In summary, a synthesis of a protected version of the C_{22}–C_{42} segment of rapamycin has been accomplished. The modular nature of the synthesis will facilitate the preparation of rapamycin derivatives that will be useful for mechanistic investigations. Current efforts are focused on optimization of the sulfone oxidation and coupling of the dienylphosphine oxide[1] to the fragment described herein. The outcome of these studies and the completion of the total synthesis of rapamycin will be the subject of future reports.

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Supplementary Material Available: Full experimental details in addition to spectral and analytical data for all reaction products (including ^1H and ^{13}C spectra for intermediates **2**, **4**, **6**, **12**, **19**, **24–28**, and degradation product **29**) (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Chemically Labile Stannylene–Nitrogen Bonds. The Chemoselective and Stereoselective Synthesis of *N,N*-Bis(trimethylsilyl)enamines and *N,N*-Dialkylenamines

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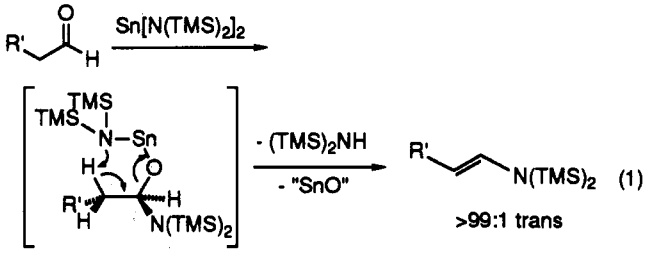
Summary: The chemoselective reaction of $Sn[N(TMS)_2]_2$ with primary aldehydes leads to the stereoselective synthesis of *trans-N,N*-bis(trimethylsilyl)enamines. More reactive $Sn(NR_2)_2$ (R = Et, iPr, or piperidine) can be generated in situ and then treated with aldehydes or ketones to give trans enamines.

Divalent tin compounds, otherwise known as stannylenes, have not been investigated as thoroughly as their carbon counterparts, the carbenes. In 1974, Lappert[1] and Zuckerman[2] both reported the synthesis of bis(trimethylsilyl)aminotin, $Sn[N(SiMe_3)_2]_2$, from the lithium amine salt and $SnCl_2$. Both groups reported this tin(II) amide to be a diamagnetic, thermally stable, distillable red-orange liquid which solidified to an orange-yellow solid. On the basis of a combination of cryoscopic, mass spectral, and X-ray crystallographic data, Lappert concluded that $Sn[N(TMS)_2]_2$ was monomeric in solution and dimeric in the solid state.[3]

Research in our group has focused on the development of new synthetic methods using stannylenes and germylenes. With regard to stannylenes, we have found that acetals may be selectively hydrolyzed to aldehydes *under mildly basic conditions* in the presence of tin(II) chloride.[4] Furthermore, aldehydes can be smoothly converted to β-keto esters via a tin(II) chloride promoted coupling with α-diazo compounds.[5] As an extension of these studies, we now report that tin(II) amides react with primary aldehydes to give the corresponding trans enamines stereoselectively (eq 1).[6] *This is the first example of transfer of a ligand from a tin(II) amide to an organic substrate.*[7]



(1)

Our initial experiments with tin(II) amides were conducted with $Sn[N(TMS)_2]_2$.[8] We were pleased to find that

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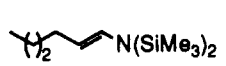
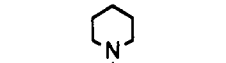
(7) Tin(II) amides have been used as substrates in ligand *exchange* reactions (Foley, P.; Zeldin, M. *Inorg. Chem.* **1975**, *14*, 2264) and in oxidative additions to alkyl and aryl halides (Gyane, M. J. S.; Lappert, M. F.; Miles, S. J.; Power, P. P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 256).

(8) Schaeffer, C. D.; Myers, L. K.; Coley, S. M.; Otter, J. C.; Yoder, C. H. *J. Chem. Educ.* **1990**, *67*, 347; see refs 1 and 2.

0022-3263/92/1957-5063$03.00/0

Table I. Enamines via Tin(II) Amides

entry	enamine	yield[a] (%)
1		27[b] (85)[c]
2		35[b] (75)[c]
3		22[b] (56)[c]
4		35[b] (58)[c]
5		40[b] (58)[c]
6		93[d]
7		70[d]
8		80[d]
9		39[d]
10		75[d]
11		60[d]

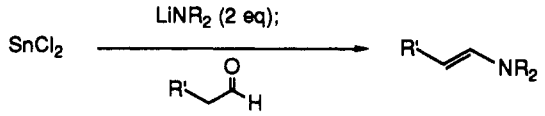
[a] Isolated yields, >99:1 trans enamines. [b] From $Sn[N(TMS)_2]_2$. [c] ^1H NMR yield versus an internal standard. [d] From in situ generated tin(II) amides.

treatment of a solution of $Sn[N(TMS)_2]_2$ with a primary aldehyde at room temperature resulted in smooth conversion to the *N,N*-bis(trimethylsilyl)enamine[9] (Table I, entries 1–5). Furthermore, $Sn[N(TMS)_2]_2$ proved to be highly chemoselective, as it did not react with ketones, nitriles, nitro compounds, epoxides, terminal acetylenes, acetals, esters, or even secondary and tertiary aldehydes. This is the first example of the conversion of an aldehyde to a silyl enamine.[10]

The first step of this reaction is thought to involve coordination of the electron-deficient tin(II) amide to the carbonyl of the aldehyde (eq 1). Transfer of a silazane ligand to the resulting oxonium ion then generates a tin(II) alkoxy amide. Finally, elimination via a six-membered ring transition state gives the trans enamine. This mechanism is supported by the following two experimental observations: (1) hexamethyldisilazane was obtained when the reaction was conducted in a sealed tube and (2) 1 equiv of the tin(II) amide was required for the reaction to go to completion.

Even though the ^1H NMR spectra of the *N,N*-bis(trimethylsilyl)enamines were clean and mass recovery was quantitative,[11] distillation of the crude material gave poor throughput. Disappointingly, all attempts to obtain analytical samples via purification by column chromatography on silica gel or on neutral alumina resulted in hydrolysis back to the aldehydes. In addition, our efforts to remove residual tin via precipitation or ligand exchange were also unsuccessful.[12]

We next turned our attention to the synthesis and reactions of tin(II) dialkylamides.[13] Enamines generated from $Sn[NR_2]_2$ were expected to be less sensitive than silyl enamines and, consequently, easier to purify. We quickly learned, however, that the starting tin(II) dialkylamides could not be easily prepared according to the procedure used for $Sn[N(TMS)_2]_2$. For example, although lithium diisopropylamide reacted with $SnCl_2$ at 0 °C to give Sn[N(diisopropyl)]$_2$, vida infra, this material could not be further purified without extensive decomposition. As an alternative, we developed an in situ procedure that both simplifies and extends the scope of this reaction (eq 2). In



(2)

the in situ procedure, 2 equiv of a lithium amide was first added to a solution of $SnCl_2$ in Et_2O at −78 °C.[14] After the reaction mixture was stirred for ca. 2 h, the appropriate aldehyde was added directly to the flask, and then the solution was allowed to warm to room temperature. Prior to workup, the crude enamine was treated with $KF{\cdot}2H_2O$, which precipitated tin and allowed for facile isolation of the desired enamine.[15] As can be seen from Table I (entries 6–11), this procedure works well with primary aldehydes and also allows for the preparation of enamines from more hindered aldehydes and ketones.

Our preliminary studies with tin(II) amides have led to a novel and stereoselective method for the preparation of trans enamines from aldehydes. In addition, it is the first example of transfer of a ligand from a tin(II) amide to an organic substrate. Further studies on amide transfer reactions are in progress.

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Supplementary Material Available: General procedures and compound characterization data (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) A stoichiometric amount of tin(II) amide is required for complete conversion of the aldehyde to an enamine. When 0.5 equiv of tin(II) amide was used, a 1:1 mixture of the enamine and aldehyde was obtained.

(10) For other syntheses of silyl enamines (a) from nitriles and imines, see: Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1990**, *55*, 4634. Corriu, Robert J. P.; Moreau, J. J. E.; Pataud-Sat, M. *J. Org. Chem.* **1990**, *55*, 2878. Picard, J. P.; Aizpurua, J. M.; Elyusufi, A.; Kowalski, P. *J. Organomet. Chem.* **1990**, *391*, 13. Cunico, R. F.; Kuan, C. P. *Tetrahedron Lett.* **1990**, *31*, 1945. Corriu, R. J. P.; Moreau, J. J. E.; Pataud-Sat, M. *Organometallics* **1985**, *4*, 623. Picard, J. P.; Elyusufi, A. A.; Calas, R.; Dunogues, J.; Duffaut, N. *Organometallics* **1984**, *3*, 1660. Ahlbrecht, H.; Dueber, E. O. *Synthesis* **1982** *4*, 273. Walter, W.; Lueke, H. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 535. Mitchell, T. N.; Kleine, B. *Tetrahedron Lett.* **1976**, *25*, 2173. (b) Via olefin isomerization, see: Paulini, K.; Reissig, H. U. *Liebigs Ann. Chem.* **1991**, *5*, 455. Murai, T.; Sakane, T.; Kato, S. *J. Org. Chem.* **1990**, *55*, 449. Corriu, R. J. P.; Huynh, V.; Moreau, J. J. E.; Pataud-Sat, M. *J. Organomet. Chem.* **1983**, *255*, 359. Corriu, R. J. P.; Huynh, V.; Iqbal, J.; Moreau, J. J. E. *J. Organomet. Chem.* **1984**, *276*, C61. (c) Other approaches, see: Murai, T.; Nonomura, K.; Kimura, K.; Kato, S. *Organometallics* **1991**, *10*, 1095.

(11) In calculating the mass recovery, we assumed that the crude product contained both the desired enamine and tin oxide. Hexamethyldisilazane and organic solvents were removed in vacuo.

(12) Neither chlorotrimethylsilane nor triethylamine added to tin; addition of sodium sulfide resulted in decomposition of the enamine.

(13) Cook, A. G. *Enamines*; Marcel Dekker: New York, 1988.

(14) The tin(II) amides of piperidine and hexamethyldisilazane can be prepared at room temperature.

(15) *CAUTION*: When the tin byproduct was filtered through paper, the filter paper smoldered. We recommend that this filtration be done using a fritted glass funnel.