



An expedient preparation of Stryker's reagent

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Abstract—A convenient and efficient preparation of Stryker's reagent, $[\text{Ph}_3\text{PCuH}]_6$, under homogeneous conditions using silanes as the reducing agent is detailed. The reaction time can be reduced to 1–2 h, and high yields of Stryker's reagent can be routinely achieved. The same method has been extended to the synthesis of $[\text{Ph}_3\text{PCuD}]_6$ using Ph_2SiD_2 . © 2002 Elsevier Science Ltd. All rights reserved.

Hydrido(triphenylphosphine)copper(I) hexamer, also known as Stryker's reagent, is a commercially available, well-characterized copper hydride.¹ It's most common application has been in the conjugate reduction of α,β -unsaturated carbonyl compounds. $[\text{Ph}_3\text{PCuH}]_6$ reduces polarized conjugated systems chemoselectively while unactivated olefins are inert. Even the highly reactive α,β -unsaturated aldehydes and conjugated systems bearing γ -leaving groups have been reduced in good yields.^{2,3} Owing to the reagent's sterically demanding structure, the hydride is usually delivered with good stereoselectivity to the less hindered face of the double bond.³ Recently, this reagent has also been shown to be effective in promoting reduction in tandem with additional carbon–carbon bond forming reactions.⁴

Nevertheless, a common complaint in the use of this reagent has been that the reduction is somewhat capricious, and the stoichiometry of the reaction was sometimes irreproducible. This is likely to be due to variations in the quality of the commercially available Stryker's reagent. Other research groups as well as ours have encountered this problem, and the most direct solution is to obtain Stryker's reagent of a good quality by preparing it in the laboratory.^{4c,5b}

Although a number of preparations of $[\text{Ph}_3\text{PCuH}]_6$ have been described,^{6,7} Stryker has published the most convenient synthesis to date by the reaction of sodium or potassium *tert*-butoxide, triphenylphosphine and

copper(I) chloride in the presence of hydrogen.^{8,9} Under these heterogeneous conditions, the reduction requires 15–24 h at room temperature. A yield of 50–65% was obtained when this reaction proceeded under one atmosphere of hydrogen. A higher yield of 80% has been reported when a similar reduction was carried out under 1500 psi of hydrogen.⁷ The Stryker protocol has been widely adopted because of its economic and operational advantages, and its ability to furnish reproducibly reagent of high purity.

The recent results of Lipshutz et al. revealed that reductions using catalytic amounts of Stryker's reagent can be carried out using silanes such as polymethylhydrosiloxane (PMHS) as the stoichiometric reductants.⁵ It then became obvious that silanes can also be used as the stoichiometric reductant in place of hydrogen to simplify further the synthesis of Stryker's reagent. The potential advantages are that the reaction time could be

Table 1. Synthesis of Stryker's reagent using silanes as reductants

Entry	Silane	CuCl:KOt-Bu:PPh ₃ :silane	Time (h)	Yield (%)
1	PMHS	1:1:1:1.2	2.2	47 ^a
2	PMHS	1:1:1:2	1.5	68 ^a
3	PMHS	1:1:2:2	1.5	82 ^a
4	Et ₃ SiH	1:1:1:1.2	2.5	30 ^a
5	Et ₃ SiH	1:1:2:2	2.75	31 ^a
6	Ph ₂ SiH ₂	1:1:2:0.75	1.0	53 ^b
7	PhMe ₂ SiH	1:1:2:2	2.0	88 ^b
8	TMDS	1:1:1:0.6	2.2	60 ^a
9	TMDS	1:1:2:1	1.0	80 ^b

^a Reaction conducted in toluene.

^b Reaction conducted in benzene.

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reduced significantly under the homogeneous reaction conditions, a liquid reducing agent is more conveniently dispensed, and the stoichiometry can be more easily controlled than hydrogenation conditions.

We found that the optimum ratio of copper chloride, potassium *t*-butoxide and triphenylphosphine was as described in Stryker's original synthesis, and the use of less than 2 equiv. of triphenylphosphine led to diminished yields (Table 1, entries 1–3). Our initial experiments employed toluene as solvent. Although the formation of Stryker's reagent proceeded smoothly, some salts appeared to be soluble in the toluene solution which precipitated out with Stryker's reagent in the isolation step. The product obtained from a benzene solution was purer. Thus benzene was the preferred solvent, in addition to the fact when the synthesis was scaled up, subsequent removal of large quantities of solvent under vacuum was easier.

We surveyed a number of silanes as reducing agents (Table 1). PMHS (entries 1–3) was one of the most efficient for generating copper hydride while triethylsilane (entries 4 and 5) was clearly the least reactive. The reactivity paralleled previous observations by Lipshutz et al.^{5b} The addition of PMHS induced a colour change immediately to give a dark red solution indicating the formation of copper hydride. With triethylsilane, a red solution was obtained after about 10–20 min at room temperature. Other silanes, including diphenylsilane, tetramethyldisiloxane (TMDS), and dimethylphenylsilane were all effective, with the latter requiring slightly longer reduction times. After some experimentation, it was found that although one hydride equiv. of silane can be used, excess silane up to 2 equiv. increased both the rate of the reaction and the yield of product.

A small-scale reaction was set up in an NMR tube and its ¹H NMR was integrated against an internal standard to measure the time for maximum hydride formation. The reaction rate was monitored for 3 h. The integration of the hydride peak (δ 3.51 ppm) was plotted against time of reaction. Although we routinely allowed reaction times of up to 2.5 h in the large-scale synthesis of Stryker's reagent, it was found that even with the less reactive dimethylphenylsilane, the rate of copper hydride formation was extremely fast, such that 90% of the maximum yield of Stryker's reagent (using the final integration of hydride as 100%) was obtained after 30 min. Therefore, it is possible to complete the reduction within 1 h, whereas 15–24 h are required for the synthesis using hydrogen.

We were concerned whether the crystallization of Stryker's reagent would be complicated by the presence of silane and silylated residues. However, the addition of acetonitrile induced the precipitation of the copper hydride as in the original Stryker procedure to yield the reagent as fine crystals. After removal of solvents, the quality of the Stryker's reagent synthesized in this manner was assessed by proton NMR spectroscopy and compared to the commercially available reagent. The hydride content was superior, as expected.

We were also concerned whether Stryker's reagent of high purity and free of silylated contaminants could be obtained using this procedure. The proton NMR spectrum of Stryker's reagent synthesized using PMHS showed extraneous broad upfield signals, probably due to silylated polymeric material. These samples were consistently less pure than those prepared using other silanes. Thus PMHS is no longer used in our routine preparations of Stryker's reagent. The use of tetramethyldisiloxane as reductant gave a reagent that was of a good quality as assessed by ¹H NMR, but its colour was more orange than that of the typical reagent. The use of dimethylphenylsilane afforded a very pure product in the form of deep red crystals characteristic of the reagent.

The preparation of Stryker's reagent on a 10 mmol scale is detailed in the following experimental procedure.

Copper(I) chloride (0.993 g, 10.03 mmol), potassium *t*-butoxide (1.124 g, 10.02 mmol) and triphenylphosphine (5.246 g, 20.00 mmol) were weighed into a dry septum-capped round-bottomed flask inside a dry-box. The flask was charged with 50 mL benzene (distilled from CaH₂ and degassed for 20 min) and the contents were stirred for 30 mins under argon to produce a slightly cloudy, yellow solution. Dimethylphenylsilane (3 mL, 19.57 mmol) was then added by syringe. The colour of the reaction mixture changed from yellow to red, to very dark red. After stirring for 2 h, the mixture was transferred to a large Schlenk filter containing 1 cm Celite via cannula. The reaction flask and the Celite pad was rinsed with 4×10 mL dry benzene. The red filtrate was concentrated in vacuo to about 20 mL. Dry, degassed acetonitrile (40 mL) was slowly layered onto the top of the benzene solution via cannula to induce crystallization of the product. After standing overnight, the red crystals thus obtained were isolated by filtration, washed with 3×10 mL dry acetonitrile and dried under vacuum to give 2.5–2.9 g (76–88%) of bright to dark red crystals. ¹H NMR (400 MHz, C₆D₆) δ 7.67 (36H, t, *J*=8.1 Hz), 6.95 (18H, t, *J*=7.3 Hz), 6.74 (36H, t, *J*=7.5 Hz), 3.51 (6H, br s).

This same procedure was conveniently extended to the synthesis of [Ph₃PCuD]₆^{9a} using Ph₂SiD₂ as the reducing agent. In this manner, using 0.55 equiv. of Ph₂SiD₂, [Ph₃PCuD]₆ was synthesized in 40% yield on a 7.0 mmol scale.

The expediency and efficiency of this procedure should promote the laboratory preparation and applications of Stryker's reagent in synthesis.

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