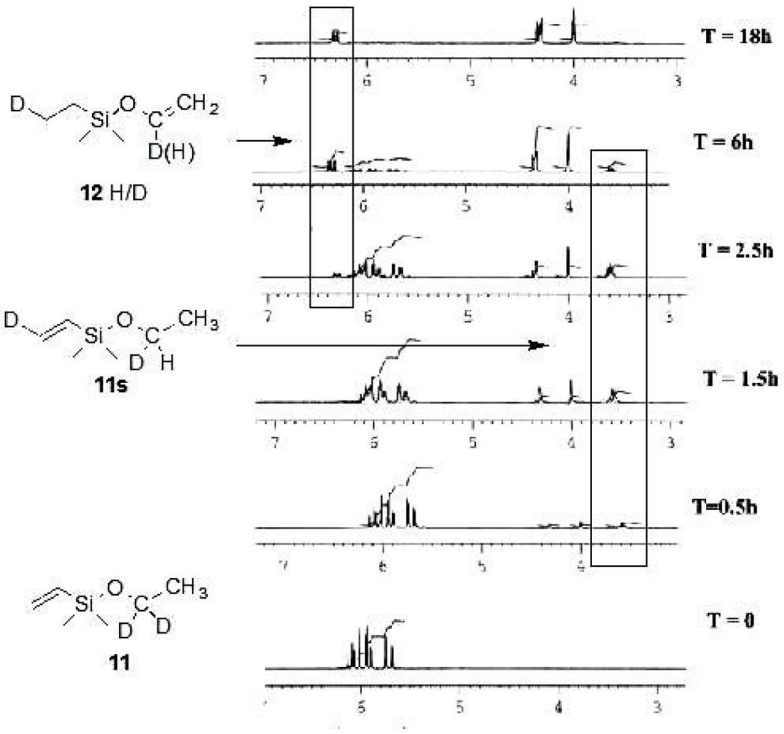


Figure 2.
^{1}H NMR spectra for conversion of **11** using catalyst **1**

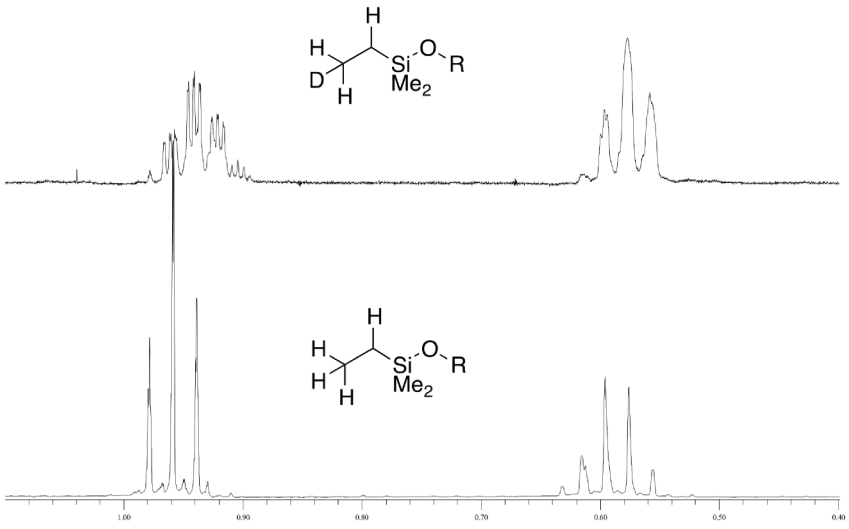


Figure 3.
Comparison of ^{1}H NMR spectra of d_2-**21/22** with unlabeled **21/22**

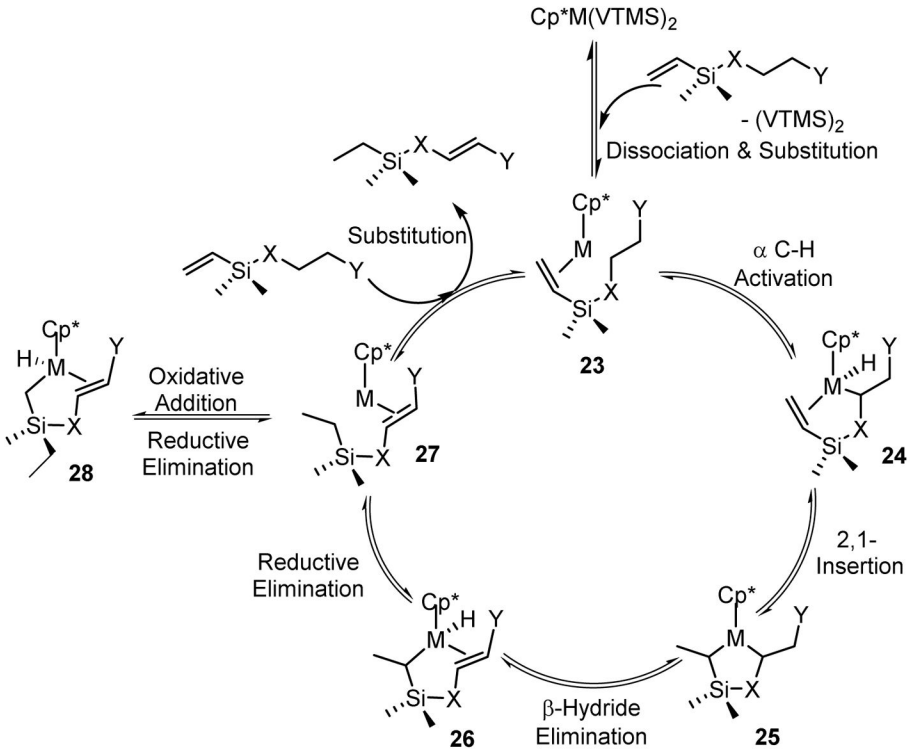
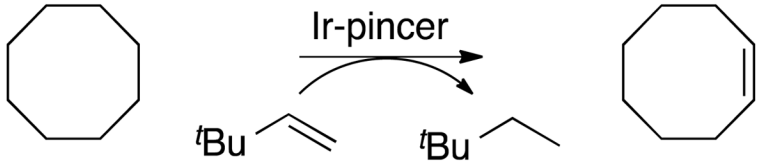
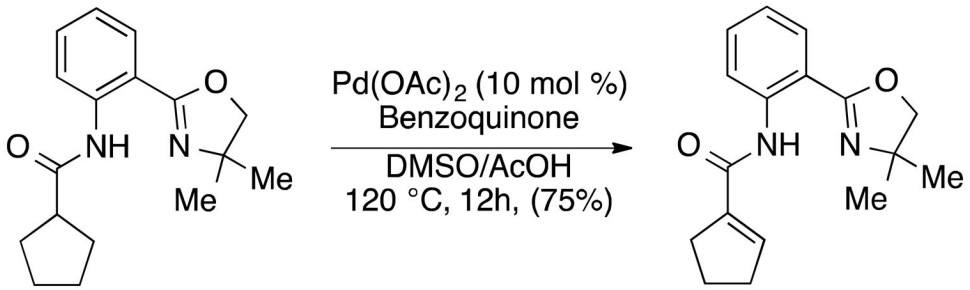


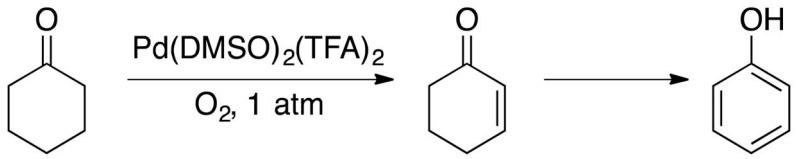
Figure 4.
General Mechanism Established for Hydrogen Transfer Catalyzed by **1** or **2**



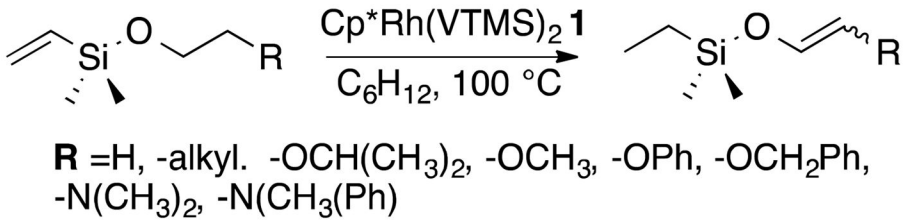
Scheme 1.
Dehydrogenation of cyclooctane with t-butylethylene.



Scheme 2.
Yu's ligand-directed dehydrogenation

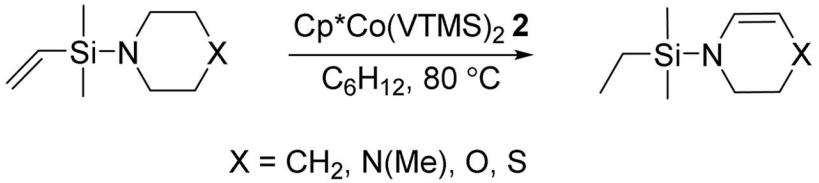


Scheme 3.
Stahl's aerobic dehydrogenation

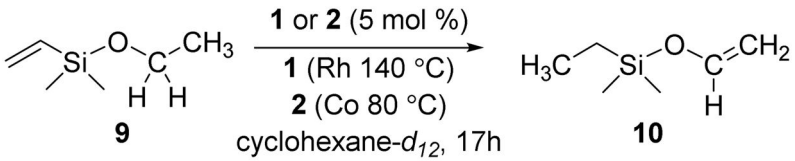


Scheme 4.

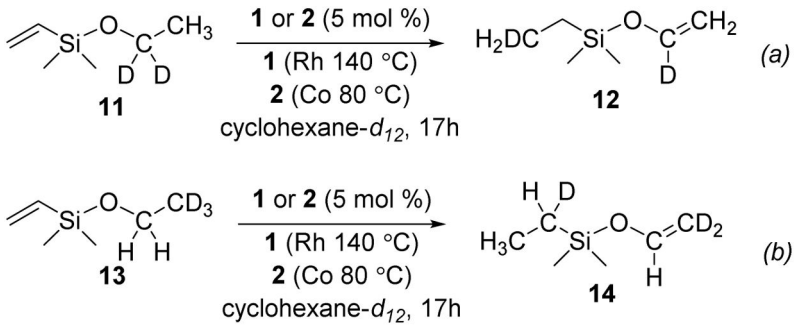
Synthesis of silyl enol ethers and 1,2-diheteroatom substituted olefins via transfer dehydrogenation.



Scheme 5.
Synthesis of enamines via transfer dehydrogenation

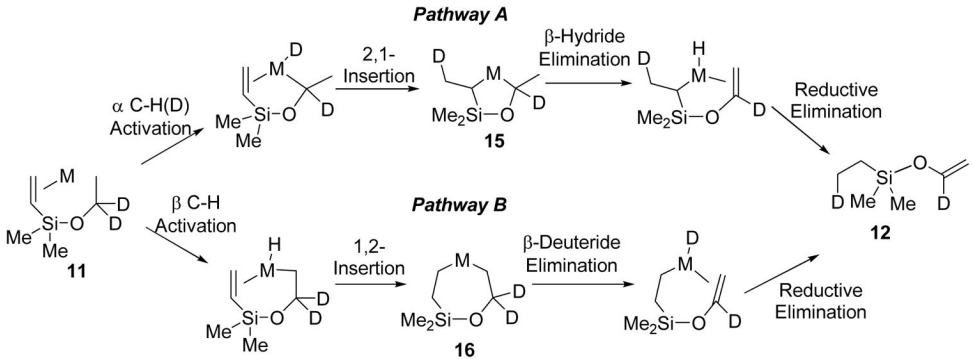


Scheme 6.
Representative example of transfer dehydrogenation with **1** or **2**



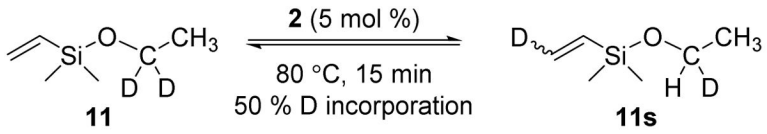
Scheme 7.

Hydrogen transfer reactions of deuterium-labeled **11** and **13**



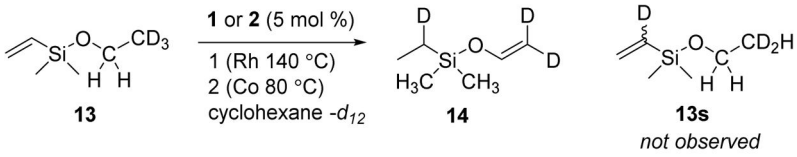
Scheme 8.

Possible pathways for regioselective hydrogen transfer illustrated for **11**.



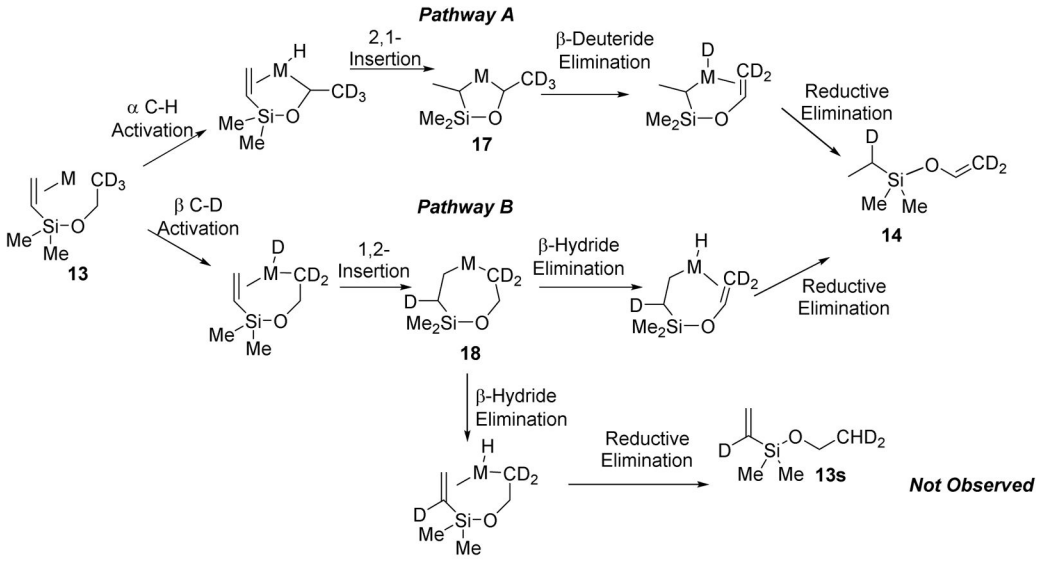
Scheme 9.

H/D scrambling results observed with **11**



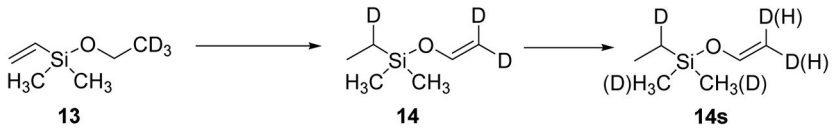
Scheme 10.

Hydrogen transfer with β-deuterium-labeled substrate.



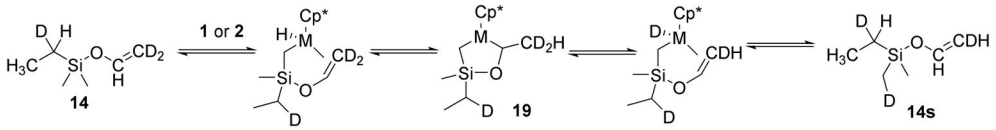
Scheme 11.

Possible pathways for regioselective hydrogen transfer of **13**.



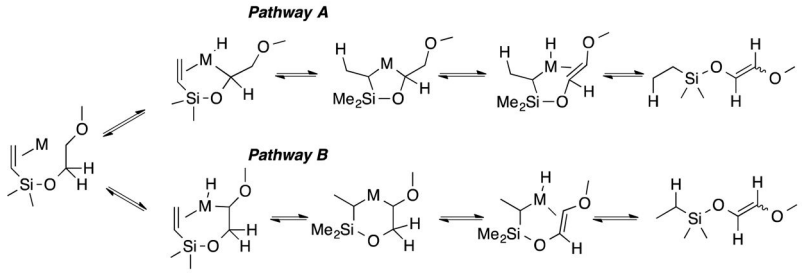
Scheme 12.

H/D Scrambling of **14** with catalyst **1**.

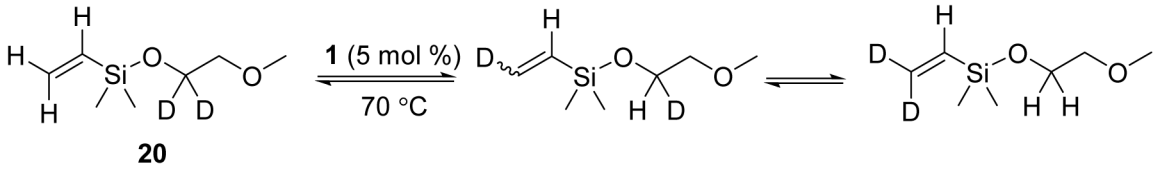


Scheme 13.

α-Si-Me Activation in **14** by **1** or **2**

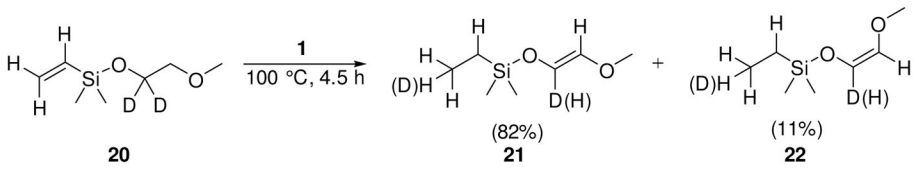


Scheme 14.
Proposed Pathways for Hydrogen Transfer using 1,2 Diheteroatom Substrates



20

Scheme 15.
H/D scrambling observed with **20**



20 21 22

Scheme 16.
Hydrogen transfer reaction with **20**