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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Iridium-Catalyzed Reduction of Secondary Amides to Secondary Amines and Imines by Diethylsilane

Chen Cheng and Maurice Brookhart*

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

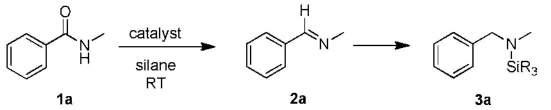
Supporting Information

ABSTRACT: Catalytic reduction of secondary amides to imines and secondary amines has been achieved using readily available iridium catalysts such as $[Ir(COE)_2Cl]_2$ with diethylsilane as reductant. The stepwise reduction to secondary amine proceeds through an imine intermediate that can be isolated when only 2 equiv of silane is used. This system requires low catalyst loading and shows high efficiency (up to 1000 turnovers at room temperature with 99% conversion have been attained) and an appreciable level of functional group tolerance.

Reduction of carboxamides is an attractive route to amines.[1] Although amides are the least reactive species among carbonyl compounds toward hydride addition, reduction of amides to amines can be achieved using stoichiometric metal hydride reducing agents such as $LiAlH_4$.[2] However, these reagents suffer from drawbacks such as limited functional group tolerance and air and moisture sensitivity.[3] Alternative methods include metal-free reduction of tertiary and secondary amides with high chemoselectivity using triflic anhydride as the activating reagent and both triethylsilane and Hantzsch ester as hydride sources.[4] Catalytic reduction of tertiary amides has been achieved using various metal catalysts and hydrosilanes as the reductant.[5] Catalytic reduction of secondary amides to secondary amines, however, has not been extensively explored.[6] For example, Nagashima reported a ruthenium cluster catalyst that produces either secondary or tertiary amines depending on the silane used.[6c] Beller has described a method using readily available zinc catalysts at high catalyst loading (20 mol%).[6d] Ohta also reported reduction of a limited number of secondary amides with Rh(I) catalysts to give a mixture of amines and imines in moderate yields.[6a] Recently we reported a highly efficient iridium pincer catalyst for reduction of tertiary amides,[5i] but the same system cannot be applied to secondary amides. Here we report catalytic reduction of secondary amides to either imines or secondary amines with high efficiency using a commercially available iridium complex, $[Ir(COE)_2Cl]_2$.

Since several group 8 and 9 metal complexes are known to catalyze addition of hydrosilanes across C=O double bonds,[5a,6a,c,7] we investigated the catalytic reactivity of some simple rhodium and iridium complexes with respect to hydrosilylation of *N*-methylbenzamide (**1a**). Using Et_2SiH_2 (4 equiv) and $[Ir(COE)_2Cl]_2$ (0.5 mol %) at room temperature in nonpolar solvents such as C_6D_6 or CD_2Cl_2, **1a** was converted to imine **2a** in 5 min and subsequently to amine **3a** within 12 h (Table 1, entries 1 and 2). Hydrogen evolution was observed upon mixing the reagents and confirmed by GC analysis. Coordinating solvents such as THF inhibit the reaction (entry 3). Other iridium(I) bis-olefin complexes showed similar or lower reactivities (entries 5 and 6). One rhodium analogue was screened but proved ineffective (entry 7). Using tertiary silanes such as Et_3SiH or tetramethyldisiloxane led to an unidentified product (entries 8 and 9).

Table 1. Catalyst Screening Experiments for Reduction of 1a



entry	catalyst (mol%)	silane (equiv)	solvent	time (h)	yield (%)^{a}
1	$[Ir(COE)_2Cl]_2$ (0.5)	Et_2SiH_2 (4)	C_6D_6	12	98
2	$[Ir(COE)_2Cl]_2$ (0.5)	Et_2SiH_2 (4)	CD_2Cl_2	11	98
3	$[Ir(COE)_2Cl]_2$ (1)	Et_2SiH_2 (4)	THF-d_8	22	80
4	$[Ir(COE)_2Cl]_2$ (0.5)	Et_2SiH_2 (4)	–^{b}	7	98
5	$[Ir(COD)(OMe)]_2$ (0.5)	Et_2SiH_2 (4)	C_6D_6	14	85
6	$[Ir(COD)Cl]_2$ (1)	Et_2SiH_2 (4)	C_6D_6	12	99
7	$[Rh(COE)_2Cl]_2$ (1)	Et_2SiH_2 (4)	C_6D_6	9	33
8	$[Ir(COE)_2Cl]_2$ (0.5)	Et_3SiH (4)	C_6D_6	34	–^{c}
9	$[Ir(COE)_2Cl]_2$ (0.5)	TMDS^{d} (2)	C_6D_6	48	–^{c}

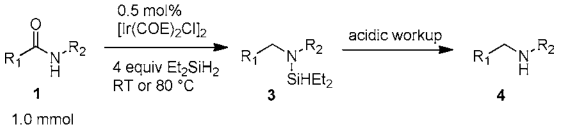
Reaction conditions: catalyst in 0.35 mL of solvent with 0.1 mmol of *N*-methylbenzamide and silane. Reactions were run at room temperature. ^{a}Yield of **3a** determined by ^{1}H NMR. ^{b}Run in neat silane. ^{c}Unidentified product. ^{d}Tetramethyldisiloxane.

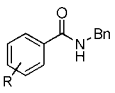
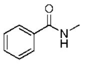
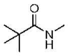
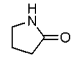
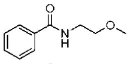
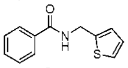
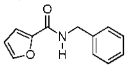
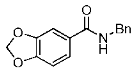
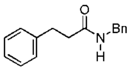
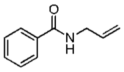
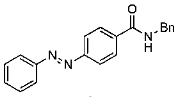
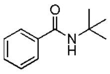
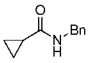
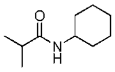
Although most secondary amides have limited solubility in Et_2SiH_2, rapid conversion to the much more soluble imines allows running the reaction in neat silane (Table 1, entry 4). Applying this condition to various secondary amides gave the corresponding *N*-silyl amines (Table 2). Aqueous HCl workup followed by neutralization afforded secondary amines **4** in good to excellent yields. This method is compatible with substrates bearing various functionalities including aryl halides, alkyl halides, ethers, heterocycles, azo and amino groups, and alkenes. High catalytic efficiencies were achieved; for example, turnovers up to 1000 at room temperature with 99% conversion were recorded for **1b** (entry 2). This system is not compatible with nitro groups and the catalytic rate is severely retarded by nitrile groups. Reaction with nitro-substituted **1i** led to unidentified products, whereas reaction with nitrile-containing **1h** resulted in full conversion to the imine but only low conversion (24%) to the amine after 50 h.[8] Reduction of amide **1s** bearing a bulky *tert*-butyl

Received: February 5, 2012
Published: July 6, 2012

dx.doi.org/10.1021/ja304547s | *J. Am. Chem. Soc.* 2012, 134, 11304−11307

Table 2. Reduction of Secondary Amides to Secondary Amines



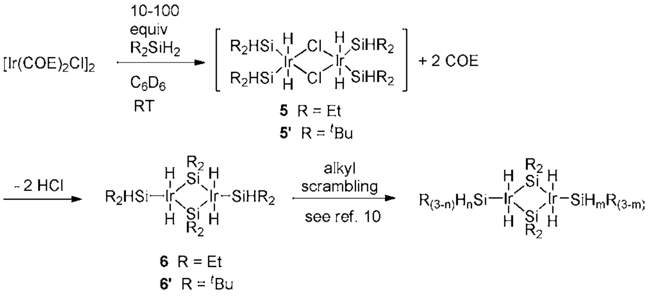
entry	substrate		T (°C)	time (h)	conversion (%)[a]	yield (%)[b]
1		**1b** R=H	23	2	>99	99(91)
2[c]		**1b** R=H	23	40	99	98(92)
3[d]		**1b** R=H	80	2	>99	98
4		**1c** R=4-F	80	1	>99	97(88)
5		**1d** R=4-Br	80	3	>99	98(79)
6		**1e** R=4-I	80	15	>99	97(76)
7[e]		**1f** R=4-N(Me)$_2$	23	6	>99	98(68)
8		**1g** R=3,5-(CF$_3$)$_2$	23	12	>99	98(85)
9[f]		**1h** R=4-CN	80	50	24	16
10[f]		**1i** R=4-NO$_2$	23	-	-	-[g]
11		**1a**	23	7	>99	98(67[h])
12		**1j**	80	72	97	85(65[i])
13		**1k**	80	12	>99	- (90[i])
14		**1l**	23	5	>99	92(75)
15		**1m**	80	2	>99	98(87)
16		**1n**	23	5	>99	90(83)
17		**1o**	80	30	>99	97(90)
18		**1p**	23	1	>99	95(84)
19		**1q**	23	24	>99	94(75[h])
20[e]		**1r**	80	36	95	88(80)
21[j]		**1s**	23	5	>99	96(74[h])
22		**1t**	23	1	>99	94(75)
23		**1u**	80	1	>99	90(81[h])

Reaction conditions: amide (1.0 mmol) with 4.5 mg (5.0 μmol) of [Ir(COE)$_2$Cl]$_2$ in 350 mg (4.0 mmol) of Et$_2$SiH$_2$. Reactions were run at room temperature or 80 °C. [a]Determined by ^{1}H NMR. [b]Yields of **3** determined by ^{1}H NMR. Numbers in parentheses are isolated yields of **4**. [c]Reaction run on a 5.0 mmol substrate scale with 2.5 μmol (0.05 mol%) of catalyst (0.1 mol% Ir). [d]Reaction run on a 0.1 mmol substrate scale in 0.35 mL of C$_6$D$_6$ in the presence of 0.1 mmol of benzyl bromide. At the end of the reaction benzyl bromide remained unreacted. [e]C$_6$H$_6$ (0.5 g) was added as cosolvent. [f]Reaction run on a 0.1 mmol substrate scale in 0.35 mL of C$_6$D$_6$. [g]Unidentified products. [h]Product is somewhat volatile. [i]Product isolated as the HCl salt. [j]6 mg (0.6 mol%) of Et$_3$NH$^+$BArF$^-$ was added at 3 h.

group requires a catalytic amount of an acid, Et$_3$NH$^+$BArF$^-$ (BArF$^-$ = B[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_4$$^-$), as additive.[9] For some substrates bearing heteroatoms, the reactions were slow at room temperature probably due to the coordinating effect of O, N, S, and halides, and the reactions were run at 80 °C to achieve rapid conversion.

To investigate the resting state of the catalyst, [Ir(COE)$_2$Cl]$_2$ was treated with ~100 equiv of Et$_2$SiH$_2$ in C$_6$D$_6$. Immediately after mixing of the reagents at room temperature, a major hydride signal at −12.98 ppm was observed, together with two low-field signals at 131.86 and 130.27 ppm in the ^{29}Si NMR spectrum, suggestive of a silylene-bridged iridium dimer **6** formed via intermediate **5** (Scheme 1).[10] In contrast to our previous report in which [Ir(COE)$_2$Cl]$_2$ was reacted with Et$_3$SiH, the chloride-bridged dimer **5** was not observed in this case.[10] With time, the major hydride signal at −12.98 ppm decreased in intensity and multiple hydride signals in the −11 to −14 ppm region appeared, which is likely caused by silane scrambling catalyzed by **6** (Scheme 1).[10] Although a single crystal of **6** could not be obtained, a model complex, **6′**,[11] derived from (^{t}Bu)$_2$SiH$_2$ was characterized by X-ray crystallography (Figure 1). While the iridium hydrides in Scheme 1 are shown as terminal hydrides they could not be located by X-ray diffraction, so bridging hydride structures cannot be ruled out, nor can binding of the terminal silanes in an η^2-fashion.[12] The short Ir−Ir distance (2.896 Å) suggests significant Ir−Ir interaction.[13]

Scheme 1. Formation of the Proposed Catalyst Resting State



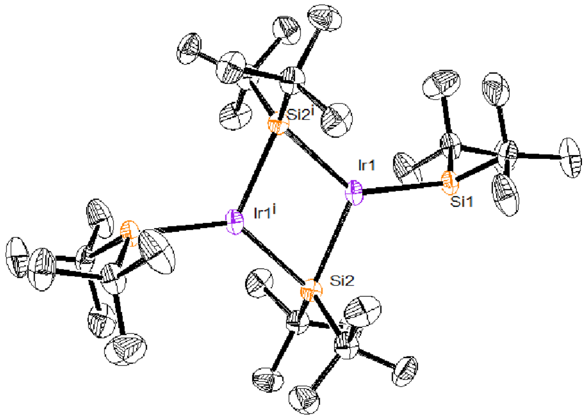
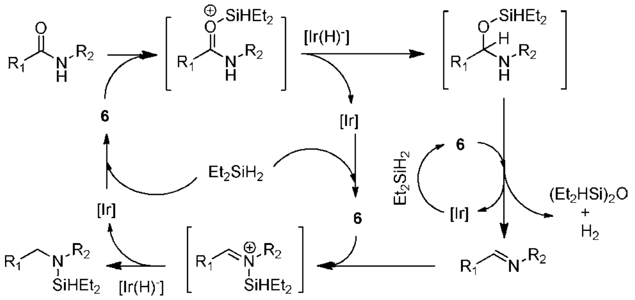


Figure 1. ORTEP drawing of **6′** at the 50% probability level. The molecule lies on a center of symmetry. Selected bond lengths (Å) and angles (deg): Ir(1)−Si(1) 2.408, Ir(1)−Ir(1′) 2.896, Ir(1)−Si(2) 2.410; Si(1)−Ir(1)−Si(2) 133.4, Ir(1)−Si(2)−Ir(1′) 73.2, Si(2)−Ir(1)−Si(2′) 106.7. Hydrogen atoms were omitted for clarity.

We propose that **6** catalyzes reduction of amides by consecutive hydrosilylations across the C=O and C=N bonds (Scheme 2).[14] Following the first hydrosilylation of the C=O bond that yields the hemiaminal, elimination of silanol gives the imine.[15]

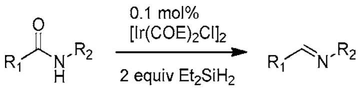
Scheme 2. Proposed Mechanism for Iridium-Catalyzed Reduction of Secondary Amides to *N*-Silylamines



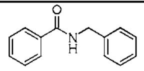
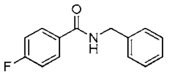
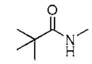
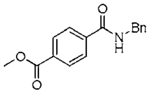
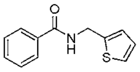
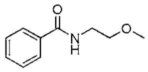
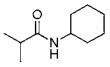
Complex **6** then catalyzes the addition of a second equivalent of silane across the imine C═N bond to give the *N*-silyl amine. In both steps the hydrosilylation is proposed to proceed by electrophilic addition of "Et_2SiH^+" followed by hydride attack at carbonyl carbon, supported by competition experiments showing that the electron-deficient substrate **1g** reacts much slower than **1b** (see Supporting Information). Following hydrosilylations, oxidative addition of Et_2SiH_2 to the iridium center regenerates the iridium silyl hydride moiety.

Because of the stepwise nature of the amide reduction and the large rate difference between the two hydrosilylations, imines can also be directly accessed by using 0.1 mol% of $[Ir(COE)_2Cl]_2$ and exactly 2 equiv of Et_2SiH_2 at room temperature (Table 3).[16]

Table 3. Reduction of Secondary Amides to Imines



1 **2**

entry	substrate		time (h)	yield (%)[a]
1		**1b**	0.2	99(86)
2		**1c**	0.5	99(77)
3[b]		**1j**	5	97
4		**1v**	1	98(63)
5		**1m**	1	98(79)
6		**1l**	0.2	98(71)
7[b]		**1u**	0.5	95

Reaction conditions: amide (1.0 mmol) in CH_2Cl_2 (3 mL) with $[Ir(COE)_2Cl]_2$ (1.0 μmol) and Et_2SiH_2 (2.0 mmol). Reactions were run at room temperature. [a]Determined by ^1H NMR. Numbers in parentheses are isolated yields of **2**. [b]Reaction run on a 0.1 mmol substrate scale in 0.35 mL of C_6D_6.

Interestingly, for amide **1v** bearing an ester group, clean reduction to the imine took place with little hydrosilylation of the ester carbonyl bond (entry 4).[17] Imines can also be conveniently transformed to aldehydes, thus increasing the usefulness of this catalytic reduction.

In summary, we report a highly efficient method for catalytic reduction of secondary amides to imines and secondary amines using diethylsilane as reductant. Side products are minimal and high efficiencies have been achieved. The simple preparation of the catalysts, mild reaction conditions, simple product isolation, and tolerance toward many functional groups render this system an attractive route for accessing secondary amines, imines, and aldehydes from secondary amides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, product characterization, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mbrookhart@unc.edu

Notes

The authors have submitted a provisional patent on this work.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the NSF as part of the Center for Enabling New Technologies through Catalysis (CENTC, Grant No. CHE-0650456).

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(8) Reduction of **1b** in the presence of 1 equiv of $NCCH_3$ or $MeNO_2$ led to results similar to those for reduction of **1h** and **1i**, suggesting that the effect was not caused solely by the electron-withdrawing properties of the nitrile and nitro groups.

(9) Without the acid co-catalyst, the reduction stopped at the imine stage. The acid is thought to activate the imine by protonating the imine nitrogen. Additives were found to be unnecessary in all other substrates screened.

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(11) Prepared by treating $[Ir(COE)_2Cl]_2$ with 15 equiv of $^tBu_2SiH_2$ in C_6D_6. **6′** is poorly soluble in pentane, C_6D_6, CD_2Cl_2, or THF and readily precipitates out of solution as red crystals.

(12) Typical Ir–Si single bond distance ranges from 2.30 to 2.40 Å, which suggests an η^1 Ir–Si bond in **6′**. See: (a) Rappoli, B. J.; Janik, T. S.; Churchill, M. R.; Thompson, J. S.; Atwood, M. J.; Holmes-Smith, R. D.; Stobart, S. R.; Bakshi, P. K.; Cameron, T. S. *Organometallics* **1988**, *7*, 1939–1944. (b) Hays, M. K.; Eisenberg, R. *Inorg. Chem.* **1991**, *30*, 2623–2630. (c) Zarate, E. A.; Kennedy, V. O.; McCune, J. A.; Simons, R. S.; Tessier, C. A. *Organometallics* **1995**, *14*, 1802–1809. (d) Calimano, E.; Tilley, T. D. *J. Am. Chem. Soc.* **2009**, *131*, 11161–11173.

(13) Typical Ir–Ir single bond distance is ca. 2.74–2.81 Å. See: (a) Stuntz, G. F.; Shapley, J. R.; Pierpont, C. G. *Inorg. Chem.* **1978**, *17*, 2596–2603. (b) McDonald, R.; Cowie, M. *Organometallics* **1990**, *9*, 2468–2478. (c) Park, B. K.; Miah, M. A.; Kang, H.; Lee, K.; Cho, Y.-J.; Churchill, D. G.; Park, S.; Choi, M.-G.; Park, J. T. *Organometallics* **2005**, *24*, 675–679.

(14) Complex **6** is stable for hours at room temperature but degrades to unknown complexes upon warming. We have assumed that **6** is the resting state, but it is quite possible that a further reaction product of **6** is the true active hydrosilylation catalyst, especially in reactions run at 80 °C.

(15) Since H_2 is formed, it appears that the iridium complex catalyzes the reaction of the silanol with silane to produce siloxane (an observed product) and H_2. These products could also result from transfer of "Et_2SiH^+" to the hemiaminal, promoting the loss of silanol and forming siloxane and an iminium ion which reacts with the resultant $[IrH]^-$ to form H_2 and imine.

(16) A small fraction of over-reduction to the amines can occur for some substrates and appears to be caused by further reduction of the imines by the byproduct of the amide reduction, $(Et_2HSi)_2O$. Optimization of the reaction time and catalyst loading can avoid or minimize over-reduction.

(17) Adding additional Et_2SiH_2 resulted in hydrosilylation of both the imine and ester.

■ NOTE ADDED AFTER ASAP PUBLICATION

After this paper was published ASAP on July 6, 2012, the note in the Author Information section was amended. The corrected version was posted July 18, 2012.