

CrossMark  
click for updatesCite this: *Chem. Sci.*, 2016, 7, 5362

## Iridium-catalyzed selective 1,2-hydrosilylation of N-heterocycles†

Jinseong Jeong,<sup>ab</sup> Sehoon Park<sup>\*ab</sup> and Sukbok Chang<sup>\*ab</sup>

A silylene-bridged Ir dimer *in situ* generated from  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  and  $\text{Et}_2\text{SiH}_2$  was found to catalyze the hydrosilylation of N-heteroaromatics to furnish dearomatized azacyclic products with high activity (up to 1000 TONs), excellent selectivity, and good functional group tolerance. The substrate scope was highly broad, including (iso)quinolines, substituted pyridines, pyrimidines, pyrazines, deazapurines, triazines, and benzimidazoles. Mechanistic studies such as a kinetic profile, rate-order assessment, and investigation of the electronic substituent effects on the initial rates were performed to access the detailed pathways. One pathway is proposed to involve an intramolecular insertion of the C=N moiety of the substrates into the Ir–H bond of a resting species to form an Ir-amido silyl intermediate, followed by reductive elimination. The synthetic utility was proven by successful application to *cinchona* alkaloids, and facile post-synthetic transformations of the 1,2-dihydroquinoline products.

Received 5th March 2016  
Accepted 26th April 2016

DOI: 10.1039/c6sc01037g

www.rsc.org/chemicalscience

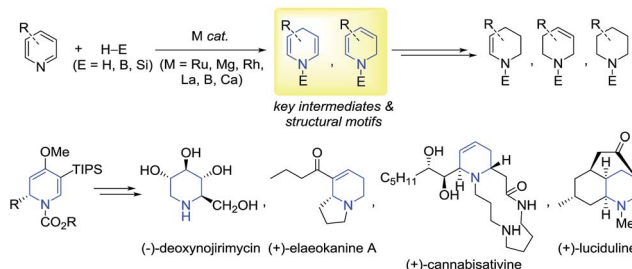
## Introduction

Dearomatization of (hetero)arenes is a kinetically unfavorable process, thus necessitating the use of efficient catalytic systems to overcome the high resonance stabilization energies.<sup>1</sup> Certain enzymes such as reductases or oxygenases are well known to catalyze dearomative transformations of arenes with excellent efficiency and selectivity,<sup>2</sup> while selective dearomatization in *synthetic chemistry* has still been a great challenge.<sup>3</sup> Compounds obtainable from the partial dearomatization of (hetero)aromatics are useful building units in synthesis, allowing for a variety of subsequent transformations. In particular, a partial reduction of pyridines can lead to 1,2- or 1,4-dihydropyridines,<sup>4</sup> which are frequently utilized as a structural motif in the synthesis of alkaloids or pharmaceutically relevant molecules (Scheme 1).<sup>5</sup> In this context, a list of elegant catalytic procedures has been developed for the reduction of pyridines to dihydropyridines with high efficiency and selectivity using  $\text{H}_2$ , boranes, or silanes as reducing agents.<sup>6</sup> For instance, Zhou and co-workers reported the 1,4-selective hydrogenation of Hantzsch pyridines to yield the corresponding dihydropyridines under a high pressure of  $\text{H}_2$ .<sup>6a</sup> Catalytic hydroboration of pyridines was recently shown to operate giving rise to 1,4- or 1,2-dihydropyridines using Lewis acidic boranes<sup>6b</sup> or metal catalysts

including Mg,<sup>6c</sup> Rh,<sup>6d</sup> or La.<sup>6e</sup> Similarly, hydrosilylation of pyridines catalyzed by cationic ruthenium species is known to produce N-silylated 1,4-dihydropyridines.<sup>6f-h</sup> In addition, Harder *et al.* developed a calcium complex-catalyzed 1,2-hydrosilylation of pyridines, albeit with limited scope.<sup>6i</sup>

On the other hand, Brookhart *et al.* reported the preparation and reactivity of a series of chloro- or silylene-bridged dimeric (hydrido)iridium silyl complexes.<sup>7,8</sup> Especially, a proposed silylene-bridged Ir dimer  $[\text{Et}_2\text{HSiR}_2(\mu\text{-SiEt}_2)]_2$ , among those complexes, was revealed to promote the reductive hydrosilylation of carbonyls and imines.<sup>8,9</sup> Given the facile *in situ* generation of this proposed complex and its notable reactivity particularly towards imines, we envisioned that this type of Ir species may catalyze the hydrosilylative dearomatization of N-heterocycles.

Herein, we report the use of an *in situ* generated silylene-bridged dinuclear Ir species as a catalyst for the hydrosilylative dearomatization of N-heteroaromatics with diethylsilane,<sup>10</sup> furnishing a wide array of partially reduced azacyclic products



Scheme 1 Partial reduction of pyridines and the use of dihydropyridines in alkaloid synthesis.

<sup>a</sup>Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305-701, South Korea. E-mail: sehoonp@kaist.ac.kr; sbchang@kaist.ac.kr

<sup>b</sup>Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, South Korea

† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization of new compounds, and X-ray analysis. CCDC 1457941. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc01037g



with excellent selectivity (Scheme 2). This catalyst system shows broad substrate scope and high efficiency (~1000 turnovers). Significantly, the present procedure does not require external ligands or additives to achieve such attractive features. Mechanistic investigations revealed details of a pathway involving C=N insertion into an Ir-H bond of a bimetallic Ir resting species.

## Results and discussion

### Optimization study

At the outset, we presumed that the type of silane would be a crucial factor governing the catalytic activity for the dearomative hydrosilylation of N-heterocycles. When quinoline (**2a**) was treated with Et<sub>2</sub>SiH<sub>2</sub> (1.5 equiv.) in the presence of 1.4 mol% of [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> in CDCl<sub>3</sub>, we were pleased to observe that 1-(diethylsilyl)-1,2-dihydroquinoline (**3a**) was formed in 62% NMR yield in 5 h at 25 °C (Table 1, entry 1). Prolonging the reaction for up to 17 h eventually led to a full conversion of the remaining **2a** to **3a**. Solvent effects were found to be significant for the catalytic performance: a reaction in THF-*d*<sub>8</sub> gave **3a** in 69% yield in 15 h (entry 2), whereas the use of nonpolar solvents such as C<sub>6</sub>D<sub>6</sub> or hexane-*d*<sub>14</sub> resulted in higher yields (85–99% in 4 h, entries 3 and 4). Notably, a reaction in *neat* Et<sub>2</sub>SiH<sub>2</sub> (3 equiv.) led to a quantitative yield within 2 h (entry 5). Performing the hydrosilylation in a reaction vial resulted in a similar catalytic efficiency (compare entries 6 and 7). It was significant to see that even 0.1 mol% of the iridium precatalyst enabled quantitative 1,2-hydrosilylation of **2a** at 55 °C in 60 h either in C<sub>6</sub>D<sub>6</sub> or *neat* silane (3 equiv.) (entries 8 and 9). While tertiary or bulky secondary silanes were ineffective (entries 10–12), some sterically less demanding secondary (MePhSiH<sub>2</sub>) and primary silanes (PhSiH<sub>3</sub>) provided **3a** with low efficiency (entries 13 and 14). Subtle structural variation of the iridium precursor also influenced the resulting catalytic activity to some extent (entries 15 and 16, and also see ESI† for details).

### 1,2-Hydrosilylation of quinolines

With the optimal conditions in hand (1.4 mol% [Ir(coe)<sub>2</sub>Cl]<sub>2</sub>, 1.5 equiv. Et<sub>2</sub>SiH<sub>2</sub>, C<sub>6</sub>D<sub>6</sub>, 55 °C), we investigated the scope for

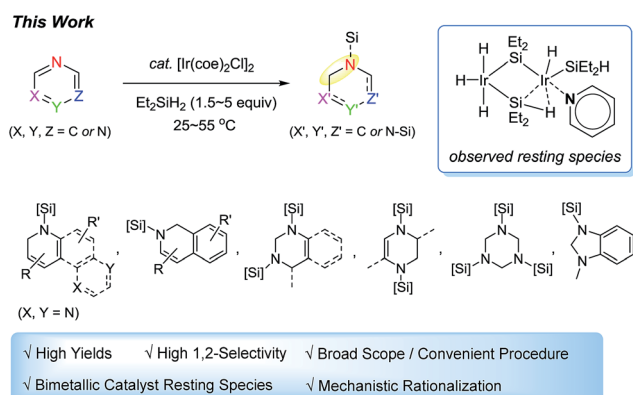
quinoline substrates (Table 2). An initial attempt to isolate **3a** using silica column chromatography failed due to its instability.<sup>11</sup> Thus, we conducted an *N*-benzoylation of **3a**, that initially provided a 99% crude yield from **2a**, to furnish **3a-PNB** (82% isolated yield over two steps). Interestingly, **3a** could also be converted to its hydrochloride salt (**3a-HCl**) in quantitative yield simply by treating the crude reaction mixture with an ether solution of HCl.<sup>12</sup>

Similarly, a range of *N*-silylated reduction products were *in situ* transformed to their isolable *N*-acyl (benzoyl or acetyl) amides or HCl salts. 3-Methylquinoline and 4-methylquinoline both reacted to give the desired products **3b** and **3c**, respectively, in quantitative yields in 3 h. 4-Chloro-2-methylquinoline (**2i**) and 6-chloro-8-fluoroquinoline (**2j**) were viable substrates for the 1,2-hydrosilylation, albeit under slightly more forcing conditions [2.8–4.2 mol% of Ir catalyst, *neat* silane (5 equiv.), and 24–48 h], affording **3i** and **3j** in 80% and 99% yield, respectively, which were subsequently converted to their benzoyl amides in good yield (**3i-PNB**; 62% and **3j-PNB**; 79% over 2 steps). Quinoline substrates bearing halides at the C-6 position were also facile substrates for this hydrosilylation, providing **3k-PNB** (80% over 2 steps) or **3l** (99% crude yield). The structure of **3k-PNB** was confirmed using X-ray crystallographic analysis.

Quinolines with electron-donating substituents at the C-6 or C-7 position were reduced to the desired *N*-silylated 1,2-dihydroquinolines (**3m–n**) in 99% NMR yields, and the former was subsequently isolated as an amide derivative (**3m-PNB**; 77%). It should be mentioned that a vinyl group remained intact during the hydrosilylation, as demonstrated by the quantitative formation of **3o** (isolated as **3o-PNB**).

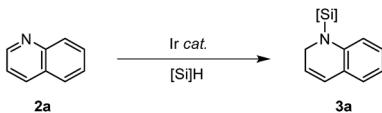
### 1,2-Hydrosilylation of substituted pyridines

Next, we turned our attention to pyridine substrates which were presumed to be more challenging than quinolines for the present partial reduction (Table 3). With the newly optimized conditions for the hydrosilylation of 4-(trifluoromethyl)pyridine **2p** in hand (see ESI† for detailed optimization study), a reaction of **2p** in *neat* Et<sub>2</sub>SiH<sub>2</sub> (5.0 equiv.) was carried out at 55 °C to provide the desired (4-trifluoromethyl)-1,2-dihydropyridine **3p** in 95% yield in 1 h, which was subsequently converted to its *N*-benzoyl derivative (**3p-PNB**, 57% isolated yield). Similarly, 4-halopyridines were selectively converted to the corresponding *N*-silyl-1,2-dihydropyridines in high yield without reductive dehalogenation (**3q–s**). Likewise, 3-halopyridines underwent the dearomative hydrosilylation with high yields obtained (**3t–v**). Interestingly, the regioselectivity for the hydrosilylation of 3-halopyridines was altered depending on the C3-substituent: 3-fluoropyridine and 3-chloropyridine were 1,2-hydrosilylated selectively (83–85% crude yields) while 3-(trifluoromethyl)pyridine underwent 1,6-hydrosilylation to afford **3v'** in 82% crude yield with only 17% of the 1,2-dihydropyridine product (**3v**). Although it is still unclear what factors influence the product regioselectivity, comparing the observed catalytic selectivity for 3-fluoropyridine [99% of 1,2-selectivity] with 3-(trifluoromethyl)pyridine [83% of 1,6-selectivity + 17% of



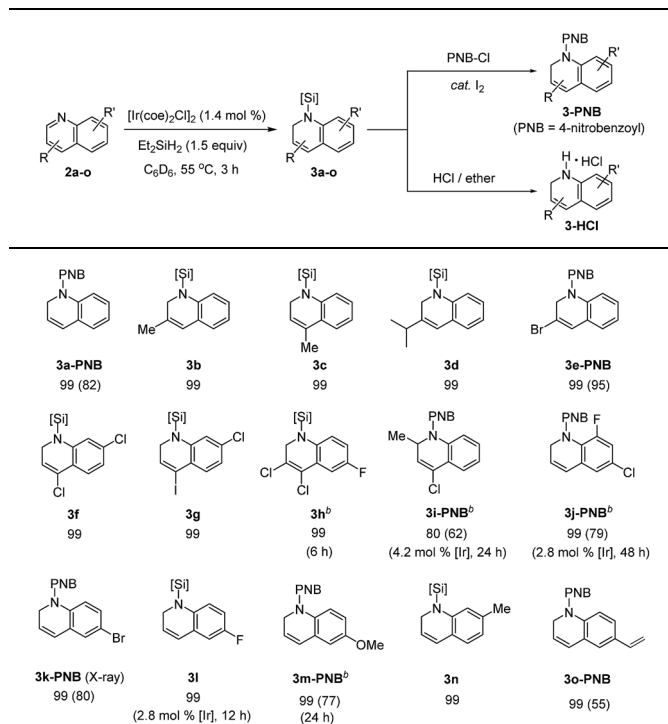
Scheme 2 This work: Ir-catalyzed selective hydrosilylation of N-heterocycles.



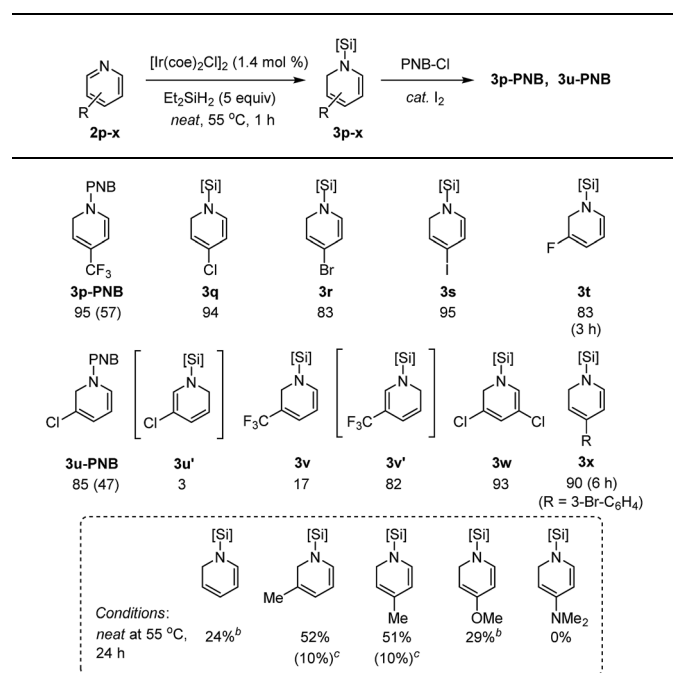
Table 1 Optimization of the 1,2-hydrosilylation of quinoline 2a<sup>a</sup>


Entry	Ir catalyst (mol%)	Silane (equiv.)	Solvent	T (°C)	Time (h)	Yield <sup>b</sup> (%)
1	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	CDCl <sub>3</sub>	25	5	62
2	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	THF-d <sub>8</sub>	25	15	69
3	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	25	4	85
4	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	Hexane-d <sub>14</sub>	25	4	99
5	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	Neat	25	2	99
6	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	55	1	99
7 <sup>c</sup>	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	55	1	99
8	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (0.1)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	55	60	99
9	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (0.1)	Et <sub>2</sub> SiH <sub>2</sub> (3.0)	Neat	55	60	99
10	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (4.2)	Et <sub>3</sub> SiH (1.5)	C <sub>6</sub> D <sub>6</sub>	85	15	<1
11	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (4.2)	Me <sub>2</sub> PhSiH (1.5)	C <sub>6</sub> D <sub>6</sub>	55	15	<1
12	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (4.2)	Ph <sub>2</sub> SiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	55	15	<1
13	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	PhMeSiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	25	4	40
14	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> (1.4)	PhSiH <sub>3</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	25	15	29 <sup>d</sup>
15	[Ir(cod)OMe] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	25	4	61
16	[Ir(cod)Cl] <sub>2</sub> (1.4)	Et <sub>2</sub> SiH <sub>2</sub> (1.5)	C <sub>6</sub> D <sub>6</sub>	25	4	58

<sup>a</sup> Carried out in a J-Young NMR tube with **2a** (0.35 mmol, 1 equiv.), Et<sub>2</sub>SiH<sub>2</sub> (1.5–3.0 equiv.) and [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> (0.1–4.2 mol%), either neat or in solvent (0.35 mL), under an argon atmosphere. <sup>b</sup> Yield of **3a** determined using <sup>1</sup>H NMR. <sup>c</sup> Performed in a reaction vial. <sup>d</sup> Unidentified side products were also formed.

Table 2 Scope of quinolines in the Ir-catalyzed 1,2-hydrosilylation<sup>a</sup>

<sup>a</sup> Substrate (0.35 mmol), Et<sub>2</sub>SiH<sub>2</sub> (1.5 equiv.), and [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> (0.005 mmol, 1.4 mol%) in C<sub>6</sub>D<sub>6</sub> (0.35 mL) at 55 °C; crude <sup>1</sup>H NMR yields based on an internal standard (mesitylene or 1,4-dioxane); numbers in parentheses are isolated yields. <sup>b</sup> With 5 equiv. of Et<sub>2</sub>SiH<sub>2</sub> (neat).

Table 3 Scope of pyridines<sup>a</sup>

<sup>a</sup> Substrate (0.35 mmol), Et<sub>2</sub>SiH<sub>2</sub> (5 equiv.) and [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> (0.005 mmol, 1.4 mol%) at 55 °C; crude <sup>1</sup>H NMR yields based on an internal standard (mesitylene or 1,4-dioxane); numbers in parentheses are isolated yields. <sup>b</sup> 4.2 mol% of [Ir(coe)<sub>2</sub>Cl]<sub>2</sub>. <sup>c</sup> Reaction in C<sub>6</sub>D<sub>6</sub> (0.35 mL).



1,2-selectivity], a steric factor seems to be involved in determining the regioselectivity. However, 3-chloropyridine was found to be converted selectively to the corresponding 1,2-dihydropyridine (97% of 1,2-selectivity). Since the steric bulkiness of a chloro group is believed to be comparable to that of a trifluoromethyl group, only steric effects of the 3-substituents cannot account for the regioselectivity observed in our study [e.g. 3-chloropyridine (97% of 1,2-selectivity) vs. 3-(trifluoromethyl)pyridine (17% of 1,2-selectivity)]. In a related study of a La-catalyzed hydroboration of pyridines,<sup>6c</sup> Marks *et al.* rationalized that appreciable bonding interactions between the C3-halogen and emerging C2–H<sub>2</sub>C might influence the dearomatization site selectivity for 3-substituted pyridines.

3,5-Dichloropyridine was reduced smoothly to the corresponding 1,2-dihydropyridine derivative (**3w**) with a 93% crude yield. A substrate with a 3-bromophenyl group at the C-4 position still displayed high reactivity to afford **3x** in good yield. However, the hydrosilylation of pyridine and substituted pyridines bearing electron-donating groups was sluggish under the present conditions as shown in the dotted box (*vide infra* for possible explanations).

### Dearomative hydrosilylation of additional N-heteroaromatics

Based on the high reactivity observed for the selective hydrosilylation of quinolines and substituted pyridines, the present iridium catalytic system was next applied to additional types of aromatic N-heterocycles (Table 4). Isoquinolines rapidly reacted with Et<sub>2</sub>SiH<sub>2</sub> (1.5 equiv.) in the presence of [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> (1.4 mol%) to provide *N*-silyl-1,2-dihydroisoquinolines in quantitative yields within 15 min at 55 °C (**5a–c**).

An *N*-silylated dihydroisoquinoline **5c** was readily transformed to its *N*-acetyl amide (**5c-Ac**, 83% isolated yield), thus demonstrating its high potential utility in synthetic chemistry. The degree of hydrosilylation was found to be controllable in the case of phenanthrolines: 1,7-phenanthroline underwent mono-hydrosilylation at the sterically more accessible C=N bond with a 94% crude yield by employing 1.5 equiv. of Et<sub>2</sub>SiH<sub>2</sub> (**5d**), whereas 4,7-phenanthroline was doubly hydrosilylated to give **5e** in high yield with 5 equiv. of Et<sub>2</sub>SiH<sub>2</sub>. We were pleased to observe that a series of pyrimidines was also selectively reduced with silane to give 1,2,3,4-tetrahydropyrimidines in excellent yields (1–6 h at 55 °C).

It is notable that the reaction of 5-bromopyrimidine was chemoselective without dehalogenation (**5h**). Similarly, pyrazines underwent double hydrosilylation with excellent selectivity to afford 1,2,3,4-tetrahydropyrazines (**5k–m**). Interestingly, a reaction of 2-methylpyrazine was regioselective leading to **5l**. The current catalytic system was also efficient for the selective hydrosilylation of 7-deazapurine to furnish a partial reduction product **5n** in quantitative yield in 24 h, while leaving another C=N moiety intact. Gratifyingly, triazine underwent triple hydrosilylation with the use of excess silane (5 equiv.) to give a saturated product **5o** in excellent yield in 12 h.<sup>13</sup> When 1-methyl-1*H*-benzo[*d*]imidazole was subjected to the present conditions, the corresponding hydrosilylated product (**5p**) was formed in high yield.

Table 4 Substrate scope using N-heteroaromatics<sup>a</sup>

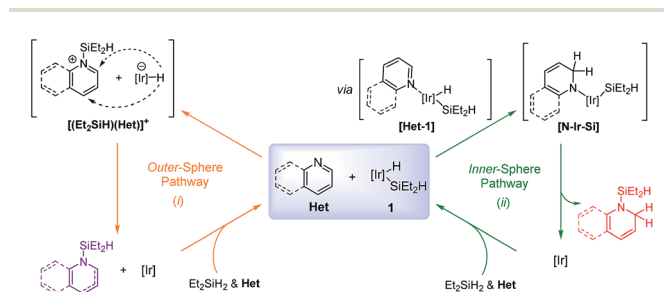
<b>5a<sup>b</sup></b> 99 (15 min)	<b>5b<sup>b</sup></b> 99 (15 min)	<b>5c-Ac<sup>b</sup></b> 99 (83) (15 min)	<b>5d<sup>b,c</sup></b> 94 (3 h in C <sub>6</sub> D <sub>6</sub> )	<b>5e<sup>d</sup></b> 92 (48 h in C <sub>6</sub> D <sub>6</sub> )
<b>5f-HCl</b> 99 (93) (1 h)	<b>5g</b> 99 (3 h)	<b>5h</b> 99 (3 h)	<b>5i</b> 99 (3 h)	<b>5j</b> 99 (6 h)
<b>5k</b> 99 (6 h)	<b>5l</b> 99 (6 h)	<b>5m<sup>e</sup></b> 94 (48 h)	<b>5n</b> 99 (24 h)	<b>5o</b> 96 (12 h)
<b>5p<sup>b</sup></b> 92 (18 h in C <sub>6</sub> D <sub>6</sub> )				

<sup>a</sup> Substrate (0.35 mmol), Et<sub>2</sub>SiH<sub>2</sub> (5 equiv.) and [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> (1.4 mol%) at 55 °C; crude <sup>1</sup>H NMR yields based on an internal standard (mesitylene or 1,4-dioxane); numbers in parentheses are isolated yields of **5c-Ac** and **5f-HCl**. <sup>b</sup> With 1.5 equiv. of Et<sub>2</sub>SiH<sub>2</sub>. <sup>c</sup> 2.8 mol% of [Ir(coe)<sub>2</sub>Cl]<sub>2</sub>. <sup>d</sup> Mono-silylated product (**5e'**, 6%) was also observed. <sup>e</sup> 4.2 mol% of [Ir(coe)<sub>2</sub>Cl]<sub>2</sub>.

### Mechanistic studies

#### (A) Kinetic studies of the Ir-catalyzed 1,2-hydrosilylation.

At the outset of the mechanistic investigations, we set two distinctive working hypotheses (Scheme 3). One process was proposed to involve the transfer of a silylium ion from a plausible silyl iridium hydride species (**1**) to a N-heteroaromatic substrate (**Het**) to form [(Et<sub>2</sub>SiH)(Het)]<sup>+</sup>, followed by hydride attack *via* an outer-sphere route at the C-2 or C-4 position to give the *N*-silylated 1,2- or 1,4-dihydropyridine [Scheme 3 (left)]. Another conceivable scenario is an inner-sphere process involving C=N insertion of **Het** into the Ir–H bond of **1** upon prior *N*-coordination *via* [**Het-1**] to form an amido silyliridium complex [**N-Ir-Si**] that eventually releases the *N*-silylated 1,2-reduction product through reductive elimination [Scheme 3 (right)].



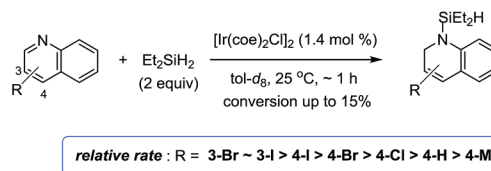
Scheme 3 Two working hypotheses for the present hydrosilylation.



In order to assess the rate-order of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$ ,  $\text{Et}_2\text{SiH}_2$ , and **2a** in the 1,2-hydrosilylation, the initial-rate ( $v_i$ ) kinetics of the individual components was studied using  $^1\text{H}$  NMR spectroscopy (Scheme 4). A plot of  $v_i$  for the formation of **3a** vs. a range of initial concentrations of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  showed that the reaction was first-order in  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$ , while the initial rate plot across a range of concentrations of  $\text{Et}_2\text{SiH}_2$  indicated zero-order for  $[\text{Et}_2\text{SiH}_2]$ . It is notable that the reaction was fractional-order in terms of the quinoline substrate (**2a**): zero-order dependence at high concentration (above  $\sim 0.5$  M), but approaching to first-order at concentrations of **2a** below  $\sim 0.5$  M (see ESI† for details). At present, however, the exact reason for the observed rate-order alteration for **2a** is not clear, and requires further rationalization.<sup>14</sup>

The reactions of a series of substituted quinolines with  $\text{Et}_2\text{SiH}_2$  were monitored using  $^1\text{H}$  NMR to compare their relative rates of hydrosilylation (Scheme 5). The observed initial rates at the early stage (up to 15% conversion of the quinoline substrate) revealed a relevance of the substituents present: 3-Br  $\sim$  3-I > 4-I > 4-Br > 4-Cl > 4-H > 4-Me (see ESI† for more details).<sup>15</sup> Although the relationship between the electron-withdrawing ability of the substituents and the observed initial rates still needs to be further rationalized, the present results at this stage suggest that: (i) softer halide substituents at the *para* position lead to a higher reaction efficiency than harder ones at the same position; (ii) electron-withdrawing ability partially contributes to the rate enhancement.

**(B) Stoichiometric reaction of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$ , 3-methylpyridine, and  $\text{Et}_2\text{SiH}_2$ .** A reaction of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  with 15 equiv. of  $\text{Et}_2\text{SiH}_2$  in toluene- $d_8$  resulted in the formation of an unsymmetrical structure of two isomeric silylene-bridged Ir dimers  $[(\text{C}_8\text{H}_{14})(\text{Et}_2\text{SiH})\text{Ir}(\text{H})_2(\mu\text{-SiEt}_2)\text{Ir}(\text{H})_3]$  (**I/I'**) in a ratio of 3 : 2 (Fig. 1A).<sup>16</sup>  $^1\text{H}$ - $^1\text{H}$  COSY analysis suggested selective interactions between the olefinic protons of the cyclooctene and the dihydrides at one Ir centre of the bimetallic species (see ESI† for details of the NMR spectroscopic data). It is noteworthy that Brookhart previously proposed a *symmetrical* structure of a silylene-bridged Ir dimer  $[(\text{Et}_2\text{SiH})\text{Ir}(\text{H})_2(\mu\text{-SiEt}_2)]_2$ , which was assumed to be generated *in situ* under similar conditions.<sup>8</sup> Subsequent addition of 3-methylpyridine (5 equiv.) as a model substrate<sup>17</sup> into a solution containing **I/I'** and excessive silane led to quantitative conversion of **I/I'** into a new bimetallic iridium species (**6a**) within 10 min at 25 °C (Fig. 1B). A set of signals assignable to the coordinated 3-methylpyridine at  $\delta$  8.85 ( $\text{H}^b$ ), 8.36 ( $\text{H}^c$ ), 6.79 ( $\text{H}^d$ ), 6.59 ( $\text{H}^e$ ), and 1.80 (methyl) appeared accordingly in the  $^1\text{H}$  NMR spectrum. The Ir-hydride signals at



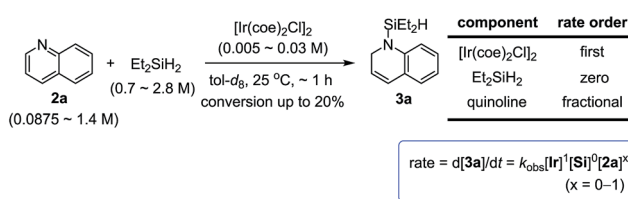
Scheme 5 Relative initial rates for substituted quinolines.

$\delta$  -13.01 and -13.20 are assignable to trihydrides and dihydrides, respectively.

As can be seen in Fig. 1B, and since the relative intensity of the  $^1\text{H}$  peaks at  $\delta$  6.59 ( $\text{H}^e$ ), -13.01, and -13.20 was determined to be 1 : 3 : 2, one molecule of 3-methylpyridine was proposed to coordinate to the bimetallic Ir species forming a pyridine adduct (**6a**), by assuming that **6a** was a pentahydride bimetallic species.<sup>18</sup> In addition, a 2D-NOESY (nuclear Overhauser effect spectroscopy) experiment for **6a** at -70 °C revealed that one 3-methylpyridine molecule coordinates *exclusively* to one Ir centre with dihydrides and a terminal silyl group, while the other metal centre does not coordinate to the excess pyridine substrates (see ESI† for the NOESY experiment). For the  $^{29}\text{Si}$  spectrum, two peaks at  $\delta$  130.4 and 44.5 were assigned to the bridged silylene and terminal silyl moieties, respectively, based on the literature.<sup>7,8,19</sup> A peak at  $\delta$  78.7 is attributable to a silicon with an  $\eta^2$  coordination mode, leading to the assignment of **6a** to a structure that contains a substructure of “-Ir-( $\text{Et}_2$ )Si-H( $\eta^2$ )-Ir-”. Indeed, a number of binuclear metal complexes with  $\eta^2$  metal-H-Si interactions have been reported,<sup>20</sup> among which a silylene-bridged dinuclear titanocene complex  $[\text{Cp}_2\text{Ti}(\eta^2\text{-H-SiHPh})(\mu\text{-H})\text{TiCp}_2]$  is known to have a  $^{29}\text{Si}$  resonance at *ca.* 87 ppm due to the  $\eta^2$ -silane moiety.<sup>20f</sup> Furthermore, regarding the Si-H coupling constant [ $^1J_{\text{Si-H}(\eta^2)}$ ] for **6a**, we observed two small peaks with a *J* value of 44 Hz at  $\delta$  -13.14 and -13.25 (see ESI† for the expanded Ir-hydride region). Fast atom bombardment mass spectrometry (FAB-MS) analysis of this stoichiometric reaction mixture showed a peak that corresponds to a fragment ion of  $[\text{6a} + \text{H}]^+$  (see ESI† for the mass analysis).

**(C) Observation of resting species in the hydrosilylation turnover.** With a prolonged reaction time, 3-methylpyridine was observed to undergo the 1,2-hydrosilylation process to afford the corresponding 3-methyl-*N*-silyl-1,2-dihydropyridine in 9% NMR yield in 18 h at 25 °C (Fig. 1C). It is notable that a constant amount of **6a** was observed throughout the reaction course. Similarly, a reaction of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$ ,  $\text{Et}_2\text{SiH}_2$ , and 3-fluoropyridine **2t** (1 : 35 : 35) at 25 °C selectively produced 3-fluoro-*N*-silyl-1,2-dihydropyridine **3t** (36% conversion in 12 h). During this conversion, an analogous resting species of a **2t** adduct was also observed, showing a peak at  $\delta$  -12.97 and multiple peaks over  $\delta$  -13.2 to -13.5 ( $^1\text{H}$  NMR) in addition to silicon peaks at  $\delta$  130.5, 87.2, and 44.4 (see ESI† for details). These results strongly indicate that N-heteroaromatic adducts of a bimetallic Ir species, such as **6a**, exist in the catalytic resting state.<sup>21</sup>

**(D) Mechanistic proposal.** Based on our mechanistic studies, in combination with the precedent literature,<sup>6c-e,i</sup> we



Scheme 4 Observed rate order for each component based on the initial-rate kinetics.



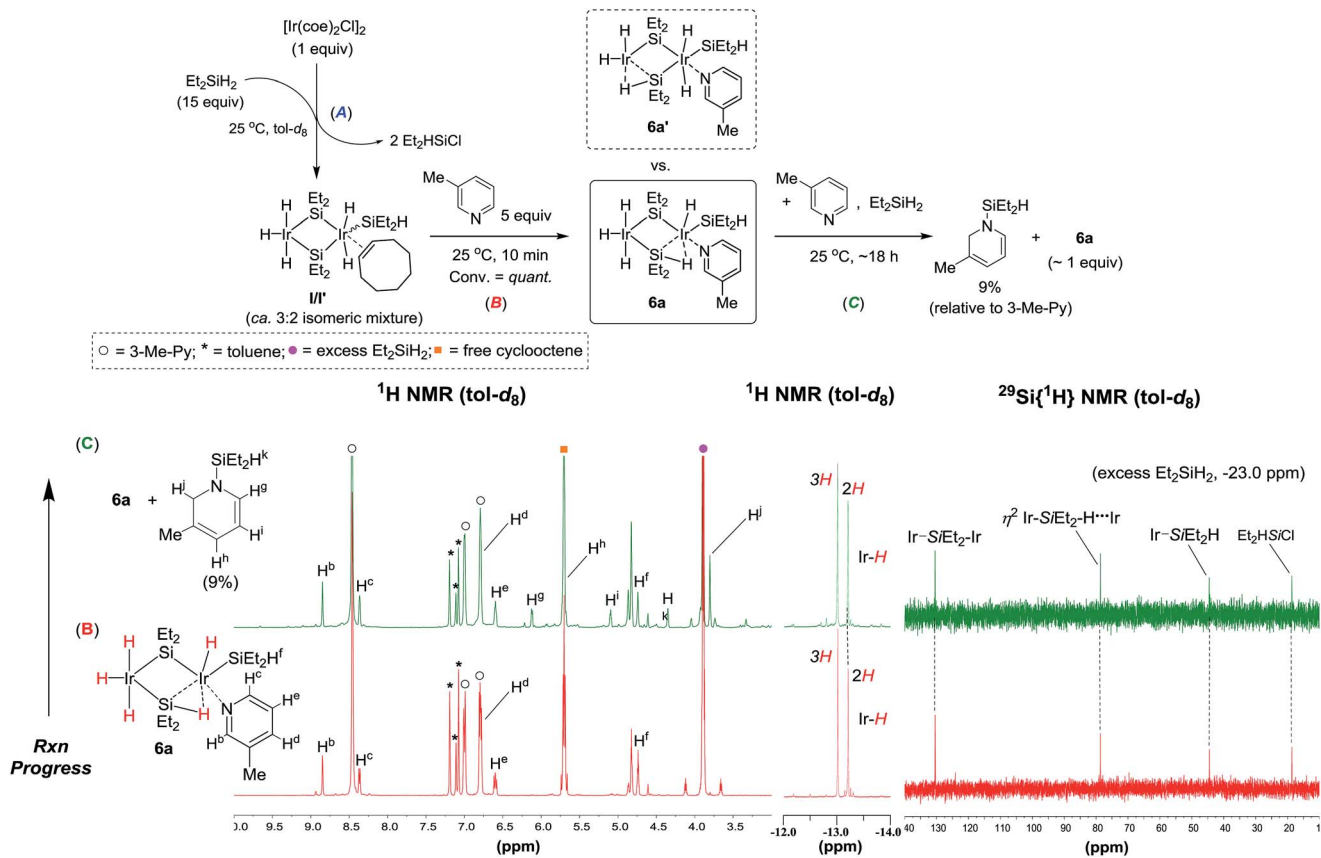


Fig. 1 The reaction of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  (1 equiv.) with  $\text{Et}_2\text{SiH}_2$  (15 equiv.) at  $25^\circ\text{C}$  for 10 min in  $\text{toluene-}d_8$  (A) blue;  $^1\text{H}$  and  $^{29}\text{Si}\{^1\text{H}\}$  NMR spectra obtained 10 min (B) red and 18 h (C) green after the addition of 3-methylpyridine (5 equiv.) at  $25^\circ\text{C}$ .

propose a catalytic cycle for the Ir-catalyzed 1,2-hydrosilylation of N-heteroaromatics (Scheme 6). The initiation step involves the generation of two isomeric iridium olefin adducts  $\text{I/I}'$  via a reaction of  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  with excess  $\text{Et}_2\text{SiH}_2$ . The *in situ* generated  $\text{I/I}'$  adducts undergo a facile ligand exchange with the heteroarene substrate to form a substrate-bound bimetallic species ( $\text{II}$ ) as the dominant catalyst resting species.

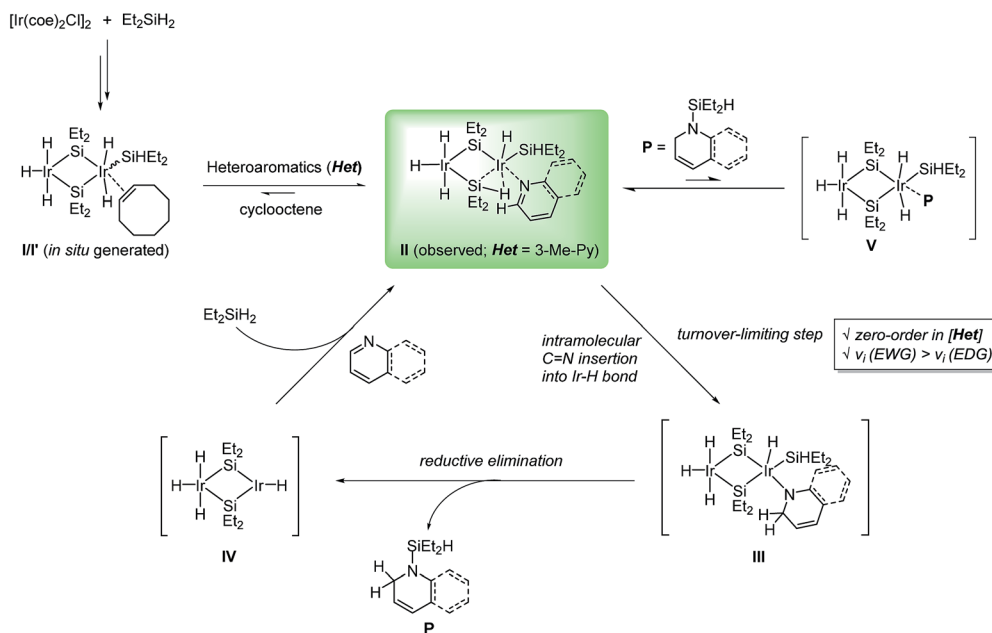
We propose that the key hydride insertion takes place within the coordinated heteroaromatic adduct species. The intramolecular  $\text{C}=\text{N}$  insertion into an Ir-H bond of  $\text{II}$  giving rise to  $\text{III}$  is believed to be turnover-limiting at high concentrations of substrates. We assume that this step is influenced by the electronic nature of the substrates, leading to higher rates with heteroarenes bearing electron-withdrawing substituents. Intermediate  $\text{III}$  will subsequently deliver the partially reduced *N*-silyl product  $\text{P}$  via reductive elimination,<sup>6d,22</sup> with the concomitant generation of an unsaturated Ir species  $\text{IV}$ . Although  $\sigma$ -bond metathesis at the Ir-amido moiety of  $\text{III}$ <sup>6e,6e,23</sup> with excess  $\text{Et}_2\text{SiH}_2$  would be an alternative product releasing path, we rather favor the reductive elimination route which would be entropically more beneficial over the metathesis process, particularly in our catalytic system. An inhibitory off-cycle process involving the coordination of  $\text{P}$  to  $\text{II}$  leading to  $\text{V}$  is assumed to be a minor occurrence in the overall process.

## Synthetic applications

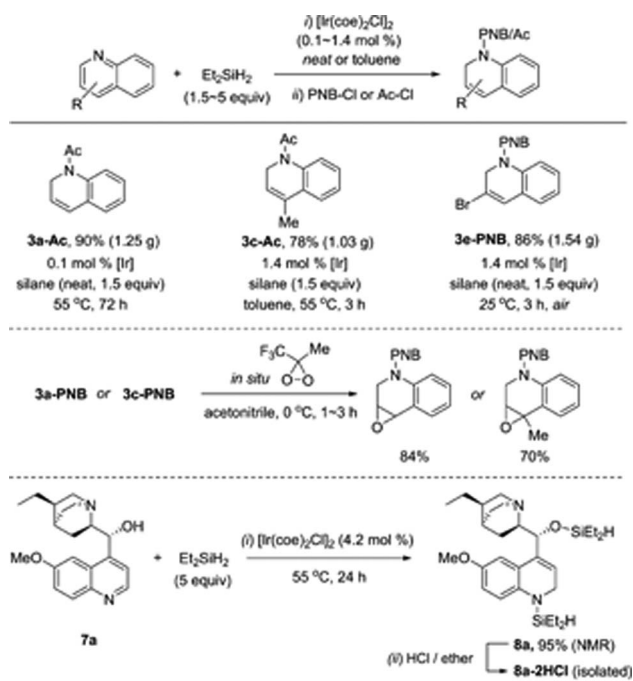
To prove the practicability of the present catalytic procedure, the 1,2-hydrosilylation of quinolines was examined on a large scale (Scheme 7). Pleasingly, the reaction of quinoline was readily amenable to gram scale synthesis, using a neat reaction mixture with only 0.1 mol% of the iridium precursor  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  at  $55^\circ\text{C}$ , to give  $\text{3a-Ac}$  in 90% yield over 2 steps. In a similar manner, the hydrosilylation of 4-methylquinoline was easily scaled up using 1.5 equiv. of  $\text{Et}_2\text{SiH}_2$  to afford the *N*-acetyl amide product ( $\text{3c-Ac}$ ) in good yield. Interestingly, a gram scale reaction of 3-bromoquinoline occurred smoothly at room temperature to give  $\text{3e-PNB}$  in 86% yield.

Epoxidation of isolated compounds  $\text{3a-PNB}$  and  $\text{3c-PNB}$  was successfully achieved using an *in situ* generated oxidant, 3-methyl-3-(trifluoromethyl)dioxirane, under mild conditions,<sup>24</sup> thus demonstrating the synthetic utility of the partially reduced products obtained through the present catalytic procedure. Cinchona alkaloids are representative compounds with biological activity bearing a quinoline moiety and, therefore, facile transformations of them are important in synthetic and pharmaceutical chemistry.<sup>25</sup> When hydroquinine ( $\text{7a}$ ) was subjected to the dearomative hydrosilylation conditions in neat  $\text{Et}_2\text{SiH}_2$  (5 equiv.), the desired *N*-silyl-1,2-reduction product ( $\text{8a}$ ) was formed with a 95% crude yield, which was subsequently transformed to the corresponding ammonium salt,  $\text{8a-2HCl}$ .





Scheme 6 Proposed mechanistic pathway for the Ir-catalyzed dearomative 1,2-hydrosilylation of heteroaromatics.



Scheme 7 Synthetic applications.

## Conclusions

We have developed a highly efficient, convenient, and scalable procedure for the Ir-catalyzed selective hydrosilylation of a wide array of N-heteroaromatics, including (iso)quinolines, substituted pyridines, pyrimidines, pyrazines, deazapurines, triazines, and benzimidazoles. The reaction occurs smoothly under mild conditions to provide diverse dearomatized azacyclic products in satisfactory yields. The catalyst system requires

a  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  precursor only, with an absence of any external ligands or additives. Mechanistic considerations of the kinetics, rate law and NMR studies led us to propose a hydrosilylation path involving intramolecular insertion of a C=N unit into an Ir-H bond of a key silylene-bridged Ir dimer. Spectroscopic analysis under various reaction conditions revealed a bimetallic structure of the catalytic resting species. The synthetic utility of the present scalable catalytic procedure was demonstrated through the facile 1,2-hydrosilylation of cinchona alkaloids and successful post-synthetic transformations (*e.g.* epoxidation) of the partially reduced azacycle products. Considering the attractive features of the present procedure, it is anticipated to find wide application in synthetic and medicinal chemistry. More detailed mechanistic studies, including DFT calculations, on the present catalytic system are now underway and the results will be communicated in due course.

## Acknowledgements

We thank Prof. Kiyong Park (KAIST) for valuable discussions. This research was supported by the Institute for Basic Science (IBS-R010-D1) in Korea.

## Notes and references

- (a) T. M. Krygowski and M. K. Cryański, *Chem. Rev.*, 2001, **101**, 1385; (b) A. T. Balaban, D. C. Oniciu and A. R. Katritzky, *Chem. Rev.*, 2004, **104**, 2777.
- (a) M. Boll, *J. Microbiol. Biotechnol.*, 2005, **10**, 132; (b) T. Hudlicky, D. Gonzalez and D. T. Gibson, *Aldrichimica Acta*, 1999, **32**, 35; (c) T. Hudlicky and J. W. Reed, *Synlett*, 2009, 685; (d) J. W. Kung, S. Baumann, M. von Bergen,



- M. Müller, P.-L. Hagedoorn, W. R. Hagen and M. Boll, *J. Am. Chem. Soc.*, 2010, **132**, 9850.
- 3 (a) A. R. Pape, K. P. Kaliappan and E. P. Kündig, *Chem. Rev.*, 2000, **100**, 2917; (b) S. P. Roche and J. A. Porco, *Angew. Chem., Int. Ed.*, 2011, **50**, 4068; (c) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642.
- 4 (a) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1; (b) W. Sliwa, *Heterocycles*, 1986, **24**, 181; (c) J.-P. Wan and Y. Liu, *RSC Adv.*, 2012, **2**, 9763.
- 5 (a) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223; (b) R. Lavilla, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1141; (c) N. Edraki, A. R. Mehdipour, M. Khohneviszadeh and R. Miri, *Drug Discovery Today*, 2009, **14**, 1058; (d) P. A. Wender, J. M. Schaus and A. W. White, *J. Am. Chem. Soc.*, 1980, **102**, 6157; (e) N. Satoh, T. Akiba, S. Yokoshima and T. Fukuyama, *Angew. Chem., Int. Ed.*, 2007, **46**, 5734; (f) H. Mizoguchi, H. Oikawa and H. Oguri, *Nat. Chem.*, 2014, **6**, 57; (g) S. Duttwyler, S. Chen, C. Lu, B. Q. Mercado, R. G. Bergman and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2014, **53**, 3877; (h) G. Zhao, U. C. Deo and B. Ganem, *Org. Lett.*, 2001, **3**, 201; (i) G. Barbe and A. B. Charette, *J. Am. Chem. Soc.*, 2008, **130**, 13873.
- 6 (a) Q.-A. Chen, M. W. Chen, C.-B. Yu, L. S. Shi, D.-S. Wang, Y. Yang and Y. G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432; (b) X. Fan, J. Zheng, Z. H. Li and H. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 4916; (c) M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kociok-Köhn and C. Weetman, *Organometallics*, 2011, **30**, 5556; (d) K. Oshima, T. Ohmura and M. Sugimoto, *J. Am. Chem. Soc.*, 2012, **134**, 3699; (e) A. S. Dudnik, V. L. Weidner, A. Motta, M. Delferro and T. J. Marks, *Nat. Chem.*, 2014, **6**, 1100; (f) D. V. Gutsulyak, A. V. D. Est and G. I. Nikonov, *Angew. Chem., Int. Ed.*, 2011, **50**, 1384; (g) S.-H. Lee, D. V. Gutsulyak and G. I. Nikonov, *Organometallics*, 2013, **32**, 4457; (h) C. D. F. Königs, H. F. T. Klare and M. Oestreich, *Angew. Chem., Int. Ed.*, 2013, **52**, 10076; (i) J. Intemann, H. Bauer, J. Pahl, L. Maron and S. Harder, *Chem.-Eur. J.*, 2015, **21**, 11452.
- 7 S. Park, B. G. Kim, I. Göttker-Schnetmann and M. Brookhart, *ACS Catal.*, 2012, **2**, 307.
- 8 C. Cheng and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 11304.
- 9 C. Cheng and M. Brookhart, *Angew. Chem., Int. Ed.*, 2012, **51**, 9422.
- 10 For our recent reports in the relevant reactions, see: (a) N. Gandhamsetty, S. Joung, S.-W. Park, S. Park and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 16780; (b) N. Gandhamsetty, J. Park, J. Jeong, S.-W. Park, S. Park and S. Chang, *Angew. Chem., Int. Ed.*, 2015, **54**, 6832; (c) N. Gandhamsetty, S. Park and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 15176.
- 11 T. P. Forrest, G. A. Dauphinee and S. A. Deraniyagala, *Can. J. Chem.*, 1985, **63**, 412.
- 12 Although the quinolinium salt **3a-HCl** slowly underwent rearomatization over time in DMSO-*d*<sub>6</sub> at 25 °C, returning to quinoline **2a**, solid **3a-HCl** was stable enough to be stored at -30 °C for over 1 week without being rearomatized.
- 13 Treatment of **4f** with 1.1 equiv. of Et<sub>2</sub>SiH<sub>2</sub> under otherwise identical conditions gave a mixture of isomeric mono-hydrosilylated products, while the reaction of **4l** led to a mixture of doubly reduced product **5l** and the remaining starting material **4l** (see ESI† for the crude NMR spectra).
- 14 Initially, we assumed an inhibition effect *via* coordination of **3a** and/or cyclooctene, which might lead to the alteration of the rate order from zero to first. However, no inhibition effect was found in terms of the reaction rate, as it was evident that hydrosilylations of **2a** with Et<sub>2</sub>SiH<sub>2</sub> in the presence of a significant amount of **3a** or cyclooctene showed a catalytic activity similar to that obtained under the standard conditions (see ESI† for details).
- 15 A similar reactivity trend was observed for the La-catalyzed 1,2-hydroboration of substituted pyridines, in which the turnover frequency (TOF) increased in the order of 3-I > 3-Cl > 3-Br > 3-F ~ 3-H, while 3-halopyridines were more reactive than the same type of 4-halopyridines (ref. 6e).
- 16 Two types of hydride resonance at -12.5 and -12.8 ppm, assignable to Ir-(H)<sub>3</sub> and Ir-(H)<sub>2</sub> respectively for both **I/I'**, were clearly separate from each other in <sup>1</sup>H NMR studies over a range of -70 to 25 °C without coalescence, suggesting that the hydrides at each Ir center are fluxional even at -70 °C, but do not undergo cross-exchange between the two Ir centers at least at 25 °C (see ESI† for this variable temperature experiment).
- 17 In order to observe the resting state(s) of the present process, we preliminarily carried out the reaction of quinoline **2a** with Et<sub>2</sub>SiH<sub>2</sub> under various conditions. It turned out that multiple Ir-hydride species were formed as the catalytic turnover increased. This rendered the resting species difficult to characterize. For this reason, 3-methylpyridine which had displayed lower reactivity under the catalytic conditions was chosen as a model substrate.
- 18 Each hydride signal at δ -13.01 and -13.20 remained sharp over a range of -70 to 60 °C without broadening and/or coalescence (see ESI† for this variable temperature experiment). This observation suggests that the hydrides of **6a** (or **6a'**) do not undergo scrambling between the two bridged Ir centers. For relevant discussions on this issue, see: (a) F. L. Taw, R. G. Bergman and M. Brookhart, *Organometallics*, 2004, **23**, 886; (b) X. Liang and R. H. Crabtree, *J. Am. Chem. Soc.*, 1989, **111**, 2527; (c) S. B. Duckett and R. N. Perutz, *J. Chem. Soc., Chem. Commun.*, 1991, 28-31; (d) R. S. Tanke and R. H. Crabtree, *Organometallics*, 1991, **10**, 415; (e) F. Delpech, S. Sabo-Etienne, B. Chaudret and J.-C. Daran, *J. Am. Chem. Soc.*, 1997, **119**, 3167; (f) S. Park and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 640; (g) T. T. Metsänen, P. Hrobárik, H. F. T. Klare, M. Kaupp and M. Oestreich, *J. Am. Chem. Soc.*, 2014, **136**, 6912.
- 19 (a) E. Calimano and T. D. Tilley, *Dalton Trans.*, 2010, **39**, 9250; (b) E. Calimano and T. D. Tilley, *J. Am. Chem. Soc.*, 2009, **131**, 11161.
- 20 For selected reviews on transition metal-silane σ-complexes, see: (a) G. Nikonov, *Adv. Organomet. Chem.*, 2005, **53**, 217; (b) J. Y. Corey, *Chem. Rev.*, 2011, **111**, 863; (c) U. Schubert, *Adv.*





- Organomet. Chem.*, 1990, **30**, 151; (d) Z. Lin, *Chem. Soc. Rev.*, 2002, **31**, 239; (e) J. I. Schneider, *Angew. Chem., Int. Ed. Engl.*, 1996, **108**, 1132; (f) R. H. Crabtree, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 789; (g) S. Lachaize and S. Sabo-Etienne, *Eur. J. Inorg. Chem.*, 2006, 2115–2127 For examples of dinuclear transition metal complexes with M–H–Si interactions in an  $\eta^2$ -mode, see: (h) M. J. Bennett and K. A. Simpson, *J. Am. Chem. Soc.*, 1971, **93**, 7156; (i) M. Ciriano, M. Green, J. A. K. Howard, J. Proud, J. L. Spencer, F. G. A. Stone and C. A. Tsipis, *J. Chem. Soc., Dalton Trans.*, 1978, 801; (j) C. T. Aitken, J. F. Harrod and E. Samuel, *J. Am. Chem. Soc.*, 1986, **108**, 4059; (k) M. D. Fryzuk, L. Rosenberg and S. J. Rettig, *Organometallics*, 1991, **10**, 2537; (l) H. Suzuki, T. Takao, M. Tanaka and Y. Moro-oka, *J. Chem. Soc., Chem. Commun.*, 1992, 476; (m) T. Takao, S. Yoshida and H. Suzuki, *Organometallics*, 2005, **24**, 521.
- 21 For examples of binuclear metal complexes in catalysis, see: (a) E. K. Van den Beuken and B. L. Feringa, *Tetrahedron*, 1998, **54**, 12985; (b) H. Li and T. J. Marks, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 15295; (c) H. Steinhagen and G. Helmchen, *Angew. Chem., Int. Ed.*, 1996, **35**, 2339; (d) M. E. Broussard, B. Juma, S. G. Train, W.-J. Peng, S. A. Laneman and G. G. Stanley, *Science*, 1993, **260**, 1784; (e) C. J. McKenzie and R. Robson, *Chem. Commun.*, 1988, 112; (f) M. J. Hostetler and R. G. Bergman, *J. Am. Chem. Soc.*, 1990, **112**, 8621; (g) M. J. Hostetler, M. D. Butts and R. G. Bergman, *J. Am. Chem. Soc.*, 1993, **115**, 2743; (h) N. Guo, C. L. Stern and T. J. Marks, *J. Am. Chem. Soc.*, 2008, **130**, 2246; (i) H. Nagashima, A. Suzuki, T. Iura, K. Ryu and K. Matsubara, *Organometallics*, 2000, **19**, 3579; (j) H. Hashimoto, I. Aratani, C. Kabuto and M. Kira, *Organometallics*, 2003, **22**, 2199.
- 22 (a) K. H. Hopmann and A. Bayer, *Coord. Chem. Rev.*, 2014, **268**, 59; (b) V. Herrera, B. Muñoz, V. Landaeta and N. Canudas, *J. Mol. Catal. A: Chem.*, 2001, **174**, 141; (c) N. Nakatani, J.-Y. Hasegawa, Y. Sunada and H. Nagashima, *Dalton Trans.*, 2015, **44**, 19344; (d) M. Brown and N. A. Cooley, *Chem. Rev.*, 1988, **88**, 1031; (e) M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1995, **117**, 4708.
- 23 L. Hao, J. F. Harrod, A.-M. Lebuis, Y. Mu, R. Shu, E. Samuel and H.-G. Woo, *Angew. Chem., Int. Ed.*, 1998, **37**, 3126.
- 24 D. Yang, M.-K. Wong and Y.-C. Yip, *J. Org. Chem.*, 1995, **60**, 3887.
- 25 (a) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483; (b) R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. S. Ojima, John Wiley & Sons, Inc., New York, 2000; (c) K. Maruoka, in *Asymmetric Phase Transfer Catalysis*, Wiley-VCH Verlag GmbH, Weinheim, 2008; (d) K. N. Houk and B. List, *Acc. Chem. Res.*, 2004, **37**, 487; (e) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (f) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (g) C.-E. Song, in *Cinchona Alkaloids in Synthesis & Catalysis: Ligands, Immobilization and Organocatalysis*, Wiley-VCH Verlag GmbH, Weinheim, 2009.

