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Mechanism of Catalytic Functionalization of Primary C−H Bonds Using a Silylation Strategy

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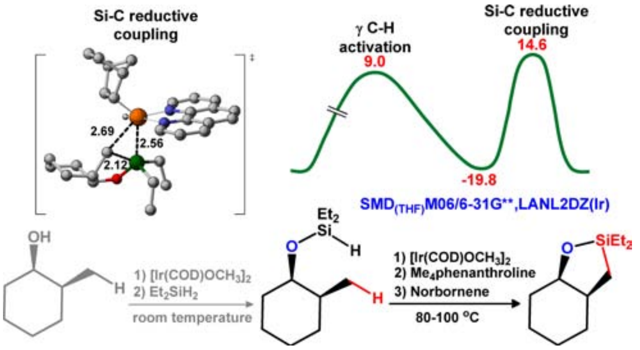
ABSTRACT



The mechanism of Ir-catalyzed γ-functionalization of a primary sp^3(C−H) bond in 2-methyl cyclohexanol is examined using the density functional theory (M06). The nature of the active catalyst for the initial silylation of alcohol is identified as the monomer derived from [Ir(cod)OMe]$_2$ while that for γ-sp^3(C−H) activation leading to oxasilolane is [IrH(nbe)(phen)]. The rate-determining step is found to involve Si−C coupling through reductive elimination.

Transition metal catalyzed C−H activation reactions have been one of the most active research areas that witnessed the right synergism between catalyst development and its application toward realizing complex organic molecules.[1] In particular, C−C coupling reactions have become incredibly popular and have offered access to a whole gamut of biaryls.[2] The current trends conspicuously indicate an increasing interest toward directed C−H activation protocols of unactivated *sp^3*(C−H) bonds such as that of an alkane.[3] While the need for newer catalysts continues to grow, efforts to impart improved efficiency to the previously known catalysts are also witnessing significant strides.

In recent years, the use of silanes in C−H functionalization reactions has been considered as a potentially valuable alternative owing to the reduced cost and environmentally benign nature of such reagents.[4] The scope for synthetic manipulation of the resulting silylated compounds is equally attractive. Although coupling of aryl *sp^2*(C−H) with Si−H bonds has been known for some time now, the practical utility has remained dormant because of the demand for relatively harsher reaction conditions.[5] A number of attractive methodologies have emerged ever since

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[5] (a) Tsukada, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5022. (b) Ureshino, T.; Yoshida, T.; Kuninobu, Y.; Takai, K. *J. Am. Chem. Soc.* **2010**, *132*, 14324.

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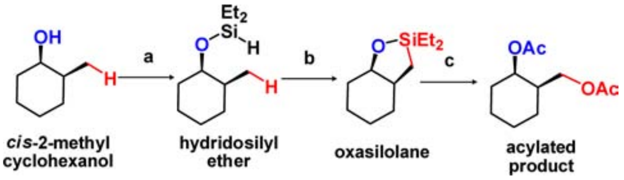
Falck's demonstration that an Ir-catalyzed silylation of heteroarenes can be achieved by using inexpensive triethylsilane.[6] For instance, Hartwig and co-workers reported a hydroxyl group directed ortho-silylation of arenes by using an $[Ir(cod)OMe]_2$ catalyst and 1,10-phenanthroline(phen) under milder reaction conditions.[7]

A more recent report from the Hartwig group has established an elegant site-selective γ-functionalization of primary unactivated sp^3(C−H) bonds using a combination of a Ir-phen catalyst and a dihydridosilane reagent (Scheme 1).[8] The reaction employs alcohol as a directing group under milder conditions and makes use of dehydrogenative cyclization. The scope of the reaction has been demonstrated to include a range of functional groups as well as diastereoselective functionalization leading to natural products. Timely rationalization of the mechanistic underpinnings of such reactions is therefore of significance toward exploiting the full potential of C−H functionalization by using catalytic silylation methods.

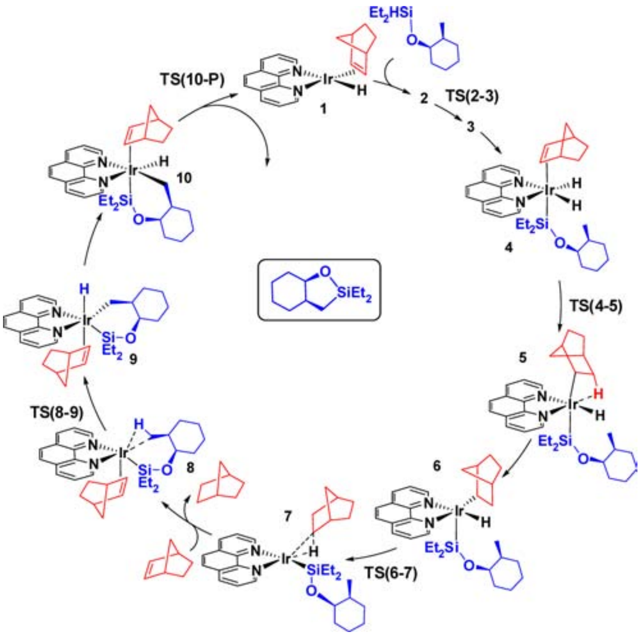
Scheme 1. γ-Functionalization of Primary C−H Bonds from (Hydrido)silyl Ether



(a) $[Ir(cod)OMe]_2$ (0.05 mol %), Et_2SiH_2(1.2 equiv), THF, room temperature. (b) $[Ir(cod)OMe]_2$ (0.5 mol %), Me_4phenanthroline (1.2 mol %), norbornene (1.2 equiv), THF, 80−100 °C. (c) $KHCO_3$, H_2O_2, THF/MeOH, 50 °C then Ac_2O, Et_3N, CH_2Cl_2, room temperature.

In line with our long-standing interest toward understanding the mechanism of transition metal catalysis,[9] we herein intend to disclose the first mechanistic investigation on Ir-catalyzed hydrosilylation and the ensuing dehydrogenative cyclization leading to oxasilolane, obtained through the density functional theory computational method. In particular, the energetics associated with the catalytic cycle, the nature of the active catalyst, and the molecular origin of the role of a hydrogen acceptor (such as norbornene) are the key highlights of this letter. The preferred mechanistic pathway is identified by locating the transition states and intermediates using the M06 density functional theory with the 6-31G** basis set, in the condensed phase (THF as the solvent).[10] The discussions are presented by using the Gibbs free energies obtained at the $SMD_{(THF)}$M06/6-31G**, LANL2DZ(Ir) level of theory.[11]

Scheme 2. Mechanism of Conversion of (Hydrido)silyl Ether to Oxasilolane Catalyzed by Neutral [IrH(nbe)(phen)]



The γ-functionalization reaction, as shown in Scheme 1, presents a number of intriguing observations. First, the catalytic silylation of the alcohol by Et_2SiH_2 is performed under relatively milder conditions in the absence of any added phen ligand. However, the activation of the primary C−H bond and the intramolecular C−Si coupling demand an elevated temperature besides the presence of phen. Although we have examined the mechanistic details of both these steps,[12] the emphasis herein is placed on the vital dehydrogenative C−Si coupling step. In view of the earlier reports that a stronger ligand such as phen could readily displace a labile ligand on an Ir(I) center, we envisaged that a neutral [IrH(nbe)(phen)] derived from the methoxy bridged precatalyst could potentially serve as the active species.[13] Another likely scenario wherein a cationic [Ir(cod)phen] acts as the active catalyst is considered as well. However, the computed energetics is found to be higher than that noted in the neutral pathway.[14]

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(10) All computations were performed using the Gaussian09 suite of quantum chemical programs. Frisch, M. J. et al. *Gaussian09*, rev. A.02; Gaussian Inc.: Wallingford, CT, 2009. See the Supporting Information (SI) for complete list of citations as well as full description of the computational methods.

(11) (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215. (b) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

(12) Complete details of the catalytic silylation of the hydroxyl group by Et_2SiH_2 are provided in Scheme S5, Figures S6−S7, and Table S8 of the SI. The barriers for the elementary steps involved in the initial silylation are found to be lower than those in silolane formation.

(13) (a) Taubmann, S.; Alt, H. G. *J. Mol. Catal. A: Chem.* **2008**, *284*, 134. (b) The conversion of the precatalyst dimer $[Ir(cod)OMe]_2$ first to [Ir(nbe)(OMe)(phen)] and subsequent reaction with the silyl ether provide an intermediate $Si(MeO)Et_2(OC_6H_4Me)$ and [IrH(nbe)(phen)]. The process exhibits a high exoergicity of −32.5 kcal/mol. More details are provided in Figure S1 in the SI.

(14) Complete details for the formation of oxasilolane with $[Ir(cod)(phen)]^+$ as the active catalytic species are provided in Scheme S9, Table S10, and Figure S11 in SI.

The catalytic cycle for the formation of oxasilolane through C–Si coupling is succinctly summarized in Scheme 2. The hydridosilyl ether obtained by the initial silylation of 2-methyl cyclohexanol is the key substrate in the catalytic cycle. The catalyst–substrate prereacting complex (**2**) between [IrH(nbe)(phen)] and silylcyclohexanol sets the stage for the initial oxidative insertion.[15] The oxidative insertion of Ir(I) to the Si–H bond gives a hexacoordinate Ir(III)–H intermediate **3**. The geometry of transition state **TS(2–3)** is provided in Figure 1. The geometric features suggest the involvement of an early transition state.[16] The interchange of axial–equatorial dispositions between the Ir-bound hydridosilyl ether and the hydride moieties in **3** provides another intermediate **4**.

A β-migratory insertion of iridium via **TS(4–5)** furnishes **5** wherein the hydrido group on the iridium gets transferred to one of the norbornenyl carbons. In this concerted hydride transfer, as shown in Figure 1, a new Ir–C bond (2.25 Å) develops at the other end of the norbornene double bond. A relatively higher strain in the four-membered ring structure of **5** results in its conversion to another intermediate **6**.[17] It is important to note at this juncture that the introduction of norbornene (nbe) as a hydrogen acceptor was reported to increase the reaction rates, alluding to its active role in the mechanism.[7] The nbe bound intermediate, as identified here, supports the direct role played by the sacrificial hydrogen acceptor.[18]

In the next step, a reductive elimination facilitated by the combination of the Ir-bound norbornyl and the hydride yields intermediate **7** through **TS(6–7)**. In intermediate **7**, one of the C–H bonds of norbornane participates in an agostic interaction with the Ir center. Displacement of the weakly bound norbornane by another norbornene molecule would then result in intermediate **8**. In this intermediate, the γ-sp^3 C–H bond is in closer proximity with a 16-electron Ir center. An agostic interaction between the γ C–H bond and iridium sets the stage for the crucial oxidative insertion step. The oxidative insertion of Ir(I) to the γ-sp^3 C–H bond gives a hexacoordinate 18-electron Ir(III) intermediate **9**. The geometry of the corresponding transition state **TS(8–9)**, as shown in Figure 1, indicates an early transition state.[19]

The intermediate **9** with a relatively bulkier silyl ether group adjacent to the norbornenyl moiety can interchange the ligand positions to another lower energy intermediate **10**. The latter intermediate appears to provide a congenial geometry for the ensuing C–Si coupling step. The coordination environment created by norbornene and the other substituents around Ir(III) in intermediate **10** is sufficiently crowded. This is a favorable condition for reductive elimination.[20] In the next step, the vital carbon–silicon coupling takes place through reductive elimination to furnish the desired oxasilolane ring. The transition state geometry of **TS(10-P)**, with longer Ir–C and Ir–Si distances, evidently suggests the departure of the active catalytic species [IrH(nbe)(phen)] **1** (Figure 1). The formation of the product and the accompanying regeneration of the active catalytic species **1** help to continue the catalytic cycle.

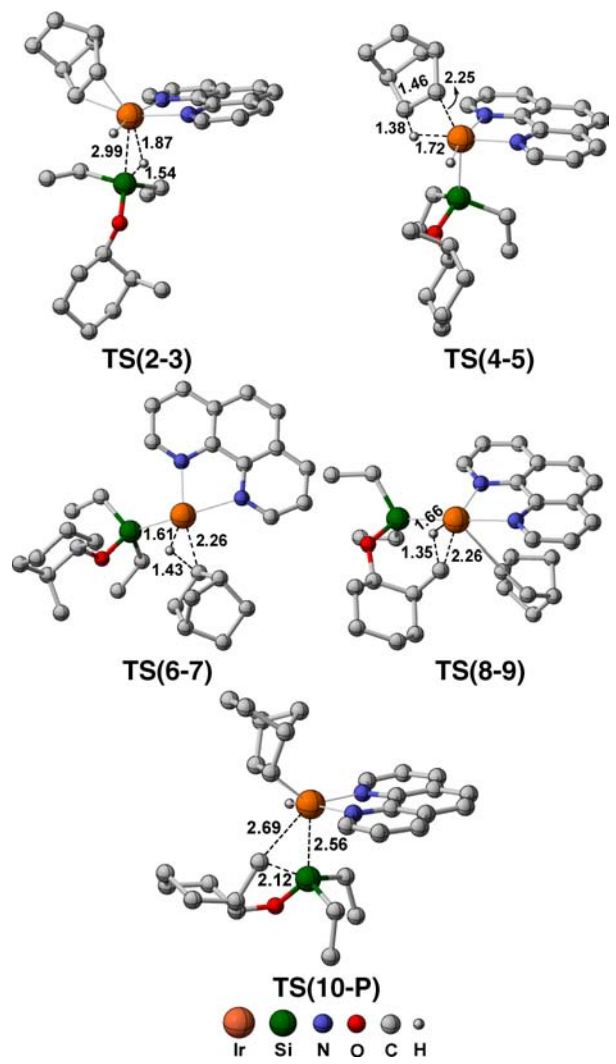

Figure 1. Optimized geometries of the transition states involved in the formation of oxasilolane using [IrH(nbe)(phen)] as the active catalyst obtained at the $\mathrm{SMD_{(THF)}M06/6\text{-}31G^{**}}$, LANL2DZ(Ir) level of theory. All distances are in Å.

The computed Gibbs free energy profile obtained at the M06 level of theory in THF continuum solvent for all the key elementary steps is summarized in Figure 2.

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(15) The optimized geometry of the prereacting complex **2** and intermediate **3** are provided in Figure S2 of the SI.

(16) The Si–H, Ir–Si, and Ir–H distances in the prereacting complex (**2**) and the product of this elementary step (**3**) are respectively 1.51, 3.59, 2.32 and 2.61, 2.36, 1.63 Å.

(17) The optimized geometry of **5** and the major electron delocalizations are provided in Figure S3 in SI.

(18) A similar role of the norbornenyl group was previously suggested in an Ir-catalyzed dehydrogenative cyclization leading to benzosiloles. See: Kuznetsov, A.; Gevorgyan, V. *Org. Lett.* **2012**, *14*, 914.

(19) The Ir–H, Ir–C, and C–H distances in intermediate (**8**) and the product of this elementary step (**9**) are respectively 1.87, 2.52, 1.15 and 1.56, 2.09, 2.58 Å

(20) (a) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (b) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936. (c) Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; Lera, A. R.; Alvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650.

The energetics reveals a series of important features of the reaction pathway beginning with the silylated 2-methylcyclohexanol. It can be noticed from Figure 2 that the activation barrier for the initial oxidative insertion of Ir(I) to the Si−H bond, calculated as the energy difference between **1** and **TS(2−3)**, is about 15.2 kcal/mol. Conspicuously, the transition state for the critical reductive elimination **TS(10-P)** leading to the oxasilolane product exhibits the highest activation barrier of 34.4 kcal/mol. One of the most important aspects at this point is the correspondence between the computed energetics and the experimental conditions. Two of the critical transition states, **TS(6−7)** and **TS(10-P)**, are of relatively higher energies and as well exhibit higher barriers for the respective elementary steps. This feature, as captured in the computed Gibbs free energy profile, is in line with the higher temperature requirement for the reaction.

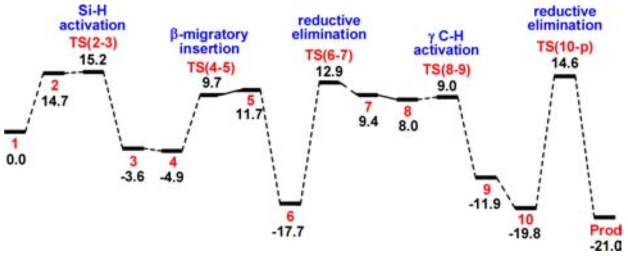

Figure 2. Gibbs free energy profile obtained at the SMD$_{(THF)}$M06/6-31G**, LANL2DZ(Ir) level of theory for the formation of oxasilolane using [IrH(nbe)(phen)] as the active catalyst. All the energies are in kcal/mol.

A comparison of the computed energies obtained using the M06/6-31G** and the M06/6-31+G** levels of theory, both in the THF continuum, is provided in Table 1. A systematic lowering of the energies of various stationary points at the M06/6-31+G** level of theory is noticeable. However, the general trends in the energetics between these two levels of theory and the conclusions remain the same.

Table 1. Relative Gibbs Free Energies (kcal/mol) of the Transition States and Intermediates with Respect to the Infinitely Separated Reactants at Various Levels of Theory[a]

	solvent phase			solvent phase	
	L1	**L2**		**L1**	**L2**
2	14.7	3.0	**7**	9.4	−2.5
TS(2−3)	15.2	3.9	**8**	8.0	−4.2
3	−3.6	1.7	**TS(8−9)**	9.0	−1.1
4	−4.9	−16.7	**9**	−11.9	−22.8
TS(4−5)	9.7	−2.2	**10**	−19.8	−30.3
5	11.7	−0.4	**TS(10-P)**	14.6	4.2
6	−17.7	−28.7	**Prod**	−21.0	−32.4
TS(6−7)	12.9	1.1			

[a] L1 = SMD$_{(THF)}$M06/6-31G**, LANL2DZ(Ir); L2 = SMD$_{(THF)}$M06/6-31+G**, LANL2DZ(Ir)//SMD$_{(THF)}$M06/6-31G**, LANL2DZ(Ir).

In conclusion, the mechanism of γ-functionalization of a primary *sp*^{3}(C−H) bond in 2-methyl cyclohexanol is identified to involve two key steps. The computed barrier for the initial silylation of the alcohol catalyzed by the monomer derived from [Ir(COD)OMe]$_2$ to give an *O*-silyl cyclohexanol is in general lower than that in the subsequent steps. The energetically favored pathway for [IrH(nbe)(phen)] catalyzed γ-*sp*^{3}(C−H) activation is found to proceed through a relatively higher energy transition state for the Si−C coupling through a reductive elimination process. The computed energetics is in concert with the experimental conditions, such as the use of a higher temperature for the dehydrogenative cylization as compared to the initial silylation as well as the rate enhancements upon introducing norbornene as a sacrificial hydrogen acceptor.

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Supporting Information Available. Details of computational methods, complete citation for ref 10, and optimized geometries of the transition states and intermediates are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.