The Development and Synthetic Application of Titanium-Mediated Carbon-Heteroatom Double Bond Hydrosilylation Methodologies

By Matthew Todd Reding

B. S. Chemistry, Northwestern University, 1988

Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN
ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

June 1997

Signature of Author _____

Department of Chemistry
May 20, 1997

Certified by _____

Stephen L. Buchwald
Thesis Supervisor

Accepted by _____

Dietmar Seyferth
Chair, Departmental Committee on Graduate Students

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Gregory C. Fu _____

Chair

Professor Stephen L. Buchwald _____

Thesis Supervisor

Professor Timothy M. Swager _____

The Development and Synthetic Application of Titanium-Mediated Carbon-Heteroatom Double Bond Hydrosilylation Methodologies

By Matthew Todd Reding

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Organic Chemistry

Abstract

Polymethylhydrosiloxane, when combined with titanium(IV) isopropoxide, provided a convenient system for the conversion of esters to the corresponding primary alcohols in the presence of a wide range of functional groups. Reactions were carried out as mixtures of the neat reaction components; work-up with aqueous alkaline THF afforded primary alcohols in good to excellent yields. The system tolerated primary alkyl bromides and iodides, olefins, and to a lesser extent epoxides and alkynes. Steric differentiation of methyl and *tert*-butyl esters was also possible. The results observed in the parent and related reactions argued against pathways involving Lewis-acid catalysis and anionic hydridosilicate-mediated reductions, and instead supported a neutral titanium hydride complex or strongly associated titanium/silane complex as the active reducing agent.

When a solution of (*S*,*S*)-ethylenebis(η^5-1,2,3,4-tetrahydroindenyl)titanium difluoride was treated with phenylsilane, heating the mixture yielded a solution which displayed catalytic activity for the asymmetric hydrosilylation of imines. A variety of *N*-methyl and endocyclic imines were hydrosilylated with high enantioselectivity. Treatment of the silylamines thus produced with aqueous acid gave highly enantiomerically enriched amines. The initial development of this system for the hydrosilylation of imines was followed by an examination of the scope of the reaction with regard to chemoselectivity in the presence of 1,2-disubstituted olefins. Although these olefins were found to be reactive under a variety of reaction conditions, a method for obtaining the desired products with high enantioselectivity and reasonable chemoselectivity was achieved. Furthermore, several important parameters of the protocol were more precisely delineated. The diasteroselectivity of the transformation of imines bearing stereogenic centers was also explored.

The first catalytic, asymmetric syntheses of the piperidine alkaloids (*S*)-coniine and (2*R*,6*S*)-*trans*-solenopsin A were carried out. The method for highly enantioselective imine hydrosilylation described above allowed for a direct and efficient route to these synthetically interesting chiral amines.

Thesis Supervisor: Stephen L. Buchwald

Title: Camille and Henry Dreyfus Professor of Chemistry

Acknowledgements

The work described in this thesis, and in fact my survival here at MIT, would have been impossible without the help and support of a large number of people.

First, I would like to thank God and my family, without whom I would never have come into this world and certainly would never have made it to MIT. From my Dad I learned the importance of hard work, and also of helping other people. My mom gave me a love for reading, and lots of enthusiastic praise and support. They both always encouraged me to make my own choices and to follow my dreams.

While here at MIT I have had the incredible blessing and great joy of meeting my best friend and future wife, Jennifer White. She has stood by me through the many storms in my life, held my hand when I was afraid, given me a shoulder to cry on when I was sad, and kicked me in the behind when I needed that, too. I cannot imagine my life without Jennifer, and I cannot imagine having finished this work without her sense of humor, warmth, and joy for life to remind me of what's really important.

I want to thank my advisor, Steve Buchwald, for sticking with me. I appreciate his patience, his candor, his high ethical standards, and his determined pursuit of scientific truth. I have become a better scientist under his expert guidance.

I owe whatever is left of my sanity to a wonderful group of close friends. I have to thank Joel for letting me follow him here in the first place, and for returning my bed. Shane was and is the friend that I should have prayed for, and that God sent anyway. You know what they say about good hearts: Shane has one. Steve, Johan, Noel, Bryan and Chad have all at one time or another been there for me, and I couldn't have asked for a better bunch of roommates.

The textbooks never mention that when you spend time in lab, you end up with an interesting assortment of labmates. Natasha was always there with a listening ear and as well as her trademark sarcasm - the better to keep me from feeling sorry for myself. Never forget seven-membered rings are hard to draw. Seble, I hope you learn to whistle, and what about breakfast at Tiffany's? To all the rest of the folks who had to share lab space with me, many thanks for all that you taught me.

I'd like to thank Dr. Bryant Yang for last-minute editorial help, as well as Marcus Hansen and Fred Hicks. Finally, I thank the National Science Foundation for a Pre-doctoral Fellowship from 1992 to 1995.

Dedication

To the Greater Glory of God

and

In Loving Memory of the Life of

Nancy Carol Reding

November 6, 1943 - December 20, 1994

Preface

Much of this thesis has been adapted from articles co-written by the author:

Reding, M. T.; Buchwald, S. L. "Short Enantioselective Total Syntheses of the Piperidine Alkaloids (*S*)-Coniine and (2*R*,6*R*)-*trans*-Solenopsin A *Via* Catalytic Asymmetric Imine Hydrosilylation" manuscript in preparation.

Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. "Highly Enantioselective Imine Hydrosilylation Using (*S,S*)-ethylenebis(η^5-tetrahydroindenyl) titanium difluoride" *J. Am. Chem. Soc.* **1996**, *118*, 6784.

Reding, M. T.; Buchwald, S. L. "An Inexpensive Air-Stable Titanium-Based System for the Conversion of Esters to Primary Alcohols" *J. Org. Chem.* **1995**, *60*, 7884.

Table of Contents

Part 1 - Titanium-Mediated Carboxylic Ester Reduction

1.0 Background

The conversion of an ester to the corresponding primary alcohol is a fundamental process in organic synthesis (Fig. 1.0.1).[1] The most popular methods for

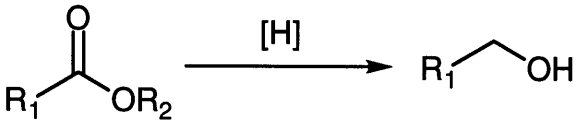


Fig. 1.0.1

accomplishing this transformation can be categorized as reactions of main group metal hydride reducing agents, especially those of boron, aluminum and silicon.[2] Many of these reagents suffer from problems such as high reactivity (including pyrophoricity), low functional group tolerance, and expense.[3] Although many of these reagents are of great utility for small-scale synthesis, their usefulness in large-scale applications is curtailed by these drawbacks.

Several methods for the direct hydrosilylation of esters and other carbonyl-containing compounds, which upon work-up afford the corresponding alcohols, have been developed. These methods fall into two main categories. Acid (Brønsted or Lewis)-catalyzed carbonyl hydrosilylations (typically of aldehydes and ketones) take place in the presence of various silanes.[4-10] This process can also give rise to appreciable amounts of symmetrical ether dimers of the desired alcohol products,[6,8] and in the case of aryl aldehydes and ketones can reduce the carbonyl to a methylene unit.[9]

The use of anionic pentacoordinate hydridosilicates (Fig. 1.0.2) represents a second method of direct carbonyl hydrosilylation *via* hydride addition to the electrophilic carbonyl carbon.[11-23] A single electron transfer pathway has also been proposed.[24] Pentacoordinate hydridosilicates are typically formed by addition of a

fluoride ion, an alkoxide, or a hydride to a silane.[5,14,15] This type of reaction has also been performed on the surface of fluoride salts.[20,22,23] The resulting reagents are

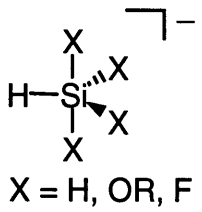


Fig. 1.0.2

powerful hydride donors which nevertheless can display good chemoselectivity; for example, ketones were selectively reduced in the presence of epoxides.[12] Also recently reported was a related hydrostannylation of aldehydes and ketones which was proposed to proceed *via* an anionic silicate formed in the presence of silica gel.[25] Reagents of this type have been shown capable of reducing esters.[23]

Transition metal-based reagents for the hydrosilylation of organic carbonyls have also been developed.[26] Of particular note here is the titanium-mediated phosphine oxide reduction that utilizes polymethylhydrosiloxane (PMHS) as the hydride source, developed by Lawrence and co-workers.[27] During the course of the work described in Section 1.1, this group also disclosed the use of stoichimetric titanium and zirconium alkoxides to effect the reduction of a limited number of carboxylic acids and esters with large excesses of PMHS.[28] Finally, a note announcing the development (by the same group) of a catalytic system involving PMHS and TBAF has appeared, but no details have as yet been forthcoming.[29]

References

1. Greeves, N. In *Comprehensive Organic Synthesis, Vol. 8*; Trost, B. M., Ed.; Pergamon Press: New York, 1991.
2. Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers, Inc.: New York, 1989.
3. Hajós, A. *Complex Hydrides*; Elsevier Scientific Publishing Co.: New York, 1979. Barrett, A. G. M. In *Comprehensive Organic Synthesis, Vol. 8*; Trost, B. M., Ed.; Pergamon Press: New York, 1991.
4. Fujita, M.; Fukuzumi, S. *J. Mol. Catal.* **1993**, *85*, 143.
5. Corriu, R.; Guérin, C.; Henner, B.; Wang, Q. *Inorg. Chim. Acta* **1992**, *198*, 705.
6. Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129.
7. Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3829.
8. Doyle, M. P.; DeBruyn, D. J.; Donnelly, S. J.; Kooistra, D. A.; Odubela, A. A.; West, C. T.; Zonnebelt, S. M. *J. Org. Chem.* **1974**, *39*, 2740.
9. West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675.
10. Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 3659.
11. Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.
12. Hojo, M.; Fujii, A.; Murakami, C.; Aihara, H.; Hosomi, A. *Tetrahedron Lett.* **1995**, *36*, 571.
13. Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371.
14. Corriu, R. J. P.; Guérin, C.; Henner, B.; Wang, Q. *Organometallics* **1991**, *10*, 2297.
15. Becker, B.; Corriu, R.; Guérin, C.; Henner, B.; Wang, Q. *J. Organomet. Chem.* **1989**, *359*, C33.

16. Becker, B.; Corriu, R. J. P.; Guérin, C.; Henner, B.; Wang, Q. *J. Organomet. Chem.* **1989**, *368*, C25.
17. Kira, M.; Sato, K.; Sakurai, H. *J. Org. Chem.* **1987**, *52*, 949.
18. Boyer, J.; Breliere, C.; Corriu, R. J. P.; Kpoton, A.; Poirier, M.; Royo, G. *J. Organomet. Chem.* **1986**, *311*, C39.
19. Fry, J. L.; McAdam, M. A. *Tetrahedron Lett.* **1984**, *25*, 5859.
20. Corriu, R. J. P.; Perz, R.; Réyé, C. *Tetrahedron* **1983**, *37*, 2165.
21. Corriu, R. J. P.; Perz, R.; Réyé, C. *Tetrahedron* **1981**, *39*, 999.
22. Boyer, J.; Corriu, R. J. P.; Perz, R.; Réyé, C. *J. Chem. Soc., Chem. Commun.* **1981**, 121.
23. Boyer, J.; Corriu, R. J. P.; Perz, R.; Poirier, M.; Réyé, C. *Synthesis* **1981**, 558.
24. Yang, D.; Tanner, D. D. *J. Org. Chem.* **1986**, *51*, 2267.
25. Figadère, B.; Chaboche, C.; Franck, X.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1994**, *59*, 7138.
26. Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989.
27. Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625.
28. Breeden, S. W.; Lawrence, S. J. *Synlett* **1994**, 833.
29. "Inexpensive Hydride Reducing Agent" *Chem. Eng. News*, September 16, 1996, p. 42.

Section 1.1 - Titanium-Mediated Carboxylic Ester Reduction

1.1.0 Introduction

The development of new titanium-mediated or catalyzed carboxylic ester reductions has been the subject of research the Buchwald laboratories for several years.[1-4] Figure 1.1.1 shows the elements which compose the titanium and hydride

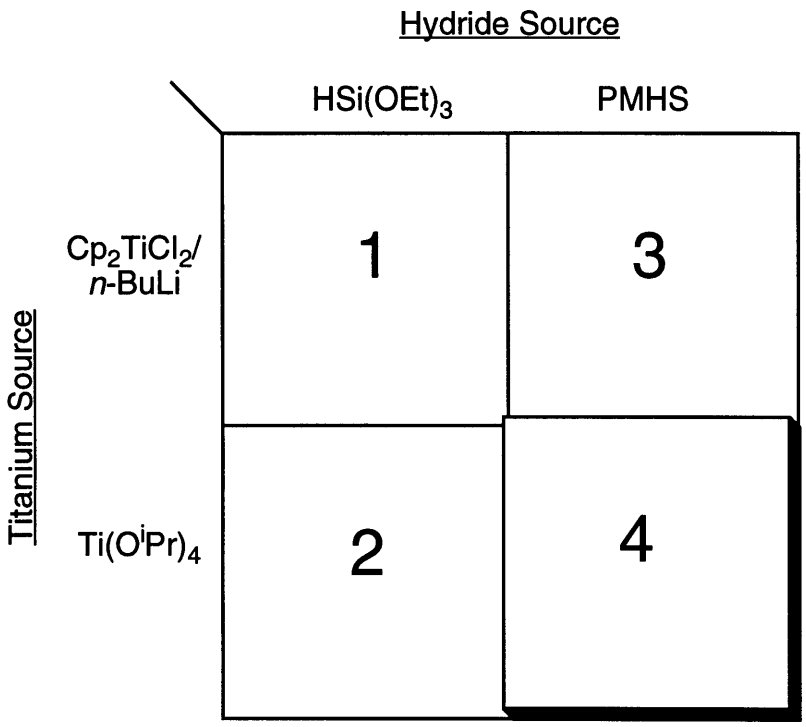


Fig 1.1.1 - Successive generations of ester reduction systems

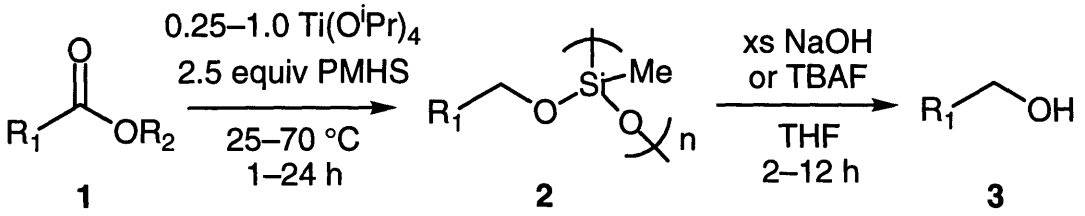
source for each of these ester reduction processes. The first generation of this type of reaction involved the use of a titanocene catalyst and a potentially toxic trialkoxysilane as the ultimate reductant.[3,4] A second generation system was produced when it was shown that the titanocene catalyst could be replaced by the much cheaper titanium(IV) tetraisopropoxide ($Ti(O^iPr)_4$), which offered the further advantage of not requiring activation by alkyllithiums.[2] Despite some effort, it was not possible to extend this work to allow for the substitution of polymethylhydrosiloxane (PMHS) for the undesirable trialkoxysilanes. However, a third-generation reduction system was developed in

which PMHS could be used with a titanocene-based catalyst as the stoichiometric reductant, thus affording an improvement both in terms of reduced toxicity and reagent cost.[1] Section 1.1.1 details the investigation of a fourth-generation reaction, in which a variety of functionalized esters were reduced with PMHS. As in the second-generation system, the reaction is promoted by $Ti(O^iPr)_4$. However, larger titanium to substrate ratios were found to be necessary. Several other titanium reagents and silane reductants were also used. This system allows for ester reduction without solvent under mild conditions, uses 0.25 to 1.0 equivalents of a very inexpensive transition metal component, and is tolerant of a wide range of functional groups.

1.1.1 Titanium-Mediated Carboxylic Ester Reduction

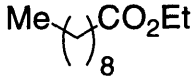
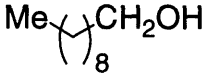
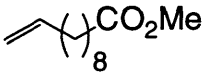
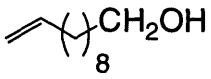
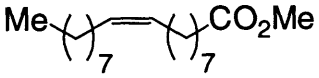
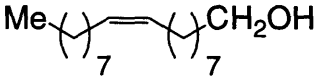
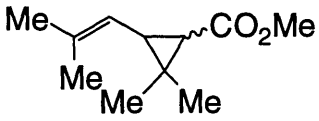
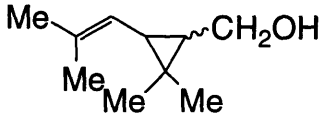
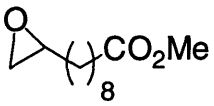
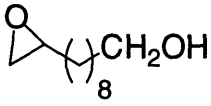
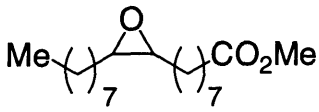
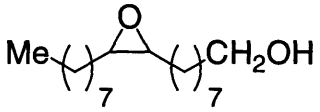
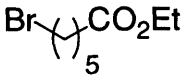
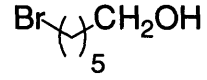
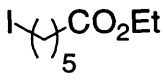
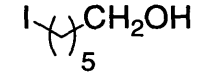
The results of a series of reactions between functionalized methyl and ethyl esters **1** and 2.5 equivalents of PMHS (monomer weight = 60) in the presence of varying amounts of $Ti(O^iPr)_4$ (Scheme 1.1.1) are presented in Table 1.1.1. These

Scheme 1.1.1



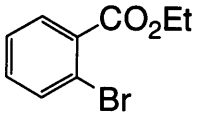
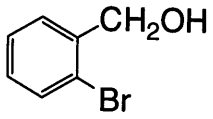
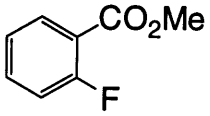
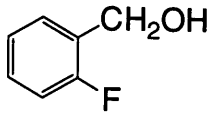
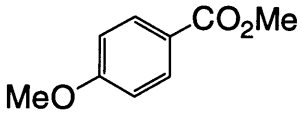
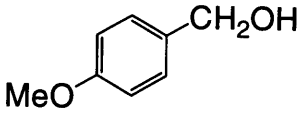
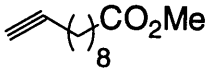
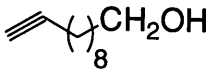
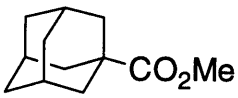
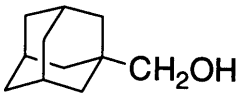
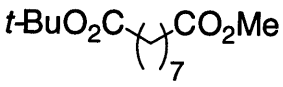
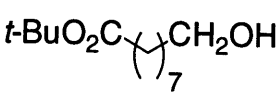
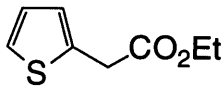
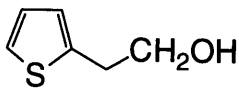
reactions were carried out simply by mixing together the neat reagents in an ordinary test tube open to the atmosphere; only a calcium sulfate drying tube was used to exclude atmospheric moisture. Often, but not always, a deep purple color was noted in the reaction mixture, although there was no noted correlation between the observation of this color and the rate or efficiency of the reaction. The reaction was judged to be complete when the starting material was no longer observable by TLC analysis. Hydrolysis with aqueous sodium hydroxide/THF (or TBAF; see Section 1.1.3) degraded the polymer backbone and freed the polymer-bound product **2** to afford primary alcohol **3**. The crude product alcohol was generally greater than 90% pure as judged by GC and ^1H NMR analysis.[5] Product was obtained (after further purification, if necessary) in good to excellent yields. It was observed that reactions of substrates containing a sterically bulky group (**1m**) or potentially coordinating functionality (e.g., **1b-f**, etc.) required heating or increased amounts of $Ti(O^iPr)_4$ to effect complete conversion on a reasonable time scale. Control experiments showed that both $Ti(O^iPr)_4$ and PMHS were necessary for reduction to occur.

Table 1.1.1 - Ester Reductions with Polymethylhydrosiloxane as the Stoichiometric Reductant

	Esters, **1**	Time (h)	T (°C)	mol% Ti	Alcohols, **3**	yield (%)[a]
a		24	65	25		93
b		24	70	25		78[b]
c		1.3	65	100		89[b]
d		8	65	100		58[c]
e		44	23	100		85[d]
f		5	65	100		85[b]
g		24	23	100		87[b]
h		24	23	100		79[b]

cont'd on next page

Table 1.1.1 cont'd - Ester Reductions with Polymethylhydrosiloxane as the Stoichiometric Reductant

	Esters, **1**	Time (h)	T (°C)	mol% Ti	Alcohols, **3**	yield (%)
i		1.25	65	100		87[b]
j		2	65	100		80[b]
k		24	65	25		89
l		22	40	100		63[e]
m		24	70	25		99
n		5.5	40	100		56[f]
o		24	65	25		8[g]

[a] Isolated yield of material greater than 95% pure as judged by GC and ^{1}H NMR. [b] No reduction of functional groups other than ester was detected. [c] No ring-opened products detected. [d] Some epoxide opening observed (see text). [e] Yield of mixture that was 93:7 alkyne to olefin by ^{1}H NMR. [f] <4% *tert*-Butyl isopropyl nonanedicarboxylate also isolated. [g] Approx. 20% yield of the self-aldol condensation/reduction product also isolated.

Under these conditions, a wide variety of functional groups were tolerated, including terminal and internal olefins (**1b** and **1c**), an α-cyclopropyl ester (**1d**), a primary alkyl bromide (**1g**) and iodide (**1h**), and an aryl bromide (**1i**) and fluoride (**1j**). The electron-rich methyl *p*-methoxybenzoate (**1k**) was also effectively reduced to *p*-methoxy benzyl alcohol (**3k**) using this protocol.

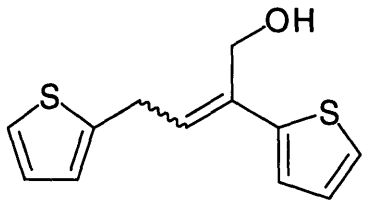
When the reduction of terminal epoxy ester (**1e**) with 2.5 equivalents of PMHS was carried out on a 40 mmol scale at 65 °C in the presence of a full equivalent of $Ti(O^iPr)_4$, both 1,10- and 1,11-undecanediol (approximately 15% diols relative to the product alcohol **3e** by integration of the GC trace of the crude reaction mixture) were observed, as a result of reduction of the epoxide. The mixture of diols could be separated from **3e** by flash chromatography and converted to the corresponding diacetates. Their identity was confirmed by ^1H NMR and low-resolution GC/MS. Close examination of GC traces of the products of small-scale (3 mmol) reactions run under identical conditions revealed varying amounts of the same diols. Similarly, reactions carried out at 40 °C evidenced the presence of approximately 7% diols by GC analysis. By adding a known amount of the diol mixture (relative to an internal standard) to crude reaction mixtures, it was established that the diols were not extracted during aqueous alkaline workup. Epoxide opening could be effectively and reliably curtailed (≤2.5% diols by GC) by carrying out the reaction at 23 °C over 44 h in the presence of a full equivalent of $Ti(O^iPr)_4$. Basic work-up (see Section 1.1.3) afforded an 85% yield (3.0 mmol scale) of **3e** after flash chromatography.

An ester bearing a terminal alkyne (**1l**) could be reduced to the corresponding alcohol if the reaction was carried out at 40 °C; less than 10% reduction of the alkyne to the olefin was observed. An ester containing a free hydroxyl group did not interfere with ester reduction if an extra equivalent of PMHS was added to the reaction mixture. However, cross-linking of the polymeric hydride occurred which caused the

solidification of the reaction mixture to an amorphous glass. The desired diol was isolated from this solid in low yield due to incomplete reaction of the ester group.

The α-trisubstituted ester methyl adamantylformate (**1m**) reacted to give 1-adamantylmethanol (**3m**) in quantitative yield at 70 °C in 24 hours; reactions carried out at 65 °C were incomplete after 24 hours. Due to the elevated temperature necessary to effect complete conversion, it was inferred that the reaction was moderately sensitive to steric effects. A fair degree of chemoselectivity between methyl and *tert*-butyl esters could be achieved as seen by the formation and isolation of *tert*-butyl 9-hydroxynonanoate (**3n**) from the reduction of *tert*-butyl methyl 1,9-nonanedicarboxylate (**1n**). A small amount of the *tert*-butyl isopropyl 1,9-nonanedicarboxylate was also isolated from this reaction;[6] no 1,9-nonanediol was detected in the crude reaction mixture.

Ethyl (2-thiophenyl)acetate (**1o**) underwent low-yield conversion to two products, 2-(2-thiophenyl)ethan-1-ol (**3o**) and allylic alcohol **4** (Fig.1.1.2), which was



4

Fig 1.1.2

identified on the basis of its ^{1}H and ^{13}C NMR spectra. Alcohol **4** was isolated as a mixture of the *cis* and *trans* isomers of the self-aldol condensation product of the presumed aldehyde intermediate (see Scheme 1.1.2), which then underwent further 1,2 reduction to the primary allylic alcohol.[7]

Table 1.1.2 delineates the flexibility of the reaction conditions, as shown by the results of a series of reactions carried out on ethyl decanoate (**1a**) as the test

substrate. Increasing the relative amount of $Ti(O^iPr)_4$ in the system allowed the rate and efficiency of the reaction to be maintained while performing the reaction at lower temperature (see Table 1.1.2, entries 1 and 2). Conversely, the reaction rate was accelerated by heating a single equivalent of $Ti(O^iPr)_4$ with the substrate in the presence of PMHS: at 65 °C, ethyl decanoate was completely and cleanly converted to decanol in 2 hours (Table 1.1.2, entry 3).

Table 1.1.2 - Reduction of Ethyl Decanoate Under Various Conditions

entry	time (h)	temp (°C)	catalyst	mol % catalyst	reductant	% conversion by GC[a]
1	24	65	$Ti(O^iPr)_4$	25	PMHS	100
2	25	23	$Ti(O^iPr)_4$	100	PMHS	100
3	2	65	$Ti(O^iPr)_4$	100	PMHS	100
4	24	65	$Ti(O^iPr)_4$	25	Ph_2SiH_2	100
5	24	23	$Ti(O^iPr)_4$	100	$HSiCl_3$	0[b]
6	24	65	$Ti(O^nBu)_4$	25	PMHS	75
7	2	65	$Ti(O^nBu)_4$	100	PMHS	90
8	96	23	$TEATi(O^iPr)$[c]	100	Ph_2SiH_2	0[b]

[a]when conversion was less than 100%, in general several products were noted. [b]only starting material was detected. [c]$TEATi(O^iPr)$ = triethoxyaminotitanium(IV) isopropoxide.

Other silanes were examined as stoichiometric reductants. Diphenylsilane (2.5 equivalents) served equally well as PMHS under standard reaction conditions (Table 1.1.2, entry 4). Phenylsilane was also effective as the stoichiometric reductant.

However, when trichlorosilane (2.5 equivalents) was combined with $Ti(O^iPr)_4$ and ethyl decanoate, a highly exothermic reaction took place that nonetheless did not result in the formation of reduction products; a GC trace of the reaction mixture quenched with aqueous acid showed only unreacted starting material after 24 hours (Table 1.1.2, entry 5).

The efficacy of two other titanium reagents was explored. Titanium(IV) *n*-butoxide ($Ti(O^nBu)_4$), in combination with PMHS, effected the reduction of ethyl decanoate; albeit at a slower rate than the analogous reaction with $Ti(O^iPr)_4$, as evidenced by the lower conversion to alcohol under identical temperatures, reaction times, and titanium/substrate ratios (Table 1.1.2, entries 6 and 7). Titanium(IV) trialkoxyamino complexes have been proposed as possibly superior catalysts for reactions involving titanium-mediated transformations.[8] However, decanol was not detected in a mixture of ethyl decanoate and PMHS in the presence of [tris(hydroxyethyl)aminato]titanium(IV) isopropoxide (THEATi(O^iPr), Fig. 1.1.3) even after prolonged exposure at room temperature (Table 1.1.2, entry 8).

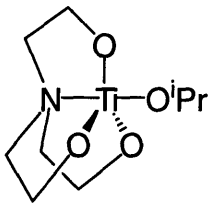


Fig 1.1.3

The primary advantage of this system is the utilization of inexpensive, readily available, stable and relatively innocuous reagents. Both components of this system are commercially available in multikilogram lots, and may be handled with little or no special precautions (in comparison to lithium aluminum hydride and other highly reactive hydride reagents which are pyrophoric and must be handled with extreme

care). In contrast with systems that employ monomeric alkoxysilanes which are poisonous and can cause blindness, PMHS, to our knowledge, is non-toxic.[3] Furthermore, although titanium complexes have been shown to catalyze the disproportionation of alkoxysilanes to silane gas, no pyrophoric products were observed to have been produced by the action of $Ti(O^iPr)_4$ on PMHS, even after prolonged heating under an inert atmosphere, either in the presence or absence of substrates.[3]

The fact that reactions may be run without solvent is a second major advantage to this system. Although these reductions may be carried out in common laboratory solvents such as THF, diethyl ether, and toluene, it is possible and often desirable to simply mix the neat reagents. The elimination of solvent from the reaction itself is a significant step toward reducing the volume of solvent waste, although it remains necessary to dissolve the reaction mixture in a small amount of THF in order to effect hydrolysis of the polymer and to facilitate extraction and isolation of the product. Furthermore, under this protocol it is unnecessary to maintain rigorously anhydrous and oxygen-free conditions. Adventitious water that may be contained in the starting ester was scavenged by the use of excess silane (2.5 equivalents of Si–H per ester). Yields and reaction times were not altered by drying the esters immediately prior to use by passing them through activity I alumina. These attributes afford an extremely simple and attractive protocol for ester reduction: simply mixing the reagents and monitoring the reaction by TLC analysis, followed by hydrolysis and extraction provides the desired primary alcohol in good yield and purity.

This system is compatible with a wide range of functional groups; functional group incompatibilities of previous protocols have been reduced or eliminated. The tolerance of aryl and alkyl bromides, alkyl iodides, and aryl fluorides is especially noteworthy, as several of these transformations were previously carried out in the presence of PMHS only with difficulty and concomitant hydrodehalogenation.[1] The

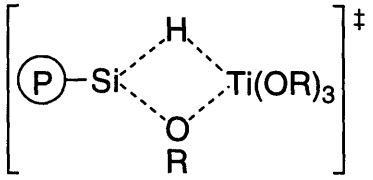
selective reduction of methyl esters in the presence of terminal alkynes and *tert*-butyl esters should be contrasted with the often non-selective highly reactive main-group hydrides. In general, the mildness of these reagents should allow successful application of this protocol to synthetic schemes with less need for complicated protection and masking strategies.

The flexibility of this method contributes to its applicability to a wide variety of substrates. As noted above, several substrates required the addition of larger amounts $Ti(O^iPr)_4$ or gentle heating in order to effect completion of the reaction in a reasonable time. The amenability of this reagent system to alteration of the variables of reaction time, temperature, titanium/substrate ratios and stoichiometric reductant make it extremely adaptable and therefore useful under a wide variety of circumstances. For example, monomeric aryl silanes can be used as stoichiometric reductants in this transformation. In cases where the product of the reaction is sensitive to the conditions required to hydrolyze the polymer, use of silanes of this type would obviate the need for aqueous alkaline workup; mild aqueous workup and removal of solvent and excess silane under reduced pressure would afford the alcohol.

PMHS has been used for many years as a stoichiometric reductant of carbonyl-containing compounds.[9] Several protocols have been advanced for the removal of the PMHS residue upon the completion of these reactions.[10] In our hands, however, only hydrolysis of the polymeric residue in the presence of aqueous alkaline THF proved reliable for the removal of the majority of polymeric reaction products. Indeed, the only impurity observed in these reactions appears to be derived from the polymer.[5]

The proposed reaction cycle, which is semi-catalytic for substoichiometric amounts of $Ti(O^iPr)_4$, involves an initial σ-bond metathesis reaction to generate a titanium hydride-like species (Scheme 1.1.2). The structure of this complex is not

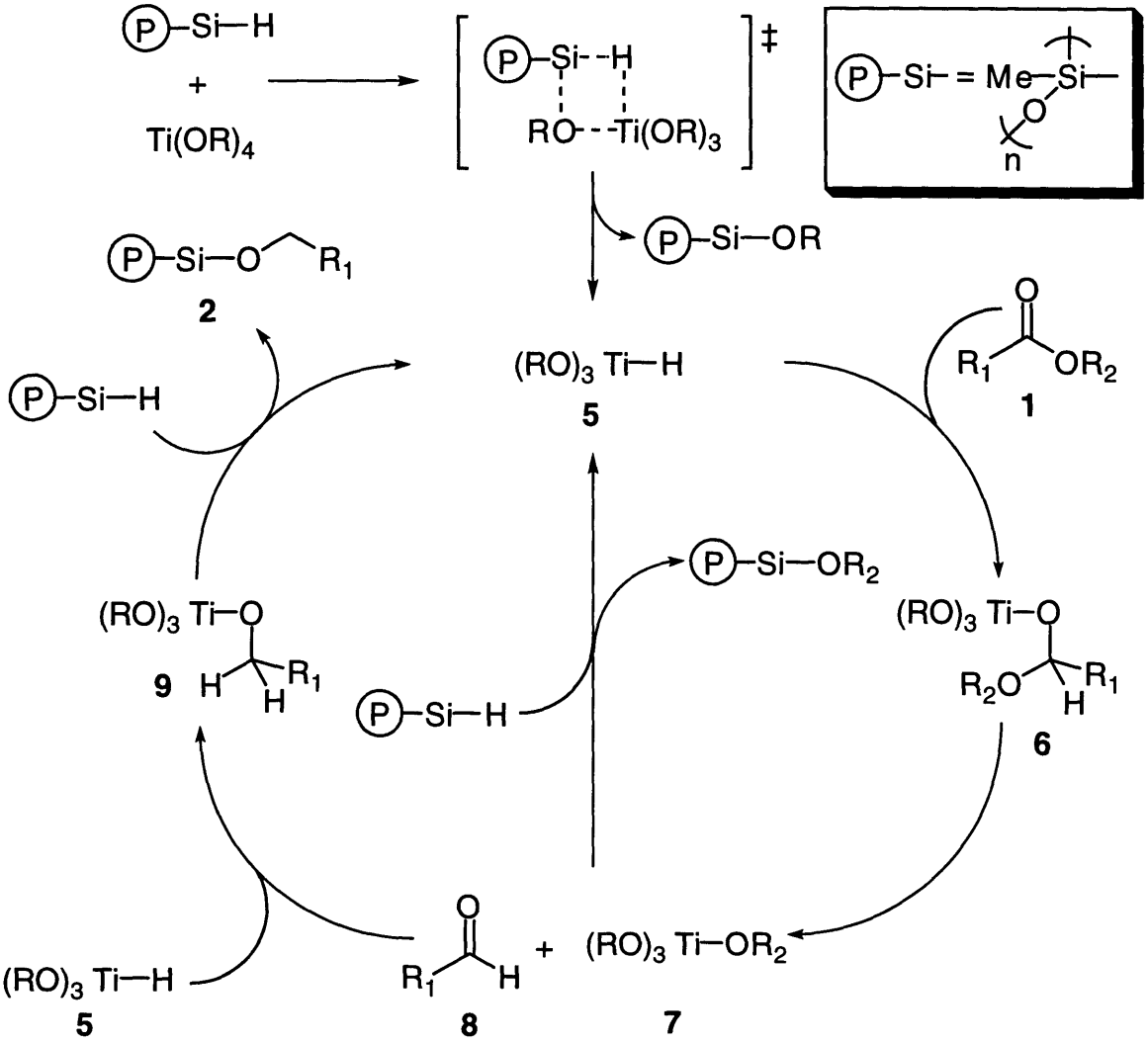
known; an intermediate Ti–H–Si bridging species such as **10** has been proposed (Fig. 1.1.4).[11] For simplicity we have formulated it as $(RO)_3TiH$ (see **5** in Scheme 1.1.2). Following the formation of **5**, ester **1** is reduced to titanium acetal **6** which then



10

Fig 1.1.4

Scheme 1.1.2



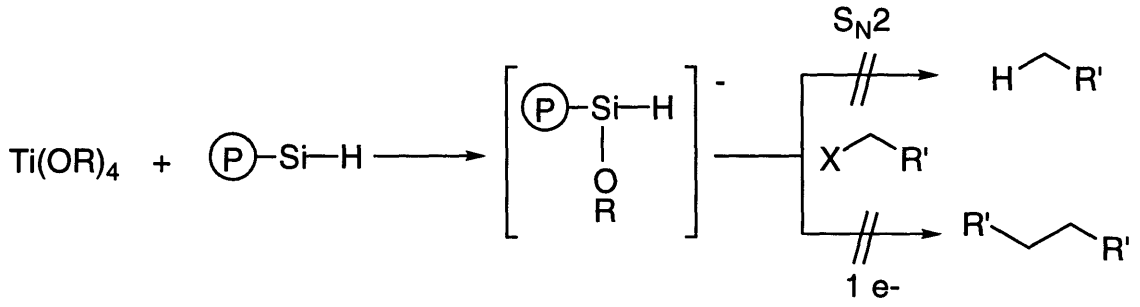
decomposes *via* β-alkoxide elimination to the titanium mixed alkoxide (**7**) and aldehyde **8**. Note that the production of allylic alcohol **4** by the reaction of 2-(2-thiophenyl)ethan-1-ol, $Ti(O^iPr)_4$, and PMHS (*vide supra*) can most easily be explained by such an aldehyde intermediate. Titanium alkoxide **7** can regenerate **5** *via* another σ-bond metathesis, while aldehyde **8** is further reduced by another equivalent of **5**. The resulting titanium alkoxide **9** undergoes σ-bond metathesis to regenerate **5** and afford the product alcohol bound to the polymer (**2**).

The observation that $Ti(O^nBu)_4$ effects the reaction of PMHS with esters more slowly than the isopropoxide analog provides insight into one aspect of the mechanism of this reaction. Based on simple steric arguments, one would expect an *n*-butoxy substituted species to react faster than the isopropoxy complex in an associative mechanism. In the present case, σ-bond metathesis between Si–H and Ti–O bonds is complicated by the fact that the Si–H bond is incorporated in a polymer. The approach of a titanium alkoxide to the polymer should therefore be especially sensitive to steric effects. On the other hand, the aggregation state of titanium(IV) branched alkoxides is generally lower than that of straight chain homologs, which is believed to explain the greater reactivity seen with $Ti(O^iPr)_4$.[12] The tetradentate chelate complex $THEATi(O^iPr)$ is presumably too sterically encumbered to interact with the polymer.

Alternatives to the hypothesis of a titanium hydride (or titanium/silane adduct) as the active reductant include Lewis-acid catalyzed silane reductions, anionic hydridosilicate reducing agents, and radical-induced reduction.[13-15] All three of these alternatives are unlikely. Several esters possessing potentially coordinating functionality reacted sluggishly, an observation which makes Lewis-acid catalyzed silane addition to the carbonyl seem plausible. However, it was observed that neither the rate nor the efficiency of the reaction was altered by the presence of 20 equivalents of pyridine (relative to titanium).

Anionic hydridosilicates are capable of reducing esters, and ligand transfer from titanium to silicon could produce an anion of this type (Scheme 1.1.3). Two

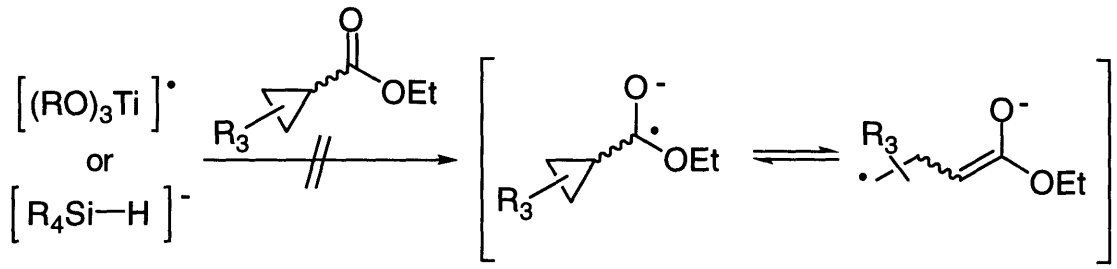
Scheme 1.1.3



observations make this alternative unlikely. First, anionic hydridosilicates react with electrophiles; that primary alkyl bromides and iodides are not reduced suggests that such species are not produced. Second, anionic hydridosilicates are known to function as electron transfer agents and halides have been shown to dimerize in their presence. Such a reaction was not observed.

Finally, any kind of radical-induced carbonyl reduction pathway would likely cause ring opening of an α-cyclopropyl ester (Scheme 1.1.4), as well as significant decomposition of alkyl and aryl halides, neither of which was observed.[16]

Scheme 1.1.4



1.1.2 Conclusion

We have shown that PMHS effects the hydrosilylation of carboxylic esters in the presence of $Ti(O^iPr)_4$; primary alcohols are obtained upon aqueous alkaline/THF work-up of the polymer-bound reaction products. This system is tolerant of a diverse set of common organic functional groups and is tunable over a range of temperatures, reaction times, and titanium/substrate ratios. The simplicity, low cost, environmental friendliness, and flexibility of this system recommend it as a promising tool for organic chemists, especially for use in large-scale applications where traditional methods are of limited utility.

1.1.3 Experimental

General. All reactions were carried out in ambient air in disposable test tubes. The tubes were capped with rubber septa through which a small drying tube containing indicating $CaSO_4$ (Drierite, W.A. Hammond Co.) had been inserted. Esters that were liquids could be passed through a short plug of activity I alumina immediately prior to use, as could PMHS (MW≈2270, Aldrich); however, it was found that both the substrates and the silane could be used as received. Solid esters were typically soluble in $Ti(O^iPr)_4$ and were used as received. $Ti(O^iPr)_4$ was handled and stored under argon and transferred by syringe to minimize hydrolysis by atmospheric moisture. Unless otherwise noted, all other reagents and solvents were either commercially available or prepared according to standard procedures, and were used as obtained from the supplier.

Flash column chromatography was performed on Kieselgel 60 (230-400 mesh). Melting points were obtained on a Haake-Buchler melting point apparatus and are uncorrected. Yields, unless otherwise stated, refer to isolated yields of compounds >95% pure as assessed by capillary GC and ^1H NMR. NMR spectra were recorded on Varian XL or Varian Unity 300 MHz spectrometers.

Method 1. General Procedure for the Reduction of Esters. Into a 15 mL test tube were weighed the ester to be reduced (3.0 mmol) and PMHS (450 mg, 7.5 mmol). A Teflon coated magnetic stirring bar was placed in the tube, which was then capped with a septum. $Ti(O^iPr)_4$ (0.75 mmol, 0.223 mL) was added via syringe, and a drying tube was inserted through the septum. The mixture was shaken to homogeneity; slight warming of the tube and the evolution of a small amount of gas were noted. In several cases the reaction mixture turned a deep purple-black for several minutes, and then returned to the usual pale yellow to orange-red color during the course of the reaction. The reaction tube was placed in an oil bath regulated at the

specified temperature to ±1 °C (all esters that were solids at room temperature dissolved to give a homogenous solution). After stirring for the specified time, the reaction mixture was cooled to room temperature and diluted with THF (20 mL) and transferred to a 100 mL round-bottomed flask. To this flask was added SLOWLY with rapid stirring 4 M aqueous sodium hydroxide (20 mL). THE MIXTURE OFTEN BUBBLED BRIEFLY BUT VIGOROUSLY UPON THE ADDITION OF THE BASE. The mixture was stirred, loosely capped, for six to twelve hours; the resulting cloudy white mixture was then extracted with diethyl ether (~20 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed (2×10 mL 1 N HCl (aq), 1×20 mL saturated brine) and dried ($MgSO_4$). The solution was filtered to remove the drying agent and concentrated on the rotary evaporator to afford the crude product, 90-100% pure by GC and/or ^1H NMR. The products were easily separable from the PMHS-derived impurities by flash column chromatography (hexane/ethyl acetate) to yield material at least 95% pure as judged by GC analysis and ^1H NMR; Kugelrohr distillation was also used as noted to remove impurities.

Method 2. Alternate Fluoride Workup. The cooled reaction mixture was diluted with THF (20 mL) and transferred to a 100 mL round-bottomed flask. A commercially available solution of tetrabutylammonium fluoride in THF (1 M, 15 mL) was added SLOWLY; THE MIXTURE BUBBLED BRIEFLY BUT VIGOROUSLY. The mixture was stirred at room temperature for 20 minutes, and the solvent was removed by rotary evaporation. The resulting viscous oil was partitioned between 1 N aqueous hydrochloric acid and diethyl ether (~20 mL ea.) and the layers were separated. The organic layer was washed (1×20 mL 1 M aqueous sodium hydroxide, 1×20 mL saturated brine); any solids which formed were disposed of with the aqueous layer. The ethereal solutions were dried ($MgSO_4$) and filtered to remove the drying agent;

concentration on the rotary evaporator afforded the crude product, which could be purified as described in Method 1.

1-decanol, 3a. Ethyl decanoate (601 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.223 mL, 0.75 mmol) was added and the reaction was carried out at 65 °C. After stirring 24 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 to afford the crude product. Kugelrohr distillation (65 °C, 8×10^{-2} Torr) afforded the product as a clear colorless oil, 443 mg, 93%. The ^1H NMR spectrum was consistent with the published spectrum.[3]

1-adamantyl methanol, 3m. Methyl 1-adamantyl formate (582 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.26b mL, 0.75 mmol) was added and the reaction was carried out at 65 °C. After stirring 24 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 and concentrated to afford the product as a white solid, 499 mg, 99%. Mp: 119-120 °C (lit. mp: 115-118 °C.)[17] The ^1H NMR spectrum was consistent with the published spectrum.[18]

10-undecen-1-ol, 3b. Methyl 10-undecenoate (595 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.26b mL, 0.75 mmol) was added and the reaction was carried out at 70 °C. After stirring 23 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 to afford the crude product. Kugelrohr distillation (65 °C, 8x10 Torr) afforded the product as a clear colorless oil, 399 mg, 78%. The ^1H NMR spectrum was consistent with the published spectrum.[3]

9-*cis*-octadecen-1-ol, 3c. Methyl oleate (890 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.890 mL, 3.0 mmol) was added and the reaction was carried out at 65 °C. After stirring 2 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 to afford the crude product. Flash column chromatography (1.5:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 718 mg, 89%. The ^1H NMR spectrum was consistent with the published spectrum.[3]

10-undecyn-1-ol, 3l. Methyl 10-undecynoate (590 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.890 mL, 3.0 mmol) was added and the reaction was carried out at 40 °C. After stirring 22 h, TLC analysis showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 to afford the crude product. Flash column chromatography (2:1 hexane/ethyl acetate) afforded the product as a 93:7 mixture (by integration of the appropriate ^1H NMR signals) of the desired alkynyl alcohol and 10-undecen-1-ol. The product was a clear colorless oil, 317 mg, 63%. The ^1H NMR spectrum was consistent with the published spectrum.[3]

chrysanthemumyl alcohol, 3d. Methyl chrysanthemumate (mixture of *cis* and *trans*, 590 mg, 3.0 mmol,) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.890 mL, 3.0 mmol) was added and the reaction was carried out at 40 °C. After stirring 8 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 to afford the crude product. By GC and ^1H NMR the only products present were the alcohol (same *cis/trans* ratio as the ester) and a trace of

isopropoxy chrysanthemumate. Flash column chromatography (2.5:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 269 mg, 58%. The ^{1}H NMR spectrum was consistent with the published spectrum.[3]

10,11-epoxyundecan-1-ol, 3e. Methyl epoxy-10-undecenoate (110 mg, 0.5 mmol) and PMHS (66 mg, 1.1 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.150 mL, 0.5 mmol) was added and the reaction was carried out at 65 °C. After stirring 2.5 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 to afford the crude product. Flash column chromatography (2:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 75 mg, 81%. The ^{1}H NMR spectrum was consistent with the published spectrum.[3]

***cis*-9,10-epoxyoctadecan-1-ol, 3f.** Methyl epoxy-oleate (160 mg, 0.5 mmol) and PMHS (75 mg, 1.25 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.150 mL, 0.5 mmol) was added and the reaction was carried out at 65 °C. After stirring 5 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to Method 1 to afford the crude product. Flash column chromatography (2:1 hexane/ethyl acetate) afforded the product as a white solid, 121 mg, 85%. Mp: 55-56 °C (lit. mp: 52-53 °C.)[17] The ^{1}H NMR spectrum was consistent with the published spectrum.[3]

6-bromohexan-1-ol, 3g. Ethyl 6-bromohexanoate (669 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.893 mL, 3.0 mmol) was added and the reaction was carried out at room temperature. After stirring 23 h, the reaction mixture was hydrolyzed (12 h) and worked up according to Method 1 to afford the crude product. Flash column chromatography (4:1 hexane/ethyl acetate)

afforded the product as a clear colorless oil, 475 mg, 87%. The ^{1}H NMR spectrum was consistent with the published spectrum.[3]

6-iodohexan-1-ol, 3h. Ethyl 6-iodohexanoate (810 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; Ti(O^{i}Pr)$_4$ (0.893 mL, 3.0 mmol) was added and the reaction was carried out at room temperature. After stirring 23 h, the reaction mixture was hydrolyzed (12 h) and worked up according to Method 1 to afford the crude product. Flash column chromatography (4:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 541 mg, 79%. The ^{1}H NMR spectrum was consistent with the published spectrum.[19]

4-methoxybenzyl alcohol, 3k. Methyl 4-methoxybenzoate (831 mg, 5.0 mmol) and PMHS (750 mg, 12.5 mmol) were mixed according to Method 1; Ti(O^{i}Pr)$_4$ (0.372 mL, 1.25 mmol) was added and the reaction was carried out at 65 °C. After stirring 23 h, the reaction mixture was hydrolyzed (12 h, 4 M NaOH), and worked up according to Method 1 to afford the crude product. Flash column chromatography (1:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 614 mg, 89%. The ^{1}H NMR spectrum was consistent with the published spectrum.[18]

2-bromobenzyl alcohol, 3i. Ethyl 2-bromobenzoate (590 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; Ti(O^{i}Pr)$_4$ (0.890 mL, 3.0 mmol) was added and the reaction was carried out at 65 °C. After stirring 1.25 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h) and worked up according to Method 1 to afford the product as a white solid, 487 mg, 87%. Mp = 80-81 °C (lit. mp: 79-82 °C).[17] The ^{1}H NMR spectrum was consistent with the published spectrum.[18]

2-fluorobenzyl alcohol, 3j. Methyl 2-fluorobenzoate (500 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.890 mL, 3.0 mmol) was added and the reaction was carried out at 65 °C. After stirring 2 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h) and worked up according to Method 1 to afford the crude product . Flash column chromatography (2:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 301 mg, 80%. The ^1H NMR spectrum was consistent with the published spectrum.[18]

***tert*-butyl 9-hydroxynonanoate, 3n.** *tert*-Butyl methyl 1,9-nonanedicarboxylate (260 mg, 1.0 mmol) and PMHS (180 mg, 3.0 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.300 mL, 1.0 mmol) was added and the reaction was carried out at 40 °C. After stirring 5.5 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h) and worked up according to Method 1 to afford the crude product . Flash column chromatography (3:1 hexane/ethyl acetate) afforded the product, as well as 8 mg of *tert*-butyl isopropyl 1,9-nonanedicarboxylate. The product was a clear colorless oil, 129 mg, 56%; ^1H NMR (300 MHz, $CDCl_3$): δ 3.63 (t, 2 H, J = 6.6 Hz), 2.20 (t, 2 H, J = 7.4 Hz), 1.58 (m, 5 H), 1.44 (s, 9 H), 1.32 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 79.9, 62.9, 35.5, 32.7, 29.2, 28.9, 28.1, 25.6, 25.0; IR (neat) (cm^{-1}): 3363, 2977, 2931, 2856, 1732, 1457, 1419, 1392, 1367, 1256, 1156, 1107, 1056. Anal. Calc'd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.81; H, 11.13.

2-(2-thiophenyl)ethan-1-ol, 3o. Methyl 2-thiophenylacetate (589 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to Method 1; $Ti(O^iPr)_4$ (0.223 mL, 0.75 mmol) was added and the reaction was carried out at 65 °C. After stirring 23 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h) and worked

up according to Method 1 to afford the crude product . Flash column chromatography (4:1 hexane/ethyl acetate) afforded the product, as well as 38 mg of the allylic alcohol **4** (identified on the basis of it's ^{1}H and ^{13}C NMR spectra). The product 2-(2-thiophenyl)ethan-1-ol was a clear colorless oil, 32 mg, 8%. The ^{1}H NMR spectrum was consistent with the published spectrum.[3]

1.1.3 References

1. Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323.
2. Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 3221.
3. Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751.
4. Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093.
5. The primary impurity observed in these reactions derived from degradation of the polymeric silane in the presence of the titanium catalyst. When PMHS was heated in the presence of $Ti(O^iPr)_4$, aqueous alkaline workup led to the isolation of a small amount of material that exhibited a multi-component ^1H NMR spectrum but which by GC analysis was a single, discrete compound with a mass-to-charge ratio of 220 (observed for the parent peak by low-resolution GC/MS). The impurity present in the product alcohols appears identical to this material. Alkaline hydrolysis of PMHS in the presence of isopropanol did not yield any material with physical characteristics similar to those of this impurity. The impurity could be removed by flash chromatography or distillation.
6. Although activated silanes (those with aryl or alkoxy substituents) have been shown to be useful in these reactions, trichlorosilane was not found to be effective as the ultimate reductant. Observation of only starting ester after an exothermic reaction between trichlorosilane and ethyl decanoate in the presence of $Ti(O^iPr)_4$ suggests that decomposition of the $Ti(O^iPr)_4$ is occurring. $Ti(O^iPr)_4$ is a known transesterification catalyst (Otera, J. *J. Chem. Rev.* **1993,** *93*, 1449; Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: New York, 1986), however, no transesterification products were detected in the reaction depicted in Table 1.1.2, entry 5.
7. A similar product was noted in the reduction of methyl phenacetate by Lawrence and Breeden: Breeden, S. W.; Lawrence, N. J. *Synlett* **1994**, 833.
8. Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 6142.

9. Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973**, *6*, 1.

10. Jaxa-Chamiec, A.; Shah, V. P.; Kruse, L. I. *J. Chem. Soc. Perkin Trans. I* **1989**, 1705. Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162.

11. Breeden, S. W.; Lawrence, S. J. *Synlett* **1994**, 833.

12. Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162.

13. Calas, R. *Pure Appl. Chem.* **1966**, *13*, 61.

14. Corriu, R. J. P.; Guérin, C.; Henner, B.; Wang, Q. *Organometallics* **1991**, *10*, 2297.

15. Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371.

16. Carey, F.A.; Sundberg, R.J. *Advanced Organic Chemistry, Third Edition, Part A: Structure and Mechanisms*; Plenum Press: New York, 1991, pp. 656-658.

17. *Catalog/Handbook of Fine Chemicals*; Aldrich Chemical Company, Inc., 1994.

18. *The Aldrich Library of NMR Spectra, Second Edition*; Pochert, C.J.; Ed.; Aldrich Chemical Company, Inc., 1983.

19. Buijs, W.; van Elburg, P.; van der Gen; A. *Synth. Commun.* **1983**, *13*, 387.

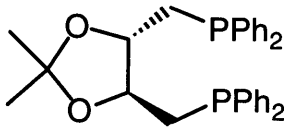
Part 2 - Titanium-Catalyzed Asymmetric Imine Hydrosilylation

2.0 Background

The deep-seated importance of molecular asymmetry within living organisms (from human beings to the tiniest organisms that infect them) lies behind the recent explosion in the development of asymmetric methods in synthetic organic chemistry.[1] The tragic historical precedent of thalidomide has shown that ignoring the 'handedness' of life can lead to disasterous results.[2] It is clear that chemists seeking to understand the function and mechanism of biological systems must learn to duplicate their seeming infinitely delicate control over chemical reactions.

Of all the possible ways of making chiral non-racemic compounds, catalytic asymmetric processes are the most efficient.[2,3] By definition, the asymmetric nature of a single catalyst molecule may be multiplied hundreds to millions of times over the course of the reaction. Reactions catalyzed by transition metal-ligand complexes are of great use in this regard, as the flexibility afforded by the variable electronic and steric environments found within a transition metal-ligand scaffold often provides fine control over chemo-, stereo-, and enantioselectivity.[4]

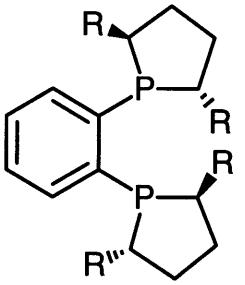
Such has been the case for catalytic asymmetric means for the production of chiral non-racemic amines from imine precursors; such amine compounds are of great importance in the pharmaceutical and agrochemical industries.[5] A number of late transition-metal catalyzed methods for the saturation of carbon-nitrogen double bonds have been developed in recent years. The first example of this type of reaction was published by Kagan and co-workers over 20 years ago.[6] This protocol involved the use of a rhodium catalyst and the chiral non-racemic bisphosphine ligand (+)-DIOP (**1**) (Fig. 2.0.1), and afforded amine products with up to 65% enantiomeric excess (ee).



(+)-DIOP **1**

Fig. 2.0.1

Several similar reactions involving rhodium catalysts and a variety of bisphosphine ligands have been reported since that time; an ee of 96% was obtained in one example.[7-12] A group of iridium catalysts for the hydrogenation of imines, also making use of bisphosphine ligands, have been reported as well; the highest ee's obtained with these systems were about 80%.[13-15] Recently, Burk and co-workers have developed a very effective and general method for the hydrogenation of *N*-acylhydrazones to the corresponding saturated chiral non-racemic compounds in high ee (many substrates greater than 90%).[16,17] This process makes use of a rhodium catalyst and the bisphosphine DuPhos (**2**) (Fig. 2.0.2). Finally, Noyori and coworkers

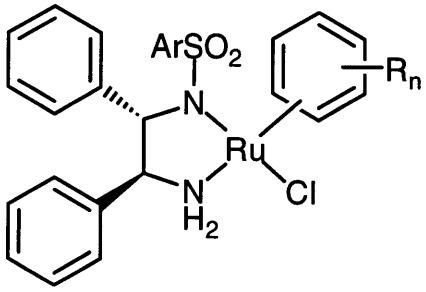


R = Me, Et, *i*Pr

DuPhos **2**

Fig. 2.0.2

have recently disclosed their asymmetric transfer hydrogenation of imines catalyzed by chiral η^6-aryl-ruthenium-diamine complexes **3** (Fig 2.0.3).[18,19] This process



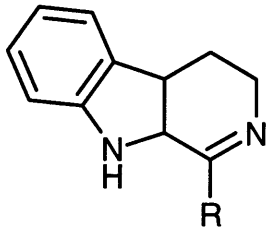
η^6-arene=*p*-cymene, benzene

Ar=*p*-tolyl, mesityl, 1-naphthyl

3

Fig. 2.0.3

hydrogenates imines of type **4** (Fig. 2.0.4) with excellent ee (generally greater than 90%), but acyclic and exocyclic imines were reduced in 72-89% ee.



R=Me, Ph

4

Fig. 2.0.4

Although these procedures represent significant advances in producing chiral non-racemic amines from achiral imines, there is still room for improvement. The rhodium-bisphosphine systems in general do not achieve the high levels of enantioselectivity required in modern asymmetric synthesis. This is also true of the iridium based methods, although these have been successfully applied to agrochemical production where lower enantioselectivity can sometimes be tolerated.[15] Although Burk's rhodium-DuPhos chemistry[16] has a broader substrate scope, it suffers from requiring the use of *N*-acylhydrazones as substrates. Here, the nitrogen substituent serves as a coordinating group which orients the organic substrate within the coordination sphere of the metal. Also, to obtain free amines, the *N*-acylhydrazines which are the products of this process are treated with superstoichiometric amounts (greater than two equivalents) of expensive samarium diiodide. The breadth of substrate scope in Noyori's ruthenium-catalyzed process has not yet been fully delineated, although it was noted that acyclic and exocyclic imines were reduced with lower enantioselectivities than the best cyclic substrates.[18]

References

1. A survey of a recent issue of *The Journal of Organic Chemistry* (**1997**, Vol. 62, No. 8), 25 of 65 published accounts involved the development or use of asymmetric methods in organic synthesis.
2. Ojima, I. In *Catalytic Asymmetric Synthesis*; I. Ojima, Ed.; VCH Publishers, Inc.: New York, 1993; pp v-vii.
3. Industrially, at present most chiral non-racemic compounds are accessed *via* resolution of racemic mixtures or from the chiral pool. However, of the chemical (as opposed to physical) methods for induction of asymmetry, catalytic methods are the most potentially efficient.
4. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059-1070.
5. For a recent review of other chemical methods for the production of asymmetric amines, see Johansson, A. *Contemp. Org. Synth.* **1995**, 393. For a review specific to asymmetric reductions of imines and other C-N double bonds, see Zhu, Q.-C. and Hutchins, R. O. *Org. Prep. Proced. Int.* **1994**, *26*, 193.
6. Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353.
7. Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 995-996.
8. Brunner, H.; Becker, R.; Gauder, S. *Organometallics* **1986**, *5*, 739.
9. Brunner, H.; Kürzinger, A.; Mahboobi, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* **1988**, *321*, 73.
10. Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684.
11. Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G.-J.; Rettig, S. J. *Inorg. Chem* **1991**, *30*, 5002.
12. Buriak, J. M.; Osborn, J. A. *Organometallics* **1996**, *15*, 3161.

13. Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558.

14. Osborn, J. A.; Chan, Y. N. C. *J. Am. Chem. Soc.* **1990**, *112*, 9400.

15. Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475.

16. Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399.

17. Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.

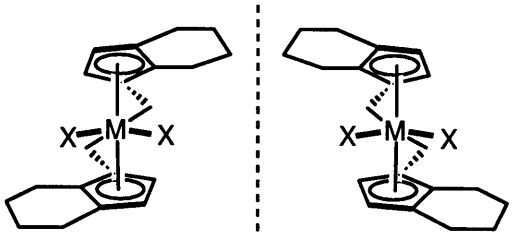
18. Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

19. Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.

Section 2.1 - Catalytic Asymmetric Imine Hydrosilylation

2.1.0 Introduction

Of the many successful metal-ligand pairs employed in enantioselective synthesis, the ethylenebis(η^5-1,2,3,4-tetrahydroindenyl)MX_2 ((EBTHI)M) system **1**, where M is a group 4 metal and X is a halide or alkoxide, has been one of the most fruitful (Fig. 2.1.1). Hoveyda and Morken have recently reviewed the chemistry of



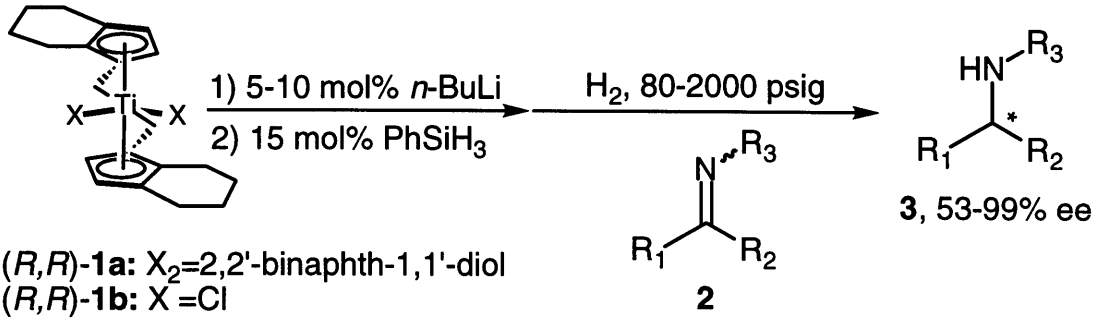
(*S,S*)-**1** (*R,R*)-**1**

Fig. 2.1.1

these complexes, which ranges from the industrially important production of isotactic polypropylene to a number of carbon-carbon bond forming reactions.[1] Also included in this context are a number of Ti–H insertion reactions, many of which were developed in the Buchwald laboratories. For example, chiral non-racemic (EBTHI)Ti complexes catalyze the asymmetric hydrogenation of unfunctionalized trisubstituted olefins[2] and enamines,[3] the asymmetric hydrosilylation of ketones,[4] and the kinetic resolution of disubstituted 1-pyrrolines.[5] Recently, a catalytic asymmetric reductive cyclization/carbonylation process has also been developed.[6] Of particular relevance to this chapter, however, is a system for the catalytic asymmetric hydrogenation of imines developed by Dr. C. A. Willoughby in our laboratories. This process makes use of the (*R,R*)-(EBTHI)Ti ligand-metal framework; the scope, limitations, and mechanism of the transformation were investigated in detail.[7-11]

Briefly, it was found that (*R,R,R*)-(EBTHI)Ti-2,2'-binaphth-1,1'-diol (**1a**) and (*R,R*)-(EBTHI)$TiCl_2$ (**1b**) could both serve as pre-catalysts for the asymmetric hydrogenation of a number of imines (**2**) (Scheme 2.1.1) under moderate to high

Scheme 2.1.1



(*R,R*)-**1a:** X_2=2,2'-binaphth-1,1'-diol
(*R,R*)-**1b:** X =Cl

2

hydrogen pressures to afford enantiomerically enriched amines **3**. Endocyclic imines were reduced with 95–99% ee, while acyclic imines were found to be reduced with somewhat poorer enantioselectivities. This was thought to be due to the presence of both *syn* and *anti* isomers for the acyclic imines, an isomerism which is impossible in the case of small-ring endocyclic imines. However, for acyclic *N*-methyl imines, high enantioselectivities were observed regardless of *syn/anti* ratio. The active reducing species was proposed to be a titanium(III) hydride, and the kinetics of the reaction were explored in detail.

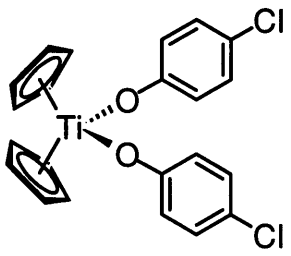
This initial reduction procedure provided many advances for the generation of enantiomerically enriched amines. However, a simpler catalyst activation protocol and elimination of the need for the use of high hydrogen pressures was sought. The pressure concern was addressed by changing the hydride source to a silane, thereby giving rise to a catalytic asymmetric hydrosilylation method. A more convenient activation procedure followed from a mechanistically related procedure for the reduction of lactones to lactols.[12] This activation procedure, which was developed primarily by Dr. X. Verdaguer in the Buchwald laboratories, proceeds *via* the

conversion of a titanium fluoride to the presumed titanium(III) hydride catalyst (see Section 2.1.1).

The initial development of this system for the hydrosilylation of imines was followed by an examination of the scope of the reaction in regard to chemoselectivity when other potentially reducible functionality was included in the substrate molecule, namely 1,2-disubstituted olefins. Although these olefins were found to be reactive under a variety of reaction conditions, a method for obtaining the desired products with high enantioselectivity and reasonable chemoselectivity was acheived. Furthermore, several important parameters of the protocol were more precisely delineated. Finally, the diasteroselectivity of the transformation of imines bearing stereogenic centers was also briefly explored.

2.1.1 Catalytic Asymmetric Imine Hydrosilylation

Verdaguer, Berk, and Buchwald's method for the reduction of lactones to lactols at room temperature involves the use of titanocene bis(*para*-chlorophenoxide) **4** (Fig. 2.1.2) as a precatalyst.[12] This complex reacts with PMHS, (see Section 1.1.1) in the

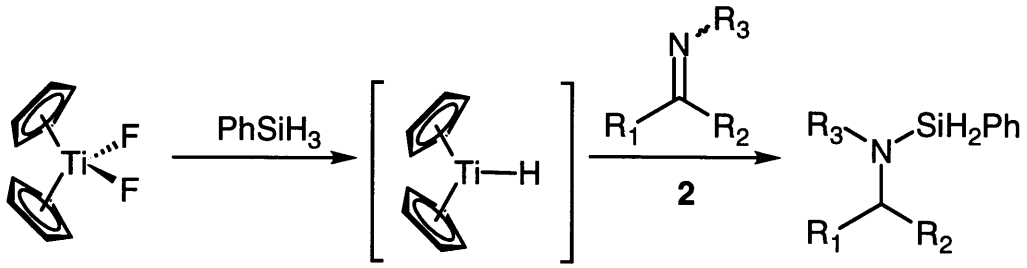


4

Fig. 2.1.4

presence of TBAF on alumina to generate the active catalyst. Investigations to clarify the role of fluoride in the activation process led to the discovery that addition of phenylsilane to a yellow solution of titanocene difluoride **5** in THF at room temperature yielded a dark blue solution which was an active catalyst for the hydrosilylation of imines (**2**) to afford racemic silylamines (**6**) (Scheme 2.1.2). Deep blue or green

Scheme 2.1.2



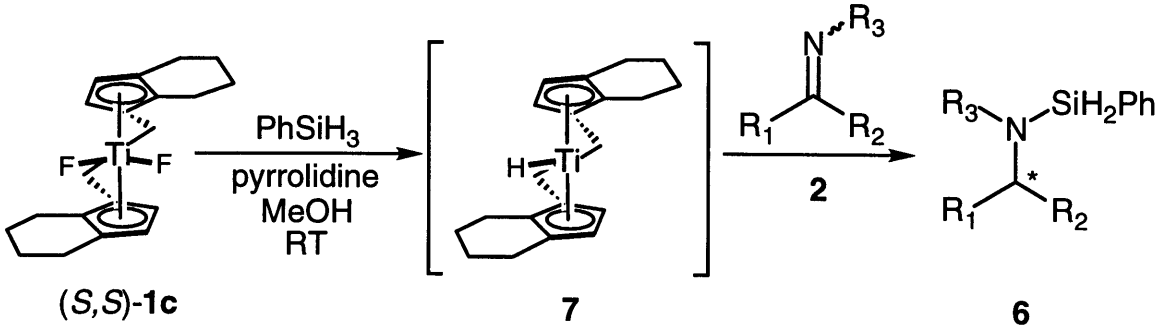
5 blue solution *rac*-**6**

colors have been noted by others upon generation of related titanium(III) species.[13] This experiment indicated that it is possible to exchange the strong Ti–F bond for a Ti–H bond under mild conditions to generate the proposed titanium(III) hydride or its

equivalent.[14-17] To our knowledge, the conversion of an early transition metal fluoride to the corresponding hydride by treatment with a silane has not previously been reported.[18] However, a process similar to the reverse of this reaction, namely, the exchange of Ti–H with Ti–F mediated by tin, has been described.[19]

The new activation technique was also applicable to the more sterically demanding (EBTHI)Ti system. When a solution of (*S,S*)-(EBTHI)TiF_2 (**1c**) was treated with phenylsilane, heating the mixture to 60 °C yielded an emerald green solution which also displayed catalytic activity for the hydrosilylation of imines. The same result was observed at room temperature when small amounts of MeOH and pyrrolidine were added to a solution of (*S,S*)-**1c** and phenylsilane (Scheme 2.1.3).[20] Subsequent

Scheme 2.1.3



(*S,S*)-**1c** **7** **6**

addition of imine **2**, followed by stirring at room temperature (or slightly warmer, *vide infra*) yielded the corresponding enantiomerically enriched silylated amine (**6**).[21] Treatment of the silylamines with aqueous acid gave the enantiomerically enriched free amine (**3**).

As mentioned above, an important feature of this hydrosilylation system is its experimental simplicity. While in the case of the related hydrogenation[9] elevated pressures (80–2000 psi) and temperatures (ca. 65 °C) were required, hydrosilylation reactions were usually carried out at room temperature under an argon atmosphere.

Furthermore, the catalyst could be activated either prior to addition of the substrate or in the presence of the imine.

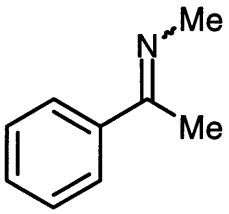
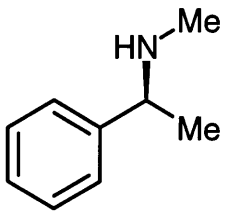
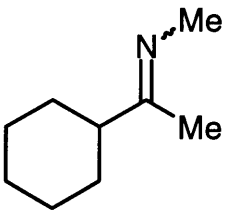
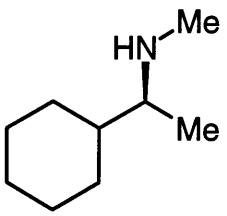
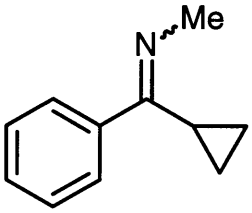
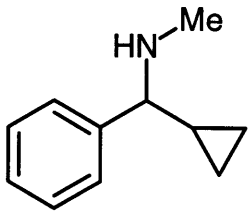
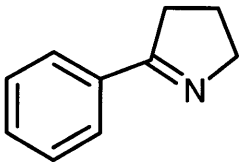
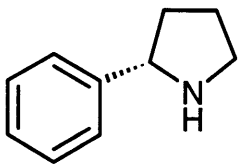
The initial substrates chosen to demonstrate the effectiveness of this protocol were all acyclic *N*-methyl or endocylic derivatives, as these types of substrates afforded high enantioselectivities with the related hydrogenation procedure (*vide supra*). Table 2.1.1 details the results of this catalytic asymmetric hydrosilylation reaction carried out in the presence of the catalyst obtained from (*S*,*S*)-**1c**. The catalyst was able to distinguish effectively (*vide infra*) between phenyl and methyl or cyclopropyl groups, or in one case, cyclohexyl and methyl; phenyl pyrroline (**2d**) was also hydrosilylated with high enantioselectivity. These results are comparable to those obtained for similar substrates reduced in the related hydrogenation protocol.[9] The substrate to catalyst ratio was also increased over the previous method, presumably due to the increased ease of handling the air-stable pre-catalyst.[22]

Other substrates which incorporated groups attached to the carbonyl carbon that were larger than phenyl and methyl or cyclopropyl required slightly more vigorous conditions to reach completion in under 12 hours. Table 2.1.2 shows two such substrates. Tetralone-derived imine **2e** reacted sluggishly in the presence of only 1 mole percent catalyst. This is somewhat surprising, since the endocyclic methylene attached to the carbonyl group would not be expected to be much more sterically demanding than a methyl group. However, the fact that this group is tied back in a ring seems rather to minimize the potential steric bulk presented to the catalyst, as it was necessary to increase the catalyst to substrate ratio and the reaction temperature (to 50 °C) to hydrosilylate acyclic phenyl-secondary imine **2f** at a comparable rate. The apparent order of steric size for differentiation by this catalyst system is thus:

methyl, cyclopropyl < 2° exocyclic < 2° acyclic < phenyl

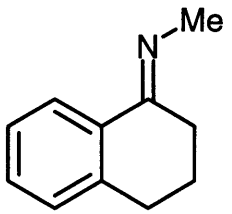
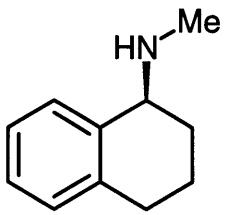
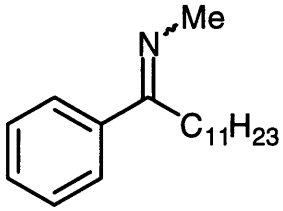
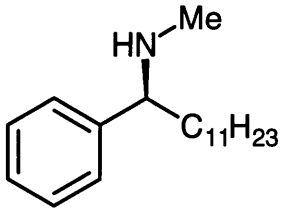
This order only holds for acyclic and exocyclic imines; in general, 5- and 6-membered endocyclic imines react with high enantioselectivity regardless of the exocyclic substituent (see Section 2.2.1).

Table 2.1.1 - Catalytic Asymmetric Hydrosilylation of Imines in the Presence of Catalyst Derived from (*S,S*)-1c[a]

	Imine, **2**	Amine, **3**[b]	mol % cat	Yield (%)[c]	ee(%)[d]
a			1	94	97
b			1	88	93
c			1	91	97
d			1	97	99

[a] These hydrosilylations were carried out by Dr. X. Verdaguer or Dr. U. E. W. Lange. [b] The absolute configurations for the product amines **3a**, **3b**, and **3d** were determined by polarimetry. [c] Yields refer to isolated compounds of >95% purity by GC and ^{1}H NMR. [d] ee's were determined by GC analysis of the corresponding trifluoroacetamides on a Chiraldex G-TA column.

Table 2.1.2 - Catalytic Asymmetric Hydrosilylation of Sterically Demanding Imines in the Presence of Catalyst Derived from (*S,S*)-1c

	Imine, **2**	Amine, **3**[a]	mol % cat	T (°C)	Yield (%)[b]	ee(%)[c]
e			2.5	23	80	96
f			2.5	50	88	95

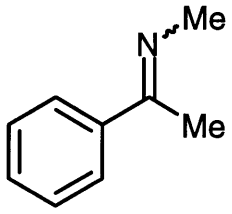
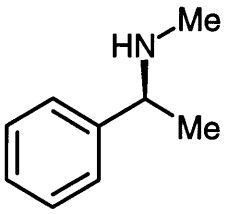
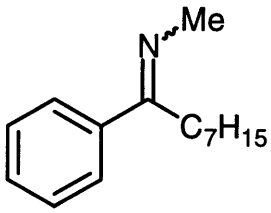
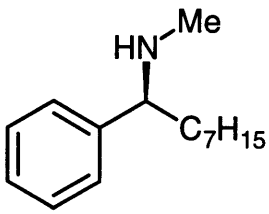
[a] The absolute configurations for the product amine **3e** was determined by polarimetry; the absolute configuration for **3f** was assigned in anaology to **3a** and **3b**. [b] Yields refer to isolated compounds of >95% purity by GC and ^{1}H NMR. [c] ee's were determined by GC analysis of the corresponding trifluoroacetamides on a Chiraldex B-PH column.

The mechanism of the activation step has not yet been determined. Thermodynamically, the formation of the unusually strong Si–F (150–166 kcal/mol) bond energy is likely the driving force responsible for the Ti–F (140 kcal/mol) bond cleavage.[23] However, the observation that a small amount of methanol and pyrrolidine enhance the rate of catalyst activation indicates that kinetic factors also play a role in this process. It has been shown that the reaction between silanes and alcohols can be catalyzed by an added base. Species such as $Ph(OMe)SiH_2$ or $Ph(OMe)SiH_2$ may possibly be generated in the $PhSiH_3$/MeOH/pyrrolidine mixture and might account for the increased rate of catalyst activation in the presence of these additives.

In the course of the study of the hydrosilylation reaction, it was discovered that the concentration of pre-catalyst during the activation process was important. If the

activation with pyrrolidine and methanol is carried out at pre-catalyst concentrations of greater than 0.0125 M, (in the range of 0.025–0.050 M) a non-selective hydrosilylation catalyst is produced, in addition to the enantioselective catalyst normally obtained. This is evidenced by the production of amines with lower ee's that are also not consistent between repeated experiments. The observations listed in Table 2.1.3 demonstrate this behavior. The ee of amine **3a** obtained from the hydrosilylation of imine **2a** varied in a non-reproducible way when the pre-catalyst concentration was 0.050 M during the activation; hydrosilylations of imine **2g** gave even more variable results. However, when the activation was carried out with pre-catalyst concentrations of 0.0125 M, consistently high ee's were obtained. After this pre-catalyst concentration effect was noted, all activations were carried out at the optimum concentration. Dilution of the activated catalyst did not appear to affect the enantioselectivity of the reaction.

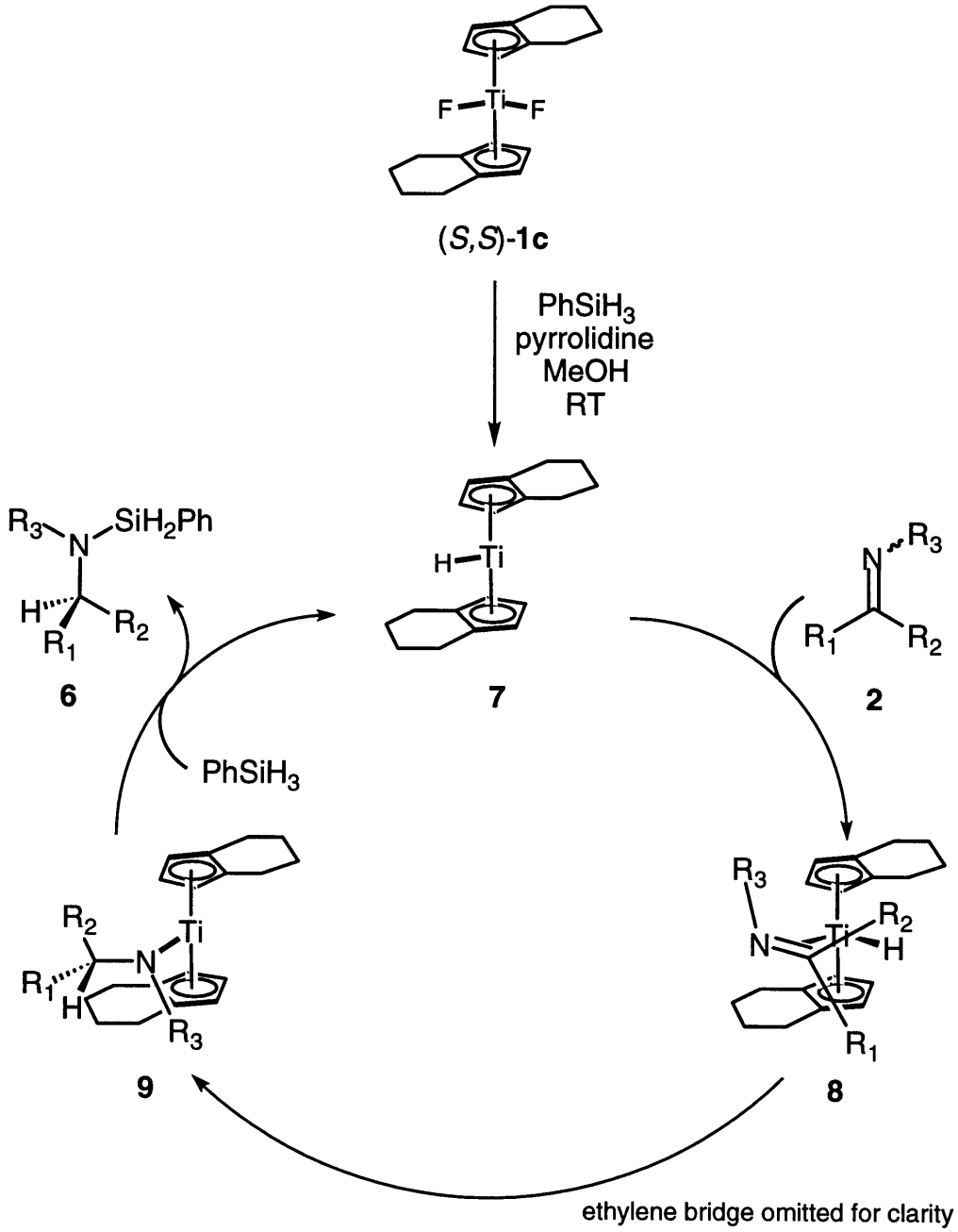
Table 2.1.3 - Effect of Pre-catalyst Concentration on Enantioselectivity of Hydrosilylation of Selected Imines

Imine, **2**	Amine, **3**[a]	[(*S*,*S*)-**1c**][b]	T (°C)[c]	ee(%)[d]
a			0.050	23	93
		0.050	23	92
		0.050	23	97
		0.0125	23	99[e]
g			0.050	23	76
		0.050	23	73
		0.050	23	68
		0.0125	50	93[e]

[a] The absolute configurations of **3g** was assigned by analogy to **3a** and **3b**. [b] Concentration of pre-catalyst in THF during the activation procedure (all activations for this table were carried out at 23 °C). [c] Reaction temperature. [d] ee's were determined by GC analysis of the corresponding trifluoroacetamides. [e] The enantioselectivities obtained at this concentration were reliably reproducible over several experiments.

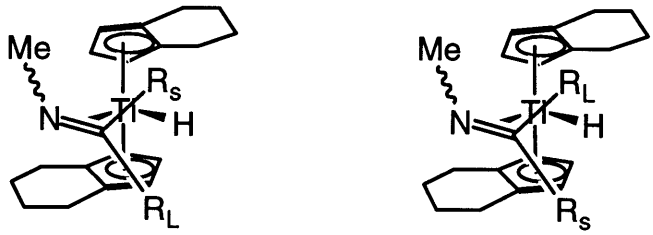
Once the active catalyst has been generated by the action of pyrrolidine and methanol in the presence of phenylsilane, it is believed that the reaction proceeds by a catalytic cycle similar to that for the titanocene-catalyzed hydrogenation of imines (Scheme 2.1.4).[10] Initial coordination of imine **2** to the catalyst gives transient

Scheme 2.1.4



π-complex **8**. Insertion of the imine into the titanium-hydrogen bond of **8** would give the corresponding amido-titanium complex (**9**). Subsequent σ-bond metathesis of **3** with phenylsilane would afford silylated amine **6** and regenerate titanium hydride **7**.

A detailed examination of the factors governing the enantioselectivity of this reaction was not carried out, and is beyond the scope of this thesis. However, in analogy to the related hydrogenation procedure it is believed that the stereochemical outcome of the reaction can be rationalized on the basis of the insertion step.[9] In the case of *N*-methyl imines the relative size of the groups attached to the carbonyl carbon have a relatively large effect on the enantioselectivity of the reaction (Fig. 2.1.5). Here, complex **8a**, in which the larger carbonyl substituent R_L is placed in the relatively



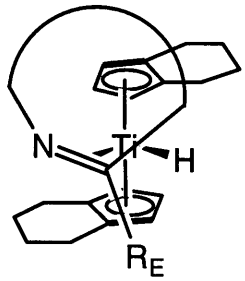
8a
favored

8b
disfavored

Fig. 2.1.5

empty lower right quadrant of the catalyst, is energetically favored over **8b**, in which the large substituent encounters the steric bulk of the saturated ring. This is in contrast to the case for imines where the nitrogen bears a group larger than methyl (e.g., benzyl), where the relative amounts of *syn* and *anti* isomers correlate more closely with the observed enantioselectivity. In that case, the interaction of the nitrogen substituent with the catalyst has a larger effect. In the case of endocyclic imines, which in all cases examined thus far are hydrosilylated with excellent enantioselectivity, the steric model predicts that the substrate approches the catalyst to form complex **8c** almost exclusively (Fig 2.1.6).[9] This is the same interaction that is predicted for *anti*

imines with large nitrogen substituents, as would be expected from the *anti*-like geometry enforced by the cyclic structure of these substrates.

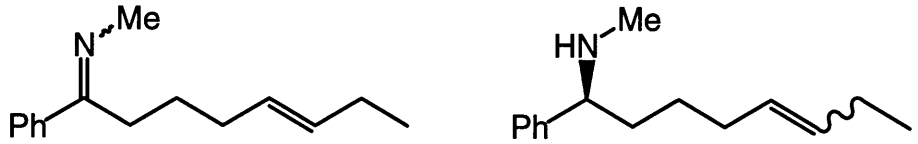


8c

Fig. 2.1.6

2.1.2 Catalytic Asymmetric Imine Hydrosilylation: Chemoselectivity

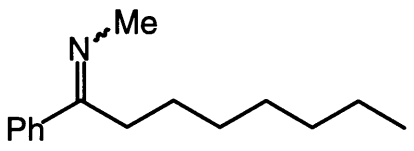
Having demonstrated the effectiveness of this new procedure for the catalytic asymmetric hydrosilylation of imines, we turned our attention to a group of substrates containing pendant olefin groups. The ability of this protocol to effect imine hydrosilylation in the presence of olefinic functionality would considerably increase the synthetic utility. It was shown in the related hydrogenation procedure that monosubstituted olefins are rapidly reduced, and 1,2-disubstituted olefins are isomerized and partially reduced.[9] In view of these observations, and the experience gained in the studies detailed in the previous section, acyclic *N*-methyl imine **2h** (Fig. 2.1.7) was chosen as an initial test substrate.



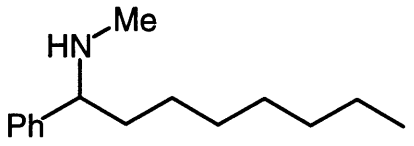
2h, >99:1 *E/Z* **3h**

Fig. 2.1.7

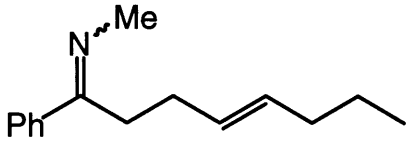
As was found to be the case for the structurally-related imine **2f** (see Table 2.1.3), the hydrosilylation of **2h** required a slightly elevated temperature (50 °C) and catalyst to substrate ratio (2.5 mol%) to reach completion in less than 12 hours. Analysis of the product of this reaction by ^{1}H NMR, GC, and chiral GC indicated that double bond isomerization and translocation had taken place.[24] This isomerization, however, did not noticeably degrade the enantioselectivity of the reaction; the ee of the resulting amine **3h** was 94%. Isomerization was confirmed by synthesizing analogs **2g**, **2i**, and **2j** and reducing them to the corresponding amines with sodium borohydride (Fig. 2.1.8). Furthermore, catalytic asymmetric hydrosilylation of these analogs gave mixtures that were nearly identical to those obtained from reactions of **2h**. Comparison of the chiral GC traces of these compounds clearly shows that the olefin functionality in **2h** is not preserved under the conditions of the reaction, but instead both the geometry and position of the double bond is altered (Fig 2.1.9). It is



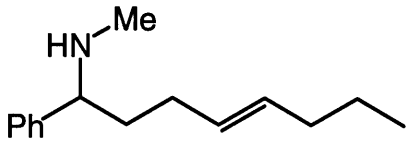
2g



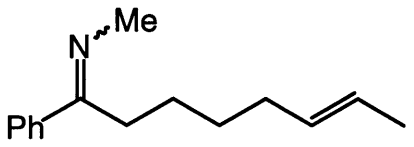
3g



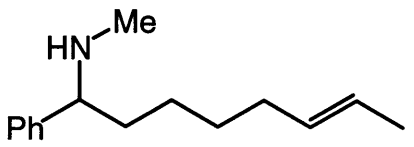
2i, 96:4 *E/Z*



3i



2j, 98:2 *E/Z*



3j

Fig. 2.1.8

noteworthy that isomerization of the olefin both toward and away from the nitrogen-bearing end of the molecule took place, and also that complete reduction of the double bond occurred for a portion of the sample. A precise quantitation of relative amounts of each product was impossible to determine due to the overlap of GC signals.

Interactions of this type between transition metal hydrides (especially of group 4 metals) and olefins are well-precedented; for example, hydrozirconation of internal olefins with Schwartz's reagent ($Cp_2Zr(H)Cl$) always leads to the formation of the thermodynamically more stable terminal alkyl zirconocene *via* a sequential olefin insertion/β-hydride elimination sequence.[25] A similar process occurs during cobalt-catalyzed hydroformylations.[25] Also, as was mentioned above, similar behavior was exhibited by the related imine reduction process - although in that case, only *E/Z*

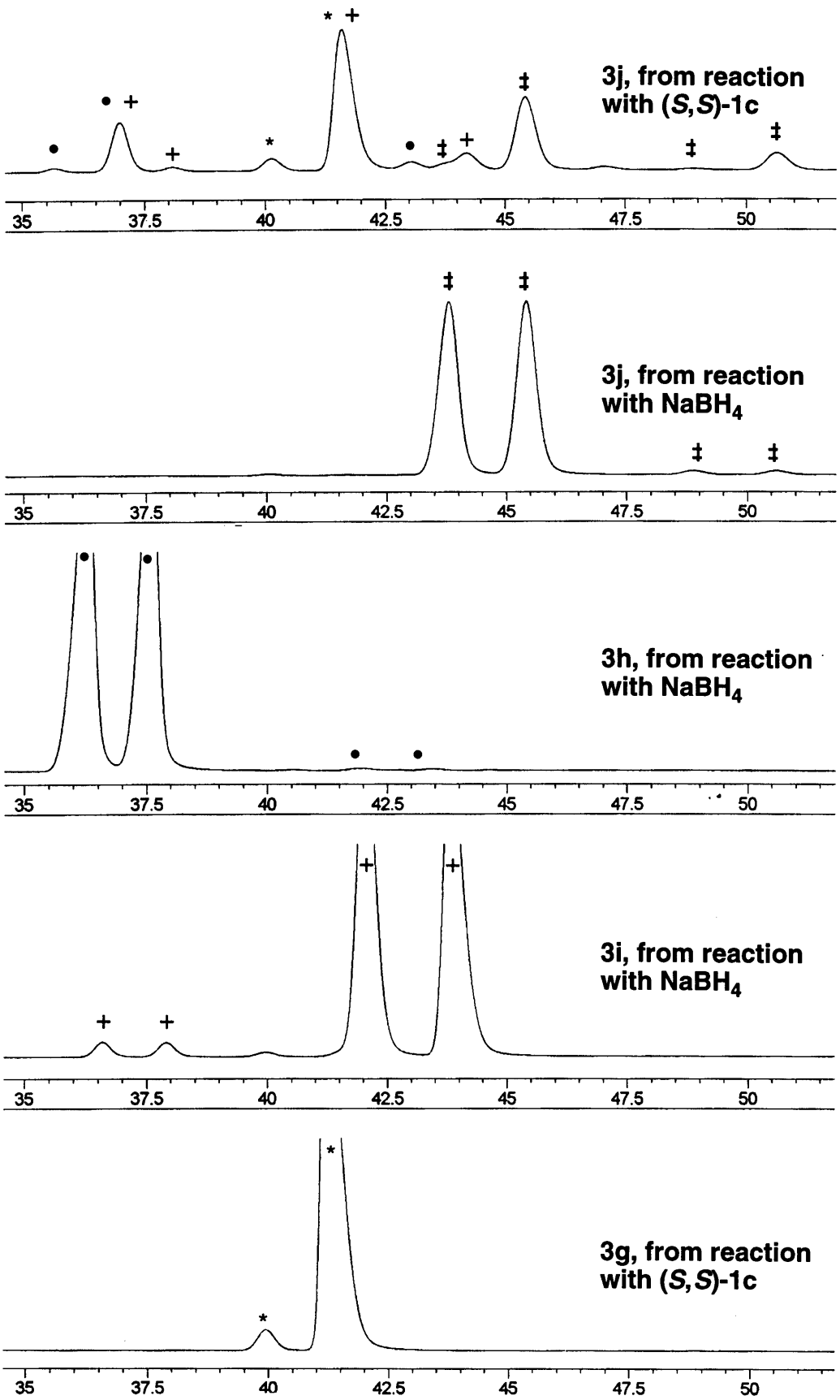


Fig. 2.1.9 - Comparison of Chiral GC Traces of Amines 3g-j

isomerization and total reduction were noted.[9] Several questions are raised by these observations:

1) Does the proximity of the double bond to the imine functionality affect the outcome of the reaction?

2) Does olefin isomerization occur before or after the imine is reduced?

3) Is the nitrogen, either as the imine or the amine, coordinating to titanium and therefore acting to direct attack on the olefin?

4) Is it possible to prevent olefin isomerization while still allowing for the efficient asymmetric hydrosilylation of the imine moiety?

As was noted above, the isomerization was indiscriminate - that is, isomers with the double bond both proximal and distal to the nitrogen-bearing carbon were observed, and further, analogs in which the olefin was separated from the imine by 4, 5, or 6 carbons gave rise to similar product mixtures. Therefore it seems unlikely that the mechanism of isomerization depends to any great extent on the location of the double bond relative to nitrogen.

In an attempt to shed light on question 2, it was necessary to monitor the enantioselectivity of the transformation as a function of reaction time. Initially, small portions of the reaction mixture were removed over the course of the reaction, and quenched with 1 M hydrochloric acid. The ee's of the amines isolated from these aliquots were found to be much lower than those isolated after the reaction was complete. This initially puzzling result was explained by noting that the acid-catalyzed hydrosilation of carbonyl compounds is well-known (see Section 1.0). Thus, when a sample containing amine (of presumably high ee), unreacted imine, and phenylsilane was treated with aqueous acid, a non-enantioselective reduction of the imine took place. This produced a final amine mixture with low ee. However, if all the initial imine had been consumed in an enantioselective manner as was normally the case, treatment with acid had no effect on the ee of the product amine.

To circumvent the action of this non-enantioselective catalyst, samples were removed from the reaction and treated directly with trifluoroacetic anhydride, and the resulting trifluoroacetamides were subjected to chiral GC analysis. By this procedure the olefin isomerization vs. time profile shown in Fig 2.1.10 was obtained. The ee of

Diastereomeric Excess as a Function of Percent Conversion for the Hydrosilylation of 2h

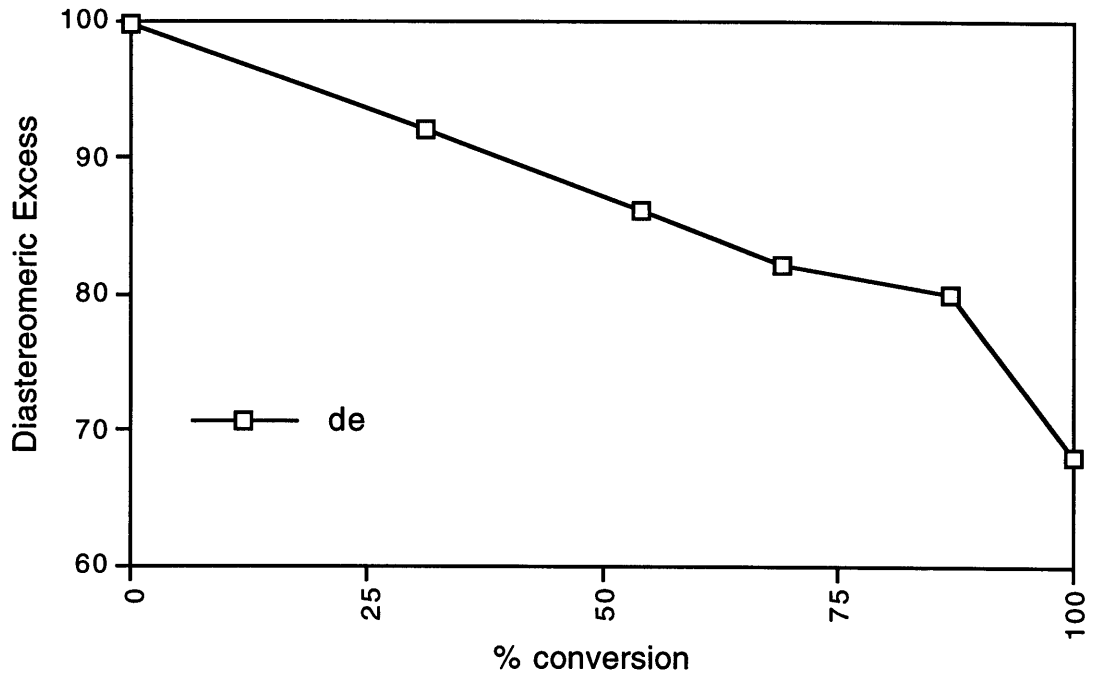
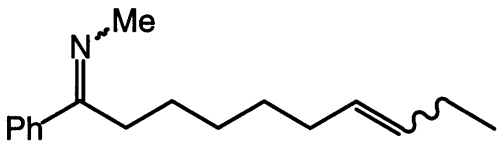


Fig. 2.1.10

the isolated product amines remained constant, within experimental error, during the course of the reaction; extent of isomerization was expressed as diastereomeric excess: de = %*E* olefin - %*Z* olefin. These results clearly showed that olefin isomerization began to take place later in the reaction, after imine hydrosilylation was nearly complete; further, the *E/Z* ratio was greater than 90:10 at 90% conversion. This was consistent with another experiment, in which a substoichiometric amount of phenylsilane was employed to hydrosilylate isomerically pure *E*-**2h**. Upon completion of the hydrosilylation, the reaction mixture (which contained a 1:1 ratio of imine to

amine) was treated with sodium borohydride to reduce the remaining imine. The resulting amine **3h** was found to be a 96:4 mixture of olefin isomers. Again, this showed that olefin isomerization was minimal up to 50% completion. Finally, when a racemic sample of amine **3h** that was 1:1 *E/Z* olefin was subjected to reaction with the catalyst under standard reaction conditions overnight, it was re-isolated with an *E/Z* ratio of 85:15. Together these results indicate that isomerization of the olefin is most likely not competitive with imine hydrosilylation, and only began to become an important side reaction when the imine was nearly consumed.

To address the fourth question of a possible nitrogen directing effect, imine **2l** was synthesized and subjected to the standard catalytic asymmetric hydrosilylation conditions (Fig. 2.1.11). As was the case for the **2h–k**, chiral GC analysis of the



90:10 *E/Z* at olefin

2k

Fig. 2.1.11

amines thus produced showed a mixture of many double-bond isomers (both geometric and positional). It proved impossible to effect adequate separation of the amine isomers to determine the ee of any particular component. It seemed unlikely that a directing effect was operating over a separation of 7 carbon atoms; the transition state for such an isomerization would involve a pseudo 10-membered ring which is less than favorable. This lends weight to the argument that this catalyst system isomerizes 1,2-disubstituted olefins indiscriminately in the absence of imine.

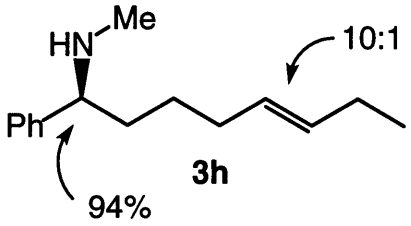
Since the preceding results indicated that the olefin isomerization process did not begin to take place while the catalyst was occupied by imine, it was hypothesized

that it might be possible to employ an additive to the reaction mixture that would allow hydrosilylation of the more reactive imine while prohibiting olefin isomerization. To this end, hydrosilylation reactions of **2h** were carried out in the presence of diphenyl acetylene and 1-hexene. In both cases, although the enantioselectivity of the reaction was unaffected, isomerization of the olefin still took place. Another possible additive that could be tried is a sacrificial imine. However, since substrates with the general structure of **2h** are less reactive than substrates with smaller groups bound to the carbonyl carbon, it is difficult to postulate an imine that would be less reactive than **2h** or its analogs, yet more reactive than a 1,2-disubstituted olefin. It is likely that any other imine added to the reaction mixture would be hydrosilylated either before or concommitantly with the desired imine, and thus would not survive to protect the olefin moiety.

In other related work,[26] it was found that PMHS (see Section 1.1.1), in combination with primary or secondary amine additives, is an effective system for the reduction of non-*N*-methyl imines, which typically react much more slowly then the corresponding *N*-methyl analogs. Hydrosilylations of **2h** carried out with PMHS in the presence of the catalyst with either *sec*-butylamine or isobutylamine additives were indeed faster than those with phenylsilane. Although these reactions proceeded with enantioselectivities similar to those obtained with phenylsilane, olefin isomerization was not attenuated. Hydrosilylations with PMHS in the absence of amine additives were very sluggish; indeed, this reaction did not go to completion even after more than 60 hours at 50 °C.

Ultimately, the information gained during the course of these studies dictated the following protocol for the hydrosilylation of *E*-**2h**: the reaction was carried out with phenylsilane in the presence of 5 mole percent catalyst at 50 °C. The reaction was monitored closely by GC analysis until the ratio of amine to unreacted imine was 9:1. The reaction was then quenched with wet THF to avoid non-selective acid-catalyzed

hydrosilylation. This protocol allowed the isolation of amine **3h** in 79% yield and 94% ee as a 10:1 mixture of olefin isomers. No other regioisomers were present at levels greater than 1%.

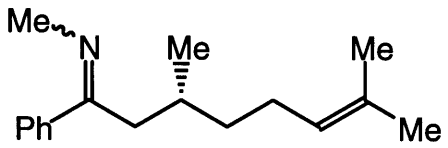


3h

Fig. 2.1.12

2.1.3 Catalytic Asymmetric Imine Hydrosilylation: Diastereoselectivity

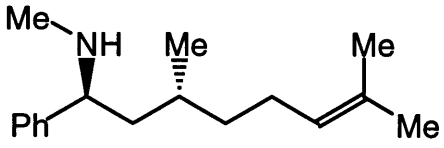
The diastereoselectivity of the reaction with subtrates that contain a stereogenic center was also of interest. To this end, the enantiomerically pure citronellyl phenone derived imine **2l** was synthesized (Fig. 2.1.13). This substrate contains a



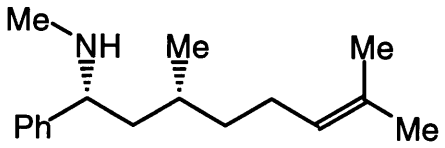
2l

Fig. 2.1.13

stereogenic center β to the imine functionality. Hydrosilylation of **2l** with phenysilane in the presence of activated (*S,S*)-**1c** afforded amine *anti*-**3l** in 94% de (Fig. 2.1.14). The absolute configuration of the nitrogen-bearing carbon in *anti*-**3l** was inferred using the model described in Section 2.1.1. No hydrosilylation of the trisubstituted double bond was observed.



anti-**3l**



syn-**3l**

Fig. 2.1.14

In order to fully examine the effect of the chiral center in **2m**, it was necesary to carry out the hydrosilylation in the presence of the enantiomeric catalyst, namely (*R,R*)-**1c**. The difluoride precatalyst was synthesized in a 2-step process from the (*R,R,R*)-**1a**. Hydrosilylation of **2m** with phenylsilane in the presence of activated (*R,R*)-**1c**

gave *syn*-**3m**, but in only 86% de. This is then an example of a matched/mismatched catalyst/substrate system.[27]

2.1.4 Conclusion

This section has detailed the development of a highly enantioselective imine hydrosilylation. This experimentally simple system features a novel activation process based on the reaction of (*S,S*)-(EBTHI)TiF_2 with phenylsilane. The concentration of precatalyst during the activation step was found to be important. The procedure converts imines to amines under mild conditions with significantly higher subtrate:catalyst ratios than previously possible. The chemoselectivity of this reaction in the presence of 1,2-disubstituted olefins was explored, and a strategy for limiting olefin isomerization was established. The diasteroselectivity of the catalyst system with an enantiomerically pure β-disubstituted imine was determined.

2.1.5 Experimental

General. Unless otherwise noted, all reagents were either commercially available and were used as obtained from the supplier, or were prepared according to published methods. Ether and THF were distilled from sodium/benzophenone ketyl under nitrogen. Pyrrolidine and methanol (Aldrich, Sure/Seal) and used as received. Flash chromatography was performed on E. M. Science Kieselgel 60 (230–400 mesh). Yields, unless otherwise stated, refer to isolated yields of compounds >95% pure as assessed by capillary GC and ^{1}H NMR. NMR spectra were recorded on Varian XL or Varian Unity 300 MHz spectrometers. Enantiomeric excesses of amines were determined by chiral GC analysis of the correspondin trifluoroacetamindes using a Hewlett Packard 5890 gas chromatograph equipped with a 20 m × 0.25 mm Chiraldex G-TA (trifluoroacetylated γ-cyclodextrin) column; hydrogen was the carrier gas. Optical rotations were measured using a Perkin-Elmer Model 241 polarimeter. Racemic amines were prepared from the corresponding imines by reduction with sodium borohydride in methanol.

1-phenyloct-5-en-1-one. Sodium ethoxide was prepared by dissolving sodium (38.6 mmol, 887 mg) in absolute ethanol (50 mL) in a 250 mL Schlenk flask. Ethyl benzoylacetate (36.8 mmol, 6.43 mL) was added *via* syringe, and the solution was stirred at room temperature for 30 min. *trans*-1-Iodo-3-hexene (40.5 mmol, 8.50 g; prepared by treating *trans*-3-hexen-1-ol with triphenylphosphine, iodine, and imidazole in dichloromethane)[28] was added *via* syringe, and the flask was equipped with a condenser/balloon unit. The mixture was stirred at reflux for 20 h. The mixture was cooled to room temperature, at which time GC analysis of a quenched aliquot showed little remaining iodide. The mixture was partitioned between ether and water (50 mL each); the layers were separated, and the aqueous layer was extracted (2×20 mL ether). The combined organic layer were washed (brine), dried ($MgSO_4$), filtered,

and concentrated *in vacuo*. The mixture was saponified by refluxing with 100 mL 2 M NaOH overnight. The mixture was cooled to room temperature, acidified with 4 M HCl, and saturated with sodium chloride (**Caution:** vigorous bubbling). The mixture was extracted (3×20 mL ether), and the combined ether layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford an orange oil. Vacuum kugelrohr distillation followed by column chromatography (20:1 hexane/ethyl acetate) afforded a clear oil, 5.06 g, 68%. The compound was later found to be an approximately 1:1 mixture of *cis* and *trans* isomers; the diastereomerically pure *trans* compound could be obtained by limiting the duration of the saponification step. ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J=7.0 Hz, 2 H), 7.51 (m, 1 H), 7.43 (m, 2 H), 5.41 (m, 2 H), 2.94 (m, 2 H), 1.99–2.15 (m, 4 H), 1.80 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 200.1, 137.1, 132.9, 132.7, 132.6, 128.4, 128.1, 128.0, 127.9, 37.7, 37.6, 31.9, 26.4, 25.4, 24.1, 24.0, 20.4, 14.2, 13.8; IR (neat, cm^{-1}): 2961, 2872, 1692, 1598, 1449, 1367, 1257, 1227, 1199, 1180, 969, 753, 739, 691. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.04; H, 8.77.

(*R*)-(–)-1-phenyl-3,7-dimethyloct-6-en-1-one. (*R*)-(+)-citronellic acid (29.4 mmol, 5.00 g) was placed in a dry 250 mL Schlenk flask and vacuum purged three times with argon. THF was then added and the solution was cooled on an ice bath. Phenyllithium (1.8 M in dibutyl ether, 58.8 mmol, 32.7 mL) was added dropwise *via* cannula. The viscous mixture was stirred and allowed to warm to room temperature during the addition. The mixture was stirred an additional 1.5 h, then cannulated into 200 mL of a rapidly stirred 1 M aqueous HCl solution. The layers were separated, and the aqueous layers were extracted (2×50 mL ether). The combined ether layers were washed (2×50 mL 1 M NaOH, 1 x brine), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil. This was purified by column chromatography (15:1 hexane/ethyl acetate) followed by kugelrohr distillation (0.02

torr, 85 °C) to give a clear oil, 2.19 g, 31%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* =7.0 Hz, 2 H), 7.41 (m, 1 H), 7.33 (m, 2 H), 5.00 (m, 1 H), 2.86 (dd, *J* = 15.6, 5.5 Hz, 1 H), 2.64 (dd, *J* =15.8, 8.1 Hz, 1 H), 2.08 (m, 1 H), 1.93 (m, 2 H), 1.58 (s, 3 H), 1.50 (s, 3H), 1.32 (m, 1 H), 1.22 (m, 1 H), 0.87 (d, *J* =6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 137.4, 132.7, 131.3, 128.4, 128.0, 124.3, 45.8, 37.1, 29.4, 25.6, 25.5, 19.8, 17.5; IR (neat, cm^{-1}): 2963, 2915, 1686, 1448, 752, 691. $[\alpha]_D$=–3.5°, c=2.6 in CH_2Cl_2. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.57; H, 9.80.

General procedure for the preparation of *N*-methylimines. The ketone (1.0 eq.) was dissolved in diethyl ether to make the solution 0.35 M in ketone, and the solution cooled to –30 °C. Methylamine (10.0 eq.) was condensed and added *via* cannula, followed by titanium tetrachloride (neat, 0.5 eq.) which was added *via* syringe. The reaction mixture was kept between –30 °C and 0 °C for 3 h and was then allowed to slowly warm to room temperature overnight. The resulting white to light-orange suspension was filtered through celite, rinsed with ether, and concentrated *in vacuo*. The resulting imine was purified if necessary by distillation and stored at –20 °C in a nitrogen-filled glovebox.

***N*-[1-(1,2,3,4-tetrahydronaphthylidene)]methylamine, 2e.** The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from 1-tetralone (34.2 mmol, 5.00 g) and purified by vacuum sublimation. The product was obtained as colorless crystals, 5.09 g, 93%. The compound existed as a single isomer about the C=N double bond. M. p.: 40–42 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10, (d, *J* = 7.2 Hz, 1H), 7.21 (m, 2H), 7.07 (d, *J* = 6.6 Hz, 1H), 3.27 (s, 3H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.49 (t, *J* = 6.3 Hz, 2H), 1.08 (m, 2 H).[29]

***N*-[1-(1-phenyldodecylidene)]methylamine, 2f.** The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from 1-phenyldodecan-1-one (38.4 mmol, 10.0 g) to afford a yellow oil, 9.86 g, 94%. The compound existed as a 2:1 mixture of isomers about the C=N double bond. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ 7.71 (br s, 2 H), 7.33 (m, 3 H), 3.38 (s, 3 H), 2.70 (t,*J* = 7.5 Hz, 2 H), 1.49 (br s, 2 H), 1.26 (m, 16 H), 0.88 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of isomers): δ 140.5, 138.6, 128.8, 128.2, 127.9, 127.8, 126.6, 126.2, 41.8, 40.2, 38.6, 31.68, 29.62, 29.35, 29.26, 29.20, 29.10, 29.07, 29.06, 27.92, 26.53, 26.05, 22.4, 13.7; IR (neat, cm^{-1}): 2924, 2853, 1634, 1466, 1444, 693. Anal. Calcd for $C_{19}H_{31}N$: C, 83.44; H, 11.43. Found C, 83.28; H, 12.32.

***N*-[1-(*trans*-1-phenyloct-5-enylidene)]methylamine, 2h.** The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from 1-phenyloct-5-en-1-one (>99:1 *trans* ; 8.65 mmol, 1.75 g) to afford a clear, colorless oil, 1.73 g, 93%. The compound existed as a 4.8:1 mixture of isomers about the C=N double bond. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ 7.70 (dd, *J* =7.5, 3.6 Hz, 2 H), 7.32 (m, 3 H), 5.38 (m 2 H), 3.36 (s, 3 H), 2.68 (m, 2 H), 2.02 (m, 4 H), 1.53 (m, 2 H), 0.95 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer): δ 170.4, 140.1, 133.1, 129.1, 128.0, 127.8, 126.5, 38.8, 32.4, 27.4, 26.3, 25.4, 13.7; IR (neat, cm^{-1}): 2960, 2930, 2871, 1633, 1460, 1444, 1297, 968, 763, 694. Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83. Found: C, 83.46; H, 9.61.

(*R*)-(+)-*N*-[1-(1-phenyl-3,7-dimethyloct-6-enylidene)]methylamine, 2l. The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from (*R*)-(–)-1-phenyl-3,7-dimethyloct-6-en-1-one (8.68 mmol, 2.00 g) to afford a slightly cloudy yellow oil, 2.07 g, 98%. The compound existed as a 3.3:1 mixture of isomers about the C=N double bond. ^{1}H NMR (300 MHz, $CDCl_3$, major

isomer): δ 7.57 (dd, J=7.5, 3.6 Hz, 2 H), 7.22 (m, 3 H), 4.92 (m, 1 H), 3.28 (s, 3 H), 2.60 (dd, J=13.5, 6.0 Hz, 1 H), 2.47 (dd, J=13.5, 8.7 Hz, 1 H), 1.87 (m, 2 H), 1.65 (m, 1 H), 1.55 (s, 3 H), 1.47 (s, 3 H), 1.25 (m, 1 H), 1.15 (m, 1 H), 0.74 (d, J=6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer): δ 170.3, 140.6, 131.2, 128.9, 128.0, 126.6, 124.1, 39.2, 37.0, 34.6, 31.0, 25.5, 25.3, 19.4, 17.4; IR (neat, cm^{-1}): 2960, 2914, 1635, 1444, 1377, 1292, 694. $[\alpha]_D$=+7.4°, c=12 in CH_2Cl_2. Anal. Calcd for $C_{17}H_{25}N$: C,83.89 ; H, 10.35. Found: C, 83.61; H, 10.59.

Imine analogs 2i–k. These compounds were prepared as described below, and identified by their ^1H NMR spectra. The corresponding amines **3i–k** were prepared by reducing their parent imines with sodium borohydride in methanol, and the corresponding trifluoroacetamide derivatives were subjected to chiral GC analysis.

General procedure for the preparation of starting ketones. Sodium ethoxide was prepared by dissolving sodium (1.1 equiv) in absolute ethanol (to make the solution 0.6 M) in an appropriate-sized Schlenk flask. Ethyl benzoylacetate (1.1 equiv) was added *via* syringe, and the solution was stirred at room temperature for 30 min. An alkyl bromide or iodide (1.0 equiv) was added *via* syringe, and the flask was equipped with a condenser/balloon unit. The mixture was stirred at reflux for 20 h. The mixture was cooled to room temperature, and the mixture was partitioned between ether and water; the layers were separated, and the aqueous layer was extracted (2× ether). The combined organic layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The mixture was saponified by refluxing with 100 mL 2 M NaOH overnight. The mixture was cooled to room temperature, acidified with 4 M HCl, and saturated with sodium chloride (**Caution:** vigorous bubbling). The mixture was extracted (3 × ether), and the combined ether layers were washed (brine), dried

($MgSO_4$), filtered, and concentrated *in vacuo* to afford an orange oil. Vacuum distillation and/or column chromatography afforded the desired ketone.

***trans*-1-phenyloct-4-en-1-one.** The compound was prepared according to the general procedure for the preparation of starting ketones from sodium (16.5 mmol, 379 mg), ethyl benzoyl acetate (17.3 mmol, 3.0 mL), and 1-bromo-2-hexene (15.0 mmol, 2.45 g, prepared by treating *trans*-2-hexene-1-ol with triphenylphosphine and NBS in dichloromethane).[28] Flash chromatography (13:1 hexane/ethyl acetate) afforded a faintly yellow oil, 2.15 g, 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J=7.2 Hz, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 5.49 (m, 2H), 3.04 (t, J=7.5 Hz, 2 H), 2.43 (m, 2H), 1.97 (m, 2H), 1.35 (m, 2 H), 0.88 (t, J=7.2 Hz, 3 H).

***trans*-1-phenyloct-6-en-1-one.** The compound was prepared according to the general procedure for the preparation of starting ketones from sodium (20.4 mmol, 469 mg), ethyl benzoyl acetate (19.5 mmol, 3.4 mL), and 1-iodo-4-hexene (21.4 mmol, 4.50 g, prepared by treating *trans*-4-hexene-1-ol with triphenylphosphine, iodine, and imidazole in dichloromethane).[28] Flash chromatography (20:1 hexane/ethyl acetate) afforded a faintly yellow oil, 1.50 g, 35%, as an 11:1 mixture of isomers. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ 8.11 (d, J=7.9 Hz, 2 H), 7.59 (m, 1H), 7.45 (m, 2 H), 5.42 (m, 2 H), 2.38 (t, J=7.1 Hz 2 H), 1.99 (m, 2 H), 1.65 (m, 2 H), 1.63 (d, J=4.7 Hz, 3 H), 1.42 (m, 2 H).

***trans*-1-phenyldec-7-en-1-one.** The compound was prepared according to the general procedure for the preparation of starting ketones from sodium (12.0 mmol, 276 mg), ethyl benzoyl acetate (11.5 mmol, 2.0 mL), and 1-iodo-5-octene (12.6 mmol, 3.0 g, prepared by treating 5-octene-1-ol with triphenylphosphine, iodine, and imidazole in dichloromethane).[28] Flash chromatography (20:1 hexane/ethyl acetate) afforded a

clear oil, 1.00 g, 38%, as an 9:1 mixture of isomers. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ 7.95 (d, *J* =7.9 Hz, 2 H), 7.57 (m, 1 H), 7.44 (m, 2 H), 5.33 (m, 2 H), 2.96 (t, *J* =7.9 Hz, 2 H), 2.03 (m, 4 H), 1.74 (m, 2 H), 1.38 (m, 4 H), 0.86 (t, *J* =7.1 Hz, 3 H).

***N*-[1-(1-phenyloctylidene)]methylamine, 2g.** The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from 1-phenyloctan-1-one (12.2 mmol, 2.50 g) to afford a clear oil, 2.54 g, 96%. The compound existed as a 2:1 mixture of isomers about the C=N double bond. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ 7.73 (br s, 2 H), 7.32 (m, 3 H), 3.41 (s, 3 H), 2.72 (t,*J* = 7.5 Hz, 2 H), 1.51 (br s, 2 H), 1.28 (m, 8 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

***N*-[1-(*trans*-1-phenyloct-4-enylidene)]methylamine, 2i.** The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from *trans*-1-phenyloct-4-en-1-one (10.0 mmol, 2.02 g) to afford a clear, colorless oil, 1.76 g, 97%. The compound existed as a 2.4:1 mixture of isomers about the C–N double bond. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ 7.72 (m, 2 H), 7.28 (m, 3 H), 5.42 (m, 2 H), 3.39, (s, 3 H), 2.78 (t, *J* = 7.7.8 Hz, 2 H), 2.18 (m, 2 H), 1.94 (m, 2 H), 1.37 (m, 2 H), 0.88 (m, 3 H).

***N*-[1-(*trans*-1-phenyloct-6-enylidene)]methylamine, 2j.** The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from *trans*-1-phenyloct-6-en-1-one (7.41 mmol, 1.50 g) to afford a yellow oil, 1.49 g, 93%. The compound existed as a 3.8:1 mixture of isomers about the C=N double bond. ^{1}H NMR (300 MHz, C_6D_6, major isomer): δ 7.73 (m, 2 H), 7.09 (m, 3 H), 5.39 (m, 2 H), 2.64 (d, *J* =4.8 Hz, 3 H), 1.93 (m, 2 H), 1.84 (m, 2 H), 1.61 (m, 2 H), 1.60 (d, *J* =4.0 Hz, 3 H), 1.31 (m, 2 H).

***N*-[1-(*trans*-1-phenyldec-7-enylidene)]methylamine, 2k.** The compound was prepared according to the general procedure for the synthesis of *N*-methyl imines from *trans*-1-phenyldec-7-en-1-one (4.34 mmol, 1.00 g) to afford a yellow oil, 1.02 g, 97%. The compound existed as a 3.6:1 mixture of isomers about the C=N double bond. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer): δ 7.71 (m, 2 H), 7.37 (m, 3 H), 5.33 (m, 2 H), 3.87 (s, 3 H), 2.71 (t, *J*=7.1, 2 H), 2.01 (m, 4 H), 1.49 (m, 2 H), 1.37 (m, 2 H), 0.95 (t, *J* =7.9 Hz, 3 H).

General procedure for the hydrosilylation of imines.

A dry sealable Schlenk flask was charged with *(S,S)*-[30] or *(R,R)*- (EBTHI)TiF_2 (1–5 mol % relative to imine) and vacuum purged three times with argon. THF was then added *via* syringe to make the solution 0.0125 M in pre-catalyst. To this solution was added *via* syringe in this order: phenylsilane (2.0 eq.), pyrrolidine (8 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol). The mixture was stirred in a 50 °C oil bath for 10–20 min, resulting in a change of color from yellow to emerald green. The flask was then sealed and transferred to a nitrogen-filled glovebox. The imine was added (neat, 1.0 eq.) and the flask was resealed and stirred either at room temperature or in a 50 °C oil bath. Extent of reaction was monitored by GC. When consumption of the starting material was complete, the reaction mixture was diluted with THF (20 mL) and stirred with 1M HCl (10 mL) for 0.5h (**Caution**: vigorous bubbling). The mixture was washed (3 x 20 mL 1 M HCl). The combined aqueous layers were made basic with 4 M NaOH and extracted (3 x 20 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the corresponding amine.

(*R,R*)-ethylenebis(η^5-tetrahydroindenyl)titanium difluoride ((*R,R*)-(EBTHI)TiF_2), (*R,R*)-1c. (*R,R,R*)-(EBTHI)Ti-2,2'-binaphth-1,1'-diol (obtained from the resolution of *rac*-(EBTHI)$TiCl_2$,[31], 1.68 mmol, 1.0 g) was suspended in ether (50

mL). Methyllithium (1.4 M in hexanes, 8.40 mmol, 6.0 mL) was added with stirring over 10 min at room temperature. The deep red mixture turned bright yellow over the next 1.25 h. The ether was removed *in vacuo*, and hexane (20 mL) was added. The supernatant was removed by cannula filtration, and the solids were rinsed with more hexane (10 mL). The combined orange filtrate was cooled on an ice bath, and pyridine•HF adduct (~5 mmol, 0.15 mL) was added *via* syringe (**Caution:** this complex will etch glass syringes; use of a plastic syringe barrel is advised). The now yellow mixture was stirred for an additional 30 min, and the reaction was quenched with saturated sodium bicarbonate. The layers were separated, and the aqueous layer was extracted (1 x dichloromethane). The combined organic layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a bright yellow solid. This was recrystallized in two crops from hot toluene/hexane as air-stable yellow plates, 481 mg, 82%.[32] The ee of this complex was determined to be ≥99%, as shown by using it as a pre-catalyst in the hydrosilylation of imine **2a**, which afforded (*R*)-*N*-methyl-1-phenylethylamine with 99% ee.[30] Mp: 235 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 (d, *J* =2.9 Hz, 2 H), 5.68 (d, *J* =3.0 Hz, 2 H), 3.16 (m, 2 H), 3.13 (m, 2 H), 2.41–2.75 (m, 8 H), 1.88 (m, 4 H), 1.58 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 133.9, 125.5, 123.8, 27.9, 23.9, 23.6, 22.0. IR (KBr disc, cm^{-1}): 3083, 2930, 2852, 1444, 1290, 832, 810, 566, 551, 499. $[\alpha]_D$=+85.2°, c=0.81 in CH_2Cl_2 (lit. for (*S,S*)-**1c** $[\alpha]_D$=–76.0°, c=0.96 in $CHCl_3$).[30] Anal. Calcd for $C_{20}H_{24}F_2Ti$: C, 68.57; H, 6.91. Found C, 68.73; H, 7.15.

(*S*)-(+)-*N*-Methyl-*N*-[1-(1,2,3,4-tetrahydronaphthyl)]amine, 3e. The compound was prepared according to the general procedure for the hydrosilylation of imines. *(S,S)*-(EBTHI)TiF_2 (32.5 μmol, 11.4 mg) was dissolved in THF (1 mL) and activated with phenylsilane (2.6 mmol, 0.32 mL), pyrrolidine (52 μmol, 4.3 μL), and methanol (52 μmol, 2.1 μL). After the addition of *N*-[1-(1,2,3,4-

tetrahydronaphthylidene)]methylamine (1.3 mmol, 207 mg) the flask was sealed and stirred at room temperature. Upon completion of the reaction, workup afforded a faintly yellow oil, 183 mg, 87%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 1H), 7.20 (m, 2H), 7.10 (m, 1H), 3.66 (t, J = 4.5 Hz, 1H), 2.77 (m, 2H), 2.50 (s, 3H), 1.92 (m, 3H), 1.77 (m, 1H), 1.24 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 137.3, 129.0, 128.8, 126.6, 125.6, 57.0, 34.0, 29.3, 27.5, 18.8. IR (neat, cm^{-1}): 3083, 3062, 3025, 2846, 2787, 1492, 1454, 1377, 1354, 1134, 700. Chiral GC of the trifluoroacetamide derivative showed an ee of 96%. $[\alpha]_D$= +12.5°, c=1.9 in ethanol. Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38. Found C, 81.74; H, 9.46.[33]

(*S*)-(–)-*N*-Methyl-*N*-1-phenyldodecylamine, 3f. The compound was prepared according to the general procedure for the hydrosilylation of imines. *(S,S)*-(EBTHI)TiF_2 (52.0 μmol, 18.2 mg) was dissolved in THF (2 mL) and activated with phenylsilane (0.46 mL, 3.75 mmol), pyrrolidine, and methanol. After the addition of *N*-(1-phenyldodecylidene)methylamine (2.6 mmol, 711 mg) the flask was sealed and heated to 50 °C. Upon completion of the reaction, workup followed by flash chromatography afforded a faintly yellow oil, 632 mg, 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 5H), 3.41 (t, J = 6.0 Hz, 1H), 2.25 (s, 3H), 1.67 (m, 1H), 1.61 (m, 1H), 1.22 (m, 19H), 0.87 (t, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.2, 128.1, 127.1, 126.7, 65.6, 37.9, 34.4, 31.8, 29.60, 29.51, 29.47, 29.40, 29.2, 26.2, 22.6. IR (neat, cm^{-1}): 3320, 3059, 3016, 2934, 2785, 1579, 1488, 1450, 1340, 1098, 740. Chiral GC of the trifluoroacetamide derivative showed an ee of 95%. $[\alpha]_D$= –11.1°, c=1.4 in CH_2Cl_2. Anal. Calcd for $C_{19}H_{33}N$: C, 82.83; H, 12.08. Found: C, 83.03; H, 12.14.

(*S*)-(–)-*N*-methyl-*N*-1-(*trans*-1-phenyloct-5-enyl)amine, 3h. The compound was prepared according to the general procedure for the hydrosilylation of imines.

(S,S)-(EBTHI)TiF_2 (25 μmol, 9 mg) was dissolved in THF (2 mL) and activated with phenylsilane (2.0 mmol, 247 μL), pyrrolidine, and methanol. After the addition of *N*-[1-(*trans*-1-phenyloct-5-enylidene)]methylamine (1.0 mmol, 215 mg) the flask was sealed and heated to 50 °C. The reaction was closely monitored until GC analysis indicated 90% conversion of starting material relative to the desired product. Workup afforded the compound as a slightly yellow oil, 156 mg, 72%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5 H), 5.34 (m, 2 H), 3.43 (dd, *J*=7.5, 6.1, 1 H), 2.26 (s, 3 H), 1.96 (m, 4 H), 1.71 (m, 1 H), 1.61 (m, 1 H), 1.47 (br. s, 1 H), 1.30 (m, 2 H), 0.94 (t, *J*=7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0 132.2, 128.7, 128.3, 127.2, 126.8, 65.4, 37.3, 34.5, 32.4, 26.3, 25.5, 13.9; IR (neat, cm^{-1}): 2961, 2931, 2847, 2787, 1453, 967, 761, 701. Chiral GC of the trifluoroacetamide derivative showed a 93:7 *trans/cis* ratio; the major (*trans*) isomer had an ee of 95%. $[\alpha]_D$=–13.7°, c=0.86 in CH_2Cl_2. Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67. Found: C, 82.61; H, 10.44.

(1*S*,3*S*)-(–)-*N*-methyl-*N*-1-(1-phenyl-3,7-dimethyloct-6-enyl)amine, *anti*-3l, matched reaction. The compound was prepared according to the general procedure for the hydrosilylation of imines. *(S,S)*-(EBTHI)TiF_2 (12.5 μmol, 4.5 mg) was dissolved in THF (1 mL) and activated with phenylsilane (0.5 mmol, 62 μL), pyrrolidine, and methanol. After the addition of (*R*)-(+)-*N*-[1-(1-phenyl-3,7-dimethyloct-6-enylidene)]methylamine (0.25 mmol, 61 mg), the flask was sealed and heated to 50 °C. Upon completion of the reaction, workup followed by flash chromatography (10:1 ethyl acetate/hexane with 2.5% v/v triethylamine) afforded a yellow oil, 55 mg, 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5 H), 5.07 (t, *J*=7.2 Hz, 1 H), 3.53 (t, *J*=7.0 Hz, 1 H), 2.25 (s, 3 H), 1.83 (m, 2 H), 1.67 (m, 1 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.40 (m, 4 H), 1.16 (m, 1H), 0.87 (d, *J* = 5.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 131.1, 128.3, 127.2, 126.8, 124.8, 63.1, 45.8, 37.1, 34.5, 29.4, 25.7, 25.3, 19.8, 17.6; IR (neat, cm^{-1}): 3025, 2922, 2789, 1492, 1474, 1453, 1132, 757, 701. Chiral GC of the

trifluoroacetamide derivative showed a 96.9% de, with greater then 99.5% chiral purity at the original chiral center. $[\alpha]_D$=–19.6°, c=0.41 in CH_2Cl_2. Anal. Calcd for $C_{17}H_{27}N$: C, 83.20; H, 11.09. Found: C, 82.98; H, 11.27.

(1*R*,3*S*)-(+)-*N* -methyl-*N*-1-(1-phenyl-3,7-dimethyloct-6-enyl)amine, *syn*-3l, mismatched reaction. The compound was prepared according to the general procedure for the hydrosilylation of imines. *(R,R)*-(EBTHI)TiF_2 (12.5 μmol, 4.5 mg) was dissolved in THF (1 mL) and activated with phenylsilane (0.5 mmol, 62 μL), pyrrolidine, and methanol. After the addition of (*R*)-(+)-*N*-[1-(1-phenyl-3,7-dimethyloct-6-enylidene)]methylamine (0.25 mmol, 61 mg), the flask was sealed and heated to 50 °C. Upon completion of the reaction, workup followed by flash chromatography (10:1 ethyl acetate/hexane with 2.5% v/v triethylamine) afforded a yellow oil, 51 mg, 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 5 H), 4.99 (t, *J*=5.9 Hz, 1 H), 3.51 (dd, *J*=8.8, 5.7 Hz, 1 H), 2.25 (s, 3 H), 1.88 (m, 2 H), 1.69 (m, 1 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 1.38 (br. s, 1 H), 1.26 (m, 2 H), 1.13 (m, 2 H), 0.90 (d, *J* = 5.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 131.0, 128.3, 127.3, 126.8, 124.7, 63.3, 45.1, 37.4, 34.4, 29.3, 25.6, 25.2, 19.8, 17.5; IR (neat, cm^{-1}): 3025, 2922, 2789, 1493, 1474, 1453, 1131, 755, 734, 701. Chiral GC of the trifluoroacetamide derivative showed a 84.5% de, with greater then 99.5% chiral purity at the original chiral center. $[\alpha]_D$=+28.8°, c=0.42 in CH_2Cl_2. Anal. Calcd for $C_{17}H_{27}N$: C, 83.20; H, 11.09. Found: C, 83.20; H, 10.95.

2.1.6 References

1. Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262.
2. Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569.
3. Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985.
4. Carter, M. B.; Schiøtt, B.; Gutiérrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667.
5. Viso, A.; Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 9373.
6. Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688.
7. Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562.
8. Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627.
9. Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952.
10. Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703.
11. Willoughby, C. A. Ph. D. Thesis, MIT, 1995.
12. Verdaguer, X.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12641.
13. Xin, S.; Aitken, C.; Harrod, J. F.; Mu, Y. *Can. J. Chem.* **1990**, *68*, 471.
14. Wolf, J. M.; Meetsma, A.; Teuben, J. H. *Organometallics* **1995**, *6*, 1381.
15. Xin, S.; Harrod, J. F.; Samuel, E. *J. Am. Chem. Soc.* **1994**, *116*, 11562.
16. Spaltenstein, E.; Palma, P.; Kreutzer, K. A.; Willoughby, C. A.; Davis, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 10308.
17. Harrod, J. H.; Yun, S. S. *Organometallics* **1987**, *6*, 1381.
18. The defluorination of perfluorohydrocarbons catalyzed by Cp_2TiF_2has been reported: Kiplinger, J. L.; Richmond, T. G. *J. Am. Chem. Soc.*, **1996**, *118*, 1805.
19. Yu, P.; Murphy, E. F.; Roesky, H. W.; Lubini, P.; Schmidt, H.-G.; Noltemeyer, M. *Organometallics* **1997**, *16*, 313.
20. For the sake of convenience, catalyst activation was generally carried out in the presence of pyrrolidine and methanol at 50 °C; the process was generally

complete in 5-10 minutes. Pyrrolidine, piperidine, and ^{t}BuONa were all successfully used as bases.

21. Silylamines **6** could be observed by NMR, but were never isolated due to their lability.
22. In some cases, this ratio could be taken as high as 1000:1; see Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784.
23. $D(F_3Ti\text{-}F)$=140 kcal/mol; $D(H_3Si\text{-}F)$=150 kcal/mol; $D(F_3Si\text{-}F)$=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.; Rappaport, Z. Eds.; John Wiley & Sons: New York, 1989. To our knowledge accurate bond energies for Ti-H have not been reported; therefore, a complete balanced thermochemical calculation is not possible.
24. *E/Z* ratios for the starting imines were measured as that of the corresponding amine produced by $NaBH_4$ reduction by chiral GC; integration of well-separated isomer peaks in the ^{1}H NMR was not possible due to peak overlap, and the isomers were not seperable by achiral GC.
25. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
26. Verdaguer, X.; Buchwald, S. L. unpublished results.
27. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
28. a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. I* **1980**, 2866. b) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473.
29. Johnson, G. P.; Marples, B. A. *J. Chem. Soc., Perkin Trans. I,* **1988**, 3399.

30. Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784.

31. Chin, B.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 5650.

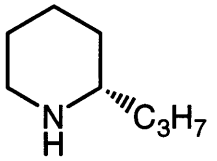
32. This compound may also be obtained by treating the binaphthol complex with KHF_2: Hansen, M. C.; Buchwald, S. L. unpublished results.

33. Cervinka, O; Dudek, V. *Coll. Czech. Chem. Commun.*, **1973**, *38*, 1159.

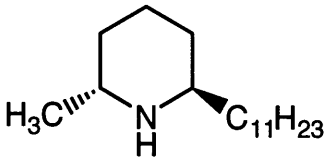
Section 2.2 - Asymmetric Syntheses of Coniine and Solenopsin A

2.2.0 Introduction

The efficient and highly enantioselective catalytic method for the hydrosilylation of imines described in Section 2.1.1 provides for the synthesis of chiral non-racemic amines.[1] (*S*)-Coniine (**1**), the poisonous hemlock alkaloid, and (2*R*,6*R*)-*trans*-solenopsin A (**2**), a myrmecological defense toxin, (Fig. 2.2.1) were selected as test cases of this technique. While these compounds have been the focus of a number of previous studies, in both cases the process described in this section provides a concise route to the desired compounds.



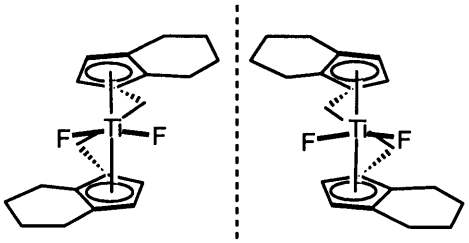
(*S*)-Coniine, **1**



(2*R*,6*R*)-*trans*-Solenopsin A, **2**

Fig. 2.2.1

Optically active piperidine alkaloids containing a stereogenic carbon atom in the 2-position are an important group of natural products and have been the target of numerous synthetic strategies. Both naturally-occurring and synthetic compounds of this type are of interest due to their often potent biological activities.[2] As noted in Section 2.1.1, the approach delineated here for the synthesis of this class of molecules makes use of the (EBTHI)Ti scaffold (Fig. 2.2.2) as the asymmetry-inducing element.

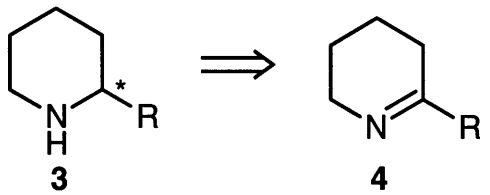


(*S*,*S*)-**5** (*R*,*R*)-**5**

Fig.2.2.2

Specifically, it was noted that in earlier work in the Buchwald labs that made use of this catalyst skeleton, endocyclic imines were reduced with excellent enantioselectivity to the corresponding cyclic amines.[3-7] Scheme 2.2.1 demonstrates the retrosynthetic

Scheme 2.2.1



3 **4**

analysis for enantiomerically enriched 2-substituted piperidines **3** from endocyclic imines **4** suggested by this observation. Prior syntheses of molecules of type **3** (*vide infra*) have generally involved the use of asymmetry derived from naturally-occurring compounds; most often this requirement directly prohibits the availability of both antipodes of a given product. However, both enantiomers of the pre-catalyst employed here ((EBTHI)TiF_2 **5**) can be obtained from a single synthetic procedure,[8] and thus centers of both *R* and *S* asymmetry may be produced at will. This is demonstrated here by the opposing sense of asymmetry required by natural coniine and solenopsin A.

Recent asymmetric syntheses of coniine have generally involved the use of auxiliaries derived from the chiral pool.[2,9-19] An asymmetric aza-Diels-Alder reaction requiring a stoichiometric amount of a chiral Lewis acid promoter has also been described,[20] as well as a chiral borohydride reducing agent which was employed in superstoichiometric amounts.[21] To date, there have been no asymmetric syntheses of this compound that have employed a catalytic enantioselective process.

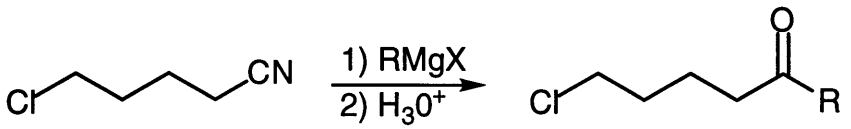
The solenopsin alkaloids were the subject of a recent exhaustive review.[22] In addition to numerous routes to the racemate of this constituent of fire-ant venom, there have also been reports of several asymmetric syntheses, all of which began with

optically active amino acids or employed chiral auxiliaries. As with coniine, the synthesis of *trans*-solenopsin A presented here (*vide infra*) is the first to take advantage of a catalytic asymmetric transformation.

2.2.1 Asymmetric Syntheses of Coniine and Solenopsin A

Endocyclic imines of the type required by our synthetic strategy (**4**) (Scheme 2.2.1) have themselves been the subject of much synthetic effort.[23-25] Attempts at direct synthesis of these compounds from δ-chlorovaleronitrile and organometallic reagents[23,26] did not afford the expected cyclic imines **4**; however, ω-chloroketones **6** which were instead obtained (Scheme 2.2.2) served as useful synthetic

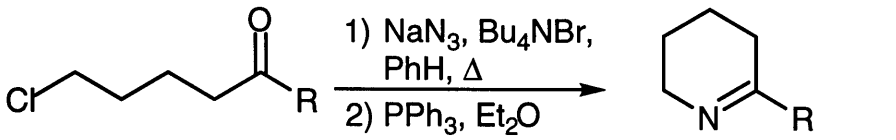
Scheme 2.2.2



6a: R=C_3H_7 (55%)
6b: R=$C_{11}H_{23}$ (29%)

intermediates.[27] Transient preparation of ω-azidoketones *via* an interesting solid/liquid phase-transfer catalysis reaction[28] followed by aza-Wittig cyclization[25,29,30] afforded the desired imines (Scheme 2.2.3).

Scheme 2.2.3



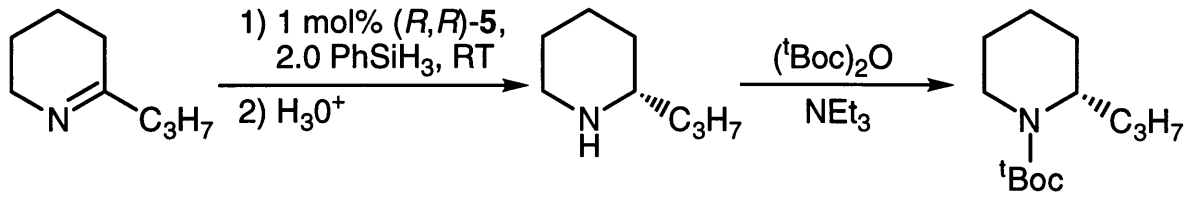
6a: R=C_3H_7
6b: R=$C_{11}H_{23}$

4a: R=C_3H_7 (62%)
4b: R=$C_{11}H_{23}$ (60%)

Our stereochemical model for the hydrosilylation of imines[1] (see Section 2.1.1) indicated that the pre-catalyst required for the production of the natural enantiomer of coniine is (*R*,*R*)-**5**. Accordingly, room-temperature reaction of imine **4a** with two equivalents of phenylsilane in the presence of 1 mol% (*R*,*R*)-**5** (which had been activated by treatment with pyrrolidine and methanol; see Section 2.2.3), followed by

acidic hydrolysis, afforded (*S*)-coniine **1** in 99% ee (Scheme 2.2.4). The free amine was immediately converted in 80% overall yield from **4a** to the *tert*-butoxycarbamate (^{t}Boc) derivative **7** to facilitate isolation.

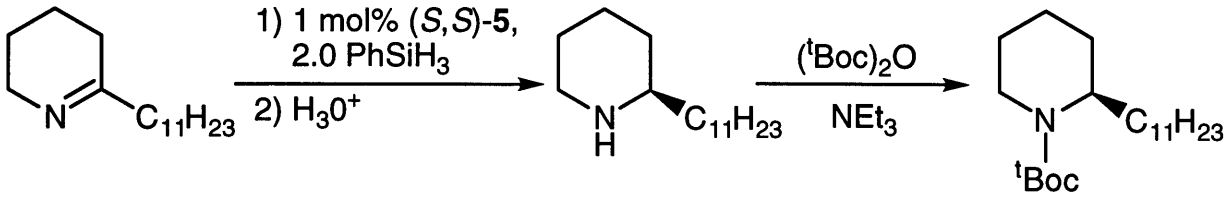
Scheme 2.2.4



4a **1** (99% ee) **7** (80% from **4a**)

In the case of *trans*-solenopsin A, the opposite sense of enantioselectivity to that required for coniine was needed. Therefore, in a similar sequence, imine **4b** was hydrosilylated in the presence of (*S*,*S*)-**5** to give (*R*)-amine **8** in 99% ee, which was again directly converted to the ^{t}Boc derivative, **9** (Scheme 2.2.5). Chiral carbamate **9**

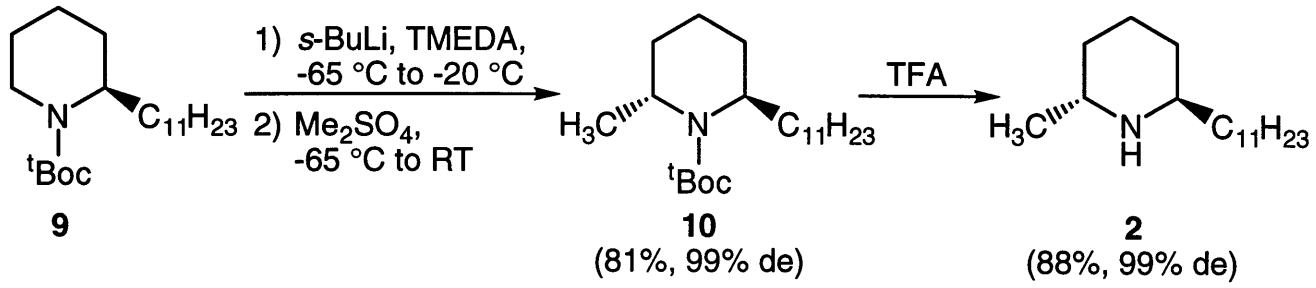
Scheme 2.2.5



4b **8** (99% ee) **9** (80% from **4b**)

was methylated in the 6-position in a stereocontrolled manner;[31] the resulting carbamate **10** was deprotected to afford (2*R*,6*R*)-*trans*-solenopsin A **2** in 88% yield (Scheme 2.2.6). This alkylation procedure was previously applied to a synthesis of racemic **2** by Beak and coworkers.[31]

Scheme 2.2.6



9

10
(81%, 99% de)

2
(88%, 99% de)

2.2.2 Conclusion

The first catalytic, asymmetric syntheses of the piperidine alkaloids (*S*)-coniine and (2*R*,6*S*)-*trans*-solenopsin A were carried out. The method for highly enantioselective imine hydrosilylation described in Section 2.1.1 allowed for a direct and efficient route to these synthetically interesting chiral amines.

2.2.3 Experimental

General. Unless otherwise noted, all reagents were either commercially available and were used as obtained from the supplier, or were prepared according to published methods. Ether and THF were distilled from sodium/benzophenone ketyl under nitrogen. TMEDA (Aldrich) was distilled from calcium hydride prior to use. All manipulations, unless otherwise specified, were carried out under an argon atmosphere using standard air-free techniques; glassware was oven-dried and cooled under vacuum. Flash column chromatography was performed on E. M. Science Kieselgel 60 (230-400 mesh). Yields, unless otherwise stated, refer to isolated yields of compounds >95% pure as assessed by capillary GC and ^{1}H NMR. NMR spectra were recorded on Varian XL or Varian Unity 300 MHz spectrometers. Enantiomeric excesses of amines were determined by chiral GC analysis of the corresponding trifluoroacetamindes using a Hewlett Packard 5890 gas chromatograph equipped with a 20 m $\times$ 0.25 mm Chiraldex G-TA (trifluoroacetylated γ-cyclodextrin) column; hydrogen was the carrier gas. Optical rotations were measured using a Perkin-Elmer Model 241 polarimeter.

1-chloro-5-octanone, 6a. To a solution of *n*-propylmagnesium bromide (1.0 M in ether, 27.0 mmol, 27.0 mL) in a 100 mL Schlenk flask was added 5-chlorovaleronitrile (27.0 mmol, 3.04 mL) dropwise *via* syringe; the solution warmed slightly and grew cloudy. The reaction mixture was stirred for 2 h, at which time GC analysis of a quenched (1 M HCl) sample showed no remaining nitrile. The vessel was cooled on an ice bath, and ice was added in portions to the reaction mixture. Vigorous bubbling took place. Upon completion of quenching, the reaction mixture was acidified (1 M HCl) and extracted multiple times with ether. The combined ether layers were washed (brine), and dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil. This was passed through a plug of silica gel (10:1 hexane/ethyl acetate) and again concentrated to give the crude product. Vacuum short-path

distillation afforded a clear oil, 2.44 g, 55%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53 (t, 2 H, J=6.4 Hz), 2.44 (t, 2 H, J=6.8 Hz); 2.38 (t, 2 H, J=7.7 Hz), 1.77 (m, 4 H), 1.59 (m, 2 H), 0.94 (t, 3 H, J=7.3 Hz); IR (neat, cm^{-1}): 2960, 2875, 1714, 1458, 1411, 1375, 1126.[25]

2-propyl-3,4,5,6-tetrahydropyridine, 4a. Sodium azide (30.0 mmol, 1.95 g) and tetrabutylammonium bromide (1.5 mmol, 0.48 g) were suspended in 10 mL benzene in a 100 mL Schlenk flask. **6a** (15.0 mmol, 2.44 g) was added as a solution in a few mL benzene, and the flask was equipped with a condenser/argon balloon unit. The mixture was heated in an 80 °C oil bath overnight. The following morning, GC analysis showed no remaining chloroketone, and the reaction mixture was cooled to room temperature. The mixture was filtered through filter paper and the solids were rinsed with ether; the filtrate was washed (water) and the aqueous layer was extracted (ether). The combined ether laters were washed (brine), dried ($MgSO_4$) and filtered. The volume of solvent was reduced to 20 mL (**Caution:** azides are potentially shock and contact explosives; azides with ratios of (C+O)/N < 3 should not be concentrated)**(ref)**, and the resulting solution was placed in a dry 100 mL Schlenk flask and purged with argon. Triphenyphosphine (15.0 mmol, 3.93 g) was added and nitrogen was evolved. After stirring overnight, GC analysis showed no remaining azide. The mixture was diluted with pentane, filtered through filter paper and the solids were rinsed with more pentane. The solution was then filtered through neutral Activity I alumina. The solution was concentrated *in vacuo* and the resulting oil was distilled (short-path, 1 atm Ar, 168 °C) to give a clear, faintly yellow, air-sensitive oil, 1.16 g, 62%. The imine was stored at -20 °C in a nitrogen-filled glovebox. ^{1}H NMR (300 MHz, C_6D_6): δ 3.55 (br. s, 2 H), 2.02 (t, 2 H, J = 3.9 Hz), 1.69 (m, 2 H), 1.61 (m, 2 H), 1.29 (m, 4 H), 0.81 (t, 3 H, J = 7.2 Hz). IR (neat, cm^{-1}): 2932, 2870, 1662, 1462, 1445, 1423, 679.[25]

1-chloro-5-hexadecanone, 6b. A 3-necked 100 mL round-bottomed flask was equipped with a stirbar, condenser, and addition funnel and purged with argon.

Magnesium turnings (30 mmol, 729 mg) and a small crystal of iodine were placed in the flask and 10 mL ether was added. A solution of undecyl bromide (30 mmol, 6.70 mL) in 10 mL ether was prepared in the addition funnel, and a few drops of this was added to the magnesium with stirring; the brown suspension immediately became colorless. An additional 10 mL ether was placed in the addition funnel, and the solution was added dropwise with stirring to the magnesium at such a rate to maintain a gentle reflux. The mixture was stirred an additional 3 h, and then cannulated into a 100 mL Schlenk flask. 5-Chlorovaleronitrile (30.0 mmol, 3.38 mL) was added dropwise *via* syringe; the solution warmed slightly and grew cloudy. The reaction mixture was stirred overnight. The reaction vessel was then cooled on an ice bath, and 1 M HCl was added in portions to the reaction mixture. Upon completion of quenching, the reaction mixture was extracted multiple times with ether. The combined ether layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil. GC analysis showed approximately 45% desired product, along with undecane and docosane as impurities. The undecane was removed by vacuum distillation, and the remaining material was purified by column chromatography (20:1 hexane/ethyl acetate) to afford a clear oil, 2.41 g, 29%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (t, 2 H, J=7.0 Hz), 2.41 (m, 4 H), 1.77 (m, 4 H), 1.57 (m, 2 H), 1.29 (br. s, 16 H), 0.88 (t, 3 H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.8, 44.9, 43.2, 42.0, 32.4, 32.3, 29.9, 29.8, 29.7, 29.6, 24.2, 23.0, 21.4, 14.4; IR (neat, cm^{-1}): 2924, 2853, 1715, 1464, 1411, 1375, 734. Anal. Calc'd for $C_{16}H_{31}ClO$: C, 69.91; H, 11.37. Found: C, 69.75; H, 11.23.

2-undecyl-3,4,5,6-tetrahydropyridine, 4b. Sodium azide (16.5 mmol, 1.07 g) and tetrabutylammonium bromide (0.82 mmol, 0.26 g) were suspended in 10 mL benzene in a 100 mL Schlenk flask. **6b** (8.2 mmol, 2.25 g) was added as a solution in a few mL benzene, and the flask was equpped with a condenser/argon balloon unit. The mixture was heated in an 80 °C oil bath overnight. The following

morning, GC analysis showed no remaining chloroketone, and the reaction mixture was cooled to room temperature. The mixture was filtered through filter paper and the solids were rinsed with ether; the filtrate was washed (water) and the aqueous layer was extracted (ether). The combined ether layers were washed (brine), dried ($MgSO_4$) and filtered. Concentration gave a yellow oil, which was placed in a dry 100 mL Schlenk flask and purged with argon, then dissolved in 15 mL ether. Triphenylphosphine (8.2 mmol, 2.15 g) was added and the solution gently bubbled. After stirring overnight, GC analysis showed no remaining azide. The mixture was diluted with pentane, filtered through filter paper and the solids were rinsed with more pentane. The solution was concentrated and the resulting oil was distilled (Kugelrohr, 10^{-2} torr, 90-95 °C) to give a clear, faintly yellow, air-sensitive oil, 1.16 g, 60%. The imine was stored at -20 °C in a nitrogen-filled glovebox. ^1H NMR (300 MHz, C_6D_6): δ 3.55 (m, 2 H), 2.10 (m, 4 H), 1.64 (m, 2 H), 1.54 (m, 4 H), 1.29 (br. s, 16 H), 0.88 (t, J =6.3 Hz, 3 H). IR (neat, cm^{-1}): 2931, 2859, 1664, 1465, 1360, 966, 733.[32]

(S)-(+)-*N*-*tert*-butoxycarbonyl-2-propylpiperidine ((S)-(+)-*N*-^{t}Boc-coniine), 7. A sealable Schlenk flask was charged with (*R,R*)-**5** (10 μmol, 3.5 mg) and vacuum purged three times with argon. THF (0.8 mL) was then added *via* syringe, followed by phenylsilane (2.0 mmol, 0.25 mL), pyrrolidine (8 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol). The mixture was stirred in a 50 °C oil bath for 10 min, resulting in a change of color from yellow to emerald green. The flask was then sealed and transferred to a nitrogen-filled glovebox. Imine **4a** was added (neat, 1.0 mmol, 125 mg) and the flask was resealed and stirred at room temperature. When GC analysis showed consumption of the starting material was complete (about 6 h), the reaction mixture was diluted with THF (20 mL) and stirred with 1M HCl (10 mL) for 0.5h (**Caution**: vigorous bubbling). The mixture was washed (3 x 20 mL 1 M HCl) and the combined aqueous layers made basic with 4 M NaOH and extracted (3 x 20 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), and filtered. To this

solution of the free amine was immediately added di-*tert*-butyl dicarbonate (1.0 mmol, 0.218 g) and triethylamine (2.0 mmol, 0.28 mL) and the mixture was stirred for several hours at room temperature. When GC analysis showed the amine had been consumed, the mixture was concentrated *in vacuo*. The residue was dissolved in THF (10 mL), and 4 M NaOH (5 mL) was added to destroy excess di-*tert*-butyl dicarbonate. After 1 hour, the mixture was acidified and extracted (5 x 15 mL ether). The combined ether layers were washed (brine), dried (Mg SO_4), filtered, and concentrated *in vacuo* to afford a slightly yellow oil. This was purified by column chromatography (15:1 hexane/ethyl acetate, 0.5% triethylamine) to give a clear oil, 183 mg, 80% from **4a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (br. s, 1 H), 3.95 (br. d, 1 H, J=11.0 Hz), 2.74 (t, 1 H, J =12.5 Hz), 1.45 (s, 9H), 1.20-1.65 (m, 10 H), 0.92 (t, 3 H, J=7.2 Hz); IR (neat, cm^{-1}): 2933, 2866, 1694, 1417, 1365, 1273, 1173, 1149. Chiral GC of the trifluoroacetamide derivative (prepared after removing the ^{t}Boc group with trifluoroacetic acid in CH_2Cl_2) showed an ee of 99%. $[\alpha]_D$=+28.7°, c=27 in CH_2Cl_2 (lit. $[\alpha]_D$=+33.5°, c=0.43 in $CHCl_3$).[15] The spectral data for this compound matched that reported in the literature.[15]

(R)-(–)-*N*-*tert*-butoxycarbonyl-2-undecylpiperidine, 9. Imine **4b** was hydrosilylated in a manner similar to that employed for **4a**. The reaction was catalyzed by (*S*,*S*)-**5** (10 μmol, 3.5 mg) which was activated with phenylsilane (2.0 mmol, 0.25 mL), pyrrolidine (8 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol). After addition of imine **4b** (1.0 mmol, 237 mg) and stirring at room temperature for at least six hours, GC analysis showed consumption of the starting material was complete, and the reaction mixture was diluted with THF (20 mL) and stirred with 1M HCl (10 mL) for 0.5h (**Caution**: vigorous bubbling). The mixture was made basic with 4 M NaOH and extracted (3 x 20 mL ether). Carbamylation, treatment with base, and workup (*vide supra*) gave a faintly yellow oil, which was purified by column chromatography (15:1 hexane/ethyl acetate, 0.5% triethylamine) to give a clear oil, 279 mg, 82% from **4b**. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 4.18 (br. s, 1 H), 3.96, br. d, 1 H, *J*=14.7 Hz), 2.74 (t, 1 H, *J* =16.4 Hz), 1.55 (s, 9 H), 1.20-1.65 (m, 26 H), 0.88 (t, 3 H, *J*=6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 78.8, 50.4, 38.7, 31.9, 29.7, 29.6, 29.5, 29.3, 28.5, 26.3, 25.7, 22.6, 19.0, 14.0; IR (neat, cm^{-1}): 2925, 2854, 1693, 1416, 1364, 1271, 1253, 1160. Chiral GC of the trifluoroacetamide derivative (prepared after removing the ^{t}Boc group with trifluoroacetic acid in CH_2Cl_2) showed an ee of 99%. $[\alpha]_D$=–21.2°, c=4.4 in CH_2Cl_2. Anal. Calc'd for $C_{21}H_{41}NO_2$: C, 74.28; H, 12.17. Found: C, 74.15; H, 11.99.

(2*R*,6*R*)-(–)-*trans*-*N*-*tert*-butoxycarbonyl-2-undecyl-6-methylpiperidine ((2*R*,6*R*)-(–)-*trans*-*N*-^{t}Boc-solenopsin A), 10. The compound was prepared according to the method of Beak.[31] Carbamate **9** (0.5 mmol, 170 mg) was placed in a dry Schlenk tube and purged three times with argon. Ether (1.7 mL) and TMEDA (0.1 mL) were added and the solution was cooled to -65 °C. *sec*-Butyllithium (1.4 M in cyclohexane, 0.65 mmol, 0.46 mL) was added dropwise. The solution was allowed to warm slowly over 1 h to –20 °C and stirred at that temperature for an addition 30 min. The solution was then re-cooled to -65 °C and dimethyl sulfate (1.0 mmol, 0.1 mL) was added. The mixture was allowed to warm to room temperature overnight. The reaction was then quenched with water (10 mL) and extracted (6 x 10 mL ether), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a clear oil. Purification by column chromatography (15:1 hexane/ethyl acetate, 0.5% triethylamine) gave a clear oil, 154 mg, 87%. ^1H NMR showed a single diastereomer. ^1H NMR (300 MHz, $CDCl_3$): δ 3.93 (m, 1 H), 3.80 (m, 1 H); 1.46 (s, 9H), 1.20-1.90 (m, 29 H). 0.88 (t, 3 H, *J*=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 78.6, 51.7, 47.0, 34.4, 31.9, 29.6, 29.5, 29.3, 28.5, 27.1, 23.5, 22.6, 20.8, 14.0; IR (neat, cm^{-1}): 2923, 2854, 1690, 1392, 1364, 1324, 1178. $[\alpha]_D$=–26.3°, c=1.3 in CH_2Cl_2. Anal. Calc'd for $C_{22}H_{43}NO_2$: C, 74.73; H, 12.26. Found: C, 74.46; H, 12.20.

(2*R*,6*R*)-(–)-2-undecyl-6-methylpiperidine ((2*R*,6*R*)-(–)-solenopsin A), 2. The compound was prepared by stirring carbamate **10** (0.08 mmol, 28.1 mg)

with excess (ca. 10 equiv) trifluroacetic acid in CH_2Cl_2 (1 mL) overnight. The reaction was quenched with saturated $NaHCO_3$, and the aqueous layers were extracted (5×10 mL ether). The combined organic layers were dried (MgSO4) and concentrated *in vacuo* to afford a clear oil, 18.4 mg, 91%. ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (m, 2 H), 2.85 (m, 2 H), 1.35-1.65 (m, 9 H), 1.25 (br. s, 18 H), 1.09 (d, J=6.3 Hz, 3 H), 0.88 (t, J =7.2 Hz, 3 H); IR (neat, cm^{-1}): 2935, 2851, 1467, 1382, 1140, 1064. Chiral GC of the trifluoroacetamide derivative showed a single diastereomer(de = 99%). $[\alpha]_D$=–1.7°, c=4.1 in CH_2Cl_2 (lit. $[\alpha]_D$=–1.3°, c=1.3 in $CHCl_3$).[33] The spectral data for this compound matched that reported in the literature.[33]

2.2.4 References

1. Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784.
2. Hammann, P. In *Organic Synthesis Highlights II*; H. Waldmann, Ed.; VCH: New York, 1995; pp 323.
3. Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703.
4. Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952.
5. Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627.
6. Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562.
7. This type of strategy has been proposed previously for the synthesis of nicotine derivatives: Brunner, H.; Kürzinger, A.; Mahboobi, S.; Wiegrebe, W. *Arch. Pharm.* **1988**, *321*, 73. Becker, R. H.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 995. Mundy, B. P.; Larsen, B. R. *Synth. Commun.* **1972**, 197.
8. Chin, B.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 5650.
9. Munchhoff, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084.
10. Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron: Asymm.* **1995**, *6*, 2651.
11. Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015.
12. Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223.
13. Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732.
14. Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 6119.
15. Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173.
16. Higashiyama, K.; Nakahata, K.; Takahashi, H. *Heterocycles* **1992**, *33*, 17.
17. Ito, M.; Maeda, M.; Kibayashi, C. *Tetrahedron* **1992**, *33*, 3765.
18. Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197.

19. Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525.
20. Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.
21. Archer, J. F.; Boyd, D. R.; Jackson, W. R.; Grundon, M. F.; Khan, W. A. *J. Chem. Soc. (C)* **1971**, 2560.
22. Leclercq, S.; Daloze, D.; Braekman, J.-C. *Org. Prep. Proced. Int.* **1996**, *28*, 499.
23. Fry, D. F.; Fowler, C. B.; Deiter, R. K. *Synlett* **1994**, 836.
24. Fukuda, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5812.
25. Vaultier, M.; Lambert, P. H.; Carrié, R. *Bull. Soc. Chim. Fr.* **1986**, 83.
26. Gallulo, V.; Dimas, L.; Zezza, C. A.; Smith, M. B. *Org. Prep. Proced. Int.* **1989**, *21*, 297.
27. The yields of these reactions were not optimized.
28. Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* **1985**, 202.
29. Khoukhi, M.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1986**, *27*, 1031.
30. Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Chem. Soc., Chem. Commun.* **1982**, 1224.
31. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
32. Bacos, D.; Célérier, J. P.; Marx, E.; Rosset, S.; Lhommet, G. *J. Heterocyclic Chem.* **1990**, *27*, 1387.
33. Jefford, C. W. *Tetrahedron Lett.* **1993**, *34*, 2911.