Reduction of Secondary Carboxamides to Imines

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Received February 12, 1996[⊗]

This article reports in detail on the discovery that zirconium(IV) salts of secondary amides and lactams are transformed by Cp_2ZrHCl to N-substituted imines in one step. The method represents the first controlled reduction of amides and lactams to the corresponding imines, a transformation that is otherwise very difficult to achieve because imines are reduced more rapidly than carboxamides by most metal hydride reagents. No products of reductive cleavage of the carboxamides are observed. Efforts to replace 2 mol equiv of Cp_2ZrHCl with simpler, less costly alternatives led to the finding that a diisobutylaluminum enolate can be substituted for the initial zirconium enolate. Such aluminum amides are smoothly reduced to the corresponding imine using Cp_2ZrHCl in good yield. Moreover, aluminum amides are also reduced to imines using either low-valent titanium species or triethylsilane. In these alternative procedures, use of Cp_2ZrHCl is eliminated altogether in the title transformation.

Introduction

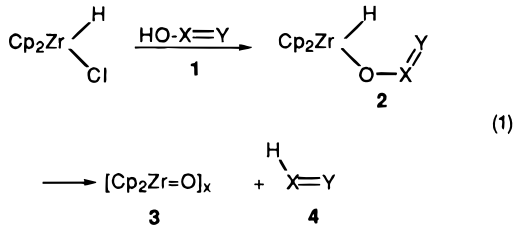
For some time, our laboratory has been interested in developing organometallic-based methods for the reductive deoxygenation of organic compounds. While the well-known reduction of simple heteroatom oxides (e.g. sulfur, selenium, nitrogen, and phosphorus) has been accomplished in numerous ways, relatively few methods are known for deoxygenating carbonyl compounds, which represent the cornerstone of most alkylation and functionalization reactions in synthesis.

We envisioned a method of carbonyl deoxygenation in which functionalized or reactive intermediates might be exploited to extend the utility of such synthetically versatile groups. Our initial efforts focused on early transition metal reagents, whose strong metal−oxygen bonds can provide a powerful driving force for reactions such as McMurry's reductive coupling of carbonyl compounds.[1] Here we present a full account of our earlier work using Cp_2ZrHCl to reduce amides to imines[2] together with variations designed to reduce or eliminate the need for zirconium(IV) reagent.

Background

Many zirconium(IV) complexes are known that are stabilized either with cyclopentadienyl (Cp) or phosphine ligands. To date, much of the synthetically interesting chemistry of such reagents can be grouped into two broad categories. The first, hydrozirconation, is a reaction that, like hydroboration, involves stereoselective *cis*-addition of Cp_2ZrHCl to alkenes and alkynes, whereupon the resulting alkyl or alkenyl−Cp_2ZrCl complexes can undergo useful coupling or alkyl transfer reactions.[3] The second, coupling of alkenes and alkynes to a wide variety of unsaturated ligands via zirconocene (Cp_2Zr) complexes, furnishes highly functionalized carbocyclic and heterocyclic systems.[4] A somewhat related family of C−C bond-forming reactions developed by Erker involves Fischer-type carbene complexes derived from zirconocene.[5]

We envisioned a third mode of reactivity in which deoxygenation of a π-unsaturated organic substrate such as **1** might generally be achieved using organozirconium hydrides (eq 1). For example, by covalently linking the oxygen of **1** directly to the metal center in Cp_2ZrHCl, an ensuing hydride addition (hydrozirconation) might trigger reductive fragmentation of the C−O bond in **2**, driven by the exothermicity of strong Zr/O binding in **3**.



In designing systems to test this hypothesis, we discovered that Cp_2ZrH enolates **6** of β-keto esters **5** (and related β-diketones), readily prepared by reacting the corresponding lithium enolates with Cp_2ZrHCl, were smoothly transformed to α,β-unsaturated esters (or α,β-enones) in good yield (eq 2).[6] Simple ketone enolates were not deoxygenated, suggesting that hydride transfer required an electrophilic alkene. Although the reaction conditions were heterogeneous, and complicated efforts to determine details of the mechanism, the intermediacy of **6** on the pathway to **7** was established by an independent synthesis. One plausible mechanism may involve intermolecular hydrozirconation of enolate **6** followed by β-elimination of a μ-oxodizirconium fragment, examples of which have been reported.[7]

We subsequently demonstrated that zirconium(IV) salts **9** or **10** (eq 3), derived from secondary amides like **8**, were transformed to *N*-substituted imines **11** under similar conditions. Although sensitive to hydrolysis, the desired imines could be isolated in good yield with a nonaqueous workup.[2] This method represents the first

⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1996.

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(4) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261,* 1696.
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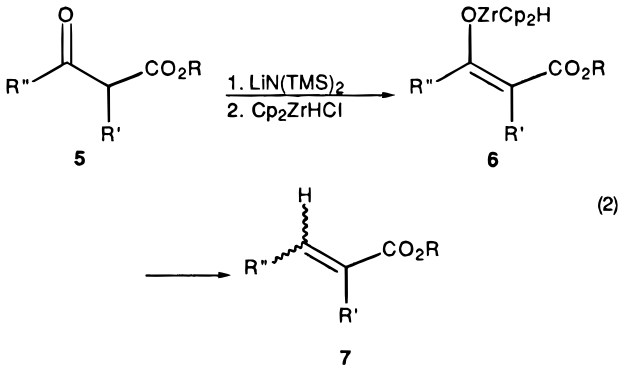
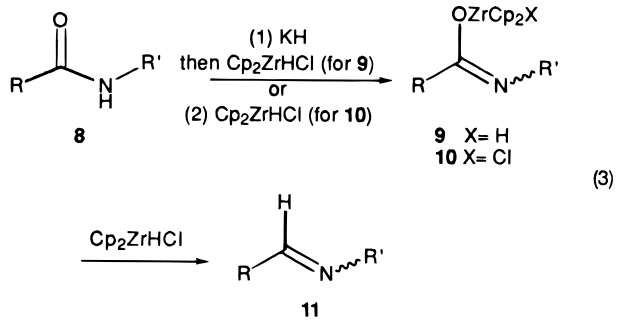
(6) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1992**, *33,* 7461.
(7) Wailes, P. C.; Coutts, R. S. P.; Wiegold, H. *Organometallic Chemistry of Titanium, Zirconium, and Hafnium*; Academic Press: New York, 1974; Chapter 4.

S0022-3263(96)00286-1 CCC: $12.00

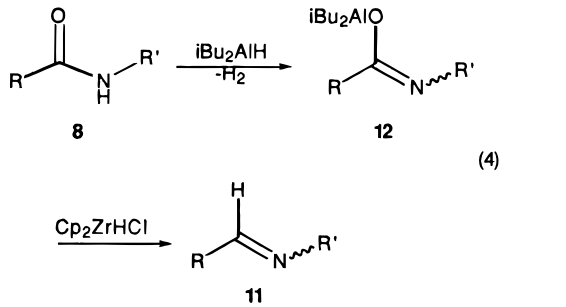


controlled reduction of amides and lactams to the corresponding imines, a transformation that is otherwise very difficult to achieve because imines are reduced more rapidly than carboxamides by most metal hydride reagents. Moreover, no products of reductive cleavage of the carboxamides were observed.



While the mechanisms of these reductions were unclear, our experiments indicated that zirconium enolates **9** and **10** required another 1 equiv of Cp_2ZrHCl to form imine, probably involving dinuclear complexes akin to those observed in carbonylation reactions.[8] From a practical standpoint, however, the overall requirement for 2 mol equiv of Cp_2ZrHCl was a major disadvantage of the method, posing cost and disposal problems on a large scale.

In attempting to replace Cp_2ZrHCl with simpler, less costly alternatives, we found that the initial zirconium enolate **10** could be replaced with a diisobutylaluminum enolate **12** (eq 4). Intermediate **12** could be smoothly reduced to imine **11** using Cp_2ZrHCl, thus replacing half the Cp_2ZrHCl with diisobutylaluminum hydride. In addition, we discovered that aluminum amides **12** could be reduced to imines using either low-valent titanium species or triethylsilane.



Results and Discussion

Initial feasibility studies of the sequence in eq 3 were conducted using *N*-decylbenzamide (**13**). To simplify product isolation from inorganic residue and to minimize imine hydrolysis, a nonaqueous workup was devised whereby hexanes were added to precipitate the inorganic byproducts, and the organic layer was filtered through Celite. Control experiments indicated that even sensitive imines survived such a workup, usually with no chromatography necessary.

Following the precedent in eq 2, prior metalation of carboxamide **13** was accomplished in the usual way with potassium hydride (THF, 0 °C), and the resulting anion was transferred by syringe to a suspension of Cp_2ZrHCl at −20 °C to generate enolate **9** ($R = C_6H_5$, $R' = C_{10}H_{21}$). Initially, 1.1 equiv of Cp_2ZrHCl was used, since that amount had been sufficient to transform β-keto esters **5** to acrylates **7** via hydridozirconocene enolates **6**. However, only traces of the desired imine **14** were formed, and starting carboxamide **13** was recovered in good yield after hydrolytic workup. As in the earlier β-keto ester reductions, an independent route to **9** ($R = C_6H_5$, $R' = C_{10}H_{21}$) was devised by reacting **13** with KH and then with Cp_2ZrCl_2 (1 equiv) followed by lithium triethylborohydride (1 equiv).[9] No imine was recovered in the hexanes extract, and only starting **13** was obtained by hydrolysis of the precipitated solids.

Although they failed to form imine spontaneously, zirconocene complexes **9** and **10** were shown to be susceptible to hydride reagents, since addition of 2−3 equiv of $LiBEt_3H$ caused overreduction to *N*-benzyldecylamine. This result prompted us to explore the reaction of intermediates **9** and **10** with an additional 1 equiv of Cp_2ZrHCl. Thus, when the potassium salt of *N*-decylbenzamide (**13**) was transferred by syringe to a suspension of Cp_2ZrHCl (2.4 equiv) at −20 °C, the reaction mixture became homogeneous after warming to rt. Nonaqueous workup afforded imine **14** in 86% yield. This procedure (method A) was successfully applied to a number of representative carboxamides and lactams, as shown in Table 1.

Imines were produced in one pot from secondary carboxamides or lactams using 2 equiv of Cp_2ZrHCl. Although *N*-alkylacetamides and other relatively nonacidic amides were best reduced by method A, prior metalation by KH proved unnecessary for relatively acidic carboxamides. Thus, hydrogen evolution was observed when **13** was added to a suspension of Cp_2ZrHCl in THF. Upon gradual warming to rt, the reaction mixture became homogeneous, whereupon addition of hexanes and filtration of the organic supernatant furnished imine **14** in 83% yield. This finding indicated that not only hydridozirconocene, but also chlorozirconocene complexes of carboxamide anions were selectively reduced to imines by Cp_2ZrHCl. Results obtained with a variety of carboxamides using the simplified procedure (method B) are summarized in Table 1. *N*,*N*-Disubstituted carboxamides such as *N*-benzoylpiperidine were not reduced by Cp_2ZrHCl. Moreover, the observed selectivity with unsaturated amide **21** (Table 1, entry 8) indicated that alkene hydrozirconation occurred much more rapidly than carboxamide reduction.

A good precedent for reduction of putative intermediates **9** and **10** by Cp_2ZrHCl was the well-known conversion of *O*-alkyl imino ethers via imines to amines using

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Table 1. Reduction of Amides to Imines Using Cp_2ZrHCl

entry	reactant	method	product (% yield)[a]	
1	$C_6H_5CONHC_{10}H_{21}$ (**13**)	A	$C_6H_5CH{=}NC_{10}H_{21}$ (**14**)	(86)
2	**13**	B	**14**	(83)
3	$C_6H_5CONHC_6H_5$ (**15**)	A	$C_6H_5CH{=}NC_6H_5$ (**16**)	(78)
4	**15**	B	**16**	(76)
5	$CF_3CONHC_{10}H_{21}$ (**17**)	A	$CF_3CH{=}NC_{10}H_{21}$ (**18**)	(61)
6	**17**	B	**18**	(42)
7	$CH_3CONHC_{10}H_{21}$ (**19**)	A	$CH_3CH{=}NC_{10}H_{21}$ (**20**)	(41)
8	$CH_2{=}CH(CH_2)_2CONH\ C_6H_5$ (**21**)	B	$(Cp_2ZrCl)(CH_2)_4CONHC_6H_5$ (**22**)	(68)
9	2-azacyclotridecanone (**23**)	A	1-azacyclotridecene (**24**)	(45)
10	**23**	B	**24**	(25)[b]

[a] Products were identified by direct comparison with authentic samples. [b] Ca. 20% of starting lactam was also recovered.

$NaBH_4$.[10] Consequently, we wondered whether *O*-alkyl imino ethers might also be reduced selectively to imines using a less reactive organozirconium hydride. In fact, however, Cp_2ZrHCl had no effect on the corresponding methyl imino ether of *N*-decylbenzamide, which was recovered in 96% yield after exposure to the usual reaction conditions. Taken together with earlier results on the overreduction of **9** and **10** with $LiBEt_3H$, the data suggest that imine formation depends on the interaction of an organozirconium hydride with an organozirconium enolate.

A labeling experiment was conducted to establish the feasibility of a mechanism involving hydride transfer from Cp_2ZrHCl to zirconocene imidates **9** and **10**. When *N*-phenylbenzamide (**15**) was reacted with Cp_2ZrDCl (90% deuterated, 2.4 equiv), hydrogen evolution proceeded much more slowly than with Cp_2ZrHCl. Nevertheless, the expected product, $C_6H_5CD{=}NC_6H_5$, was formed in 50% yield. The complete absence of unlabeled imine was rationalized on the basis of a kinetic isotope effect that preferentially consumed unlabeled Cp_2ZrHCl in the initial, metalation step.

When **15** was first treated with Cp_2ZrHCl (1.1 equiv), hydrogen evolution was rapid at room temperature. However, reduction of the intermediate imidate **10** (R, R′ = Ph) with Cp_2ZrDCl (1.4 equiv) led, in a very sluggish reaction, to a 1:2 mixture of unlabeled:labeled **16** (35% yield). The formation of unlabeled **16** was attributed to reduction of imidate **10** by adventitious Cp_2ZrHCl from two sources. First, approximately 10 mol % residual Cp_2ZrHCl was likely present from the initial metalation of **15**. Second, commercially available Cp_2ZrDCl (Aldrich Chemical Co.) contained approximately 10% Cp_2ZrHCl.

Thus, the overall transformation of carboxamides to imines outlined in eq 3 involved (i) a formal activation of the amide function as a zirconium-metalated carboxamide anion such as **9** or **10**, followed by (ii) hydride transfer from Cp_2ZrHCl and concomitant deoxygenation leading to imine. Each step in eq 3 consumed 1 equivalent of Cp_2ZrHCl. To address this drawback, we decided to look for alternative reagents by which either the activation or reduction step (or both) might be carried out without the use of organozirconium hydrides.

We decided to investigate whether aluminated amides **12** (eq 4) could replace Cp_2ZrHCl in the activation stage of amide-to-imine reduction. An inexpensive and convenient route to species like **12** was envisioned by direct metalation of secondary amides **8** with diisobutylaluminum hydride (DIBAL). Using *N*-phenylbenzamide as a test case, a toluene solution of DIBAL (1.05 equiv) was added to **15** in THF at 0 °C, whereupon hydrogen evolution was observed. Treatment of the homogeneous aluminum amidate **12** (R, R′ = Ph) with Cp_2ZrHCl (1.2 equiv) as before furnished imine **16** in 71% yield. Initial application of the DIBAL modification to several additional carboxamides listed in Table 1 confirmed the generality of the method. However, in no case did the yield of imine ever exceed 70% and some carboxamide was always recovered.

Table 2. DIBAL−Cp_2ZrHCl Reduction of Amides to Imines

entry	reactant	product (% yield)[a]	
1	$C_6H_5CONHC_{10}H_{21}$ (**13**)	$C_6H_5CH{=}NC_{10}H_{21}$ (**14**)	(90)
2	$C_6H_5CONHC_6H_5$ (**15**)	$C_6H_5CH{=}NC_6H_5$ (**16**)	(93)
3	$CF_3CONHC_{10}H_{21}$ (**17**)	$CF_3CH{=}NC_{10}H_{21}$ (**18**)	(53)
4	$CF_3CONHC_{10}H_{21}$ (**17**)	$CF_3CH{=}NC_{10}H_{21}$ (**18**)	(NR)

[a] Products were identified by direct comparison with authentic samples.

After varying several experimental parameters to optimize the DIBAL modification, a dramatic improvement in yield of imine was achieved simply by inverting the order of mixing in the metalation step. Thus, addition of the THF solution of carboxamide **15** to DIBAL in toluene followed by addition of Cp_2ZrHCl gave imine **16** in 93% yield. Table 2 presents the results when this procedure was applied to several representative secondary amides.

Benzamides and trifluoroacetamides were acidic enough to undergo rapid metalation with DIBAL below rt, whereupon Cp_2ZrHCl reduction occurred smoothly. However, the reaction of DIBAL with less acidic amides such as *N*-decylacetamide (**19**) did not spontaneously evolve hydrogen, even after prolonged heating at 50 °C.

With diisobutylaluminum amidate anions **12** serving as suitable surrogates for zirconated carboxamides **9** or **10**, we next tried to find a more acceptable substitute for Cp_2ZrHCl in the reduction stage of eq 3. Reagents based on titanium, another Group IVa metal, seemed like obvious possibilities. Especially noteworthy was the fact that imines could be prepared, without overreduction, by treatment of oximes with $TiCl_3$.[11] A solid, lower-valent Ti reagent prepared by the reaction of $TiCl_3$ with DIBAL in toluene was recently reported to transform oxime *O*-methyl ethers to ketones via imines.[12] Other, low-valent titanium species have been prepared from mixtures of $TiCl_3-LiAlH_4$ [Ti(0) or Ti(I)][13] or $TiCl_4-LiAlH_4$[14] and display useful reducing properties.

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Table 3. Other Reductions of Amides to Imines

entry	reactant	reagent	product (% yield[a]	
1	$C_6H_5CONHC_6H_5$ (**15**)	DIBAL−$TiCl_3$/DIBAL	$C_6H_5CH{=}NC_6H_5$ (**16**)	(38)
2	**15**	DIBAL−Et_3SiH	**16**	(34)
3	$C_6H_5NHC_{10}H_{21}$ (**13**)	DIBAL−Et_3SiH	$C_6H_5CH{=}NC_{10}H_{21}$ (**14**)	(33)
4	$CH_3CONHPh$ (**26**)	DIBAL−Et_3SiH	$CH_3CH{=}NPh$ (**27**)	(NR)

[a] Products were identified by direct comparison with authentic samples.

The reduction of amide **15** was therefore attempted by treating aluminated amide **12** (R, R′ = Ph) with $TiCl_3$/DIBAL. The most promising results were obtained using THF as solvent, where imine **16** was obtained in 38% yield, along with recovered **15** after aqueous workup (Table 3). No trace of *N*-benzylaniline was observed. Parallel experiments using $TiCl_4$−DIBAL produced significant quantities (35−55%) of *N*-benzylaniline, together with recovered carboxamide **15**. In an attempt to bypass the initial metalation step, carboxamide **15** was treated directly with $TiCl_3$−DIBAL, but no imine (and only starting material) was recovered under those conditions.

Amides **15** and **13** could also be reduced via the corresponding imidates using triethylsilane in THF at rt to furnish imines **16** and **14** in 33−34% yield, with about 30% of starting amide also recovered (Table 3). Addition of catalysts such as $ZnCl_2$, $AlCl_3$, or BF_3 diminished the yield of imine, whereas $PdCl_2$ gave *N*-benzylaniline instead of imine.

Conclusion

With its demonstrated scope and generality, the selective reduction of carboxamides to imines using either Cp_2-ZrHCl (Table 1) or DIBAL−Cp_2ZrHCl (Table 2) illustrates new roles for early transition metal hydrides in synthesis. By prior formation of an aluminated carboxamide, it is possible to reduce by half the amount of organozirconium reagent necessary to accomplish this transformation (Table 2). Moreover, promising results with other reagent combinations such as DIBAL−Et_3SiH (Table 3) suggest that it may eventually be possible to eliminate the use of Cp_2ZrHCl altogether in this process.

To our knowledge, the transformations reported herein represent the first controlled reductions of carboxamides and lactams to the corresponding imines, a transformation that is otherwise very difficult to achieve since imines are reduced very rapidly to amines by most metal hydride reagents. Moreover, no products of reductive cleavage of the amides were observed. Since imines are readily hydrolyzed to amines and aldehydes, the method may prove to be a useful alternative to the partial reduction of carboxamides, or to known reductive or hydrolytic deprotection procedures for amides, especially in situations where more drastic hydride reagents must be avoided.

Experimental Section[15]

Reduction of *N*-Decylbenzamide (13) to Benzaldehyde *N*-Decylimine (14) Using KH−Cp_2ZrHCl: Representative Example of Table 1−Method A Reduction. A solution of *N*-decylbenzamide (0.15 g, 0.59 mmol) in anhydrous THF (2 mL) was added dropwise to a suspension of KH (25 mg, 0.62 mmol) in THF (1 mL) at 0 °C. After stirring 10 min, the clear, colorless solution of the enolate was transferred by syringe to a −20 °C suspension of Cp_2ZrHCl (Aldrich Chemical Co., freshly sublimed, 0.37 g, 1.46 mmol) in THF (0.5 mL). The reaction mixture was gradually warmed to rt over 2 h and then pipetted into cold hexanes (10 mL) with vigorous stirring. The heterogeneous mixture was filtered under vacuum through Celite (hexane rinsing), and the combined filtrates were concentrated on a rotary evaporator to afford pure **14** (0.124 g, 86%) as a pale yellow oil. ^{1}H- and ^{13}C-NMR and IR spectral data of the product were identical with an authentic sample prepared by the method of Stork and Dowd.[16]

Reduction of *N*-Decylbenzamide (13) to Benzaldehyde *N*-Decylimine (14) Using Cp_2ZrHCl: Representative Example of Table 1−Method B Reduction. A solution of **13** (0.10 g, 0.38 mmol) in anhydrous THF (1 mL) was added dropwise to a suspension of Cp_2ZrHCl (0.24 g, 0.91 mmol) in THF (1 mL) at −20 °C and after 10 min the reaction mixture was gradually warmed to rt. After 4 h, the reaction mixture was pipetted into cold hexanes (10 mL) with vigorous stirring. The heterogeneous mixture was filtered under vacuum through Celite (hexane rinsing), and the combined filtrates were concentrated on a rotary evaporator to afford pure **14** (78 mg, 83%) as a pale yellow oil, which was spectroscopically identical (^{1}H-, ^{13}C-NMR, IR) with an authentic sample.

Reduction of *N*-Phenylbenzamide (15) to Benzaldehyde *N*-Decylimine (16) Using DIBAL−Cp_2ZrHCl. To a toluene solution of DIBAL (Aldrich, 0.28 mmol) in anhydrous THF (1 mL) at −10 °C was added a solution of **15** (50 mg, 0.25 mmol) in THF (1 mL) over 20 min. After 10 min, the reaction mixture was warmed to 0 °C and stirred 20 min. The resulting clear solution of aluminum amide was cooled to −20 °C, and Cp_2ZrHCl (83 mg, 0.30 mmol) was added. After warming gradually to rt and stirring for 7 h, the solution was cooled to 0 °C, and dry hexanes (10 mL) were added, forming a turbid mixture that was filtered through Celite (hexane rinsing). The filtrate was concentrated in vacuo to afford *N*-decylimine **16** (58 mg). The crude product was filtered through column of silica gel (2 cm × 2 cm) eluting with 1:1 ether:hexanes (20 mL) to afford pure imine **16** (43 mg, 93%), which was spectroscopically identical (^{1}H-, ^{13}C-NMR, IR) with an authentic sample.

Reduction of *N*-Phenylbenzamide (15) to Benzaldehyde *N*-Phenylimine (16) Using DIBAL−$TiCl_3$/DIBAL. To a toluene solution of DIBAL (Aldrich, 0.17 mmol) was added dropwise over 5 min a solution of *N*-phenylbenzamide (**15**) (32 mg, 0.16 mmol) in anhydrous THF (2 mL) at −20 °C. After 10 min at 0 °C the solution was cooled to −20 °C and treated with a suspension of low-valent titanium reagent prepared[12] by adding DIBAL (0.50 mmol) dropwise to $TiCl_3$ (7.5 mg) in THF (1 mL) over 5 min and then stirring an additional 10 min.

Following transfer of the DIBAL−$TiCl_3$ reagent, the reaction mixture was warmed to rt, stirred for 8 h and then treated with cold hexanes (10 mL). The resulting slurry was filtered through hexane-rinsed Celite, and the colorless filtrate was concentrated to one-half the volume, whereupon a suspension appeared that was refiltered through Celite. The final, clear filtrate was concentrated in vacuo to afford pure **16** (11 mg, 38%) as a pale yellow oil that was spectroscopically identical (^{1}H-, ^{13}C-NMR, IR) with an authentic sample.

Reduction of *N*-Decylbenzamide (13) to Benzaldehyde *N*-Decylimine (14) Using DIBAL−Et_3SiH. To a toluene solution of DIBAL (Aldrich, 0.84 mmol) was added dropwise over 10 min a solution of *N*-decylbenzamide (**13**) (200 mg, 0.77 mmol) in anhydrous THF (3 mL) at −20 °C. After stirring 20 min at 0 °C, the clear, colorless solution was cooled to −20 °C, and Et_3SiH (0.15 mL, 0.94 mmol) was added dropwise. The solution was stirred for 20 min at −20 °C and then warmed

(15) For general experimental procedures, see King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562.

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to rt for 3 h. Addition of cold hexane (1 mL) with vigorous stirring produced a heterogeneous mixture that was filtered through hexane-rinsed Celite. The filtrate was concentrated in vacuo to ca. 3 mL, whereupon a suspension appeared that was refiltered through Celite. The final, clear filtrate was concentrated in vacuo to afford pure **14** (63 mg, 33%) that was spectroscopically identical (^{1}H-, ^{13}C-NMR, IR) with an authentic sample.

Acknowledgment. We thank the National Institutes of Health (GM 35712) for generous financial assistance. Support of the Cornell Nuclear Magnetic Resonance Facility by the NSF (CHE 7904825; PGM 8018643) and NIH (RR02002) is gratefully acknowledged.

JO960286J