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# 2-Pyridylsilyl Group as a Multifunctional "Phase Tag" for Solution Phase Synthesis

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***Abstract:*** 2-Pyridyldimethylsilyl (2-PyMe$_2$Si) group was found to serve as effective "phase tag" for acid-base extraction for solution phase synthesis. Acid-base extraction of octyl(2-pyridyl)dimethylsilane gave rise to 98% recovery. The introduction of 2-PyMe$_2$Si group to organic molecules was easily accomplished by Rh catalyzed hydrosilylation of alkenes with 2-PyMe$_2$SiH. The removal of 2-PyMe$_2$Si group was achieved by the oxidation with $H_2O_2$/KF (Tamao oxidation). In order to demonstrate the utilitiy of 2-PyMe$_2$Si group as a "phase tag", a sequential multi-step transformation was conducted. The products of each steps were easily isolated by acid-base extraction, and were sufficiently pure for the direct use in the next step of the sequence. 

Solid phase[1] has emerged as the medium of choice for automated synthesis of chemical libraries[2] while solution phase synthesis[3] has not been widely utilized as a viable alternative. This is probably because of the key advantage of product isolation of solid phase synthesis (simple filtration). However, solid phase synthesis often suffers from disadvantages of limited scale, high price of solid support, low reactivity, and limited reaction repertoire in the resin bound media, and difficulties on product analysis. Therefore, the development of new solution phase protocols having the advantages of solid phase synthesis is strongly needed. In such protocols, a range of reactions can be conducted under homogeneous traditional conditions, yet the products can still be easily separated by a simple operation. One of the most attractive techniques for this purpose is liquid/liquid extraction, and the development of effective and general "phase tags"[4] for liquid/liquid separation has become especially important. Recently, epoch-making fluorous groups[5] have emerged as powerful "phase tags" for solution phase synthesis and their potential utility in automated combinatorial synthesis has been demonstrated. We have been interested in the development of "phase tag" based on different principles, because solution phase synthesis will enjoy rich chemistry and versatile applications using several orthogonal phase separation protocols. Thus, we focused on acid-base extraction[6] because this traditional protocol has still high potentiality from view points of effectiveness, operation, safety, economy, and environment. In this communication, we introduce a new prototypical example of silicon based "phase tags" for acid-base extraction in solution phase synthesis.

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We designed 2-pyridyldimethylsilyl (2-PyMe$_2$Si) group as a "phase tag", because the silyl group is widely utilized in organic synthesis[7] and the presence of a pyridyl group on silicon would enable easy purification of products by simple acid-base extraction (Figure 1). We also envisioned that the pyridyl group would assist both the introduction of the silyl group and its removal after transformations by virtue of its strong coordinating ability.

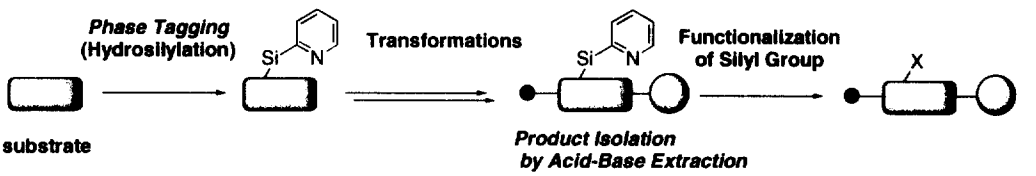



**Figure 1.** Synthetic strategy using 2-PyMe$_2$Si group as a "phase tag".

In order to test the effectiveness of 2-PyMe$_2$Si group as a "phase tag", we first examined acid-base extraction of octyl(2-pyridyl)dimethylsilane (**1**) as a model compound (Figure 2). Acid extraction (1*N aq* HCl, 6 times[8]) of a solution of **1** in $Et_2O$ transfers **1** to the aqueous phase. The neutralization of the aqueous phase (pH = ca. 7) followed by the extraction with $Et_2O$ (3 times) transfers **1** to the organic phase (98% recovery). Therefore, 2-PyMe$_2$Si group proved to be quite effective and efficient for this "phase switching" technique.[9] It is also noteworthy that 2-PyMe$_2$Si group is quite stable under both acidic conditions and basic conditions.

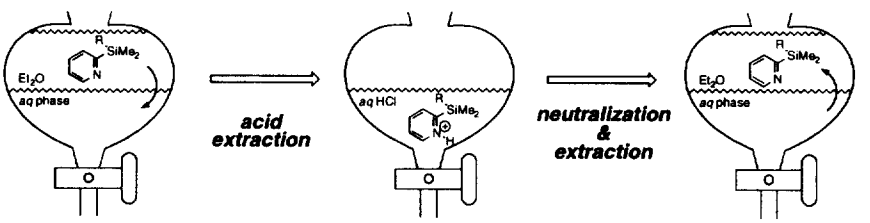
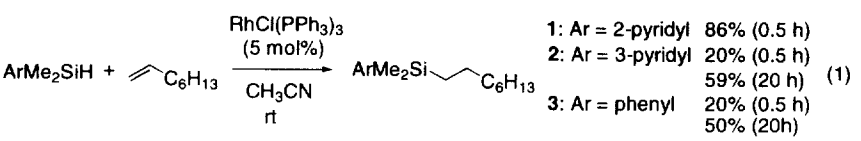



**Figure 2.** Acid-base "phase switching" technique using 2-PyMe$_2$Si group as a "phase tag"

The introduction of 2-PyMe$_2$Si group was accomplished quite easily by transition metal catalyzed hydrosilylation[10] of alkenes with 2-pyridyldimethylsilane[11] (eq 1). Preliminary screening of the catalysts, including palladium(0), platinum(0), and rhodium(I) complexes, revealed that $RhCl(PPh_3)_3$ was most effective in terms of catalytic activity and regioselectivity. The hydrosilylation product was easily isolated by simple acid-base "phase switching" technique with >95% purity as shown in eq 1. It is interesting to note that the hydrosilylation with 3-pyridyldimethylsilane and phenyldimethylsilane proceeded much more slowly under similar conditions,[12] indicating the acceleration by the 2-pyridyl group. Probably the pyridyl group pre-coordinates to the metal center[13] prior to the oxidative addition of the Si-H bond, thereby enhancing the rate of the catalytic cycle (Figure 3).



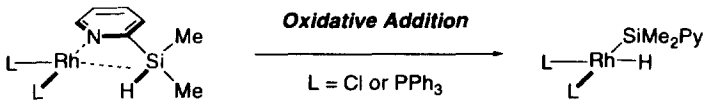
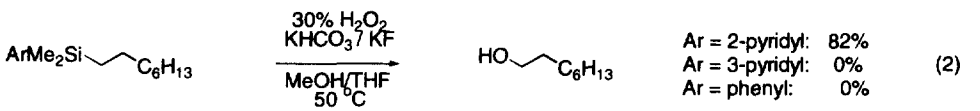



**Figure 3.** Pre-coordination of the pyridyl group to the metal in hydrosilylation

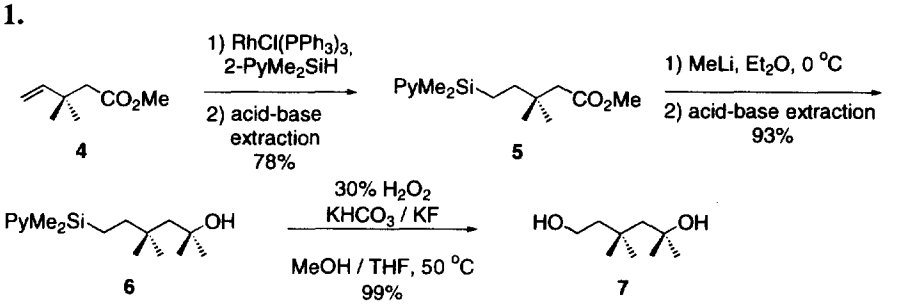
The removal of 2-PyMe$_2$Si group was easily accomplished by Tamao oxidation.[14] Although Fleming developed the two-step procedure for the cleavage of PhMe$_2$Si group,[15] we were delighted to find that 2-PyMe$_2$Si group was cleaved in a single step under much milder conditions. Thus, the treatment of octyl(2-pyridyl)dimethylsilane with *aq* 30% $H_2O_2$ (30 equiv) in the presence of KF (2 equiv) and $KHCO_3$ (2 equiv) in THF/MeOH afforded 1-octanol in 82% yield (eq 2). The presence of 2-pyridyl group is essential for this transformation, because neither octyl(3-pyridyl)dimethylsilane nor octylphenyldimethylsilane gave 1-octanol under the same conditions. The reason for the unique reactivity of 2-PyMe$_2$Si group has not been fully clarified as yet and more data should be accumulated before the elucidation of the precise reaction mechanism.[16]




(2)

To illustrate the possibilities of 2-PyMe$_2$Si group as a "phase tag" in conventional and combinatorial solution phase synthesis, we conducted a sequential multi-step transformation shown in Scheme 1. Methyl 3,3-dimethyl-4-pentenoate (**4**) was treated with 2-pyridyldimethylsilane in the presence of 5 mol% of RhCl(PPh$_3$)$_3$ in $CH_3CN$ at room temperature for 1 h. Simple acid-base extraction afforded hydrosilylated product **5** in 83% yield with >95% regioselectivity. In the next step, **5** was treated with MeLi (5 equiv) in $Et_2O$ at 0 °C for 1 h to obtain tertiary alcohol **6** (93% yield) which was purified by acid-base extraction. The products (**5** and **6**) were quite pure (no identifiable starting materials or side products as judged by $^1$H NMR and capillary GC) and were used directly in the next step of the sequence. It is also noteworthy that satisfactory data of elemental analysis was obtained for **6** after simple acid-base extraction. In the final step, Tamao oxidation of **6** gave the corresponding diol **7** in 99% isolated yield.

**Scheme 1.**



In summary, we have developed 2-Py$Me_2$Si group as a novel "phase tag" that enables the simple isolation of the product by acid-base extraction. It is noteworthy that 2-Py$Me_2$Si group can be introduced to various organic molecules by well-established hydrosilylation reaction and easily removed by reliable Tamao oxidation using the unique reactivity of the pyridyl group. The silicon based "phase tag" demonstrated herein would serve a new protocol for the emerging field of solution phase synthesis. Its adaptation to automation and parallel synthesis of chemical libraries, as well as the development of other related "phase tags" are currently under investigation.

## References and Notes

(1) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
(2) For reviews on combinatorial chemistry, see: (a) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. (b) Borman, S. *Chem. Eng. News* **1996**, *Feb. 12*, 29. (c) Balkenhohl, F.; Von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2289. (d) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (e) Borman, S. *Chem. Eng. News* **1997**, *Feb. 24*, 43. (f) Czarnik, A. W.; DeWitt, S. H. Eds; *A Practical Guide to Combinatorial Chemistry*, American Chemical Society, Washington DC, 1997.
(3) For liquid phase combinatorial syntheses, see: (a) Carell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2059. (b) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 6419. (c) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842. (d) Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109. (e) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539.
(4) Curran, D. P. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1174.
(5) (a) Horvath, I. T,; Rabai, J. *Science* **1994**, *266*, 72. (b) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. (c) Curran, D. P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480. (f) Curran, D. P. *ChemTracts-Org. Chem.* **1996**, *9*, 75. (d) Hughes, R. P.; Trujillo, H. A. *Organometallics* **1996**, *15*, 286. (e) DiMagno, S. G.; Dussault, P. H.; Schultz, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5312. (f) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823. (g) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681.
(6) For example, Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567.
(7) For example, Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988.
(8) For organo(2-pyridyl)dimethylsilane having polar funcitonal groups, the number of extraction would be decreased to two or three.
(9) 3-Pyridyldimethylsilyl group was also found to be quite effective as a "phase tag" for acid-base extraction.
(10) For example, Marciniec, B. *Comprehensive Handbook on Hydrosilylation*; Pergamon Press: Oxford, 1992.
(11) Ang, H. G.; Kwik, W. L. *J. Organomet. Chem.* **1989**, *361*, 27.
(12) In 1,2-dichloroethane 3-pyridyldimethylsilane gave the hydrosilylation product in 90% yield, although the reaction was still very slow (20 h).
(13) For pyridylsilyl group coordination to the metal, see: (a) Jutzi, P.; Heusler, H. *J. Organomet. Chem.* **1975**, *102*, 145. (b) Jutzi, P.; Heusler, H. *J. Organomet. Chem.* **1976**, *114*, 265. (c) Wright, M. E. *Tetrahedron Lett.* **1987**, *28*, 3233. (d) Wright, M. E.; Lowe-Ma, C. K. *Organometallics* **1990**, *9*, 347.
(14) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96. For excellent reviews on oxidative cleavage of silicon-carbon bond, see: (a) Tamao, K. in *Organosilicon and Bioorganosilicon Chemistry: Structure, Bonding, Reactivity and Synthetic Application*, Sakurai, H., Ed. Halsted Press: New York, 1985; pp 231. (b) Tamao, K. *Advances in Silicon Chemistry*; JAI Press Inc., 1996; Vol. 3, pp 1.
(15) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.
(16) Pioneering work of Chan revealed that the aminomethylsilyl group is cleaved under 'standard conditions' of Tamao oxidation: Chan, T. H.; Pellon, P. *J. Am. Chem. Soc.* **1989**, *111*, 8737. It is also noteworthy that the interaction of C-Si $\sigma$ orbital with the nonbonding p orbital of the nitrogen raises the HOMO level which in turn enhances the susceptibility toward oxidation. (a) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962. (b) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589.