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Precipiton Reagents: Precipiton Phosphines for Solution-Phase Reductions

Todd Bosanac and Craig S. Wilcox*

Department of Chemistry and The Combinatorial Chemistry Center, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

daylite@pitt.edu

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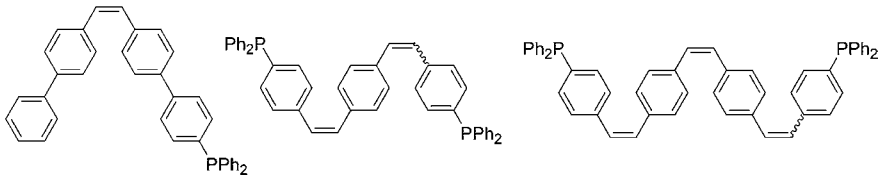
ABSTRACT



Several Precipiton phosphines were prepared and employed in the Staudinger reaction and in the reduction of secondary ozonides. Both amines and aldehdyes were obtained in good to excellent yields and purities. After use of the phosphine, isomerization and precipitation of the spent phosphorus reagent were induced by exposure to visible light in the presence of erythrosin B, a triplet sensitizer. Products were isolated by simple filtration. The use of the triplet sensitizer has the added advantage of eliminating [2 + 2] cycloaddition reactions between *trans*-Precipitons.

The rate at which useful new molecules are prepared has dramatically increased over the past decade due to advances in high-throughput screening and parallel synthesis. Often, the rate-limiting step in a reaction sequence is separation of desired product(s) from excess reagent(s), byproduct(s), and/or catalyst(s). Polymers derived from polystyrene have been used as supports for reagents so that expended reagents can be conveniently separated from a reaction mixture by filtration.[1] Although the insoluble nature of the resin is required at the filtration stage, it is a disadvantage during the reaction stage; it causes delayed reaction times and difficulties in monitoring reaction progress. To circumvent these disadvantages, chemists have developed alternative phase tags,[2] also called solubility control auxiliaries,[3] that alter the affinity of an attached compound for one phase over another. Reagents, catalysts, and scavenger reagents have been attached to phase tags, both polymeric[4] and nonpolymeric, which include fluorous tags,[5] polyaromatic tags,[6] Brønsted or Lewis acid/base tags,[7] and norbornenyl tags.[8] Reagents bearing such tags can be removed from solution by a phase transfer event.[9]

Many of the phase tags currently employed are structurally "static". By this we mean that the phase tag is not actively modified (chemically or structurally) during the separation process. (Exceptions include the traditional ionizable group

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(2) (a) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174. (b) Flynn, D. L.; Deraj, R. V.; Naing, W.; Parlow, J. J.; Weidner, J. J.; Yang, S. *Med. Chem. Res.* **1998**, *8*, 219−243.

(3) Link, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4039.

(4) (a) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325. (b) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345. (c) Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Chem. Rev.* **2002**, *102*, 3301.

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(6) Warmus, J. S., da Silva, M. I. *Org. Lett.* **2000**, *2*, 1807.

(7) (a) Ley, S. V.; Massi, A.; Rodríguez, F.; Harwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1053. (b) Perrier, H.; Labelle, M. *J. Org. Chem.* **1999**, *64*, 2110. (c) Yoshida, J.; Itami, K.; Mitsudo, K.; Suga, S. *Tetrahedron Lett.* **1999**, *40*, 3403.

(8) Barrett, A. G. M.; Roberts, R. S.; Schröder, J. *Org. Lett.* **2000**, *2*, 2999.

(9) (a) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964. (b) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693. (c) Also see: *Chem. Rev.* **2002**, *102* (10) (thematic issue: Heterocycles).

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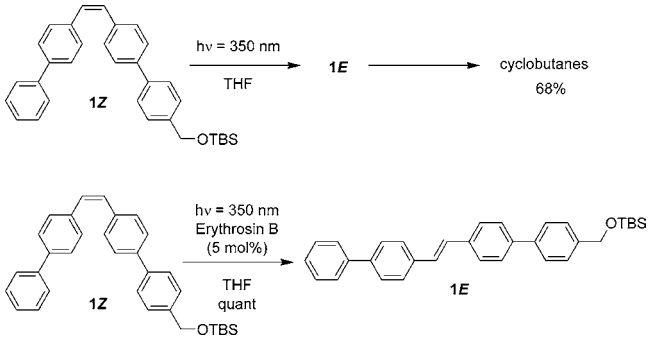


Figure 1. Irradiation of TBS ether **1*Z***.

and metal chelating tags, which are modified by introduction of new components to the tag solution, and the norbornene tags.) In other cases, precipitation or phase transfer is caused by a change in environment (a solvent change or a change in temperature).

Precipiton phase tags undergo activation and structural modification prior to the separation event. Precipitons exist in two isomeric forms, one form (*Z*) is soluble in common organic solvents (up to 0.3 M), whereas the other form (*E*) is insoluble.[10] The solubility change is caused by a structural isomerization of the phase tag. Precipitons have been used for product isolation,[10a−c] reagent sequestration,[10d] and removal of metals[10e] from polymerization solutions. Herein we describe the preparation and some uses of phosphine Precipiton reagents.

Phosphines are employed for a wide variety of transformations in organic synthesis, and the difficulty associated with separating phosphine oxide from products is well recognized. To address this, we chose to prepare several Precipiton phosphines and examine their use for reductions of azides (the Staudinger reaction[11]) and secondary ozonides.

We examined the effects that appended solubilizing groups might have on both the physical and photochemical properties of the phase tag. *tert*-Butyldimethylsilyl ether **1*Z*** (Figure 1) was prepared by standard procedures. Ether **1*E*** (the (*E*)-isomer of TBS-ether **1*Z***) was partially soluble in THF (4.2 mg/mL, 8.8 mM). (The saturated solution was prepared by irradiation of a THF solution containing 0.024 M TBS-ether **1*Z*** with 350 nm light.) As expected, the (*E*)-isomer underwent an irreversible (at 350 nm) [2 + 2] cycloaddition reaction[12] leading to a 8.7:1 ratio of very soluble *syn*- and *anti*-cyclobutanes **2**−**5**, respectively (up to 1.0 M in hexanes, THF, ether, CH_2Cl_2, $CHCl_3$, EtOAc). The *syn*- and *anti*-

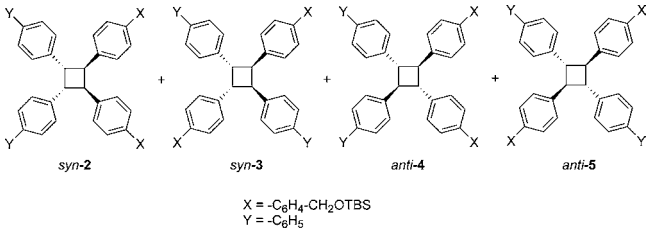


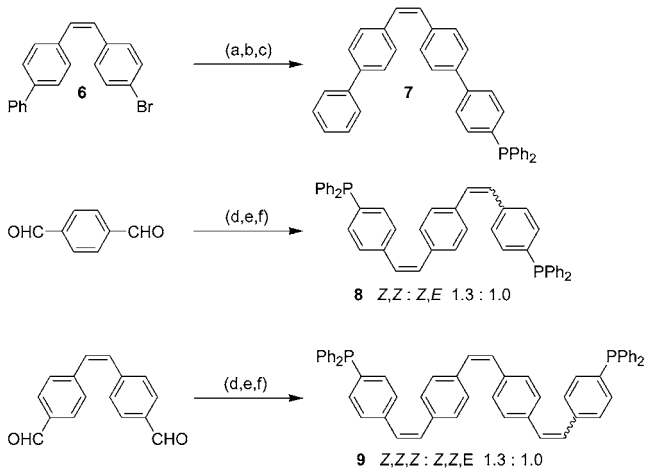
Figure 2. Cyclobutanes.

cyclobutanes were obtained as a 1:1 ratio of regioisomers (Figure 2). On long irradiation, this undesired cycloaddition product was the major product. Cyclobutane formation, which was not observed with other less-soluble derivatives related to **1*E***, was facilitated by the higher accessible concentrations of this derivative.

Such cycloadditions are known to occur via the singlet excited state, while isomerization occurs through both the singlet and triplet states.[13] Thus, a general solution to this problem is to use a triplet sensitization of the isomerization. We found erythrosin B (5 mol %) to be effective. Erythrosin B can be easily removed from reaction solution by filtration through SiO_2 or by sequestration using MP-carbonate,[14] a polymeric basic resin.

Phosphine **7** was prepared from bromide **6** by conversion to the boronic acid, which was subsequently subjected to a Suzuki cross-coupling reaction with 4-bromo phenyldiphenylphosphine (Scheme 1). Phosphines **8** and **9** were prepared

Scheme 1[a]



[a] Reagents and conditions: (a) *t*-BuLi, −78 °C, THF; (b) $(MeO)_3B$, −78 to 23 °C, 69%; (c) 4-bromophenyldiphenylphosphine, $Pd(PPh_3)_4$, THF/aq Na_2CO_3, 34%; (d) KOH, 18-crown-6, 4-bromobenzyltriphenylphosphonium bromide, CH_2Cl_2, −78 °C, 77% (**8**), 67% (**9**); (e) *n*-BuLi, −78 °C, THF; (f) $ClPPh_2$, −78 to 23 °C, 74% (**8**), 51% (**9**).

via Wittig olefination reactions.[15] Treatment of terephthaldehyde with 18-crown-6, 4-bromophenyltriphenylphospho-

(10) (a) Bosanac, T.; Yang, J.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1875. (b) Bosanac, T.; Wilcox, C. S. *Tetrahedron Lett.* **2001**, *42*, 4309. (c) Bosanac, T.; Wilcox, C. S. *Chem. Commun.* **2001**, 1618. (d) Bosanac, T.; Wilcox, C. S. *J. Am. Chem. Soc.* **2002**, *124*, (e) Pallack, M. E.; Brittain, W. J.; Bosanac, T.; Wilcox, C. S. *Macromolecules* **2002**.

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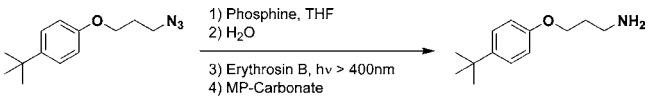
(12) (a) Green, B. S.; Heller, L. *J. Org. Chem.* **1974**, *39*, 196. (b) Ito, Y.; Kajita, T.; Kunimoto, K.; Matsuura, T. *J. Org. Chem.* **1989**, *54*, 587. (c) Leigh, W. J.; Lewis, T. J.; Lin, V.; Postigo, J. A. *Can. J. Chem.* **1996**, *74*, 263.

Table 1. Comparison of Precipiton Phosphines



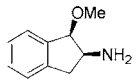
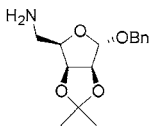
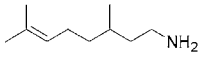
phosphine	irradiation time (h)	% yield (% purity)[a]
7	3.5	77 (93)
8	2	83 (>95)
9	1	88 (>95)

[a] Yields refer to the isolated product. Purities were determined by ^{1}H NMR and GC-MS.

nium bromide, and powdered potassium hydroxide afforded a 1.3:1.0 separable mixture of *Z*,*Z* and *Z*,*E* isomeric bromides. This mixture was treated with *n*-butyllithium followed by chlorodiphenylphosphine to afford phosphine **8** as a 1.3:1.0 mixture of separable (*Z*,*Z*)- and (*Z*,*E*)-isomers. (*Z*)-4,4′-Formylstilbene was treated with 18-crown-6, 4-bromophenyltriphenylphosphonium bromide, and powdered potassium hydroxide to generate a 1.3:1.0 separable mixture of *Z*,*Z*,*Z* and *Z*,*Z*,*Z* isomeric bromides that were subsequently treated with *n*-butyllithium followed by chlorodiphenylphosphine to yield phosphine **9** as a 1.3:1.0 mixture of separable (*Z*,*Z*,*Z*)- and (*Z*,*Z*,*E*)-isomers.

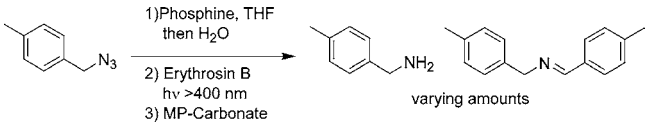
The Staudinger reduction of 3-(*p*-*tert*-butylphenoxy)propyl azide was studied to compare the effectiveness of isomeric phosphines **7**−**9** (Table 1). The reactions were conducted by heating a solution of phosphine (1.1 equiv of **7**, and 0.55 equiv of **8** and **9**) and azide in THF until azide was consumed (2 h). The resulting phosphorimine was hydrolyzed by the addition of water, and heating was continued until hydrolysis was complete (∼12 h). The phosphine oxide was precipitated from solution by irradiation at >400 nm in the presence of erythrosin B, which was subsequently removed by the addition of MP-carbonate. All phosphines afforded product in good yields and purities; the only difference was in the time of isomerization. Phosphine **7** required irradiation for 3.5 h and therefore was no longer used for additional experiments since we saw no advantage compared to the other phosphines.

Table 2. Reduction of Azides to Amines

Product	Phosphine	Yield (purity) %
	**9**	86 (>95)
	8	80 (>95)
	**9**	61(>95)
	8	54 (83)
	**9**	78 (>95)
	8	79 (>95)

[a] Yields refer to the isolated products. Purities were determined by ^{1}H NMR and GC-MS.

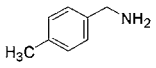
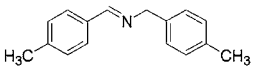
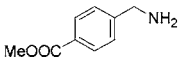
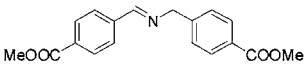
Scheme 2



Other azido substrates were reduced employing both phosphines **8** and **9** to afford the corresponding amines in good yields and purities. The reaction works equally well with secondary azides (Table 2, entry 1) and is compatible with functionalized azides (Table 2, entry 2). However, other azides were either reluctant to undergo reduction or not tolerant of the isomerization conditions (see below). Adamantyl azide, after 24 h, afforded only starting material.

An unexpected product was obtained with benzylic azides. We observed that upon reduction of 4-methylbenzyl azide followed by isomerization, a mixture of expected 4-methylbenzylamine and symmetrical imine was obtained (Scheme 2). The imine product is formed via a photooxidation of the expected amine product. The oxidation is catalyzed by erythrosin B.[16] By carrying out the isomerization reaction in acetonitrile and irradiating for 5 h, one may obtain solely the imine product from the azide in good yields and excellent purities (Table 3). Upon completion of isomerization, the sensitizer was removed by filtration through a plug of SiO_2.

Table 3. Synthesis of Imines from Azides

Amine	Imine	Yield[a] (%) (Phosphine)
		63 (**8**) 63 (**9**)
		61 (**8**) 64 (**9**)

[a] Yields are for the isolated products. Purities were determined to be >95% in all cases by ^{1}H NMR and GC-MS.

Reduction of secondary ozonides is often accomplished with triphenylphosphine. The workup of a reaction that employs triphenylphosphine often requires column chromatography to separate the product from excess phosphine and phosphine oxide. Use of Precipiton phosphines affords

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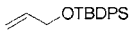
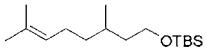
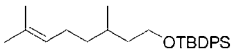
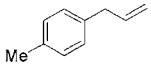
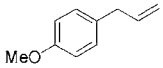
(14) Argonaut Technologies (Foster City, CA).
(15)) Bellucci, G.; Chiappe, C.; Lo Moro, G. *Tetrahedron Lett.* **1996**, *37*, 4225.
(16) (a) Pandey, G. *Synlett* **1992**, 546.

Table 4. Reduction of Secondary Ozonides

Alkene	Phosphine	Yield (purity) %
	**8**	87 (>95)
	9	92 (>95)
	**9**	94 (75)
	**9**	92 (>95)
	**9**	89 (>95)
	**9**	91 (>95)

[a] Purity determined by ^{1}H NMR and GCMS.

phosphorus containing byproducts that, after isomerization, can be easily removed by filtration. Ozonolysis products can then be isolated without need for chromatography.

Each of several alkenes was treated in a solution of dichloromethane with a stream of ozone at −78 °C until a blue color persisted. Excess ozone was removed by passing a stream of nitrogen through the solution, and the resulting secondary ozonide was reduced with Precipiton phosphine (0.55 equiv of **8** or **9**). Photoisomerization with visible light in the presence of erythrosin B followed by filtration through a plug of SiO_2 with ether afforded the aldehydes in excellent yields and purities (Table 4). The *tert*-butyldimethylsilyl protecting group did not tolerate ozonolysis as well as the *tert*-butyldiphenylsilyl protecting group (Table 1, entries 2 and 3).

We conclude from these experiments that reductions with Precipiton phosphines can afford amines and aldehydes in good to excellent yields, free of phosphine oxide, without resorting to extractions or chromatography. A triplet sensitizer, erythrosin B, was shown to be an effective catalyst for the photoisomerization and to eliminate [2 + 2] cycloaddition byproducts that can form upon long irradiation at 350 nm. The sensitizer allows use of light of wavelengths >400 nm. The sensitizer was easily removed from solution by addition of MP-carbonate or filtration through SiO_2. Benzylic amines are not compatible with the erythrosin B-catalyzed photoisomerization conditions. However, conditions were developed to take advantage of this side reaction and provide a useful method for preparing symmetrical imines from the corresponding azides.

Acknowledgment. This work was supported by a grant from the National Institute of General Medical Sciences.

Supporting Information Available: Experimental details, copies of ^{1}H and ^{13}C NMR spectra, and complete characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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