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Hydrocarbon Soluble Recyclable Silylation Reagents and Purification Auxiliaries

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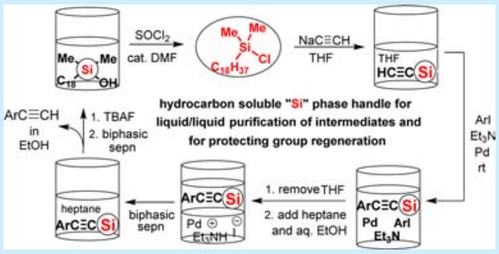
Ⓢ *Supporting Information*

ABSTRACT: Procedures using heptane-phase-selectively soluble octadecyldimethylsilyl groups to facilitate separations and silyl reagent regeneration are described. These results show that alcohols and alkynes protected by these groups are phase-selectively soluble in hydrocarbon solvents. In a thermomorphic cyclohexane/DMF system, >96% of the silylated alcohols are in the cyclohexane phase, allowing these compounds to be purified by a simple liquid/liquid extraction. Applications of these silylating agents in a Grignard synthesis and Sonogashira reaction are described.



Chlorosilanes are widely used in organic synthesis as protecting groups.[1] For example, trialkylsilyl chlorides are used to form silyl ethers to protect alcohols, and trimethylsilyl groups are used to monoprotect one C−H of ethyne in cross-coupling chemistry. These organosilicon reagents are particularly useful because their installation and removal can be performed with high chemoselectivity under mild conditions. However, when a silyl group is removed, often with a fluoride reagent, it is typically discarded. Here, we show how techniques we developed for the separation and recycling of phase-selectively soluble homogeneous catalysts can be adapted to recycle protecting groups. We also show that these same protecting groups can serve as phase handles in a simple extractive purification method for silyl-protected alcohols and alkynes, a strategy that has precedent in liquid/liquid separations that employ fluorous silyl groups.[2]

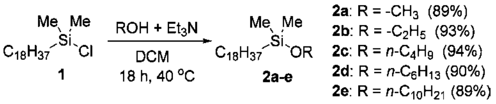
The chemistry described here highlights the potential of heptane soluble silyl groups in recycling as well as purification. Surprisingly few studies have been carried out to recycle organosilyl species by regenerating chlorosilanes. Lickiss showed that *tert*-butyldimethylsilanol (TBS−OH) could be recycled and converted to *tert*-butyldimethylchlorosilane. However, in this chemistry, the volatility of the hemihydrate of TBS−OH leads to losses of product during distillation.[3] Darling and co-workers described cross-linked polystyrene supported chlorosilanes that could be used as protecting groups in solid-phase synthesis and regenerated by treatment with BCl_3. However, the heterogeneity of the support resulted in low loading of the silicon reagent, difficult characterization, and modest efficiency in subsequent silylation chemistry.[4] Our experience with hydrocarbon soluble catalyst ligands and others' work with hydrocarbon phase tags that employ octadecyl groups suggested alternative biphasic schemes for separating and recycling silicon reagents might be useful alternatives.[5−7]

Our group has a longstanding interest in phase-selectively soluble polymer-supported catalysts.[7] We have shown that it is possible to prepare catalysts or ligands that effect homogeneous reactions and a separation without affecting reactivity by anchoring catalysts or ligands onto soluble polymers.[8] In this strategy, separations are most often effected after completion of the reaction, using a biphasic liquid/liquid separation where the soluble polymer supported species is by design selectively soluble in a phase that does not contain the product. Alternatively, separations can be carried out using an extractive workup. These methods have been used by us and others to recycle precious metal catalysts and in synthesis.[7,9−12] Here we show how a similar strategy can address the issue of recycling organosilicon species and as a strategy in purification of intermediates.

Our initial studies showed the feasibility of using a hydrocarbon phase anchored silylating agent—octadecyldimethylchlorosilane (**1**)—as an analog of trimethylchlorosilane. After synthesizing silyl ethers of a variety of alcohols, we showed that the products of silylation that either had an *n*-octadecyl group or contained a mixture of octadecyl isomers are soluble in alkanes such as hexane and heptane, but poorly soluble in common polar organic solvents such as dimethylformamide, 90% aqueous ethanol, and acetonitrile. We further showed that this phase-selective solubility can be used to assist in the extractive purification of compounds containing this protecting group and to subsequently separate and recycle a spent organosilyl species.

To study the separability of silyl ethers of **1** and the recyclability of octadecylsilyl groups of **1**, we first prepared silyl ethers from a series of primary alcohols. As shown in Scheme 1, alcohols with side chains of various sizes reacted with **1** under

Scheme 1. Synthesis of Silyl Ethers 2a−e



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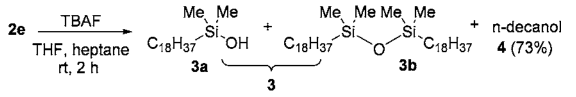
mild conditions to give the corresponding silyl ethers with excellent yields. Notably, these products could be purified by a simple liquid/liquid separation using heptane and 90% aqueous ethanol due to the phase-selective solubility of the products in heptane. In these cases, the products could be isolated by removal of the heptane under reduced pressure. After the ethers were synthesized, we next quantitatively determined the phase-selective solubility of silyl ethers in a thermomorphic system of DMF and cyclohexane, which is biphasic at room temperature but forms a monophasic solution on heating. We then analyzed the leaching of the silyl ethers into the polar phase of this thermomorphic system using ^{1}H NMR spectroscopy. Using methoxy(octadecyldimethyl)silane (**2a**), ethoxy(octadecyldimethyl)silane (**2b**), and butoxy(octadecyldimethyl)silane (**2c**) as examples, we found that **2a** showed 3.8% leaching, **2b** showed 2.1% leaching, and **2c** showed 2.0% leaching into the DMF phase of a cyclohexane/DMF thermomorphic system. Similar results were seen in ^{1}H NMR experiments using **2c** in cyclooctane/DMF, hexane/DMF, heptane/DMF, and cyclooctane/90% aqueous ethanol where 2.2%, 4.6%, 3.2%, and 0.7% leaching of **2c** into the polar phase was seen. These results show that **1** is effective at forming products that are reasonably phase-selectively soluble in nonpolar solvents and suggest that **1** can be used as a purification auxiliary.

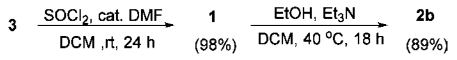
Next, we examined ways to reform the alcohol and to recycle the octadecyldimethylsilyl group (Scheme 2). In this case, we used **2e** as an example, cleaving the silyl ether using TBAF in a heptane/THF solution. The octadecyldimethylsilyl groups were recovered as a mixture of the silanol and silyl ether (**3**) in 94% yields. The decanol (**4**) yield was lower, as some decanol was lost during the extractions that were used to remove the TBAF residues. The octadecyldimethylsilyl residue mixture **3** could be further purified to form **3b**, but the mixture of **3a** and **3b** was typically used directly in recycling experiments.

Scheme 2. TBAF Cleavage of 2e To Form 3 and Decanol



There are a number of reactions that could in principle regenerate **1** from **3**. Some, like Sommer's route using chlorine gas, are likely experimentally inconvenient.[13] Other procedures including chlorination with acetyl chloride,[14] thionyl chloride,[15] oxalyl chloride,[16] phosphorus pentachloride,[17] and concentrated hydrochloric acid[18] are better choices. In our case, we found that **1** can be regenerated quantitatively from **3** by allowing **3** to react with thionyl chloride in the presence of a catalytic amount of DMF (Scheme 3). With these results in hand, a procedure for the cleavage of organosilyl protecting groups and regeneration of **1** was established (Figure 1).

Scheme 3. Regeneration of 1 from 3



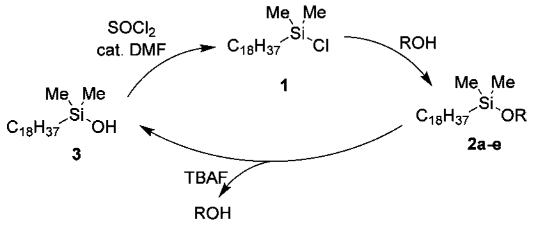
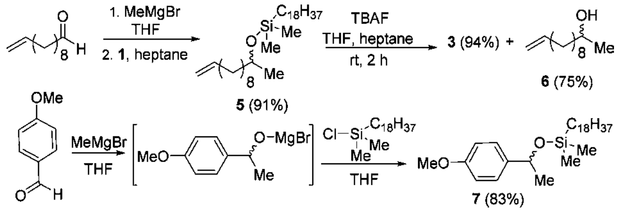


Figure 1. Recycling of **1** after a protection/deprotection sequence.

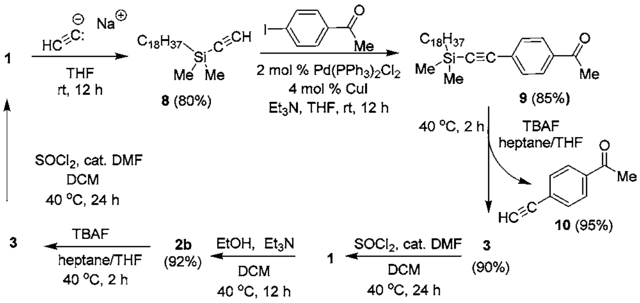
Scheme 4. Use of 1 To Trap Intermediates in Grignard Reactions



These recyclable hydrocarbon-soluble silylating reagents can also be used in other types of reactions. For example, regenerable **1** can be used to phase tag the alkoxide product of a Grignard reaction. This is shown in Scheme 4 where 10-undecenal was allowed to react with methylmagnesium bromide. Addition of **1** to the alkoxide product solution formed (dodec-11-en-2-yloxy)(octadecyldimethyl)silane (**5**) which after a workup using heptane afforded a 91% yield of **5**. A subsequent fluoride deprotection and liquid/liquid separation procedure afforded dodec-11-en-2-ol (**6**) in 75% yield that was pure by ^{1}H and ^{13}C NMR spectroscopy. This same strategy was used to form an 83% yield of (1-(4-methoxyphenyl)ethoxy)(octadecyldimethyl)silane (**7**) when **1** was added to the product of the reaction of methylmagnesium bromide and 4-methoxybenzaldehyde

The Sonogashira reaction is a widely used catalytic reaction that leads to alkynes via a Pd-catalyzed cross-coupling reaction.[19] A common variant of this procedure uses trimethylsilyl-protected ethyne as a reagent to form terminal alkyne products.[20,21] In these cases, the protected alkyne coupling products are purified by column chromatography to separate them from catalyst residues. To illustrate the broader potential of **1**, we have shown that **1** can replace trimethylsilyl groups in these sorts of Sonogashira coupling reactions, providing both recyclable silyl protecting groups and a simpler way to isolate the intermediate protected alkyne product.

Scheme 5. Use of 1 in a Sonogashira Reaction Followed by Regeneration and Reuse of 1



As shown in Scheme 5, the reaction of **1** with sodium acetylide[22] formed octadecyldimethylsilylacetylene (**8**) which could then be coupled with 4-iodoacetophenone to obtain 4-(dimethyloctadecylsilyl)ethynylacetophenone (**9**). While a trimethylsilyl analog of **9** previously had to be purified by column chromatography,[23] **9** was purified by simple liquid/liquid extraction. The result shows that **8** is a potential replacement for Me$_3$SiC≡CH and a purification handle for the intermediate product. In this example, 4-ethynylacetophenone (**10**) was obtained in 95% yield after cleavage of the silyl group. The starting **1** was then regenerated from **3**. We also showed that regenerated **1** could be used in other chemistry, specifically in a reaction with ethanol to afford a 92% yield of **2b**. The product **2b** formed from regenerated **1** was identical to that formed from fresh **1** and contained no Sonagashira coupling products.

While we were successful in using **1** as a phase anchor as shown in the examples above, **1** has limitations. If the substrate that is appended to **1** has a molar mass comparable to **1** and is significantly polar, leaching levels will exceed 10%. This is illustrated visually in Figure 2 with an octadecyldimethylsilyl-protected derivative of the azo dye **11**. This silylated dye is soluble in a hot homogeneous thermomorphic solvent mixture, but cooling produced a biphasic mixture with a significant amount of the dye derivative in the polar phase. Separate experiments with the alcohol precursor of **11** show it is predominantly in the polar phase of this thermomorphic mixture. We believe this is because the azo dye portion of **11** is both polar and has a mass that is approximately the same as the silyl phase anchor and the hydrophobic groups in **1**.

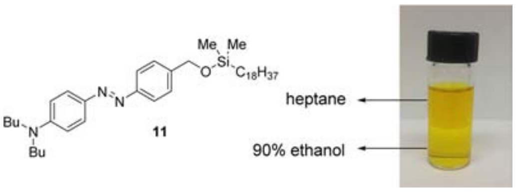


Figure 2. Phase selectivity of **11** at 25 °C in a thermomorphic 1/1 (v/v) mixture of heptane and 90% aqueous ethanol.

In summary, this work shows that hydrocarbon phase anchored silyl protecting groups can serve both as regenerable protecting groups and as purification handles. Using commercially available and inexpensive octadecyldimethylsilyl chloride **1**, we showed that a variety of silyl ethers are >95% phase-selectively soluble in the heptane phase of a heptane/DMF mixture when alcohols are converted into silyl ethers using **1**. We further show that the octadecyldimethylsilyl products formed in the deprotection can be used to reform **1**. Other experiments show that **1** can be used directly to silylate alkoxides produced in reactions to form silyl ether products that facilitate purification and separation of the products. The broader utility of **1** is shown by the successful use of an ethyne derivative of **1** in a Sonogashira coupling reaction. While our experiments mostly used a well-defined *n*-octadecyldimethylsilyl chloride reagent, we also showed that a less expensive commercially available silyl chloride containing octadecyl silyl isomers is similarly effective. We anticipate that in future work we can design more phase-selectively soluble silylating agents to ameliorate the modest losses due to leaching of silylated intermediates seen here and to address issues that may come up with protection of more polar or larger polar substrates. We also expect that adaptations of this strategy will be generally useful in recycling stoichiometric protecting groups and reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00263.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Wuts, P. G. M.; Greene, T. W. *Greene's protective groups in organic synthesis*; Wiley-Interscience: Hoboken, NJ, 2007.
(2) Zhang, W. *Tetrahedron* **2003**, *59*, 4475.
(3) Lickiss, P. D.; Stubbs, K. M. *J. Organomet. Chem.* **1991**, *421*, 171.
(4) Stranix, B. R.; Liu, H. Q.; Darling, G. D. *J. Org. Chem.* **1997**, *62*, 6183.
(5) (a) Encinas, L.; Chiara, J. L. *Eur. J. Org. Chem.* **2009**, *2009*, 2163. (b) Guo, J.; Lu, Y.-J.; Zhang, L.; Ye, X.-S. Ye *Synlett* **2012**, *23*, 1696. (c) Fujita, Y.; Fujita, S.; Okada, Y.; Chiba, K. *Org. Lett.* **2013**, *15*, 1155. (d) Aihara, K.; Komiya, C.; Shigenaga, A.; Inokuma, T.; Takahashi, D.; Otaka, A. *Org. Lett.* **2015**, *17*, 696. (e) Okada, Y.; Wakamatsu, H.; Sugai, M.; Kauppinen, E. I.; Chiba, K. *Org. Lett.* **2015**, *17*, 4264. (f) Matsuno, Y.; Shoji, T.; Kim, S.; Chiba, K. *Org. Lett.* **2016**, *18*, 800.
(6) McBride, K.; Gaide, T.; Vorholt, A.; Behr, A.; Sundmacher, K. *Chem. Eng. Process.* **2016**, *99*, 97.
(7) Bergbreiter, D. E.; Tian, J.; Hongfa, C. *Chem. Rev.* **2009**, *109*, 530.
(8) Yang, Y.-C.; Bergbreiter, D. E. *J. Org. Chem.* **2010**, *75*, 873.
(9) Yang, Y.-C.; Bergbreiter, D. E. *Pure Appl. Chem.* **2013**, *85*, 493.
(10) Behr, A.; Turkowski, B.; Roll, R.; Schoebel, R.; Henze, G. *Top. Organomet. Chem.* **2008**, *23*, 19.
(11) Rackl, D.; Kreitmeier, P.; Reiser, O. *Green Chem.* **2016**, *18*, 214.
(12) Hobbs, C.; Yang, Y.-C.; Ling, J.; Nicola, S.; Su, H.-L.; Bazzi, H. S.; Bergbreiter, D. E. *Org. Lett.* **2011**, *13*, 3904.
(13) (a) Sommer, L. H.; Frye, C. L.; Parker, G. A.; Michael, K. W. *J. Am. Chem. Soc.* **1964**, *86*, 3271. (b) Naka, A.; Matsumoto, Y.; Itano, T.; Hasegawa, K.; Shimamura, T.; Ohshita, J.; Kunai, A.; Takeuchi, T.; Ishikawa, M. *J. Organomet. Chem.* **2009**, *694*, 346.
(14) Daudt, W. H.; Hyde, J. F. *J. Am. Chem. Soc.* **1952**, *74*, 386. Savela, R.; Zawartka, W.; Leino, R. *Organometallics* **2012**, *31*, 3199.
(15) Tacke, R.; Kornek, T.; Heinrich, T.; Burschka, C.; Penka, M.; Pülm, M.; Keim, C.; Mutschler, E.; Lambrecht, G. *J. Organomet. Chem.* **2001**, *640*, 140.
(16) Metz, S.; Nätscher, J. B.; Burschka, C.; Götz, K.; Kaupp, M.; Kraft, P.; Tacke, R. *Organometallics* **2009**, *28*, 4700.
(17) Hoffmann, F.; Wagler, J.; Roewer, G. *Eur. J. Inorg. Chem.* **2010**, *2010*, 1133.
(18) Masaoka, S.; Banno, T.; Ishikawa, M. *J. Organomet. Chem.* **2006**, *691*, 174.
(19) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
(20) Handa, S.; Fennewald, J. C.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3432.
(21) Xu, C.; Du, W.; Zeng, Y.; Dai, B.; Guo, H. *Org. Lett.* **2014**, *16*, 948.
(22) Plater, M. J.; Aiken, S.; Bourhill, G. *Tetrahedron* **2002**, *58*, 2405. Ishikawa, M.; Sakamoto, H.; Tabuchi, T. *Organometallics* **1991**, *10*, 3173.
(23) (a) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551. (b) Bracher, F.; Krauß, J. *Eur. J. Org. Chem.* **2001**, *2001*, 4701.