Highly Enantioselective Imine Hydrosilylation Using (*S,S*)-Ethylenebis(η^5-tetrahydroindenyl)titanium Difluoride

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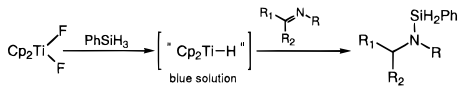
In the past few years we have developed a number of titanocene-catalyzed methods for the reduction of imines and carbonyl containing compounds.[1−3] In these procedures the active catalyst was generated by the addition of 2 equiv of *n*-BuLi to the corresponding dichloro or binaphthdiolate titanocene derivative.[4] In this communication we report a more convenient catalyst activation protocol which proceeds *via* an unprecedented conversion of a Ti−F to a Ti−H. We have utilized this activation process as an integral step in the development of the first highly enantioselective catalyst system for the hydrosilylation of imines.

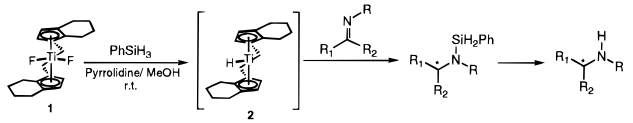
We recently reported a method for the reduction of lactones to lactols at room temperature.[5] In this system, $Cp_2Ti(p\text{-}ClC_6H_4O)_2$ reacts with polymethylhydrosiloxane (PMHS) in the presence of TBAF/alumina to afford the active catalyst. Investigations to clarify the role of the fluoride ion in the activation process led to a surprising finding. The addition of phenylsilane to a yellow solution of Cp_2TiF_2 at room temperature yielded a dark blue solution[6] which is catalytically active for the hydrosilylation of imines (Scheme 1). This experiment indicated that it is possible, under very mild conditions, to break the strong Ti−F bond and generate what we believe is a titanium(III) hydride or its equivalent.[6,7] To our knowledge, the conversion of an early transition metal fluoride to the corresponding hydride by treatment with a silane has not been reported.[8]

The new activation methodology is also applicable to more sterically demanding titanocene systems. When (*S,S*)-ethylenebis(η^5-tetrahydroindenyl)titanium difluoride[9] **1** was treated with $PhSiH_3$ (Scheme 2), heating to 60 °C yielded a green solution which was also catalytically active. The same result was observed at room temperature when a small amount of

Scheme 1



Scheme 2



MeOH and pyrrolidine[10] were added to **1** and phenylsilane (*vide infra*). Subsequent addition of the imine and stirring at room temperature or 35 °C yielded the corresponding silylated amines[11] which upon treatment with acid and workup afforded the enantiomerically enriched free amines.

To date only a few asymmetric hydrosilylations of imines, all catalyzed by late transition metal complexes, have been reported.[12] None of these afford amines with high levels of enantioselectivity. In the light of the efficiency demonstrated by the Brintzinger-type catalysts for the hydrogenation of prochiral imines,[13] we decided to explore the hydrosilylation of these substrates using (*S,S*)-(EBTHI)TiF_2 as a precatalyst. The results obtained for a series of *N*-methyl and cyclic imines are shown in Table 1. An important feature of this system is its experimental simplicity.[14] While in the case of the hydrogenation elevated pressures (80−500 psi) and temperatures (∼65 °C) were required, hydrosilylation reactions are usually carried out at room temperature under an argon atmosphere. The catalyst can be activated prior to addition of the substrate or more conveniently in the presence of the imine (entries 2 and 8). After the reaction is complete, an acidic workup provides the product secondary amines in high yields and >95% purity (GC and ^{1}H NMR analysis). The enantioselectivities achieved in the hydrosilylation of the imines listed in Table 1 are very high. It is important to point out that the new activation protocol

(1) (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323.

(2) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562.

(3) Carter, M. B.; Schiøtt, B.; Gutierrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667.

(4) (a) Brintzinger, H. H. *J. Am. Chem. Soc.* **1966**, *88*, 4305. (b) Brintzinger, H. H.; Bercaw, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 6182.

(5) Verdaguer, X.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12641.

(6) A similar color is observed when Cp_2TiMe_2 reacts with a silane at room temperature: Xin, S.; Aitken, C.; Harrod, J. F.; Mu, Y. *Can. J. Chem.* **1990**, *68*, 471.

(7) For examples of titanium(III) hydrides and silyl titanium hydrides, see: (a) Xin, S.; Harrod, J. F.; Samuel, E. *J. Am. Chem. Soc.* **1994**, *116*, 11562. (b) Wolf, J. M.; Meetsma, A.; Teuben, J. H. *Organometallics* **1995**, *14*, 5466. (c) Harrod, J. H.; Yun, S. S. *Organometallics* **1987**, *6*, 1381. (d) Spaltenstein, E.; Palma, P.; Kreutzer, K. A.; Willoughby, C. A.; Davis, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 10308.

(8) During the preparation of this manuscript the defluorination of perfluorocarbons catalyzed by Cp_2TiF_2 was reported: Kiplinger, J. L.; Richmond, T. G. *J. Am. Chem. Soc.* **1996**, *118*, 1805.

(9) (*S,S*)-(EBTHI)TiF_2 is a crystalline, air-stable yellow-orange solid and was prepared from the corresponding dichloride derivative in one step, see: (a) Schäfer, A.; Karl, E.; Zsolnai, L.; Gottfried, H.; Brintzinger, H. H. *J. Organomet. Chem.* **1987**, *328*, 87. (b) Bruce, P. M.; Kingston, B. M.; Lappert, M. F.; Spalding, T. R.; Srivastava, R. C. *J. Chem. Soc. (A)*, **1969**, 2106.

(10) (a) **1**:base:MeOH = 1:4:4. (b) Pyrrolidine, piperidine, and ^{t}BuONa were all successfully used as bases.

(11) The product silylamines could be observed (NMR) but were never isolated due to their lability.

(12) (a) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353. (b) Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*. 995. (c) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1973**, *14*, 2475.

(13) (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703

(14) (a) Typical experimental procedure: A dry resealable Schlenk flask under argon was charged with *(S,S)*-(EBTHI)TiF_2 (9 mg, 0.025 mmol) and 2 mL of dry THF. To this solution were added *via* syringe in this order: $PhSiH_3$ (0.45 mL, 3.75 mmol), pyrrolidine (8 mL, 0.1 mmol), and methanol (4 mL, 0.1 mmol). The mixture was stirred at room temperature for 30−60 min resulting in a color change from yellow to green. At this point, the sealed Schlenk flask was brought into a nitrogen filled glovebox and *N*-(1-phenylethylidene)methylamine (332 mg, 2.5 mmol) was added. The Schlenk was removed from the glovebox, and the reaction mixture was stirred at room temperature. When consumption of the starting material was complete (∼12 h), the reaction mixture was diluted with Et_2O (20 mL) and stirred with 1 M HCl (10 mL) for 0.5 h (**caution**: vigorous bubbling). The aqueous layer was separated, made basic with 3 M NaOH, and extracted with ether (3 × 20 mL). The combined ether layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield 319 mg of *(S)*-(−)-*N*-methyl-1-phenylethylamine (94% yield, 97% ee). (b) An alternative procedure with *in situ* activation of the catalyst proceeds as follows: A dry resealable Schlenk flask under argon was charged with (*S,S*)-(EBTHI)TiF_2, the imine, and THF. To this solution were added *via* syringe in this order: $PhSiH_3$, pyrrolidine, and methanol. The reaction mixture was stirred at 35 °C until complete consumption of starting material was observed. After cooling the reaction mixture to room temperature, workup and isolation were conducted as before. (c) *N*-Methylimines were prepared from the corresponding ketones with methylamine and $TiCl_4$, see: Evans, D. A.; Domeier, L. A. *Organic Syntheses;* Wiley: New York, Collect. Vol. VI, p 818. (d) All imines were stored in a nitrogen filled glovebox. (e) For reactions employing a 1 mol % catalyst loading crude *N*-methylimines and commercially available grade $PhSiH_3$ (Aldrich) were used. For lower catalyst loadings, imines and $PhSiH_3$ were distilled and stored in an inert atmosphere.

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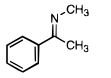
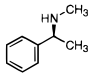
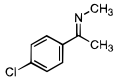
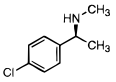
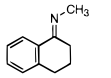
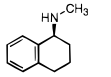
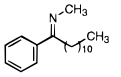
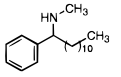
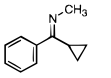
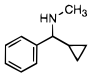
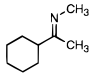
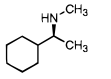
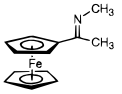
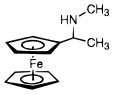
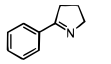
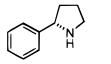
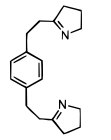
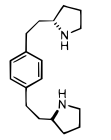
Table 1. Catalytic Hydrosilylation of Imines Using (*S,S*)-(EBTHI)TiF_2

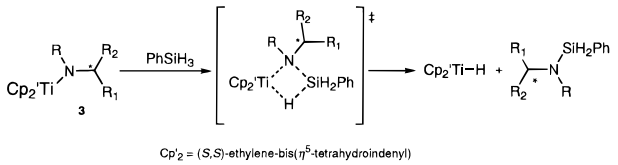
Entry	Imine	Amine[a]	mol % cat.	T (°C)	Yield(%)[b]	ee(%)[c]	(+/-)
1			1 0.02	r.t. 35	94 95	97 99	(–)
2			1 0.1	r.t. 35	85 87	99 98[g]	(–)
3			2.5	r.t.	80	96[d]	(+)
4			2.5	50	88	95[d]	(–)
5			1	r.t.	91	97	(+)
6			1 0.02	r.t. 35	88 96	93 92	(+)
7			2.5	r.t.	89	86	(+)
8			1 0.1	r.t. 35	97 96	99[f] 98[g]	(–)
9			2	r.t.	64	98[e]	(–)

[a] The absolute configurations for the product amines in entries 1, 2, 3, 6, and 8 were determined by polarimetry. The absolute configuration for the product in entry 9 was assigned by analogy to 2-phenylpyrrolidine in entry 8. [b] Yields refer to isolated compounds of >95% purity by GC and ^{1}H NMR. [c] Unless otherwise noted ee (%) were determined by GC analysis of the corresponding trifluoroacetamides on a Chiraldex G-TA column. [d] Enantiomeric excess determined by GC analysis of the trifluoroacetamide derivative on a Chiraldex B-PH column. [e] Enantiomeric excess determined by combined analysis of the bis(trifluoroacetamide) derivative on a Chiralcel OD HPLC column and HP-1 GC column. [f] Chiral GC analysis revealed 1100/1 ratio of the corresponding enantiomers. [g] *In situ* catalyst activation was used.

has allowed us to decrease the catalyst loading to as little as 0.02−0.1 mol % with no effect on the yield or the enantiomeric purity of the resulting amines (entries 1, 2, 6, and 8). Furthermore, the reaction tolerates an aromatic chloride (entry 2) and the presence of a ferrocenyl moiety (entry 7). In addition, the successful reduction of a cyclopropyl imine is evidence against a radical process (entry 5).[15] Finally, as shown in entry 9 this procedure can be also applied to the synthesis of chiral amines which contain multiple stereogenic centers.

At the present time the nature of the activation process is unclear. From a thermochemical point of view, the unusually high Si−F (150−166 kcal/mol) bond energy could be considered the driving force responsible for the Ti−F (140 Kcal/mol) bond cleavage.[16,17] Related with this is the observation that a small amount[10a] of methanol and a base such as pyrrolidine enhance the rate of catalyst activation. It is known that the reaction between silanes and alcohols can be catalyzed by an added base.[18] Involvement of a species such as $Ph(MeO)SiH_2$ or $Ph(MeO)_2SiH$ generated in the $PhSiH_3$/MeOH/pyrrolidine mixture could account for the faster rate of catalyst activation. Once the active catalyst has been generated, the reaction presumably proceeds by a catalytic cycle similar to that for the titanocene-catalyzed hydrogenation of imines.[13b] Insertion of the imine into the titanium−hydrogen bond of **2** would give the corresponding amido-titanium complex **3**. Subsequent σ-bond metathesis of **3** with $PhSiH_3$ *via* a four center transition state[19] would afford the silylated amine and regenerate the titanium hydride (Scheme 3). As previously reported, the stereochemical outcome of the reaction can be rationalized on the basis of the insertion step.[20]

Scheme 3



Cp'$_2$ = (*S,S*)-ethylene-bis(η^5-tetrahydroindenyl)

In summary, we have developed the first highly enantioselective method for the catalytic hydrosilylation of imines. This experimentally simple system features a novel activation process based on the reaction of (*S,S*)-(EBTHI)TiF_2 with phenylsilane. The procedure converts imines to amines under mild conditions with significantly higher subtrate:catalyst ratios than previously possible. Further work aimed at the elucidation of the mechanism and broadening the scope of these reactions is currently in progress.

Acknowledgment. This work was supported by the National Institutes of Health. X.V. thanks the Spanish Ministry of Education and Science for a postdoctoral fellowship. U.L. thanks the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship. We are grateful to B. Chin for the preparation of **1**. We thank N. Radu for insightful comments and Professor Mark Burk for information on chiral GC analysis.

Supporting Information Available: Detailed experimental procedures and spectral data for (*S,S*)-ethylenebis(η^5-tetrahydroindenyl)-titanium difluoride and compounds listed in Table 1 (10 pages). See any current masthead page for ordering and Internet access instructions.

JA960808C

(15) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

(16) *D* (F_3Ti-F) = 140 kcal/mol, *D* (H_3Si-F) = 150 kcal/mol, *D* (F_3Si-F) = 166 kcal/mol, see: (a) Connor, J. A. *Top. Curr. Chem.* **1977**, *71*, 71. (b) Schock, L. E.; Marks, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 7701. (c) Walsh, R. in *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989.

(17) To our knowledge accurate bond energies for Ti−H have not been reported; therefore, a complete balanced thermochemical calculation is not possible.

(18) For examples of base-catalyzed dehydrocondensation of silanes with alcohols, see: (a) Lukevics, E.; Dzintara, M. *J. Organomet. Chem.* **1984**, *271*, 307. (b) Gilman, H.; Dunn, G. E.; Hartzfeld, H.; Smith, A. G. *J. Am. Chem. Soc.* **1955**, *77*, 1287. (c) Bazant, V.; Chvalovsky, V.; Rathousky, J. In *Organosilicon Compounds*; Publishing House of the Czechoslovak Academy of Science: Prague, 1965; pp 54−56.

(19) Woo, H-G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 8043.

(20) The absolute configuration of the major enantiomer observed in the hydrosilylation coincides with the one obtained from the hydrogenation reaction.[13b]