Article

Selectivity and Mechanism of Iridium-Catalyzed Cyclohexyl Methyl Ether Cleavage

Caleb D. Fast, Caleb A. H. Jones, and Nathan D Schley

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.0c01718 • Publication Date (Web): 12 May 2020

Selectivity and Mechanism of Iridium-Catalyzed Cyclohexyl Methyl Ether Cleavage

Caleb D. Fast, Caleb A. H. Jones, and Nathan D. Schley*

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 27235 United States

ABSTRACT: Cationic bis(phosphine)iridium complexes are found to catalyze the cleavage of cyclohexyl methyl ethers by triethylsilane. Selectivity for C−O cleavage is determined by the relative rates of S_N2 demethylation versus S_N1 demethoxylation, with the axial or equatorial disposition of the silyloxonium ion intermediate acting as an important contributing factor. Modulation of the electron-donor power of the supporting phosphine ligands enables a switch in selectivity from demethylation of equatorial methyl ethers to 2° demethoxylation. Applications of these accessible catalysts to the selective demethoxylation of the 3α-methoxy group of cholic acid derivatives are demonstrated, including a switch in observed selectivity controlled by 7α-substitution. The resting state of the catalyst has been characterized for two phosphine derivatives, demonstrating that the observed switch in C−O cleavage selectivity likely results from electronic factors rather than from a major perturbation of catalyst structure. ***Keywords***: silyloxonium, demethoxylation, cyclohexyl ether, methyl ether, sterol, iridium hydride.

Introduction

Nature provides complex, stereochemically-rich organic feedstocks in oxygenated molecules including lignins and carbohydrates. The efficient utilization of such materials as valuable organic building blocks relies on the availability of selective methods for their reduction. Traditional methods for the cleavage of C–O bonds in biomass rely on direct hydrogenolysis over heterogeneous catalysts, which lack design features necessary for selective processes.[1-2] The conversion of alcohol derivatives to a leaving group followed by reduction in a second step offers enhanced opportunities for selectivity in complex substrates.[3-9] However in recent years, a more-direct catalytic approach has emerged allowing alkyl- and silyl ether cleavage via reduction of a silyloxonium ion generated in situ.[10-12]

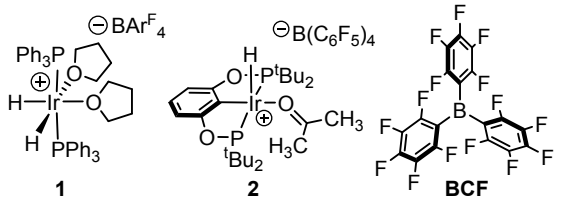
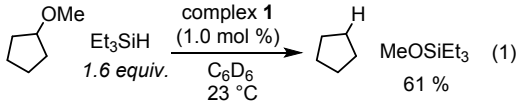


Figure 1. Reported catalysts for ether silylation.[10, 12-13]

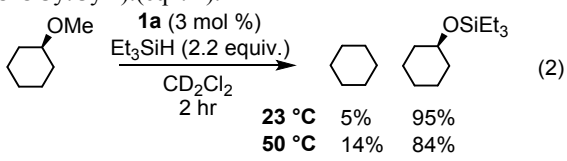
The reductive cleavage of ether-derived silyloxonium ions requires a catalyst capable of effecting hydrosilane heterolysis. Yamamoto reported that the electron deficient triaryl borane tris(pentafluorophenyl)borane (**BCF**) catalyzes the deoxygenation of alcohols with silanes via initial dehydrosilylation to the silyl ether and showed that this system also cleaves dialkylethers.[10-11] (Figure 1). Gagné has applied this catalyst to both the partial and complete deoxygenation of carbohydrate substrates.[14-16] Work by Brookhart showed that a cationic pincer-supported iridium complex (**2**) operates by a similar mechanism,[12] however attempts by Gagné to apply this system in complex polyether substrates provided products resulting from unselective C-O cleavage.[14, 17] In recent work we have shown that a simple cationic bis(phosphine)iridium dihydride complex (**1**) is capable of effecting the selective cleavage of alkyl ethers with silane.[13] Crucially, the resulting silyl ethers are stable with respect to further reduction, unlike in the Brookhart system.



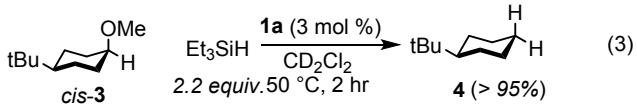
Furthermore, in our previous study of the preliminary reactivity of complex **1**, we discovered that cyclopentyl methyl ether (CPME) underwent cleavage at the secondary position to give cyclopentane (eqn. 1).[13] This observation contrasts with the selectivity observed from tris(pentafluorophenylborane) which gives preferential cleavage at the methyl position.[10, 18] As secondary cyclic alcohols and ethers are common functional groups in biologically-relevant compounds including carbohydrates, we were encouraged to develop a catalytic system capable of the direct demethoxylation of cyclohexyl methyl ethers.

Results and Discussion

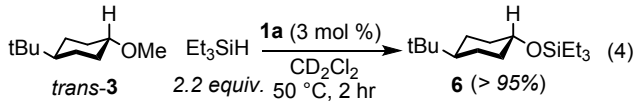
Previous efforts from our group identified that in a single example, the iridium complex **1** could effect the selective cleavage of CPME at the secondary position in preference to demethylation (eqn. 1).[2] Complex **1** is synthesized by hydrogenation of the air-stable 1,5-cyclooctadiene complex **1a** in THF solvent, but this step has been found to be unnecessary, as complex **1a** serves as a comparably competent precatalyst to **1**. Surprisingly, the homologated substrate cyclohexyl methyl ether does not show the same preference, giving triethylsiloxycyclohexane as the major product (95:5 TES-OCy:CyH).(eqn. 2).



The difference in selectivity for cleavage of cyclohexyl and cyclopentyl methyl ethers provided an impetus to examine the factors that influence the selectivity of iridium-catalyzed cyclohexyl methyl ether cleavage in detail. The conformationally-biased pair of substrates *cis*- and *trans*-(tert-butyl)-4-methoxycyclohexane were prepared (*cis*-**3** and *trans*-**3**). By virtue of the 1,3-diaxial interactions with the tertiary butyl group, these substrates adopt conformations that place the methoxy substituent axial and equatorial in the *cis* and *trans* isomers respectively.[19-20]



(3)



(4)

Under catalytic conditions, we observe that *cis*-**3** is cleaved to **4** and that *trans*-**3** is selectively demethylated to give silyl ether **6** (eqns. 3 and 4). These observations appear to argue for the importance of substrate conformation in hydrosilylative ether cleavage by **1a**.

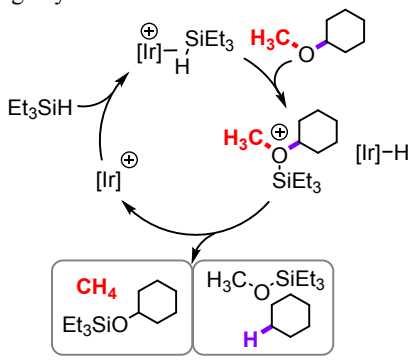
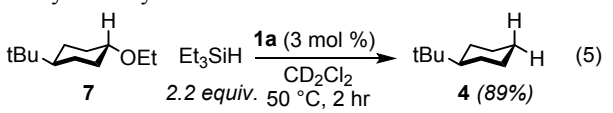


Figure 2. Demethylation versus demethoxylation of ethers.

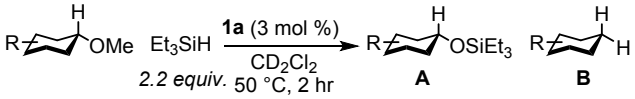
The selectivity obtained for *cis*-**3** and *trans*-**3** can be interpreted in the context of the simplified proposed mechanism given in Figure 2. Based on mechanistic work on related catalysts, the cationic catalyst promotes silane heterolysis via formal transfer of a silylium ion-equivalent to the ether.[12-13] The selectivity-determining step is proposed to be attack by a neutral iridium hydride on the incipient silyloxonium ion.[12-13] The important reactivity difference between *cis*-**3** and *trans*-**3** should stem from different reactivity of the silyloxonium ions formed *in situ*. A computational approach was used to determine the relative energies of the chair conformations of triethylsilyloxonium ions in Table 1. The experimentally-determined yields of demethylation versus 2° cleavage track well with the computed difference in energies, confirming that substrates with a strong energetic preference ($\Delta E_{ax\text{-}eq}$ > ~5 Kcal) for an equatorial silyloxonium ion conformation undergo preferential demethylation by **1a**.

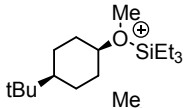
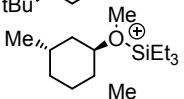
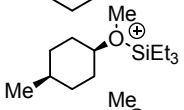
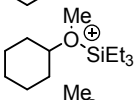
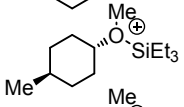
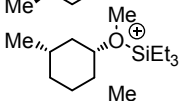
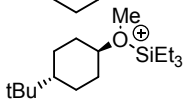


(5)

The selectivity for methyl versus 2° C−O cleavage is likely dictated by the relative rates of S_N1 cleavage of the silyloxonium versus S_N2 cleavage of the methyl group. The apparent preference for S_N1 reactivity at substrates with significant axial silyloxonium populations can be rationalized on the basis of the known increased rate of solvolysis of axial cyclohexane substituents relative to their equatorial isomers.[19, 21] Evidence for an S_N1 mechanism for 2° C−O cleavage has been obtained through the reduction of *cis*-**3** using Et_3SiD, which gives a near-1:1 mixture of *cis* and *trans* **4**-d_1.[22] Demethylation appears to occur via an S_N2 mechanism, as the ethyl derivative **7** undergoes selective deethoxylation. (eqn. 5) This outcome is expected given the much lower rate of S_N2 reactions of ethyl groups versus methyl groups, shifting the reactivity towards S_N1 substitution.

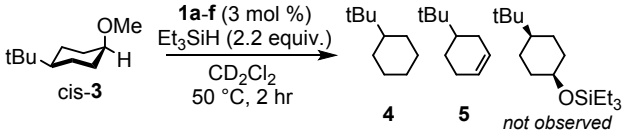
Table 1. Computed energies (kcal·mol^{-1}) for chair conformations that place the OMe group axial versus equatorial compared with experimental selectivity for ether cleavage.



Ether	Silyloxonium	E_{ax}-E_{eq}	Yield **A**	Yield **B**
cis-**3**		-0.6	-	>95
trans-**8**		3.1	32	68
cis-**9**		3.2	31	69
CyOMe		4.9	84	14
trans-**9**		8.3	>95	-
cis-**8**		10.7	>95	-
trans-**3**		11.3	>95	-

Our observations on the S_N1/S_N2 selectivity in cyclohexyl methyl ether cleavage with **1a** inspired the synthesis of an array of catalyst variants in the hopes of finding derivatives with an increased preference for 2° C−O cleavage. The six complexes examined are given in Figure 3. **1a-1c** differ by variation of the phosphine substituents from PPh_3 to $PMePh_2$ to PMe_2Ph (**1a**, **1b** and **1c**) which decrease the steric demand of the catalyst while increasing the electron-richness of the metal center. The phosphine substituents in complexes **1d-1f** are varied from meta-xylyl to 3-methyl-5-(trifluoromethyl)phenyl to 3,5-bis(trifluoromethyl)phenyl (**1d**, **1e** and **1f**). This second set represents an attempt to prepare an isosteric set of catalysts that would give intermediates with progressively decreasing hydride nucleophilicity in the expectation that this would lead to decreased rates of S_N2 demethylation.

Table 2. Catalyst-controlled reduction of *cis*-**3**.



Entry	Catalyst	Yield of **4**	Yield of **5**
1	**1a**	> 95%	-
2	**1b**	> 95%	-
3	**1c**	95%	3%
4	**1d**	> 95%	-
5	**1e**	> 95%	-
6	**1f**	91%	9%

When the suite of catalysts **1a-f** were examined with *cis*-**3**, all six gave the product of 2° C–O bond cleavage **4** (Table 2). The same selectivity is not observed with the borane catalyst **BCF** which gives largely the product of elimination **5**. In contrast, the equatorially-predisposed methyl ether substrate *trans*-**3** shows varying selectivity across the selection of catalysts tested (Table 3). In cases where triphenylphosphine catalyst **1a** was highly selective for demethylation, the electron-deficient catalysts **1e** and **1f** promote selective demethoxylation. Considering the quasi-isosteric set of catalysts **1d**, **1e**, and **1f**, the replacement of one of the methyl groups on the xylyl substitutent (**1d**) by trifluoromethyl (**1e**) is sufficient to flip the observed selectivity.

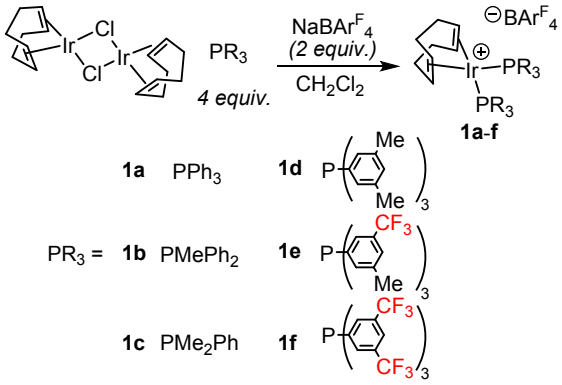


Figure 3. Synthesis of bis(phosphine) precatalysts tested.

Another direct comparison of catalysts **1a-f** can be made using the *trans* decalin-based substrates **10** and **11**. These substrates cannot undergo a ring flip and thus their product distributions should directly telegraph the relative rates of S_N1 and S_N2 processes for **1a-f** for both an axial and equatorial case. The selectivity trends for complexes **1a-f** established with substrates *cis*-**3** and *trans*-**3** appear to hold for both **10** and its axial epimer **11**. (Tables 4 and 5). Additionally, when the substrates shown in Table 1 are examined with the electron-deficient precatalyst **1e**, products of 2° C–O cleavage are obtained in all cases (Table S10). Thus we have found that the experimental selectivity for cyclohexyl methyl ether cleavage with **1a** depends strongly on the axial or equatorial disposition of the incipient silyloxonium ion, while less electron-rich catalyst variants prefer 2° C–O cleavage in all cases tested.

Table 4. Catalyst-controlled reduction of **10**.

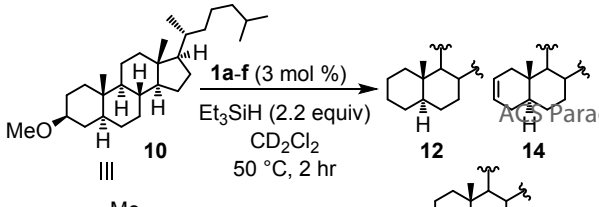


Table 5. Catalyst-controlled reduction of **11**.

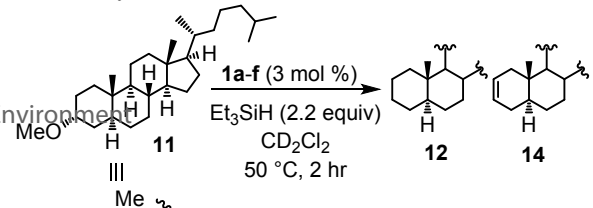
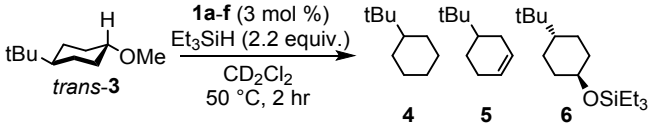
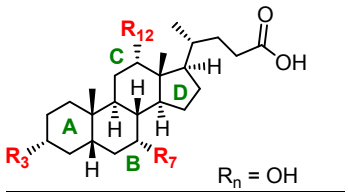


Table 3. Catalyst-controlled reduction of *trans*-**3**.



Entry	Catalyst	Yield of **4**	Yield of **5**	Yield of **6**
1	**1a**	-	-	> 95%
2	**1b**	45%	-	54%
3	**1c**	58%	12%	28%
4	**1d**	-	-	74%
5	**1e**	95%	4%	-
6	**1f**	92%	-	-



cholic acid	n = 3, 7, 12
chenodeoxycholic acid	n = 3, 7
deoxycholic acid	n = 3, 12
lithocholic acid	n = 3

Figure 4. Hydroxylation pattern of cholic acids.

Our success in developing selective catalysts for equatorial cyclohexyl methyl ether C–O cleavage encouraged the examination of more-complex substrates derived of cholic acid (Figure 4).[5] Cholic acid and its derivatives are synthesized in the liver from cholesterol[23] and play an important role in cholesterol homeostasis[24] and lipid metabolism.[25] In particular, they function as signaling molecules for nuclear receptors[26] with unnatural variants occasionally possessing desirable target selectivity.[27-28] The sites of hydroxylation, their stereochemistry, and the degree of polyhydroxylation are species-dependent, with the parent cholic acid being hydroxylated on the α face at the 3, 7, and 12 positions on the A, B and C rings respectively (Figure 4). Their biological relevance has inspired studies of the relative reactivity of each site of hydroxylation. Deoxycholic acid has been previously prepared by B-ring deoxygenation via selective oxidation of the 7α-hydroxyl to the mono ketone[29-30] followed by Wolff-Kishner reduction.[31] A similar strategy has been used to deoxygenate the C ring of 6,12-dihydroxy-cholanoic acid.[32] For the unprotected triols, the A-ring hydroxyl is considered to be the least reactive site with respect to oxidation by chromic oxide.[33-35]

When methyl ether substrates **15-18** were subjected to optimized catalytic conditions using complex **1a** as a catalyst we observed in all cases selective reaction at the 3α-methoxy substituent of the A ring. (Figure 5) This observation is particularly noteworthy given the number of potential positions for reduction in cholanol derivative **18**.

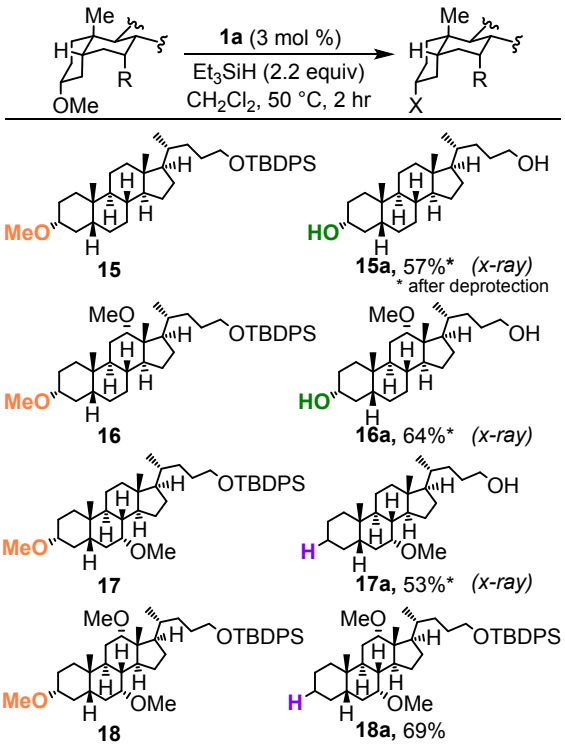


Figure 5. Isolated yields for cholic acid-derived methyl ether silylation. Single crystal X-ray data for **15a, 16**, **16a**, and **17a** is provided as supplemental information.

While all four cholanol derivatives **15**-**18** undergo selective reaction at the 3α-substituent on the A ring, the fate of this methyl ether appears to be dictated by substitution on the neighboring B ring. For both the protected lithocholanol and deoxycholanol derivatives **15** and **16**, the 3α-methoxy group undergoes demethylation – an outcome consistent with the selectivity expected for an equatorial methyl ether with **1a** as the catalyst. With the same catalyst however, chenodeoxycholanol **17** and cholanol **18** undergo 2° cleavage of the 3α-methoxy substituent. When examining the four cholanol substrates together it appears that the presence or absence of the 7α-methoxy substituent on the B ring controls the fate of the 3α-methoxy group under our silylation conditions with **1a**.

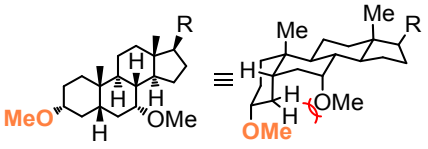
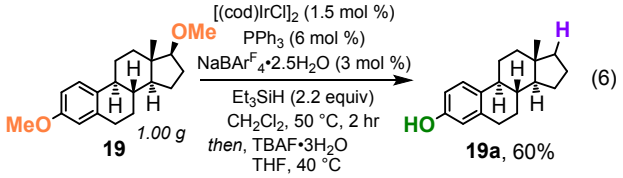


Figure 6. Depiction of the interaction of the 7α substituent with the cis-fused A ring.

A depiction of the cis-fusion of the A and B rings of cholic acids is shown in Figure 6. The 7α group is spatially located to participate in a pseudo syn-pentane interaction with the C_4 methylene of the A ring. This steric interaction likely destabilizes the chair conformation of the A-ring relative to the twist-boat. Since the ionization of cyclohexane substituents is believed to proceed through the twist-boat and not directly from the chair in many cases,[21, 36-37] our hypothesis is that differential destabilization of the chair by the 7α-OMe group in **17** and **18** increases the rate of S_N1 substitution of the 3α-silyloxonium intermediate and thus promotes demethoxylation.

Catalysis with catalyst generated in situ. To test the robustness of catalysis by **1a**, we undertook a series of reactions conducted in air where the catalyst is generated entirely *in situ* from commercially-available reagents. A previous report showed that mixtures of $NaBAr^F_4$ and $[(cod)IrCl]_2$ were inactive for ether silylation on their own,[17] however we speculated that the addition of triphenylphosphine would allow for direct synthesis of complex **1a** *in situ*.



Prior to setup of the catalytic reaction, solid samples of $[(cod)IrCl]_2$, $NaBAr^F_4$, and triphenyl phosphine were left open to the air for 24 hours. On small scales (0.040 mmol) the catalyst generated *in situ* gave comparable outcomes for reduction of *cis*-**3** and *trans*-**3** respectively. The reduction of 1.0 gram of dimethylestradiol (**19**) could also be accomplished in air using catalyst generated *in situ*. Under these conditions dimethylestradiol undergoes both demethylation of the anisole functional group and demethoxylation of the D ring to give 17-deoxyestradiol (**19a**) in 60% isolated yield after deprotection (eqn. 6). It is interesting to note that although cleavage of the 17β-OMe group in **19** is observed, this group occupies a pseudo-*equatorial* position by virtue of the C/D ring fusion.[38] As further evidence for the important role of local conformation, trimethylestriol (**22**) (differing from **19** by addition of a methoxy substituent at C16) is not reduced at C17 under our conditions (see Supporting Information).

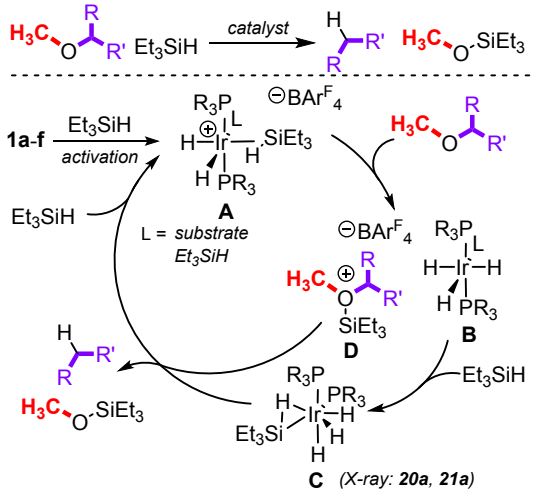
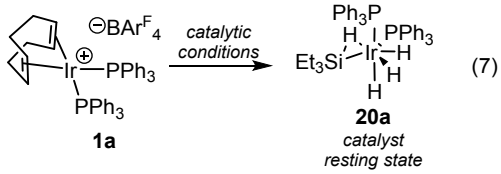


Figure 7. Proposed mechanism for 2° ether cleavage.

Reaction mechanism. A proposed mechanism for ether cleavage by bis(phosphine) iridium catalysts is given in Figure 7 and is based on work by Brookhart and our own previous study.[12-13] A cationic σ-silane compound (**A**) is believed to transfer an equivalent of triethylsilyllium ion to substrate ether to give a silyloxonium ion (**D**) and a neutral metal hydride (**B**/**C**). Since silyloxonium ions undergo silyllium exchange with ethers,[12] the selectivity-determining step should be C-O

bond cleavage, whether by ionization of- or hydride delivery to the silyloxonium ion (**D**).

In our previous report we showed that complex **1** operates by a mechanism analogous to the Brookhart system, with a neutral tetrahydridosilyl species $[(PPh_3)_2IrH_4SiEt_3]$ (**20a**) serving as both the catalyst resting state (**C**) and plausible hydride source in silyloxonium cleavage.[13] Although we previously characterized this species by NMR spectroscopy after independent synthesis from $(PPh_3)_2IrH_5$,[39] the lack of structural data led us to propose a *trans* arrangement of the two triphenylphosphine ligands to account for the single resonance observed by ^{31}P NMR spectroscopy.[13] We now find that under our optimized conditions for ether silylation, the precatalyst **1a** gives the same catalyst resting state (**C**/**20a**) (eqn. 7) (Figures S4 and S5).

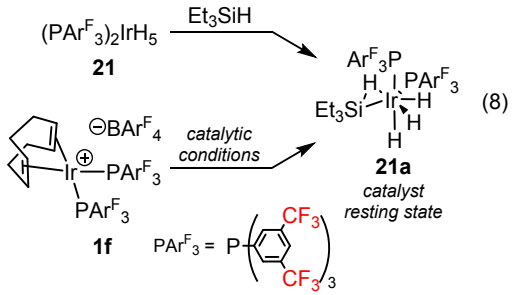


(7)

The observation that complex **20a** serves as the catalyst resting state when **1a** is the precatalyst implies that the turnover-limiting step occurs after silane heterolysis. Thus the concentration of **D** should be equal to that of **B** (not observed) + **C**. In the case of S_N2-type demethylation, a bimolecular turnover-limiting step between **C** and **D** is expected to give a rate law with 2nd order dependence on the iridium concentration. Indeed, kinetic analyses of the cleavage of *trans*-**3** by **1a** are consistent with a 2nd order dependence on **1a** loading (Figure S3). With 2 mol % **1a**, the reduction of *trans*-**3** takes 5 minutes to reach 40% yield and only 60 seconds to reach the same point when the **1a** loading is doubled to 4 mol %. Direct NMR evidence for a free silyloxonium ion (**D**) during catalysis is complicated by rapid exchange with substrate ether, however, Brookhart has been able to characterize a relevant silyloxonium ion under related conditions.[12]

Furthermore we have been successful in obtaining single-crystal samples of the resting state species **C**/**20a** suitable for X-ray crystallography. Our X-ray crystallographic analysis demonstrates that the two phosphine ligands occupy *cis* sites in the solid state, with one being *trans* to the silyl ligand. (Figure 8, left) The high quality of the structural data has allowed us to locate and refine the four metal hydride atom positions. (See Supporting Information for additional details) This analysis shows that one of the hydride ligands occupies a bridging position between the iridium ion and the silyl ligand. By using the refined, restrained hydrogen atom positions as initial coordinates for a DFT calculation, we find that this results in calculated bond lengths of 1.70 Å and 1.80 Å for the Ir-H and H-Si bonds respectively. The latter represents a significantly elongated Si-H bonding contact but does not rule out some non-classical, σ-silane character.[40]

At present it is unknown whether the solid state structure of **20a** aligns with its structure in solution. Samples of **20a** generated *in situ*, under catalytic conditions, or by dissolution of the recrystallized solid give identical ^{31}P NMR spectra in solution. The observed singlet is suggestive of a structure with equivalent phosphines like the *trans* arrangement we proposed previously.[13] However, rapid silane dissociation or other exchange processes could also be responsible for the higher symmetry ^{31}P NMR signal observed in solution.



(8)

The characterization of the catalyst resting state when **1a** is used as a precatalyst inspired us to pursue a similar study on the less electron-releasing phosphine variants that gave rise to distinct selectivity profiles in C–O bond cleavage of cyclohexyl methyl ethers (*vide supra*). Like **1a**, the tris(3,5-bis(trifluoromethyl)phenyl)phosphine-ligated complex **1f** also gives a single resonance by ^{31}P NMR spectroscopy during catalysis (Figure S6). Independent preparation of the tetrahydridosilyl compound **21a** from **21** (eqn. 8) allows us to confirm that **21a** is the catalyst resting state when **1f** is used as a precatalyst. Characterization of **21a** by single-crystal X-ray diffraction confirms that **20a** and **21a** share a similar solid-state geometry (Figure 8). Thus we can conclude that the changes in selectivity on moving from complex **1a** to **1f** stem from differences in reactivity of comparable catalytic intermediates rather than a switch in overall catalyst structure resulting from modification of the phosphine ligands.

The apparent structural similarity of **20a** and **21a** extends to their DFT-optimized hydrogen positions. The Si–H bond distance in **21a** is calculated to be identical to that in **20a** (1.82 Å versus 1.80 Å). Given the less electron-releasing ligands in **21a**, we had expected to see a contraction of the Si–H bond distance resulting from reduced backdonation into the Si–H σ*. The lack of such an observation is telling given that the potential energy surface for elongation of the Si–H bond in σ-silane complexes is known to be shallow.[40] Accordingly, **20a** and **21a** appear to have comparable degrees of σ-silane character, despite representing two extremes of a highly-tunable hydride equivalent for silyloxonium-ion reduction.

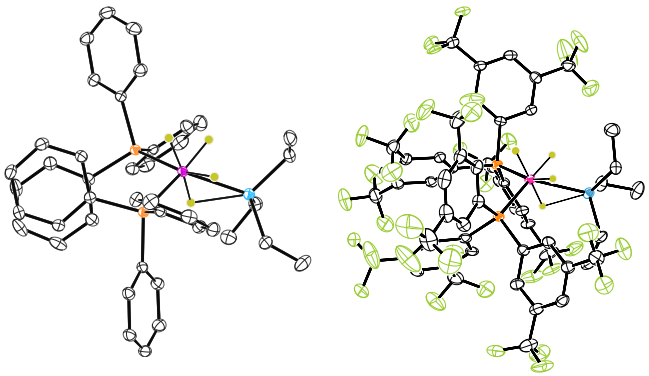


Figure 8. ORTEP diagrams of **20a** (left) and **21a** (right) shown at 50% probability.

Conclusion

In summary we have demonstrated that cationic bis(phosphine)iridium complexes function as tunable and selective catalysts for the cleavage of C–O bonds in cyclohexyl methyl ethers. For the parent bis(triphenylphosphine) precatalyst **1a** the selectivity for demethylation versus 2° C–O cleavage is determined

primarily by the axial versus equatorial preference of the silyloxonium substituent in the intermediate ion. This selectivity can be overridden by the use of less electron-rich precatalysts **1e** and **1f**. These findings are confirmed in *trans*-decalin substrates. The outcome of a deuterium incorporation experiment is consistent with 2° alkyl ether cleavage occurring via an S_N1-type substitution reaction of the silyloxonium intermediate, while the relative reactivity of an ethoxy derivative is indicative of an S_N2 process for demethylation.

This class of catalysts has been extended to cholic acid derivatives bearing a *cis* fusion at the A and B rings. In these cases the 3α-OMe group undergoes reduction in preference to other positions, with the selectivity for demethoxylation versus demethylation being controlled by the presence or absence of a 7α-OMe substituent respectively. Studies of the structure of the catalyst resting state demonstrate that both the PPh_3 and 3,5-tris(bis(trifluoromethyl)phenyl)phosphine variants of the catalyst adopt a comparable tetrahydridosilyliridium structure with similar degrees of σ-Si−H character. The significant change in ligand electronics leads to a switch in selectivity of the resulting catalysts without major perturbation of the resting-state structure, presumably by modulation of the hydride nucleophilicity and thus its preference for S_N1 versus S_N2 reactivity.

Finally, we find that catalysis by this class of cationic bis(phosphine) complexes is remarkably robust. The catalysts can be generated from commercially-available materials directly in air. In total, we find that cationic bis(phosphine)iridium complexes are operationally simple and tunable catalysts for the selective reduction of 2° methyl ethers. Our ongoing efforts aim to extend the scope of suitable substrates for selective reduction from sterols to complex carbohydrate-derived polyethers.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at the ACS publications website at "http://pubs.acs.org."

Experimental procedures, X-ray crystallographic data, Compound characterization data, the results of DFT Calculations, and Cartesian coordinates for the calculated structures.

ACKNOWLEDGMENT

The authors thank Dan Xiaoyu Tong for helpful discussion and preliminary experiments related to this work. Scott Chapp is acknowledged for the initial synthesis and crystallization of **21**. Funding from Vanderbilt University is gratefully acknowledged. This material is based upon work supported by the National Science Foundation under grant no. CHE-1847813. Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research.

REFERENCES

(1) Duzee, E. M. v.; Adkins, H., Hydrogenation and Hydrogenolysis of Ethers. *J. Am. Chem. Soc.* **1935**, *57*, 147-151.

(2) Zaheer, M.; Kempe, R., Catalytic Hydrogenolysis of Aryl Ethers: A Key Step in Lignin Valorization to Valuable Chemicals. *ACS Catalysis* **2015**, *5*, 1675-1684.

(3) Hartwig, W., Modern methods for the radical deoxygenation of alcohols. *Tetrahedron* **1983**, *39*, 2609-2645.

(4) Herrmann, J. M.; König, B., Reductive Deoxygenation of Alcohols: Catalytic Methods Beyond Barton–McCombie Deoxygenation. *Eur. J. Org. Chem.* **2013**, *2013*, 7017-7027.

(5) Dai, X.-J.; Li, C.-J., En Route to a Practical Primary Alcohol Deoxygenation. *J. Am. Chem. Soc.* **2016**, *138*, 5433-5440.

(6) Bauer, J. O.; Chakraborty, S.; Milstein, D., Manganese-Catalyzed Direct Deoxygenation of Primary Alcohols. *ACS Catalysis* **2017**, *7*, 4462-4466.

(7) Yang, S.; Tang, W.; Yang, Z.; Xu, J., Iridium-Catalyzed Highly Efficient and Site-Selective Deoxygenation of Alcohols. *ACS Catalysis* **2018**, *8*, 9320-9326.

(8) Barton, D. H. R.; McCombie, S. W., A new method for the deoxygenation of secondary alcohols. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574-1585.

(9) Burwell, R. L., The Cleavage of Ethers. *Chem. Rev.* **1954**, *54*, 615-685.

(10) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y., A novel reduction of alcohols and ethers with a $HSiEt_3$/catalytic $B(C_6F_5)_3$ system. *Tetrahedron Lett.* **1999**, *40*, 8919-8922.

(11) Gevorgyan, V.; Rubin, M.; Benson, S.; Liu, J.-X.; Yamamoto, Y., A Novel $B(C_6F_5)_3$-Catalyzed Reduction of Alcohols and Cleavage of Aryl and Alkyl Ethers with Hydrosilanes. *J. Org. Chem.* **2000**, *65*, 6179-6186.

(12) Yang, J.; White, P. S.; Brookhart, M., Scope and Mechanism of the Iridium-Catalyzed Cleavage of Alkyl Ethers with Triethylsilane. *J. Am. Chem. Soc.* **2008**, *130*, 17509-17518.

(13) Jones, C. A. H.; Schley, N. D., Selective alkyl ether cleavage by cationic bis(phosphine)iridium complexes. *Organic & Biomolecular Chemistry* **2019**, *17*, 1744-1748.

(14) Adduci, L. L.; McLaughlin, M. P.; Bender, T. A.; Becker, J. J.; Gagné, M. R., Metal-Free Deoxygenation of Carbohydrates. *Angew. Chem. Int. Ed.* **2014**, *53*, 1646-1649.

(15) Hein, N. M.; Seo, Y.; Lee, S. J.; Gagné, M. R., Harnessing the reactivity of poly(methylhydrosiloxane) for the reduction and cyclization of biomass to high-value products. *Green Chemistry* **2019**, *21*, 2662-2669.

(16) Seo, Y.; Lowe, J. M.; Gagné, M. R., Controlling Sugar Deoxygenation Products from Biomass by Choice of Fluoroarylborane Catalyst. *ACS Catalysis* **2019**, *9*, 6648-6652.

(17) McLaughlin, M. P.; Adduci, L. L.; Becker, J. J.; Gagné, M. R., Iridium-Catalyzed Hydrosilylative Reduction of Glucose to Hexane(s). *J. Am. Chem. Soc.* **2013**, *135*, 1225-1227.

(18) Yang, J.; Brookhart, M., Iridium-Catalyzed Reduction of Alkyl Halides by Triethylsilane. *J. Am. Chem. Soc.* **2007**, *129*, 12656-12657.

(19) Winstein, S.; Holness, N. J., Neighboring Carbon and Hydrogen. XIX. t-Butylcyclohexyl Derivatives. Quantitative Conformational Analysis. *J. Am. Chem. Soc.* **1955**, *77*, 5562-5578.

(20) Buchanan, G. W.; Ross, D. A.; Stothers, J. B., A New Approach to Conformational Analysis. Carbon-13 Nuclear Magnetic Resonance1,2. *J. Am. Chem. Soc.* **1966**, *88*, 4301-4302.

(21) Nordlander, J. E.; Blank, J. M.; Jindal, S. P., Solvolysis rates of 4,4-dimethylcyclohexyl tosylate. Evidence on conformational reactivities. *Tetrahedron Lett.* **1969**, *10*, 3477-3479.

(22) Deuterium scrambling into other positions on the substrate is also observed to a lesser extent.

(23) Bloch, K.; Berg, B. N.; Rittenberg, D., The biological conversion of cholesterol to cholic acid. *J. Biol. Chem.* **1943**, *149*, 511-5I7.

(24) Russell, D. W.; Setchell, K. D. R., Bile acid biosynthesis. *Biochemistry* **1992**, *31*, 4737-4749.

(25) Qi, Y.; Jiang, C.; Cheng, J.; Krausz, K. W.; Li, T.; Ferrell, J. M.; Gonzalez, F. J.; Chiang, J. Y. L., Bile acid signaling in lipid metabolism: Metabolomic and lipidomic analysis of lipid and bile acid markers linked to anti-obesity and anti-diabetes in mice. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2015**, *1851*, 19-29.

(26) Li, T.; Chiang, J. Y. L., Nuclear receptors in bile acid metabolism. *Drug Metab Rev* **2013**, *45*, 145-155.

(27) Festa, C.; Renga, B.; D 'Amore, C.; Sepe, V.; Finamore, C.; De Marino, S.; Carino, A.; Cipriani, S.; Monti, M. C.; Zampella, A.; Fiorucci, S., Exploitation of Cholane Scaffold for the Discovery of Potent and Selective Farnesoid X Receptor (FXR) and G-Protein Coupled Bile Acid Receptor 1 (GP-BAR1) Ligands. *J. Med. Chem.* **2014**, *57*, 8477-8495.

(28) Yu, D. D.; Sousa, K. M.; Mattern, D. L.; Wagner, J.; Fu, X.; Vaidehi, N.; Forman, B. M.; Huang, W., Stereoselective synthesis, biological evaluation, and modeling of novel bile acid-derived G-protein coupled Bile acid receptor 1 (GP-BAR1, TGR5) agonists. *Biorg. Med. Chem.* **2015**, *23*, 1613-1628.

(29) Gallagher, T. F.; Long, W. P., PARTIAL OXIDATION OF CHOLIC ACID. *J. Biol. Chem.* **1943**, *147*, 131-134.

(30) Fieser, L. F.; Rajagopalan, S., Selective Oxidation with N-Bromosuccinimide. I. Cholic Acid. *J. Am. Chem. Soc.* **1949**, *71*, 3935-3938.

(31) Hoehn, W. M.; Linsk, J., 3,12-Dihydroxy-7-ketocholanic Acid1. *J. Am. Chem. Soc.* **1945**, *67*, 312-314.

(32) Sonders, R. C.; Hsia, S. L.; Doisy, E. A.; Matschiner, J. T.; Elliott, W. H., Bile acids. XXVI. Metabolism of 12 α -hydroxycholanoic acid-24-14C in the rat. *Biochemistry* **1969**, *8*, 405-413.

(33) Fieser, L. F.; Rajagopalan, S., Oxidation of Steroids. III. Selective Oxidations and Acylations in the Bile Acid Series1. *J. Am. Chem. Soc.* **1950**, *72*, 5530-5536.

(34) Bergström, S.; Haslewood, G. A. D., 122. Substituted ketocholanic acids. *Journal of the Chemical Society (Resumed)* **1939**, 540-541.

(35) Kaziro, K.; Shimada, T., Partielle Oxydation der Cholsäure und der Desoxycholsäure durch CrO_3. - Über eine Farbreaktion der Ketocholansäuren mit *m*-Dinitrobenzol. *Hoppe-Seyler´s Zeitschrift für physiologische Chemie* **1937**, *249*, 220.

(36) Kwart, H.; Takeshita, T., Evaluation of the Relative Importance of Charge-Dipole Interactions and Steric Strain Acceleration in Conformationally Mobile Systems. *J. Am. Chem. Soc.* **1964**, *86*, 1161-1166.

(37) Shiner, V. J.; Jewett, J. G., Nonchair Transition State Conformation in trans-4-t-Butylcyclohexyl Brosylate Solvolysis. *J. Am. Chem. Soc.* **1965**, *87*, 1383-1384.

(38) Barton, D. H. R., The conformation of the steroid nucleus. *Experientia* **1950**, *6*, 316-320.

(39) Loza, M.; Faller, J. W.; Crabtree, R. H., Seven-Coordinate Iridium(V) Polyhydrides with Chelating Bis(silyl) Ligands. *Inorg. Chem.* **1995**, *34*, 2937-2941.

(40) Nikonov, G. I., Recent Advances in Nonclassical Interligand Si···H Interactions. In *Adv. Organomet. Chem.*, West, R.; Hill, A. F.; Stone, F. G. A., Eds. Academic Press: 2005; Vol. 53, pp 217-309.

Graphical Abstract