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Efficient and selective hydrosilylation of secondary and tertiary amides using an iridium(III) metallacycle catalyst: development and mechanistic investigation.

Yann Corre,^[a,b] Xavier Trivelli,^[c] Frédéric Capet,^[a] Jean-Pierre Djukic,^[d] Francine Agbossou-Niedercorn^{*[a,b]} and Christophe Michon^{*[a,b]}

Dedicated to Professor Jérôme Lacour at the occasion of his 50th birthday.

Abstract: In the present study, we show accessible cationic Ir(III) metallacycles catalyse efficiently the chemoselective hydrosilylation of tertiary and secondary amides to amines. The catalyst described herein operates at low loadings using inexpensive 1,1,3,3-tetramethyldisiloxane and allows fast reactions with high yields, selectivities and turnover numbers. Whereas a transient iminium intermediate has been observed for the first time by mass spectrometry, the activations of the catalyst and the silane reagent have been studied by DFT calculations. These fundamental insights support present and future improvements of Ir(III) metallacycles through proper ligand modifications and enable further broad applications of catalysts based on metallacycles.

Introduction

Amines are ubiquitous in natural products, building blocks or targets for fine chemicals, farming-related chemicals and biologically active compounds.^[1] They can be prepared by numerous synthetic methodologies including reductive aminations,^[1c] alcohol aminations,^[1d] hydroaminations^[1e] and transaminations.^[1f,g] However, when the preparation of more functionalised amines is required by pharmacy and fine chemistry, the reduction of amides is often preferred. Nowadays, such reaction still involves the sub-stoichiometric use of metal hydride reagents which are air and moisture sensitive and produce large amounts of waste.^[2] Whereas the reduction of amides can be performed by hydrogenation using heterogeneous catalysts under harsh conditions, the use of homogeneous catalysts allow more active and selective hydrogenation reactions by operating in milder conditions.^[3] Alternatively, the use of hydrosilanes as reductants is an area of growing interest for the mild and selective reduction of carboxylic acid derivatives by using transition metal or Lewis acid catalysts.^[4,5] Indeed, hydrosilylation, which operates without any high pressure equipment and high temperature, can be an interesting alternative to hydrogenation, provided that

inexpensive and abundant hydrosilanes are used. Because the reactivity of such reagents and related intermediates is modular and depends on the substituents of the silicon atoms, the hydrosilylation reaction can be a highly chemo- and regioselective reduction method which tolerates various other reducible functional groups. However, whereas several organometallic or organic catalysts were shown to hydrosilylate tertiary and secondary amides,^[5] the hydrosilylation of primary amides remains challenging.^[5i,j] Moreover, to the best of our knowledge, only few publications have reported effective hydrosilylation of amides by using affordable silanes and highly active catalysts operating at low loadings.^[5b,d,h,i,k] Following our past studies on hydrosilylation reactions of unsaturated carbon-carbon and carbon-heteroatom compounds using Ir(III) metallacycle catalysts,^[6] we report herein the first application of accessible Ir(III) metallacycles to catalyse at low loadings and high turnover numbers the hydrosilylation of secondary and tertiary amides using inexpensive 1,1,3,3-tetramethyldisiloxane.

Results and Discussion

Following our previous investigations on hydrosilylation reactions,^[6] screening of Ir(III) metallacycle precursors, additives and reaction conditions was performed on the hydrosilylation of tertiary amide **5a** (Table 1). In presence of 2 mol% of trityltetra(pentafluorophenyl)borate (Ph₃CBARF₂₀) and triethylsilane, chromiumtricarbonyl-bound iridacycle **2** provided a more active catalyst as compared to iridacycle **1** affording amine **6a** in yields of 48 versus 33% (entries 1, 2). Addition of an NMe₂ donating substituent to the chelating 2-phenyl-pyridine ligand resulted overall in more active catalysts. Whereas chromiumtricarbonyl-bound iridacycle **4** led to **6a** in a 91% yield, iridacycle **3** allowed the hydrosilylation of amide **5a** in a nearly quantitative yield (e.g. 98% yield) (entries 3, 4). Hence, considering the effect of the Cr(CO)₃ moiety, a reverse trend was observed compared to iridacycle **1** and **2**. The use of [IrCp*Cl₂]₂ as pre-catalyst resulted in a less efficient and selective reaction with the formation of unidentified side-products (entry 5). Changing the additive to sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate (NaBARF₂₄) or *N,N*-dimethylanilinium tetra(pentafluorophenyl)borate (Me₂PhHNBARF₂₀) led to a significant decrease of yields (entries 6 and 7). Finally, triethylsilane was replaced by inexpensive and green hydrosilylation reagents. Whereas polymethylhydroxysiloxane (PMHS) afforded amine **6a** in a lower yield (65%), we were glad to reach a quantitative yield using 1,1,3,3-tetramethyldisiloxane (TMDS) reagent (entries 8, 9).

Interested by the results obtained in the presence of pre-catalyst **3** and TMDS, the reaction conditions were studied in more details (Table 2). We focused first on the activity of our catalytic system by changing the loadings of the pre-catalyst **3** and Ph₃CBARF₂₀ additive.

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Supporting information for this article is available on the web.

Table 1. Catalytic study.

$\text{Ph-C(=O)-N(Bn)}_2 + \text{silane} \xrightarrow[\text{TCE, 100 } ^\circ\text{C, 15 h}]{\text{pre-cat. Ir (1 mol\%)} + \text{additive (2 mol\%)}} \text{Ph-CH}_2\text{-N(Bn)}_2$

5a, 1 eq. $\xrightarrow{\text{3 eq.}}$ **6a** (then hydrolysis)

Entry	pre-cat.	Additive	Silane	Yield (%) ^[a]
1	1	Ph ₃ CBArF ₂₀ ^[b]	Et ₃ SiH	33
2	2	Ph ₃ CBArF ₂₀	Et ₃ SiH	48
3	3	Ph ₃ CBArF ₂₀	Et ₃ SiH	98
4	4	Ph ₃ CBArF ₂₀	Et ₃ SiH	91
5	[IrCp*Cl ₂] ₂	Ph ₃ CBArF ₂₀	Et ₃ SiH	68 ^[c]
6	3	NaBArF ₂₄ ^[d]	Et ₃ SiH	37
7	3	Me ₂ PhHNBArF ₂₀ ^[e]	Et ₃ SiH	76
8	3	Ph ₃ CBArF ₂₀	TMDS ^[f]	100
9	3	Ph ₃ CBArF ₂₀	PMHS ^[g]	65 ^[h]

[a] yield measured by GC; TCE: 1,1',2,2'-tetrachloroethane. [b] Ph₃CBArF₂₀: trityl tetra(pentafluorophenyl)borate. [c] with unidentified side-products. [d] NaBArF₂₄: sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate. [e] Me₂PhHNBArF₂₀: *N,N*-Dimethylanilinium tetra(pentafluorophenyl)borate. [f] TMDS: 1,1,3,3-tetramethyldisiloxane. [g] PMHS: Polymethylhydroxysiloxane. [h] 91% yield after 45 h reaction.

A control experiment proved the additive was not catalysing itself the hydrosilylation of amide **5a** (entry 1). In the presence of 1 mol% of pre-catalyst **3**, quantitative yields were obtained at 100 and 80°C (entries 2, 3) but a reaction at 60°C resulted in a significant decrease of the yield (entry 4). When the pre-catalyst loading was reduced from 1 to 0.5 mol%, the yield was still quantitative at 100°C (entry 5), while a reaction performed at 80°C resulted in a 58% yield (entry 6). By operating at 0.1 mol% loading of **3**, the yield was again quantitative within 15h providing a turnover number (TON) of 1000 (entry 7). We noticed the same catalytic performances could be maintained decreasing the amount of TMDS to 2 equivalents, an excess of silane reagent still being required in order to reach a full conversion of tertiary amide **5a** (entries 8, 9). A further decrease of the pre-catalyst loading to 0.05 mol% resulted in a complete reaction within 0.5h with a TON of 2000 (entry 10). Finally, the use of a 0.01 mol% pre-catalyst loading afforded a quantitative yield with a TON of 10000 provided the reaction was run for 24 hours (entry 11). A part the decrease of the pre-catalyst loading from 1 to 0.01 mol%, it was worth to note a higher concentration of the reaction medium had no effect on the yield or the catalyst activity. Whereas solvents like toluene, 1,4-dioxane or CPME implied much lower yields (entries 12-14), the use of anisole resulted in a 73% yield for amine **6a** with a TON of

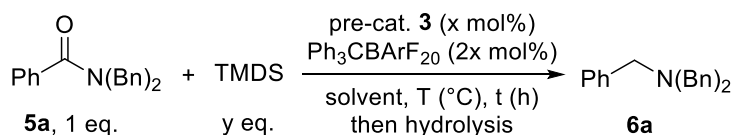
Table 2. Screening of reaction conditions.

1460 provided the reaction was run over 24 hours (entries 15-16). Depending on the reaction time, various amounts of a possible iminium species (*vide-infra*) could be observed along with product **6a** (entries 15-16).

The scope of the hydrosilylation reaction was studied with aromatic and aliphatic tertiary amides **5a-v** (Table 3). Under the optimised conditions determined above, the corresponding amines **6a-v** were obtained generally in high to quantitative yields. Substrates **5a-e** bearing only aromatic substituents were reduced smoothly and the desired products were readily recovered in 0.5 to 2 hours of reaction (entries 1-5). The hydrosilylation reaction was effectively working with heterocyclic substrates **5f-g** (entries 6, 7) but compounds **5h-k** (entries 8-11) bearing alkyl cycles on whichever side of the amide required 2 to 8 hours to be reduced in good yields. If the reaction was apparently not limited by some alkyl substituents (reagents **5h,l** – entries 8, 12), the hydrosilylation of tertiary amides **5m-o** bearing either bulky isopropyl groups or just an ethyl fragment required up to 48 hours to reach average to good yields (entries 13-15). The same trend was also observed for aromatic amides **5p** and **5r** bearing a fluoro or a methoxy substituent in ortho-position (entries 16, 18). Moreover, the developed catalyst allowed highly chemoselective hydrosilylation reactions tolerating other reducible functional groups like nitro, cyano and ester. If substrates **5u-v** functionalised by an ester or a nitrile group in para-position required more time to react completely (entries 21, 22), other para-substituted derivatives **5q** and **5s-t** could be reduced smoothly within 2 to 8 hours in high yields (entries 17, 19-20).

The reaction scope was further studied with the hydrosilylation of the less reactive secondary amides **7a-t** (Table 4).^[5d,5m,5o] To our delight, high yields of the corresponding amines **8a-t** could be obtained at 100°C with 2 equivalents of TMDS through a simple increase of loadings of pre-catalyst **3** and trityl tetra(pentafluorophenyl)borate additive to respectively 0.5 mol% and 1 mol%. Similar to the reduction of tertiary amides **5a-v**, aromatic secondary amides **7a-b** and **7d-i** were quickly hydrosilylated with high to quantitative yields (entries 1, 2, 4-9). As the allyl substituent of substrate **7d** was not reduced, we confirmed again the high chemoselectivity of the catalyst developed here (entry 4). The hydrosilylation of secondary amide **7c** bearing a bulky *tert*-butyl group needed 24 hours in order to reach an average yield (entry 3). A decrease of reactivity was also observed for aromatic amide **7j** bearing an ethyl substituent in ortho-position, 8 hours being required to obtain a good yield (entry 10). Other ortho- or para-substituted derivatives **7k-n** could be reduced readily, like *O*-heterocyclic substrate **7o** (entries 11-15). If the hydrosilylation of aliphatic secondary amides **7p** and **7t** was also straightforward (entries 16, 20), the reaction of sterically hindered substrates **7q-s** bearing cyclohexyl or isopropyl groups required 24 to 48 hours to reach average to good yields (entries 17-19).

In an attempt to improve our catalytic system, we prepared a new iridacycle by changing the chelating 2-phenyl-pyridine ligand for a 1-phenyl isoquinoline one while keeping the NMe₂ donating substituent on the phenyl group (See the Supporting Information). The resulting iridacycle **9** was first applied to the hydrosilylation of the sterically hindered tertiary amide **5n** (Scheme 1). Though this substrate was reduced in 48 hours using pre-catalyst **3**, the use of iridacycle **9** allowed us to obtain the related tertiary amine **6n** with a 95% yield in only 8 hours. The hydrosilylation of the bulky secondary amide **7r** was subsequently studied (Scheme 1).



Entry	pre-cat. (mol%)	TMDS (eq.)	[5a] (mmol.l ⁻¹)	Solvent	T (°C)	Time (h)	Yield (%) ^[a]	TON ^[b]
1 ^[c]	0	3	0.077	TCE	100	15	0	-
2	1	3	0.077	TCE ^[d]	100	15	100	100
3	1	3	0.077	TCE	80	15	100	100
4	1	3	0.077	TCE	60	15	26	26
5	0.5	3	0.154	TCE	100	15	100	200
6	0.5	3	0.154	TCE	80	15	58	116
7	0.1	3	0.770	TCE	100	15	100	1000
8	0.1	2	0.770	TCE	100	15	100	1000
9	0.1	1	0.770	TCE	100	15	57	570
10	0.05	2	1.540	TCE	100	0.5	100	2000
11	0.01	2	3.850	TCE	100	24	100	10000
12	0.05	2	1.540	toluene	100	2	17	340
13	0.05	2	1.540	1,4-dioxane	100	2	6	120
14	0.05	2	1.540	CPME ^[e]	100	2	16 ^[f]	320
15	0.05	2	1.540	anisole	100	0.5	45 ^[g]	900
16	0.05	2	1.540	anisole	100	24	73 ^[h]	1460

[a] yield measured by GC; Ph₃CBArF₂₀: trityl tetra(pentafluorophenyl)borate. [b] TON, turnover number (mol product / mol catalyst). [c] 2 mol% of Ph₃CBArF₂₀ and no pre-catalyst. [d] TCE: 1,1',2,2'-tetrachloroethane. [e] CPME: cyclopentylmethylether. [f] 91% yield in 24h. [g] 100% conversion with 55% of possible iminium species (vide-infra) and 45% of **6a**. [h] 100% conversion with 27% of possible iminium species (vide-infra) and 73% of **6a**.

Whereas the reaction was performed with a 47% yield in 24h using pre-catalyst **3**, we were glad to obtain a quantitative yield of secondary amine **8r** in only 6 hours while applying pre-catalyst **9**. In order to understand such a ligand effect on the catalyst activity, we put all our efforts into investigating the mechanism of these Ir(III) catalysed hydrosilylation reactions.

As a preliminary study regarding the possible active intermediate species involved in the catalytic process and the mechanism of such hydrosilylation reaction, we performed analyses by electrospray ionization mass spectrometry (ESI-MS) in acetonitrile of the crude reaction mixture issued from the hydrosilylation of tertiary amide **5a** at 100°C in 30 minutes (Table 3, entry 1 and the Supporting Information Figures S1-S4). The hydrolysed tertiary amine product **6a** was clearly identified and dechlorinated Ir(III) complex **10b** could be deduced through the observed cationic fragments **10b₁-b₃** combined with BArF₂₀ anion, with or without coordination of acetonitrile which was the solvent used for the analyses (Figures S2-S4). Hence, though the reaction mixture was not quenched, the simple use of wet acetonitrile for the solvation of the mass analysis sample led to the hydrolysis of the hydrosilylated reaction product and afforded amine **6a**. In addition, the mass analysis conditions did not allow any iridium-hydride complex to be observed, probably because of the possible ionisation of such species during the analysis or because of reaction with water and air atmosphere. A further analysis by ESI-MS of the crude mixture resulting from the hydrosilylation of reagent **5a** in anisole allowed us to observe a mixture of tertiary amine product **6a** and iminium species **C** (Figure S1, Scheme 2). Though the latter was already suggested as a key transient intermediate in amide

hydrosilylation reactions,^[5] it was, to the best of our knowledge, never evidenced before.

Regarding the reaction mechanism, a ionic hydrosilylation^[7] pathway could be presumed. However, some of us had already shown through a combination of organometallic syntheses and DFT calculations a cohesive hydrido-iridium(III) → silylium donor-acceptor complex could exist.^[8] Hence, we assumed our reaction pathway could differentiate from the others^[4,7] by the activation mode of the silane. Thermochemical data inferred from singlet state gas phase DFT-D calculation (ZORA-PBE-D3(BJ)/all electron TZP basis set) provided a solid basis for establishing a reasonable mechanistic scheme (Scheme 2) of the therein reported catalysis particularly for its initiation stage. For convenience we extended our considerations to precatalysts **1**, **3** and **9**. The computed thermochemistry clearly suggested that the necessary dechlorination of precatalyst **3** to yield putative electron deficient cationic intermediate **10b** results from a reaction with an in-situ-produced form of a stabilised silylium cation generated by the reaction of the tritylium cation with the silane reagent.^[9] For instance, the reaction of Et₃SiH with Ph₃C⁺ is expected to produce triphenylmethane and cation [Et₃Si-H-SiEt₃]⁺ according to Heinekey,^[9a] with a Gibbs enthalpy of -9 kcal/mol according to our DFT-D computations (Scheme 2, Scheme 3a). Worthy to note, the hypothesis of the formation of an elusive “naked” trigonal planar silylium cation^[10] by the stoichiometric 1:1 reaction of the tritylium with Et₃SiH was ruled out owing to its high endoergonicity (ΔG₂₉₈= +17 kcal/mol). The dechlorination of **3** by [Et₃Si-H-SiEt₃]⁺ to give intermediary **10a**, Et₃SiCl and Et₃SiH was found

Table 3. Hydrosilylation of tertiary amides catalysed by iridacycle **3**.

$$\text{R}^1\text{-C(=O)-N(R}^2\text{)(R}^3\text{)} + \text{TMDS} \xrightarrow[\text{TCE, 100 }^\circ\text{C, } t \text{ (h) then hydrolysis}]{\text{pre-cat. Ir } \mathbf{3} \text{ 0.05 mol\% Ph}_3\text{CBArF}_{20} \text{ 0.1 mol\%}}$$

$$\text{R}^1\text{-CH}_2\text{-N(R}^2\text{)(R}^3\text{)}$$

Entry	Amide	R ¹	R ²	R ³	t (h)	Yield ^[a] (isolated yield %) ^[b]
1	5a	Ph	Bn	Bn	0.5	6a 100 (92)
2	5b	Ph	Me	Me	0.5	6b 100 (96)
3	5c	Ph	Ph	Ph	2	6c 100 (80)
4	5d	Ph	Ph	Me	0.5	6d 100 (93)
5	5e	Ph	Bn	Me	0.5	6e 100 (97)
6	5f	Ph	-(CH ₂) ₂ -O-(CH ₂) ₂ -		0.5	6f 100 (87)
7	5g	1-furane	Bn	Bn	0.5	6g 100 (99)
8	5h	Cy	Bn	Bn	8	6h 83 (81)
9	5i	Ph	-(CH ₂) ₅ -		8	6i 85 (82)
10	5j	H	-(CH ₂) ₅ -		6	6j 100 (99)
11	5k	-(CH ₂) ₄ -		Bn	2	6k 100 (45)
12	5l	PhCH ₂ CH ₂ -	Bn	Bn	2	6l 100 (92)
13	5m	Et	Bn	Bn	24	6m 49 ^[c] (39)
14	5n	<i>i</i> Pr	Bn	Bn	48	6n 78 (60)
15	5o	Ph	<i>i</i> Pr	<i>i</i> Pr	48	6o 81 (65)
16	5p	(<i>o</i> -MeO)C ₆ H ₄ -	Bn	Bn	48	6p 79 (69)
17	5q	(<i>p</i> -MeO)C ₆ H ₄ -	Bn	Bn	8	6q 100 (99)
18	5r	(<i>o</i> -F)C ₆ H ₄ -	Bn	Bn	24	6r 50 (43)
19	5s	(<i>p</i> -F)C ₆ H ₄ -	Bn	Bn	4	6s 99 (92)
20	5t	(<i>p</i> -NO ₂)C ₆ H ₄ -	Bn	Bn	2	6t 93 (77)
21	5u	(<i>p</i> -CN)C ₆ H ₄ -	Bn	Bn	20	6u 98 (91)
22	5v	(<i>p</i> -CO ₂ Me)C ₆ H ₄ -	Bn	Bn	24	6v 100 (90)

[a] Yield measured by GC. [b] Isolated yield after flash chromatography.

[c] **6m** along with 17% of dibenzylamine resulting from the hydrolysis of the related iminium intermediate.

in this case to be largely exoergonic with a Gibbs enthalpy of -31 kcal/mol (Scheme 3b).

The alternative dechlorination of **3** by the tritylium was found to be endoergonic with a Gibbs enthalpy ΔG_{298} of ca. +6 kcal/mol and was therefore not considered further. The reaction of iridium catalyst **10b** with Et₃SiH produces the silane-iridium adduct **11b** with a Gibbs enthalpy of -13 kcal/mol (Scheme 3c).^[10,11] Worthy to note here the production of **11b** is by ca. 5 kcal/mol less exoergonic, that is less favorable than those of the adducts resulting from **1** and **9**, i.e. **11a** and **11c**. Still, the silylium fragment has a greater affinity for the hydrido-iridium unit in **11c** than in **11a** and **11b**, the latter two displaying identical relative silylicity (Scheme 3d). It must be pointed out here that ongoing research is focused on the mechanism of formation of intermediates **11** from **10** that will be disclosed elsewhere: preliminary results from DFT investigations point to a barrier-less process corresponding to a concerted hydride transfer and silylium trapping from Et₃Si-H.

The term silylicity proposed here is more general than the specific TMSA (Trimethyl silyl affinity) introduced by Villingier et al. for computing thermodynamic parameters of model

reaction implying the formation of molecular complexes of the trimethylsilylium cation;^[10a] silylicity characterises in analogy with hydricity^[11] the capability of a given silyl-metal complex to release a silylium group.

The isodesmic reaction depicted in Scheme 3d shows the hypothetical transfer of silylium from **11b** and **11c** respectively towards **12a**, which is nearly isoergonic for the former pyridyl derivative and endoergonic by ca. 4 kcal/mol for the latter quinoline derivative. This higher affinity of the silylium group for the hydrido-iridium unit in **11c** cannot be exclusively assigned to the strong donor effect of the *N,N*-dimethylamino group because such an effect is not observed with **11b**. We speculate that the non-coplanarity of the aryl fragments in the quinoline derivative **11c** might restrict the extent of the mesomeric electron delocalisation operated by the amino group towards the quinoline group, allowing a slightly larger charge density to concentrate at the metal centre than in the pyridyl analogue **11b**, which contains a planar iridacycle. A Ziegler-Rauk energy decomposition analysis (EDA)^[12] was performed on **11a**, **11b** and **11c** to probe the intrinsic bonding energy of the silylium Et₃Si⁺ cation, or intrinsic silylicity, with the hydrido-iridium fragment; it shows clearly that the interaction energy ΔE_{int} of

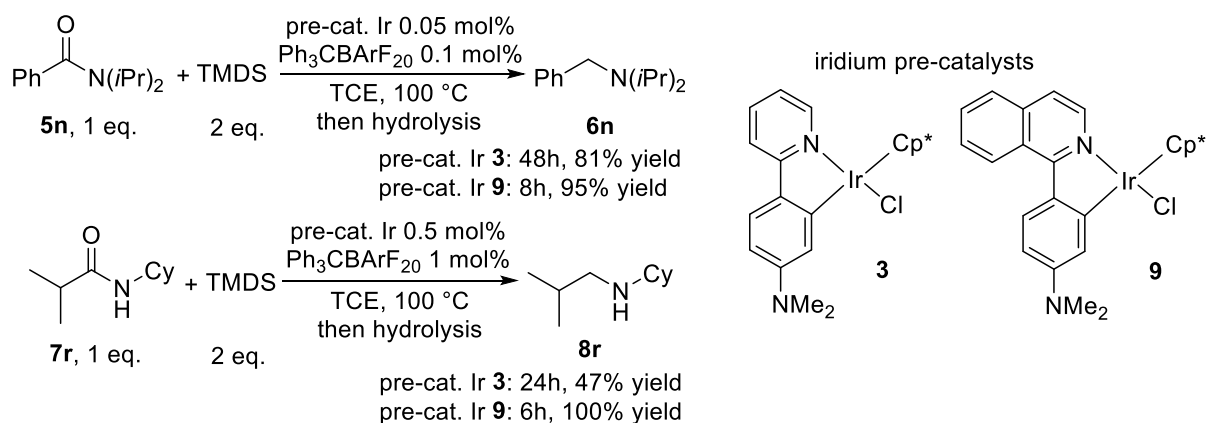
Table 4. Hydrosilylation of secondary amides catalysed by iridacycle **3**.

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{R}^1-\text{C}-\text{N}-\text{R}^2 \\
 | \\
 \text{H} \\
 \mathbf{7a-t} \text{ 1 eq.}
 \end{array}
 + \text{TMDS} \text{ 2 eq.}
 \xrightarrow[\text{TCE, 100 }^\circ\text{C, t (h)}]{\text{pre-cat. Ir } \mathbf{3} \text{ 0.5 mol\%}}
 \xrightarrow[\text{then hydrolysis}]{\text{Ph}_3\text{CBArF}_{20} \text{ 1 mol\%}}
 \begin{array}{c}
 \text{R}^1-\text{CH}_2-\text{N}-\text{R}^2 \\
 | \\
 \text{H} \\
 \mathbf{8a-t}
 \end{array}$$

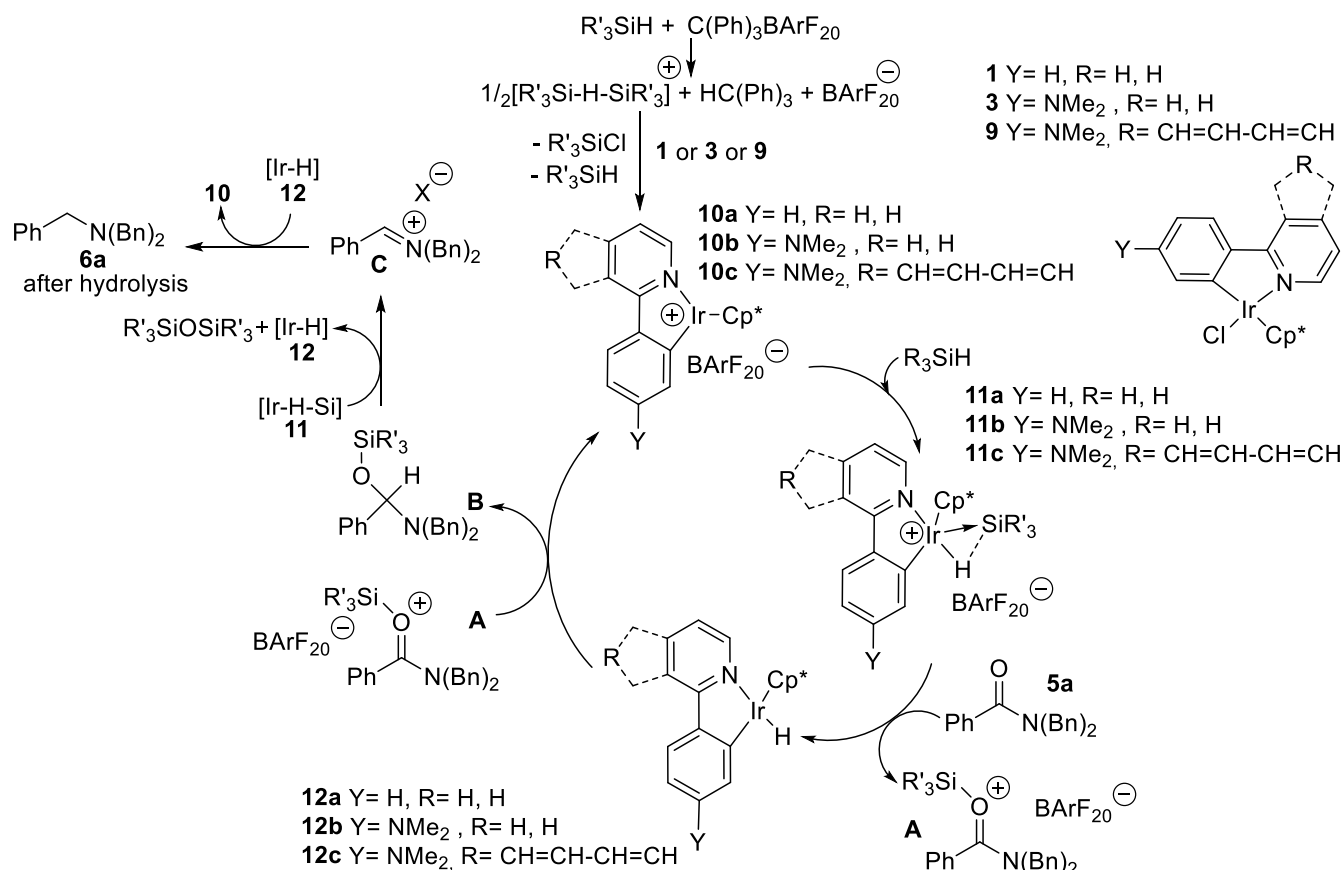
Entry	Amide	R ¹	R ²	t (h)	Yield ^[a] (isolated yield %) ^[b]
1	7a	Ph	Bn	0.5	8a 100 (quant.)
2	7b	Ph	Me	0.5	8b 100 (85)
3	7c	Ph	<i>t</i> Bu	24	8c 49 (46)
4	7d	Ph	allyl	0.5	8d 100 (82)
5	7e	Ph	-CH ₂ -1-thiophene	0.5	8e 100 (86)
6	7f	Ph	cyclohexyl	2	8f 47 (45)
7	7g	Ph	Ph	0.5	8g 98 (92)
8	7h	Ph	(<i>p</i> -MeO)C ₆ H ₄	0.5	8h 100 (96)
9	7i	Ph	(<i>p</i> -F)C ₆ H ₄ -	0.5	8i 96 (75)
10	7j	Ph	(<i>o</i> -Et)C ₆ H ₄ -	8	8j 83 (82)
11	7k	(<i>o</i> -MeO)C ₆ H ₄ -	Bn	2	8k 94 (76)
12	7l	(<i>p</i> -MeO)C ₆ H ₄ -	Bn	0.5	8l 96 (96)
13	7m	(<i>o</i> -F)C ₆ H ₄ -	Bn	0.5	8m 99 (86)
14	7n	(<i>p</i> -F)C ₆ H ₄ -	Bn	0.5	8n 100 (quant.)
15	7o	1-furane	Bn	0.5	8o 100 (79)
16	7p	PhCH ₂ CH ₂ -	Bn	0.5	8p 100 (quant.)
17	7q	cyclohexyl-	Bn	24	8q 68 (44)
18	7r	<i>i</i> Pr	cyclohexyl	24	8r 47 (40)
19	7s	<i>i</i> Pr	Bn	48	8s 81 (65)
20	7t		-(CH ₂) ₄ -	2	8t 100 (76)

[a] Yield measured by GC. [b] Isolated yield after flash chromatography.

Scheme 1. Improved catalyst for the reduction of tertiary and secondary amides.

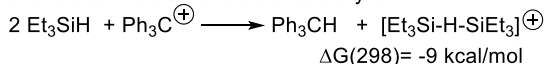


Scheme 2. Proposed catalytic cycle for the reduction of tertiary and secondary amides.

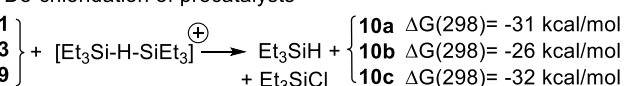


Scheme 3. Thermochemical data computed (298.15 K) at the ZORA-PBE-D3(BJ)/all electron TZP level with gas phase ground state molecules devoid of counter anion BARF₂₀.

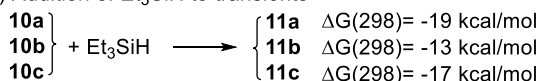
a) Silane's conversion to a stabilised silylium



b) De-chloridation of precatalysts

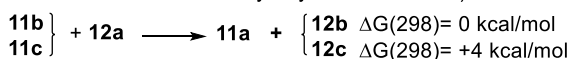


c) Addition of Et₃SiH to transients **10a-c**

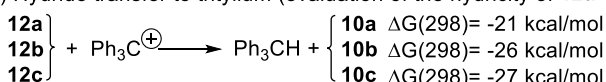


d) Isodesmic silylium transfer reaction

(evaluation of the relative silylicity of **11a** and **11c**)



e) Hydride transfer to tritylium (evaluation of the hydricity of **12a-c**)



the silylium group with the neutral hydrido-iridium fragment is by ca. 8 kcal/mol stronger in **11b** ($\Delta E_{\text{int}} = -127 \text{ kcal/mol}$)

and in **11c** ($\Delta E_{\text{int}} = -127 \text{ kcal/mol}$) than in **11a** ($\Delta E_{\text{int}} = -119 \text{ kcal/mol}$). Consistently the total natural charge (Natural Population Analysis) borne by the Et₃Si group in **11a** ($q = +0.29$) is slightly higher than that in **11b** ($q = +0.25$) for example.

In the framework of the mechanism depicted in Scheme 2, adducts **11a-c** are sources of hydrido-iridium intermediates **12a-c** and silylium cation R₃Si⁺.^[9,10,13] The latter may activate the carbonyl group of amide substrate **5a** and generate silyloxy carbonium species **A**. At this stage, elimination of a silyloxy fragment may be helped by any electrophilic species present in the medium to lead to the iminium intermediate **C**. The latter can then react with a second equivalent of the iridium hydride complex **12** and affords the amine product **6a** along with the cationic iridium catalytic species **10** (Scheme 2). As mentioned in Table 2 (entries 8, 9), 2 equivalents of TMDS were added in order to get a quantitative hydrosilylation of amide **5a**. At the end of reaction, we could isolate the silicon residue from the resulting crude mixture. Interestingly, a ¹H NMR analysis revealed the presence of a hydride silicon species and suggested only one hydride from the two of TMDS reagent may participate to the reaction (see the Supporting Information Figures S5, S6). Further characterisation by ESI-MS of such a silicon residue formed at the end of reaction showed several silicon compounds were formed during the catalysis (Figure S7).

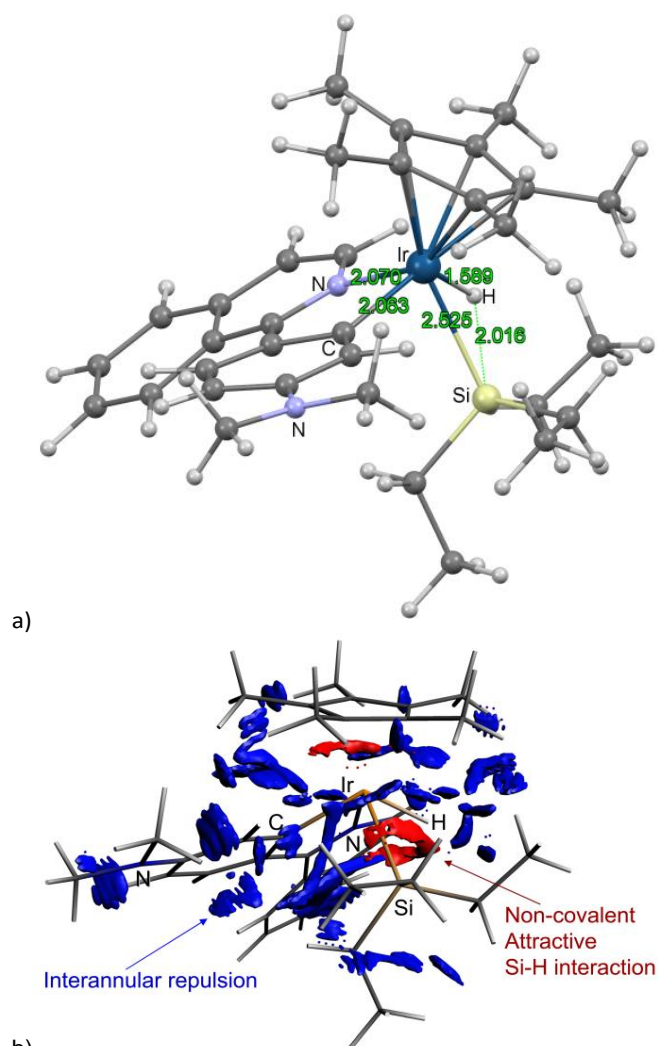


Figure 1. a) Gas phase singlet state geometry of **11c** optimised at the ZORA-PBE-D3(BJ)/all electron TZP level (interatomic distances printed in green are expressed in Å); b) Similarly to **11b** the NCI plot^[14] of **11c** depicts a rather non-covalent attractive H...Si interaction in this computed model were covalent and donor acceptor interactions are identical to those already pointed out for **11b**^[14]; ADFview2013 plot of non-covalent interaction (NCI) regions (ZORA-PBE-D3(BJ)/ae-TZP) materialised by reduced density gradient isosurfaces (cut-off value $s = 0.02$ a.u., $\rho = 0.05$ a.u.) colored according to the sign of the signed density $\lambda_2\rho$, that is red (attractive) and blue (Pauli repulsive or non-bonded van der Waals) isosurfaces are associated with negatively and positively signed terms respectively.

Addressing the difference in reactivity of the two amino-substituted precatalysts **3** and **9** as compared to **1** is a difficult task in such a catalysis where a great number of species like substrate and cocatalysts coexist. Nevertheless, even though further efforts will be needed in the future, thermochemistry of possible reactions can be calculated by DFT computations and offer sufficient clues to attempt a rationalisation. At this stage, assuming the reactions to be mostly driven by favourable initiation and catalytic event under thermodynamic control, we can only elaborate on four points of crucial importance that are the readiness of: 1) the precatalyst's dechlorination, 2) the reaction of silane with transient **10** to give **11**, 3) silylium abstraction from **11**, and 4) the hydride transfer from the hydrido-Ir transient.

Point 1: all three pre-catalysts **1**, **3** and **9** can be dechlorinated readily, with a somewhat larger exoergonicity for **3** and **9** (Scheme 3b).

Point 2: **10a** gives less exo-ergonically a silane-iridium adduct than **10c** (Scheme 3c); this rather counter-intuitive result can be explained by the major inter-annular tensions that exist within **10c** and which are somewhat released upon return of the Ir(III) center to a hepta- or hexa-coordinate geometry like in **11c** and **12c** respectively (Figure 1). According to the X-ray structure determination, it is worth to note inter-annular tensions are also observed for chlorinated pre-catalyst **9** (Figure S8).

Point 3: **11a** and **11b** have nearly the same relative silylicity ($\Delta G = 0$ kcal/mol, Scheme 3d) whereas **11c** displays a lower one ($\Delta G = +4$ kcal/mol, Scheme 3d and Figure 1).

Point 4: both **12a** and **12c** display similar hydricity (Scheme 3e and Figure 1).

It seems therefore tempting to state that the outstanding performance of **9** could be related to the easier formation of silane-iridium adduct **11c** combined with its relatively lower silylicity and to a relatively higher hydricity of its related hydrido complex **12c**. A high hydricity is intuitively related to a faster reduction of an electrophile of reference. A slightly lower relative intrinsic silylicity might sensibly contribute in decreasing the weight of the pathway detrimental to the catalysis that entails the formation of catalytically inactive μ -hydrido bridged bis-iridium species. It was shown that such species are formed almost unavoidably in rather large amounts when a cationic solvato-iridacycle derived from 2-phenylpyridine is treated with Et_3SiH at room temperature.^[8]

Conclusions

To summarise, we have described a highly efficient catalytic process for the hydrosilylation of tertiary and secondary amides. The combination of an accessible Ir(III) metallacycle complex and trityltetra(pentafluorophenyl)borate in the presence of 1,1,3,3-tetramethyldisiloxane allowed, at low loadings, the chemoselective reduction of a large array of amide substrates in high yields and turnover numbers tolerating a wide range of substituents. According to DFT calculations, silane-iridium adduct is a source of hydrido-iridium intermediate and silylium cation. The latter activates the carbonyl group of the amide substrate and generates a silyloxy carbonium species. Reaction with a first equivalent of the iridium hydride complex affords silyl hemiacetal along with the cationic catalytic species. The further elimination of silyloxy fragment leads to an iminium intermediate which has been observed by mass spectrometry for the first time. Reaction with a second equivalent of the iridium hydride complex affords the amine product along with the cationic catalytic species. On the whole, the work described herein demonstrates the reactivity of Ir(III) metallacycles can be improved through proper ligand modifications to allow the straightforward catalytic hydrosilylation of challenging amide substrates. Such developments foresee clearly future broad and significant applications of catalysts based on metallacycles.

Experimental Section

General Procedure for the catalysis

In a Schlenk tube, amide reagent (1.54 mmol, 1 eq.) and iridium (III) catalyst (0.05 mol%, 0.0005 eq.) are introduced. BARF salt (0.1 mol%) is then added in a glovebox. Under nitrogen, 1 mL of TCE and TMDS (2 eq.) are transferred by syringe and the reaction mixture is heated at 100 °C under stirring for 2 hours (the Schlenk tube being closed under N₂). Afterwards, the solvent is evaporated under vacuum (using a Schlenk line) and the reaction mixture is hydrolysed following method A or B.

Method A: acid hydrolysis (examples: hydrosilylation of amines 5a, 5b, 5e, 5f, 5g). After complete evaporation of the solvent, the reaction mixture is diluted with diethylether (4 mL) and HCl 4M (4 mL) is added. The resulting solution is stirred vigorously during 10 minutes to afford the protonated amine as a precipitate which was recovered by filtration and washed with diethylether. The resulting solid was then dissolved in CH₂Cl₂ and neutralized with an aqueous solution of NaOH 1M (for tertiary amines) or of saturated NaHCO₃ (for secondary amines) until pH > 7. After extraction (3 times with CH₂Cl₂), the organic phase was dried with MgSO₄ and evaporated to afford the desired amine.

Method B: basic hydrolysis (examples: hydrosilylation of amines 5c, 5d). After complete evaporation of the solvent, the reaction mixture is diluted with methanol (4mL) and NaOH 1M (4 mL) is added. After extraction (3 times with Et₂O), the organic phase was dried with MgSO₄ and evaporated to afford the desired amine which was further purified by flash chromatography using mixtures of petroleum ether and ethyl acetate with 5% NEt₃.

Computational details

Computations were performed with methods of Density Functional Theory, i.e the PBE^[15] GGA functional implemented in the Amsterdam Density Functional package (ADF2013^[16] version) and augmented with Grimme's DFT-D3(BJ)^[17] implementation of dispersion with a Becke-Johnson (BJ) damping function. Scalar relativistic corrections with the Zeroth Order Regular Approximation^[18] were applied with ad hoc all-electron (AE) basis sets consisting of polarised triple- ζ (TZP) Slater type orbitals. Geometry optimisation by energy gradient minimisation was carried out in all cases with a numerical grid accuracy comprised between 4.5 and 8, an energy gradient convergence criterion of 10⁻³ au and a very tight SCF convergence criterion. Vibrational modes were computed to verify that the optimised geometries were related to energy minima not considering residual modes comprised between 0 and 100i cm⁻¹. Fragment interaction energies were extracted from a conventional Energy Decomposition Analysis according to the Ziegler-Rauk method implemented in ADF.^[11] By extension, intrinsic hydricity and silylicity have been determined by considering the disruption of a hydrido-metal and silyl-metal intermediate by conferring to the hydrogen a negative charge (hydride) and to the silyl fragment a positive charge (silylium in its prepared geometry). This arbitrary choice of fragmentation, although artificial, gives an intuitive direct access to the intrinsic affinity of the metal center for those ligands that are suspected to play a central role in the catalysis depicted here according to a recent report.^[8]

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Keywords: iridium • metallacycles • hydrosilylation • amides • amines.

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