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Iridium-Catalyzed Silylation of C−H Bonds in Unactivated Arenes: A Sterically Encumbered Phenanthroline Ligand Accelerates Catalysis

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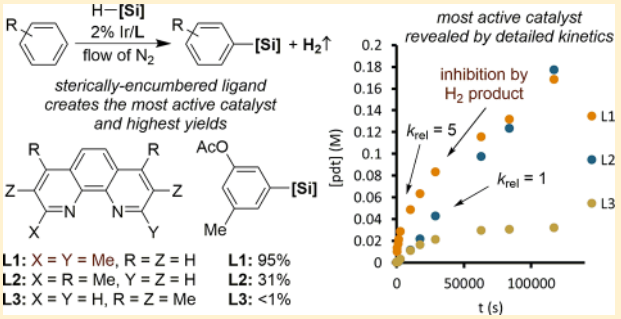
Supporting Information

ABSTRACT: We report a new system for the silylation of aryl C−H bonds. The combination of $[Ir(cod)(OMe)]_2$ and 2,9-Me_2-phenanthroline (2,9-Me_2-phen) catalyzes the silylation of arenes at lower temperatures and with faster rates than those reported previously, when the hydrogen byproduct is removed, and with high functional group tolerance and regioselectivity. Inhibition of reactions by the H_2 byproduct is shown to limit the silylation of aryl C−H bonds in the presence of the most active catalysts, thereby masking their high activity. Analysis of initial rates uncovered the high reactivity of the catalyst containing the sterically hindered 2,9-Me_2-phen ligand but accompanying rapid inhibition by hydrogen. With this catalyst, under a flow of nitrogen to remove hydrogen, electron-rich arenes, including those containing sensitive functional groups, undergo silylation in high yield for the first time, and arenes that underwent silylation with prior catalysts react over much shorter times with lower catalyst loadings. The synthetic value of this methodology is demonstrated by the preparation of key intermediates in the synthesis of medicinally important compounds in concise sequences comprising silylation and functionalization. Mechanistic studies demonstrate that the cleavage of the aryl C−H bond is reversible and that the higher rates observed with the 2,9-Me_2-phen ligand are due to a more thermodynamically favorable oxidative addition of aryl C−H bonds.



INTRODUCTION

The functionalization of C−H bonds in arenes and alkanes is becoming a valuable methodology for the synthesis of pharmaceutical drug candidates,[1] and the reactions of boranes and diboranes with arenes catalyzed by transition-metal complexes have proven particularly useful. These reactions occur at the most electron-poor C−H bond that is sterically accessible, and this regioselectivity is complementary to electrophilic aromatic substitutions, which generally occur at the most electron-rich position.[2] The products of these reactions are versatile synthetic intermediates that undergo further halogenation, cyanation, etherification, hydroxylation, amination, and trifluoromethylation,[3] as well as cross-coupling reactions to form carbon−carbon bonds that are widely employed in medicinal chemistry.[4]

Although the functionalizations of aryl C−H bonds with boron reagents are useful, several features of these reactions could limit broad utility. For example, the reagents can be expensive relative to the value of the products, some heteroarylboronates are unstable to proto-deboronation, and the lengthy synthesis of diboron reagents can lead to large amounts of waste.[5] The functionalization of C−H bonds with silanes is an attractive alternative to the functionalization with boranes because many silanes are produced and consumed on a large scale,[6] silylarenes containing heteroatom substituents attached to silicon can be employed in a wide range of coupling reactions and oxidative transformations,[7] and the heteroarylsilanes are more stable than heteroarylboronates.[7d,8] Several groups have reported silylations of the C−H bonds of arenes with trialkylsilanes, difluoroalkylsilanes, silatrane, or siloxysilanes catalyzed by complexes that are similar to those that catalyze the borylation of C−H bonds. However, these reactions require a large excess of the arene[9] or a directing group.[10]

Our group has reported silylations of aryl C−H bonds with the arene as limiting reagent catalyzed by rhodium and iridium complexes with the silane $HSiMe(OTMS)_2$, which is available in bulk at low cost (Scheme 1A).[11] Due to the presence of two heteroatoms attached to the central silicon, the silylarenes produced from the functionalization of aryl and heteroaryl C−H bonds with this reagent undergo a wide variety of cross-coupling and functionalization reactions.[8] The silylations catalyzed by a rhodium−bisphosphine complex we reported functionalize arenes with high sterically derived regioselectivity. However, a series of functional groups, including Lewis basic groups, such as nitriles, most basic heterocycles, and reducible groups, such as aryl iodides, aryl bromides, aryl esters, and ketones, did not undergo silylation (Scheme 1B).[12] In contrast, the silylations catalyzed by an iridium complex of 2,4,7-trimethylphenanthroline occurred with exceptionally high functional group tolerance. Yet, reactions catalyzed by this

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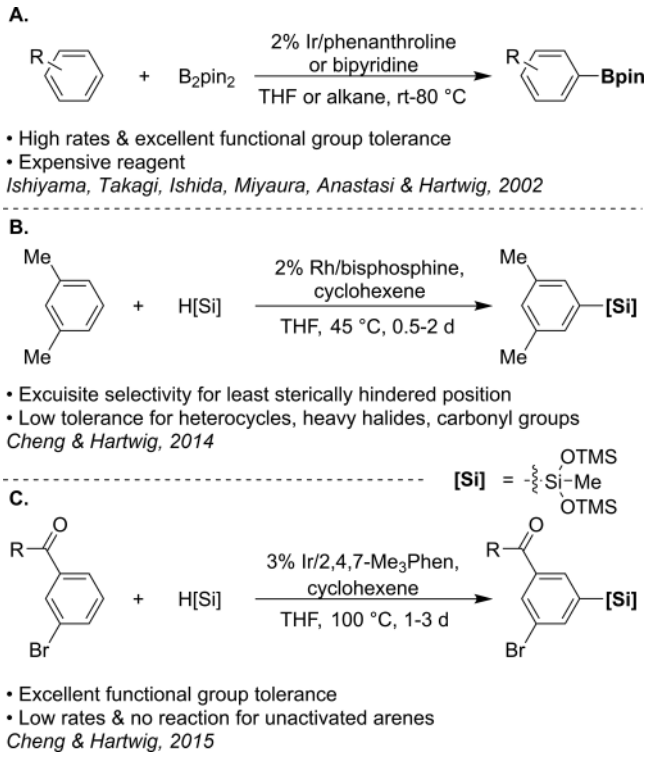
system required long times and required high temperatures to reach high conversion of starting material. Furthermore, the reactions of electron-neutral arenes occurred in only modest yields, and the reactions of electron-rich arenes formed little to no product (Scheme 1C).[13]

Scheme 1. Functionalization of Aryl C−H bonds with Boron and Silicon Reagents



Here, we describe a new iridium catalyst and conditions for the silylation of arenes with hydrosilanes that together lead to reactions of electron-rich arenes and much faster reactions of heteroarenes and electron-poor arenes, along with experimental mechanistic studies that reveal the origin of this high reactivity. This catalyst contains 2,9-dimethylphenanthroline (2,9-Me_2-phen) as ligand. The high activity of this catalyst is masked under standard conditions by its susceptibility to inhibition by the hydrogen byproduct. The high activity is evident from initial rates and becomes practical when the product inhibition is alleviated by removing the hydrogen from the system. Cleavage of the aryl C−H bond is reversible, and the higher rates, counterintuitively, appear to result from a more thermodynamically favorable oxidative addition of a C−H bond to the iridium complex of this hindered ligand than to complexes of ligands lacking substituents in the 2 and 9 positions. Applications to the synthesis of a series of intermediates to medicinally important compounds demonstrate the value of this new system.

RESULTS AND DISCUSSION

1. Initial Rates and Reaction Development. To identify highly active catalysts for the silylation of aryl C−H bonds, including those of electron-rich arenes, we first measured the rates of the silylation of benzene in the presence of an iridium precatalyst and phenanthrolines possessing varied steric properties. The initial rate of the reaction of $HSiMe(OTMS)_2$ and benzene was determined by measuring the amount of silylarene produced at 80 °C with a 1:1.5 ratio of benzene to silane (Figure 1). The rates of reactions catalyzed by the combination of 1 mol% $[Ir(COD)(OMe)]_2$ and 3 mol% of four phenanthroline ligands (**L1**−**L4**, Figure 1) containing methyl substituents in different quantities and positions were measured. The initial rates of the reactions catalyzed by the combination of iridium and a phenanthroline containing methyl groups in the 2 and the 9 positions (**L1** and **L4**) are higher than those of the reactions catalyzed by the combination of iridium and phenanthroline ligands lacking one or both of the methyl groups in the 2 and the 9 positions (**L2** and **L3**) (Figure 1). The silylation reactions of aryl C−H bonds catalyzed by iridium complexes of phenanthrolines bearing methyl groups in the 2 and the 9 positions were more than 5 times faster than those catalyzed by iridium complexes of the 2,4,7-substituted phenanthroline (**L2**) previously reported for the silylation of C−H bonds.

Despite the high initial rate of the silylation catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and 2,9-Me_2-phen, the overall yield of this reaction was reported to be lower than that of the reaction catalyzed by complexes containing other ligands.[13] Indeed, when the reaction of benzene and silane catalyzed by iridium and this ligand approached 5% conversion, the rate began to decrease (Figure 1), and after 15% conversion, the amount of silylbenzene produced by the reaction conducted with 2-methyl ligand **L2** is greater than that produced by the catalyst containing 2,9-dimethyl ligand **L1** or **L4**. We hypothesized that inhibition of the catalyst by the hydrogen produced by the reaction could cause the observed decrease in rates during reactions catalyzed by complexes ligated by **L1** or **L4**.

To determine whether hydrogen inhibited the silylation reaction, we first measured the amount of silylbenzene formed in the presence of $[Ir(COD)(OMe)]_2$ and **L1** with added dihydrogen. The rate at which silylbenzene is formed is 10 times lower under an atmosphere of hydrogen than under an atmosphere of nitrogen (see Supporting Information (SI)). We examined whether a series of hydrogen acceptors could prevent inhibition by hydrogen formed in the course of the reaction. The profile of the reaction of benzene and silane was the same in the presence or absence of cyclohexene or tetramethylethylene as hydrogen acceptors (Figure 2). Consistent with this observation, the ^1H NMR spectrum of the crude reaction catalyzed by iridium and 2,9-Me_2-phen with cyclohexene as the hydrogen acceptor contained signals corresponding to less than 0.05 equiv of cyclohexane, even though 16% of the starting material was converted to product. This result shows that the rate of the reduction of cyclohexene is much lower than the rate of the silylation of benzene. The conversion of silane in the reaction conducted with the strained alkene norbornene (nbe) was higher in less time than that in reactions conducted with other hydrogen acceptors, but the silylation of the alkene C−H bond of nbe to form vinylsilane was faster than silylation of the C−H bond of benzene, and a low yield of silylarene was observed. Thus, the complex formed by the combination of iridium and 2,9-Me_2-phen and silane does not reduce unstrained internal alkenes with hydrogen at a rate that is commensurate with the rate of the silylation of benzene, and this complex leads to the silylation of the C−H bond of a strained alkene. For this reason, a different approach to removing hydrogen from the reaction was required to prevent the inhibition of the catalysts by hydrogen.

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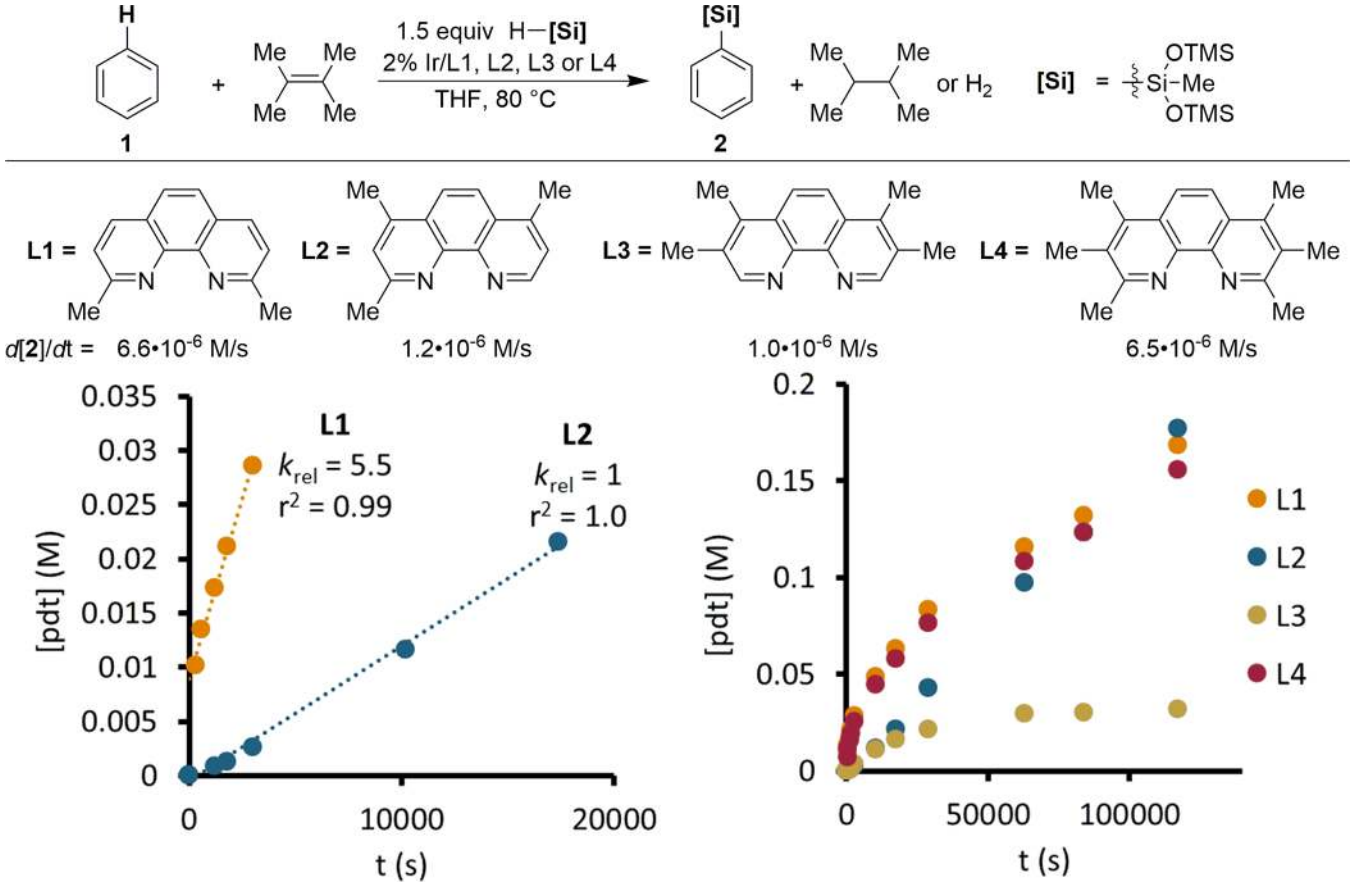

Figure 1. Measurement of rate of silylation and reaction profile with different iridium catalysts. Conditions: benzene (**1**, 0.25 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), tetramethylethylene (1.0 equiv), $[Ir(cod)(OMe)]_2$ (1.0 mol%), ligand (3.0 mol%), dodecane (1.0 equiv), THF (1 M). Silylarene (**2**) concentration was determined by GC using *n*-dodecane as an internal standard.

To test further the effect of the hydrogen byproduct, the reaction was run in a closed system, as is typically done for reactions on small scale, as well as a system containing a flow of nitrogen. The reaction of *o*-xylene and silane catalyzed by $[Ir(cod)(OMe)]_2$ and 2,9-Me_2Phen in a closed vial produced the silylarene in only 18% yield. However, the same reaction conducted in a vessel equipped with a nitrogen inlet and gas outlet formed silylarene **4** in 77% yield within 20 h. It appears that the flow of nitrogen gas through the system prevents catalyst inhibition by removing hydrogen gas and allows reactions catalyzed by iridium complexes ligated by 2,9-Me_2Phen to reach high conversion.

2. Scope of the Silylation of Aryl C—H Bonds. Having identified a ligand that generates a highly active catalyst, and having gained evidence that the catalyst activity is inhibited by the hydrogen byproduct, we explored the scope of the reactions catalyzed by the complex of 2,9-dimethyl ligand **L1** under conditions in which hydrogen is removed by a flow of nitrogen. Most reactions were conducted in a Radley carousel reactor equipped with nitrogen inlet and outlets, heating block, and cooling jacket. Under these conditions, electron-rich, electron-neutral, electron-poor, and heteroaromatic silylarene products were obtained in high yields from reactions catalyzed by iridium complexes of **L1**. Silylarenes also were produced in high yield from reactions conducted in a simple round-bottom flask fitted with a reflux condenser and a nitrogen inlet and gas outlet.

The dramatic increase in rates of reactions catalyzed by the complex of 2,9-Me_2-phen enabled the first iridium-catalyzed silylations of electron-rich arenes with the arene as limiting reagent. Arenes containing alkyl, methoxy, and dimethylamino substituents were obtained in yields ranging from 66% to 94% (Table 1). The silylation of 1,3-dimethoxybenzene occurred with >10:1 selectivity for functionalization at the meta C—H bond over the ortho C—H bond. In all other cases, the sole C—H bond that reacted was distal to functional groups on the arene. To assess whether the influence of the steric properties of the C—H bonds on the selectivity of the silylation reaction was larger than the effect of the electronic properties of the arene and whether reactions would occur at particularly electron-rich C—H bonds, the reaction of 2,6-dimethylanisole was conducted. The C—H bond that is *para* to the electron-donating methoxy group in this arene is particularly electron rich, due to the presence of three substituents that are electron-donating to the C—H bond at the sterically accessible 5-position. Despite the high electron density at this C—H bond, the reaction occurred exclusively to form the 5-silylarene **8** in a high 83% yield.

To assess the effect of the ligand on the reactions of electron-rich arenes, we also conducted the silylations with the catalyst generated from 2,4,7-Me_3-phen and 3,4,7,8-tetramethylphenanthroline. The reactions of electron-rich arenes conducted with 2,4,7-Me_3-phen instead of 2,9-Me_2-phen formed silylarenes in low yields, whether the reaction was conducted under a flow of nitrogen or in a closed system with

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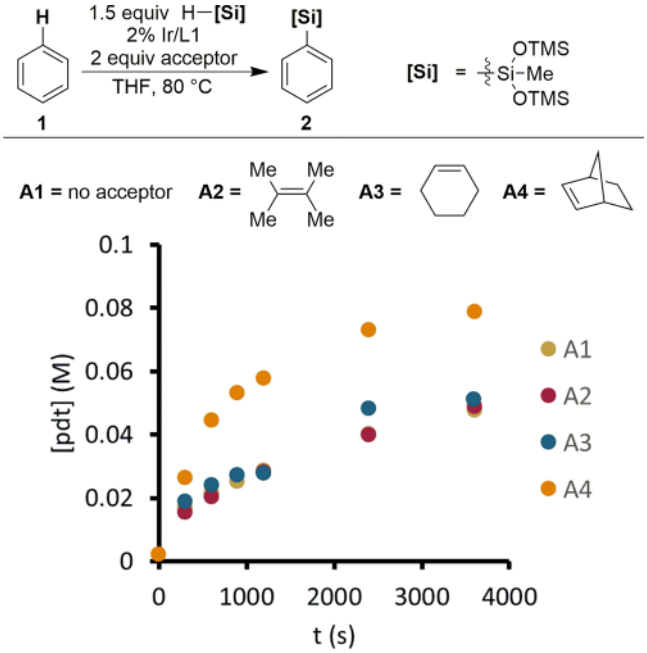


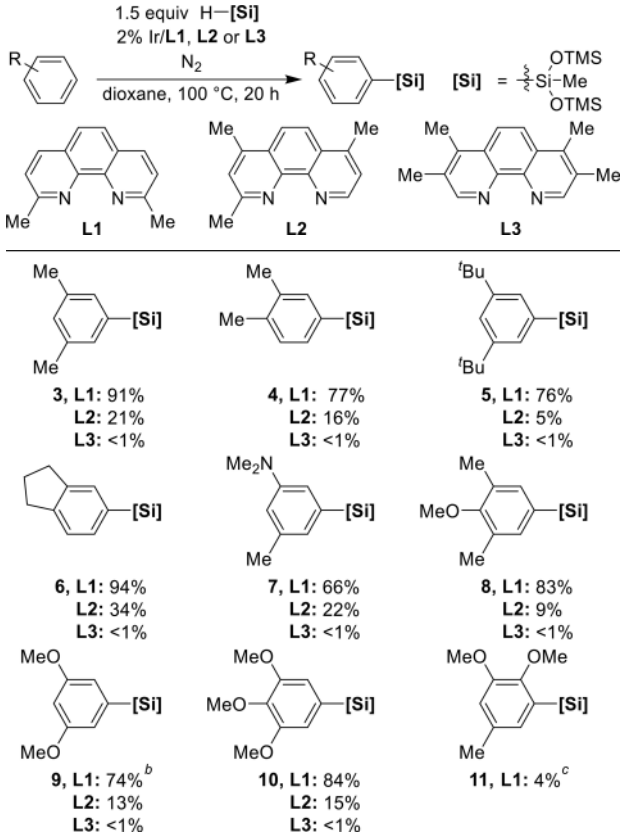
Figure 2. Measurement of rate of silylation and reaction profile with a series of hydrogen acceptors. Conditions: benzene (**1**, 0.25 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), hydrogen acceptor (1.0 equiv), $[Ir(cod)(OMe)]_2$ (1.0 mol%), 2,9-Me_2Phen (2.0 mol%), dodecane (1.0 equiv), THF (1 M). Silylarene (**2**) concentration was determined by GC using *n*-dodecane as an internal standard.

alkene hydrogen acceptor. The yields from reactions of these arenes under a flow of nitrogen catalyzed by iridium and 2,4,7-Me_3-phen (**L2**) ranged from 5% (**5**) to 34% (**6**). No electron-rich silylarene products were obtained from reactions catalyzed by iridium and Me_4 phen (**L3**). These results demonstrate that previously reported systems for the iridium-catalyzed silylation of aryl C−H bonds would require unacceptably high catalyst loadings to produce reasonable yields of electron-rich silylarenes.

Electron-neutral and electron-poor arenes underwent C−H silylation in yields that ranged from 56% to 99% (Table 2). The reactions of these substrates occurred with high functional-group tolerance in less than 20 h. Esters were tolerated; no products from reduction of this functionality were observed (**13**, **16**, and **20**). Likewise, two representative benzonitriles underwent silylation in 84% (**15**) and 97% (**18**) yield without any detectable reduction of the cyano groups. These reactions occurred with >10:1 selectivity for functionalization at the *meta* C−H bond over the *ortho* C−H bond. Borylation of benzonitriles often occurs to give mixtures of products from reaction *ortho* and *meta* to the cyano group.[14] Silylarenes containing iodo, bromo, or chloro substituents were obtained in high yield without hydrodehalogenation (substrates: **12**, **14**, **18**, **20**−**23**).

The reactions catalyzed by complexes of the previously reported ligands (**L2** or **L3** with added hydrogen acceptor) form electron-neutral silylarene products in much lower yields under similar conditions. Most of these electron-neutral silylarenes (Table 2, top) were produced in acceptable yield from reactions catalyzed by iridium ligated by **L2**, but these reactions required days to reach high conversion. The conversion of electron-neutral arenes to the corresponding silylarenes catalyzed by the complex of **L2**, after 20 h, ranged from low (**16**, 31%) to modest (**14**, 58%). In contrast, the

Table 1. C−H Silylation of Electron-Rich Arenes[a]



[a]Conditions for reactions with **L1**: arene (0.5 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), $[Ir(cod)(OMe)]_2$ (1 mol%), ligand (2 mol%), 1,4-dioxane (200 μL), 100 °C, under a stream of N_2, 20−24 h. Isolated yields are reported. Conditions for reactions with **L2** and **L3**: arene (0.5 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), $[Ir(cod)(OMe)]_2$ (1 mol%), ligand (2 mol%), 1,4-dioxane (200 μL), 100 °C, under a stream of N_2, 20 h. Yield was determined by NMR spectroscopy relative to CH_2Br_2 internal standard. [b]Conducted at 80 °C. [c]Yield was determined by NMR spectroscopy relative to CH_2Br_2 internal standard.

conversion of electron-neutral arenes into the corresponding silylarenes was complete after 20 h when catalyzed by the complex of **L1**.

Arenes in which all C−H bonds are *ortho* to a substituent were silylated, but the rates of these reactions were low. For example, the reaction of 3,4-dimethoxytoluene formed the silylarene resulting from C−H activation *ortho* to the methoxy group. However, only 4% yield of **11** was observed after 2 d, even with a higher catalyst loading of 4%.

In some cases, running the silylation reaction in a closed system with a hydrogen acceptor is more convenient than running the reaction under a flow of nitrogen. We hypothesized that the rates of the silylation of heteroarenes might be significantly faster than the rate of the competitive silylation of a norbornenyl C−H bond, allowing this alkene to be employed as hydrogen acceptor in a closed system. As shown in Table 3, both 5-membered and 6-membered ring heterocycles underwent silylation with norbornene as acceptor or in an open system in high yields under conditions that are milder than those for the silylation of aromatic substrates. As was observed for reactions of aryl halides, reactions of heteroaryl halides occurred without protodehalogenation.

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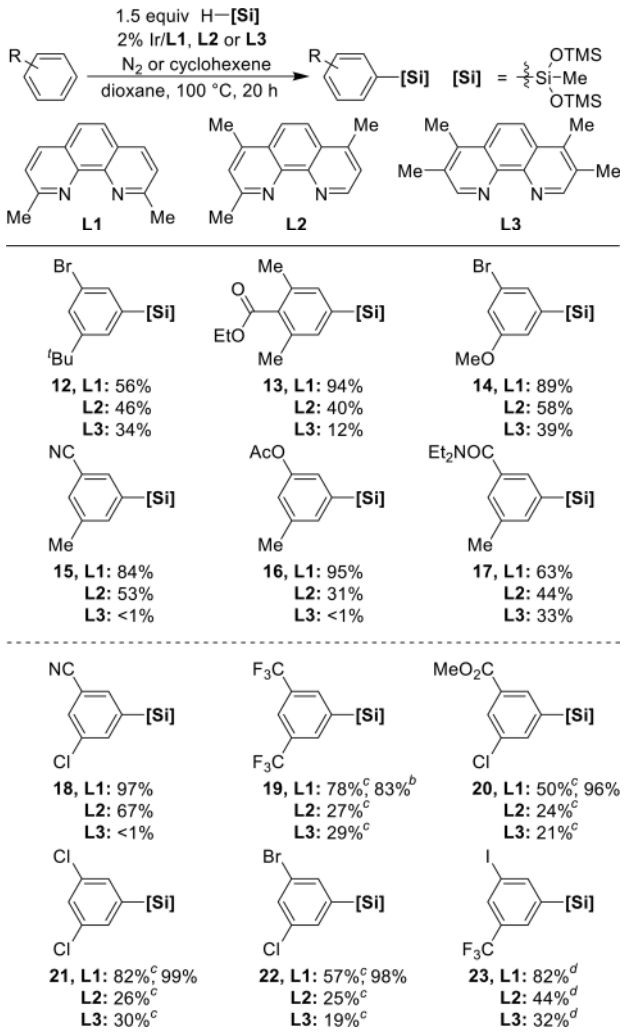
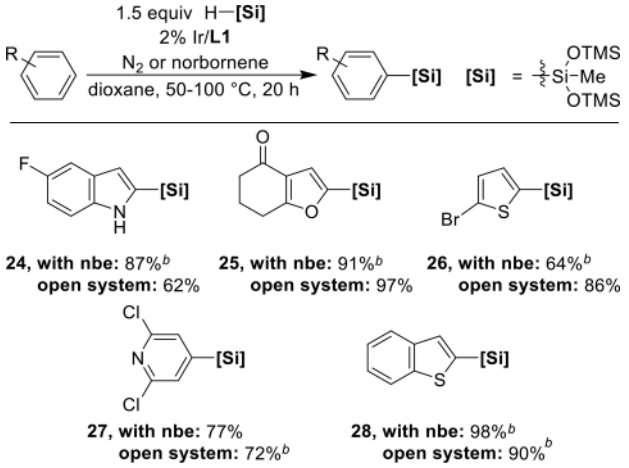
Table 2. C−H Silylation of Electron-Neutral Arenes (Top) and Electron-Poor Arenes (Bottom)[a]



[a]Conditions for reactions with **L1**: arene (0.5 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), $[Ir(cod)(OMe)]_2$ (1 mol%), ligand (2 mol%), 1,4-dioxane (200 μL), 100 °C, under a stream of N_2, 6−24 h. Isolated yields are reported. Conditions for reactions with **L2** and **L3**: arene (0.1 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), cyclohexene (1.5 equiv), $[Ir(cod)(OMe)]_2$ (1 mol%), ligand (2 mol%), THF (100 μL), 100 °C. Yield was determined by NMR spectroscopy relative to CH_2Br_2 internal standard. [b]Conducted at 80 °C. [c]Yield was determined by NMR spectroscopy relative to CH_2Br_2 internal standard; reaction used 0.2−0.25 mol% $[Ir(cod)(OMe)]_2$, 18 h. [d]Reaction used 4 mol% $[Ir(cod)(OMe)]_2$, 20 h.

Table 3. C−H Silylation of Heteroarenes[a]



[a]Conditions with norbornene: arene (0.25 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), norbornene (1 equiv), $[Ir(cod)(OMe)]_2$ (1 mol%), ligand (2 mol%), THF (100 μL), 100 °C, 2 h. Isolated yields are reported. Conditions with open system: arene (0.5 mmol), $HSiMe(OTMS)_2$ (1.5 equiv), $[Ir(cod)(OMe)]_2$ (1 mol%), ligand (2 mol%), 1,4-dioxane (200 μL), 50−60 °C, under a stream of N_2, 20 h. Isolated yields are reported. [b]Yield was determined by NMR spectroscopy relative to CH_2Br_2 internal standard.

The reactions of heteroarenes also occurred with the same tolerance for carbonyl groups observed in the reactions of arenes. Furyl ketone **25** underwent silylation in 97% yield without any reduction of the carbonyl group. The silylation of thiophenes and furans occurred exclusively at the 2-position. Indole **24** underwent silylation with high selectivity for the 2-position over the 3-position (2-Si:3-Si = 17:1). 2,6-Dichloropyridine underwent silylation exclusively at the 4-position in 77% yield.

3. Functionalizations of Silylarenes. The transformations of the silyl group of these silylarenes into common functional groups are well documented and underscore the value of these silylation reactions (Scheme 2). Silylarene **21** has undergone cross-coupling reactions mediated by copper with a broad range of nitrogen nucleophiles including anilines, pyrroles, amides, sulfonamides, and alkyl amines, with yields of aniline products that range from 41% to 78%. The coupling of **4**, **15**, and **20** with amides has also been reported.[15] Tamao−Fleming oxidation of silylarene **9** has been reported to form 3,5-dimethoxyphenol in 69% yield.[12] Silylarene **15** also has been iodinated using ICl.[13] Silylarene **19** has been coupled with 3-iodoanisole in a reaction catalyzed by palladium to produce biaryl product in 58% yield.[12] Finally, **4**, **15**, **20**, and **21** have been converted into the corresponding trifluoromethyl arenes in 34% to 75% yield by reaction with (phenanthroline)-$CuCF_3$ in the presence of fluoride activator.[16] Clearly, the silylarenes formed by the reactions reported here are versatile intermediates that can be transformed into aryl halides and phenols in good yields and coupled with haloarenes, amines, anilines, and sources of trifluoromethyl groups in modest to good yields.[12,13,15,16]

4. Synthesis of Pharmaceutical Intermediates. To demonstrate the applicability of the silylation of C−H bonds, we synthesized arenes and heteroarenes that are intermediates in the synthesis of medicinally relevant molecules, as shown in Scheme 3. Doravirine is the active ingredient in Pifeltro and the combination tablet Delstrigo recently approved by the FDA for the treatment of HIV. 1,3,5-Substituted arenes **29** and **30** containing multiple *ortho*−*para* directing groups are intermediates in two different process-scale routes to doravirine.[17] Arenes with such substitution patterns are well suited to being prepared by the silylation of C−H bonds. A second medicinally relevant compound, Ozenoxacin, is an antibiotic discovered by Toyama Chemical Co., developed by Maruho Co.,[18] and approved in Japan for the treatment of acne and skin infections. Heteroaryl bromide **31** is an intermediate in the synthesis of Ozenoxacin. Because electron-poor heteroarenes, such as **36**, do not undergo electrophilic aromatic bromination, C−H bond functionalization is well suited to the synthesis of this class of heteroarenes, *vide supra*.

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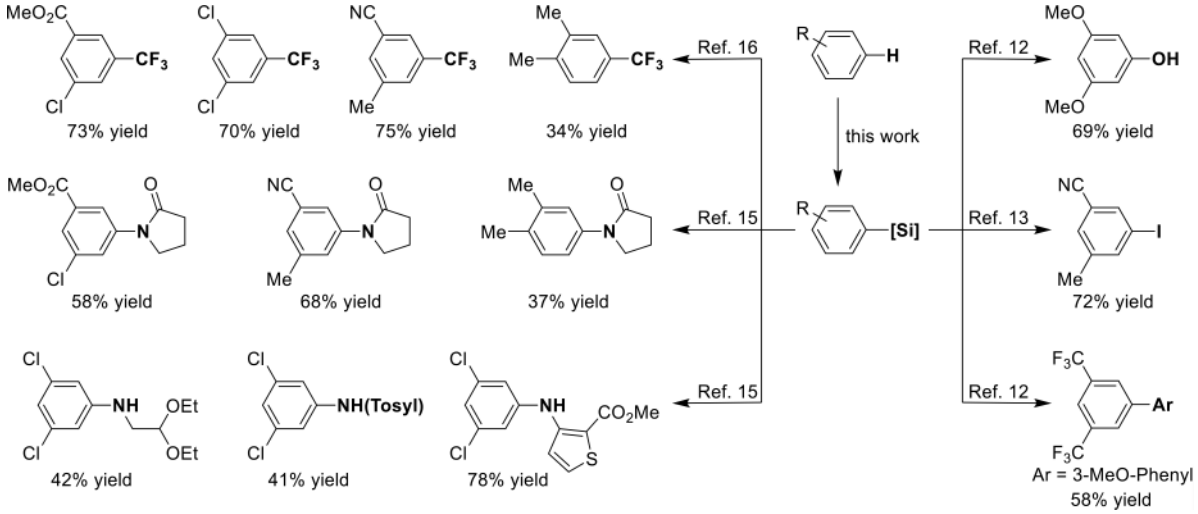
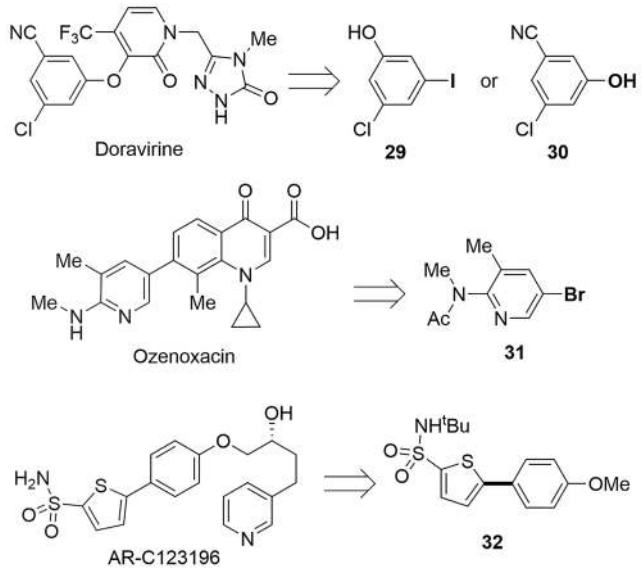
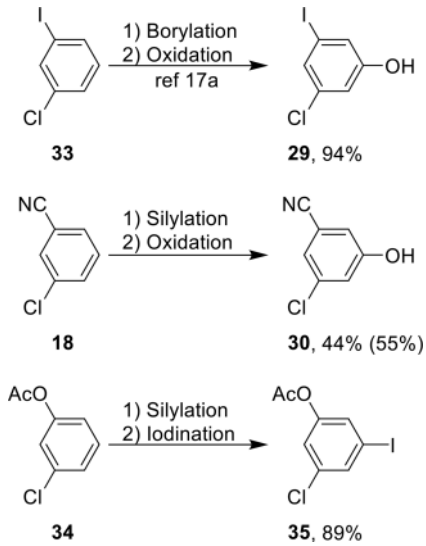
Scheme 2. Reported Functionalizations of Silylarene Products



Scheme 3. Disconnections of Doravirine (Top), Ozenoxacin (Middle), and AR-C123196 (Bottom)



Scheme 4. Synthesis of Doravirine Intermediates[a]



[a]See SI for reaction conditions. Isolated yields are reported. Yield was determined by ^{1}H NMR spectroscopy relative to CH_2Br_2 internal standard in parentheses.

A third medicinally relevant compound, AR-C123196, was produced on multikilogram scale by AstraZeneca to furnish studies on its anti-inflammatory properties and as a treatment for asthma.[19] Heterobiaryl **32** is an intermediate in the synthesis of AR-C123196 assembled by Pd-catalyzed coupling of a heteroaryl bromide and an arylboronic acid. The nucleophile and electrophile can be reversed when C−H bond silylation is used because the boronate for the coupling is generated from an aryl bromide. In contrast, the heteroaryl silane can be used directly as nucleophile, whereas the corresponding heteroarylboronic acid undergoes spontaneous proto-deboronation.

Three routes to related intermediates in the synthesis of doravirine are shown in Scheme 4. The first route, reported by Merck, starts from *m*-chloroiodobenzene and comprises the borylation of the C−H bond of the arene in the 5-position and oxidation to generate 1,3,5-chloroiodophenol. Aryl iodides are produced on a smaller scale than phenols, and the iodide in this molecule is ultimately transformed into a nitrile. Thus, it might be preferable to start the synthesis from an arene that contains the nitrile or to install the iodide by C−H activation. However, the borylation of 3-chlorobenzonitrile generates a mixture of products, which result from monoborylation *ortho* and *meta* to the nitrile and from diborylation. An alternative synthesis by the borylation of a protected phenol, such as **34**, would form a single arylboronate, but iodination of arylboronic esters generally occurs in only modest yield.[20] In contrast, entry 7 of Table 2 shows that the silylation of 3-chlorobenzonitrile occurred with excellent selectivity for the meta position without formation of any product from disilylation. We found that arene **18** undergoes the combination of silylation and oxidation with hydrogen peroxide to generate phenol **30** in 55% yield from the arene over two steps. Alternatively, acyl-protected 3-chlorophenol, **34**, underwent silylation in high yield. Iodination with ICl afforded iodoarene **35**, an acyl-protected form on the intermediates in 89% isolated yield over two steps.

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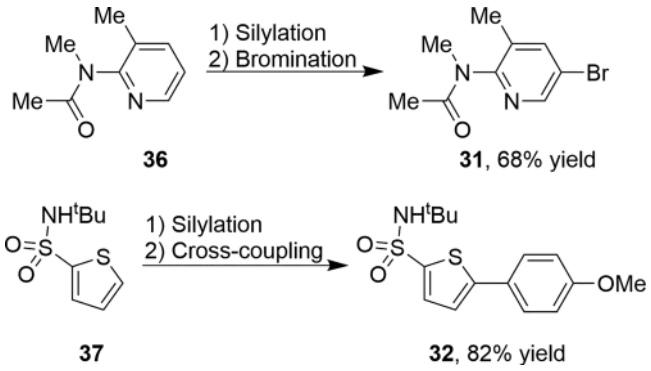
Heteroaryl bromide **31**, an intermediate in the synthesis of Ozenoxacin, was prepared in 68% yield by the combination of silylation of pyridine **36**, with the catalyst containing **L1**, followed by treatment with *N*-bromosuccinimide (Scheme 5).

Scheme 5. Synthesis of Ozenoxacin Intermediate and AR-C123196 Intermediate[a]



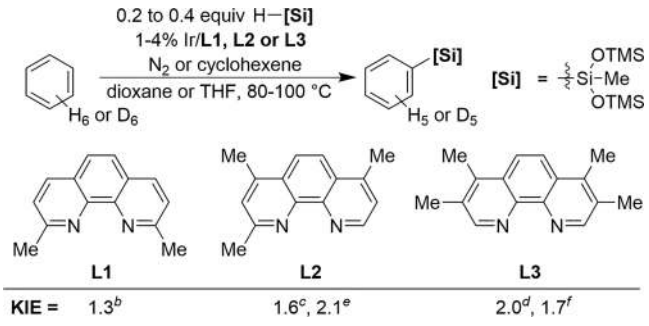
[a]See SI for reaction conditions. Isolated yield is reported.

Although direct bromination of **36** is challenging, the *ipso* bromination of the silylheteroarene occurs under mild conditions. Heterobiaryl **32**, an intermediate in AstraZeneca's anti-inflammatory for asthma AR-C123196, was prepared by silylation and coupling. Silylation of the thienyl sulfonamide **37** occurred in quantitative yield, and coupling of the resulting silylarene with 4-bromoanisole occurred in the presence of catalytic amounts of $Pd(P^tBu_3)_2$ to produce **32** in 82% yield. In contrast to the reported instability of 5-boryl analogues of **37**, the silylated heteroarene was stable to chromatography and storage on the benchtop. These reaction sequences comprising silylation of a C−H bond and functionalization at the C−Si bond demonstrate that the system we report here for the silylation of C−H bonds is useful for the synthesis of medicinally important compounds.

5. Mechanistic Studies. To gain information on the steps of the catalytic process influenced by the steric properties of the methyl-substituted phenanthrolines, we measured kinetic isotope effects (KIEs) for the silylation reactions of benzene and conducted studies on H/D exchange between the silane and benzene catalyzed by complexes of the series of phenanthrolines. To probe if C−H bond cleavage was rate-limiting, we first measured the KIE for reactions of benzene in separate vessels with catalysts containing 2,9-dimethyl-, 2,4,7-trimethyl-, and 3,4,7,8-tetramethylphenanthrolines (ligands **L1**, **L2**, and **L3**). The initial rates were determined by monitoring the silylarene product in the reactions catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and ligand. As shown in Table 4, the KIEs were 1.3, 1.6, and 2.0 for the silylation of benzene and deuterobenzene catalyzed by the combination of iridium and **L1**, **L2**, and **L3**, respectively, with silane as the limiting reagent. Similar KIEs of 1.6 or 1.7 were measured for the silylation of benzene and deuterobenzene catalyzed by the combination of iridium and **L2** or **L3** with arene as the limiting reagent. These KIEs are too small to be considered simple primary values and more likely indicate that cleavage of the C−H bond is fully or partially reversible.

To gain further information about the potential reversibility of the reaction, we studied H/D exchange between the Si−H bond of the silane and deuterated arene. These data are shown in Figure 3. H/D exchange between the silane and benzene-d_6 was evidenced by the growth of ^{1}H NMR signals of the arene.

Table 4. Kinetic Isotope Effects Determined from Independent Reactions[a]



[a]See SI for conditions. Rates from reactions containing **L1** were determined by GC-FID relative to dodecane internal standard. Rates from reactions containing **L2** and **L3** were determined by ^{1}H NMR spectroscopy relative to dodecane internal standard. [b]Arene (7.5 equiv), $HSiMe(OTMS)_2$ (1 equiv). [c]Arene (5.6 equiv), $HSiMe(OTMS)_2$ (1 equiv). [d]Arene (17 equiv), $HSiMe(OTMS)_2$ (1 equiv). [e]Arene (1 equiv), $HSiMe(OTMS)_2$ (1.4 equiv), average of three experiments (KIE = 1.6 ± 0.3). [f]Arene (1 equiv), $HSiMe(OTMS)_2$ (1.4 equiv).

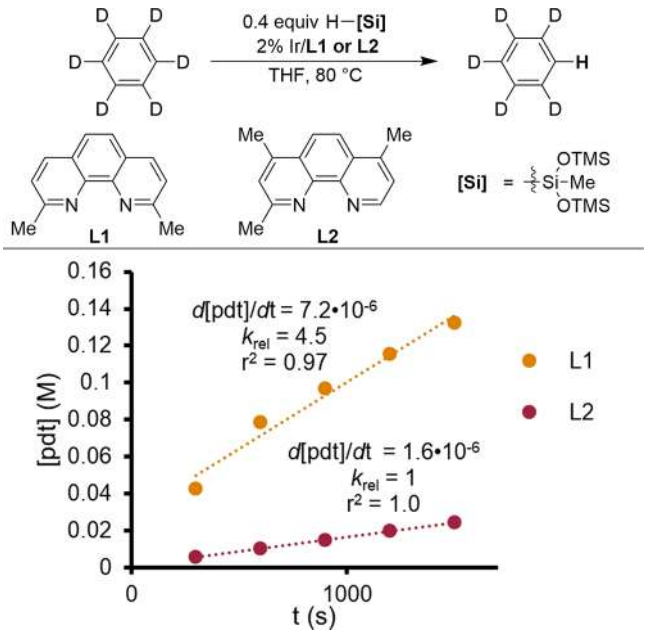


Figure 3. Rate of protiation of deuterobenzene. Conditions: $HSiMe(OTMS)_2$ (0.4 mmol), $[Ir(cod)(OMe)]_2$ (1.0 mol%), ligand (2.0 mol%), dodecane (0.5 equiv), benzene-d_6 (100 μL), THF, 80 °C. Silylarene concentration was determined by ^{1}H NMR spectroscopy using *n*-dodecane as an internal standard.

The rates at which the benzene-d_6 was transformed into benzene-d_5 under the catalytic reaction conditions with ligand **L1** and with ligand **L2** were measured. The incorporation of protons into deuterated benzene catalyzed by the combination of iridium and **L1** was nearly 5 times faster than that catalyzed by the combination of iridium and **L2**. These relative rates closely mirror the 5-times greater rates for the silylation reaction catalyzed by the complex of **L1** than by the complex of **L2**.

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The faster rate of the silylation catalyzed by the complex of **L1** versus that of the silylation catalyzed by the complex of **L2** could result from faster cleavage of the C−H bond, a more favorable equilibrium for cleavage of the C−H bond, or a larger effect of the ligand on the formation of the C−Si bond than on the cleavage of the C−H bond. The small KIE value observed for reactions of benzene and the observation of H/D exchange between the silane and benzene imply that cleavage of the C−H bond in benzene is reversible. In this case, a difference in the equilibrium constant for cleavage of the C−H bond or a difference in the rate of formation of the C−Si bond could lead to the difference in rates of reaction catalyzed by complexes of **L1** and **L2**. The similarity between the difference in the rates of H/D exchange between the silane and benzene catalyzed by the two complexes and the difference in rates of the overall silylation of benzene catalyzed by the two complexes implies that the cleavage of the C−H bond is the step that leads to the difference in rates of reaction of the two catalysts. These conclusions can be shown in the reaction coordination diagram of Figure 4. In this diagram, the rate and

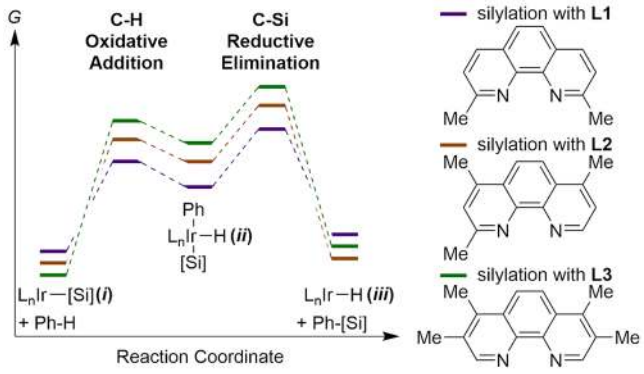

Figure 4. Proposed reaction coordinate.

equilibrium constant for cleavage of the C−H bond in the arene are larger for the reaction of the complex of **L1** than of the complex of **L2**, as suggested by our mechanistic data.

Faster and thermodynamically more favorable oxidative addition of a C−H bond to a more sterically hindered complex seems counterintuitive in a system that is unlikely to involve dissociation of the hindered ligand. We suggest that the seven-coordinate product from oxidative addition, counterintuitively, suffers less steric hindrance than the starting square pyramidal complex. As shown in Figure 5, seven coordinate complexes in a geometry like a capped trigonal prism likely contain fewer ligands in the plane of the substituted phenanthroline ligand. The five-coordinate square-based pyramidal geometry of a d^6 iridium complex contains two ligands in the equatorial plane

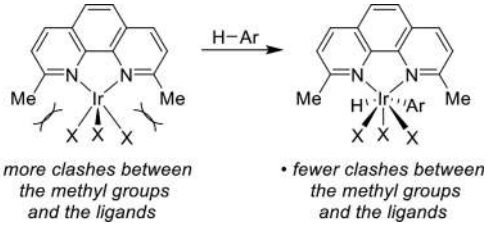

Figure 5. Model for the relief of steric hindrance upon oxidative addition of C−H bonds.

(shown as the plane of the page in Figure 5) in addition to the nitrogens of the phenanthroline, whereas the seven-coordinate complex contains just one additional ligand in the equatorial plane. This model implies that the destabilization of the resting state of the catalyst by the methyl groups of **L1** is greater than the destabilization of the intermediate following oxidative addition. This analysis is consistent with our assertion that the difference in energy between these two species is responsible for the high rate of the silylation of aryl C−H bonds observed in reactions catalyzed by the iridium complexes containing the 2,9-dimethylphenanthroline ligand.

CONCLUSION

In summary, we report an iridium catalyst for the silylation of arenes with hydrosilanes revealed by measuring the difference between initial rates and overall conversion. These measurements distinguished between catalysts that react with low rates and those that react with high rates but are short-lived. By determining the origin of inhibition of a catalyst that reacts with high initial rates, we have developed the combination of a highly active catalyst and appropriate reaction conditions to achieve a large increase in scope of the silylation of arenes and a large increase in rates for arenes that reacted with catalysts reported previously. The new system tolerates most common functional groups, and the reactions occur with high sterically derived regioselectivity. The products of these reactions can be transformed into many common functional groups, and the utility of this method was demonstrated by constructing intermediates in the syntheses of medicinally important molecules. This method significantly increases the utility of C−H silylation by allowing reactions to be conducted on convenient time scales under mild conditions and with inexpensive reagents.

Studies on isotopically labeled arenes showed that the cleavage of the C−H bond is reversible. The relative rates of H/D exchange catalyzed by complexes of 2,9-dimethylphenanthroline and 2,4,7-trimethylphenanthroline mirrored those of the initial rates of the silylation. These data imply that the difference in activity observed for reactions of arenes and silane with the two catalysts results from a difference in the equilibrium constant for addition of the arene to the two catalysts. More favorable oxidative addition of the arene to the complex of the more hindered ligand is counterintuitive but likely results from the difference in geometry of a five-coordinate square-planar d^6 complex and a seven-coordinate intermediate that would contain fewer ligands in the plane of the phenanthroline ligand. Further experimental mechanistic studies to prepare potential intermediates and detailed computational studies on the reactivity of these intermediates to gain further insight in to the mechanism and to create even more active catalysts are in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b01972.

Experimental procedures, characterization of new compounds, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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