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ROMPgel-Supported Triphenylphosphine with Potential Application in Parallel Synthesis

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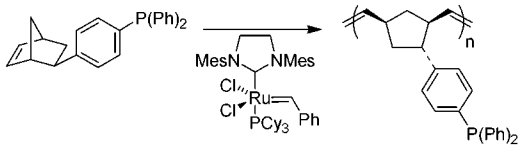
ABSTRACT



ROMPgel-supported triphenylphosphine was synthesized in three steps (67%) from norbornadiene, 4-bromoiodobenzene, and chlorodiphenylphosphine. The supported reagent has a high loading (2.5 mmol/g) and favorable swelling properties in organic solvents. It has been utilized for the conversion of alcohols to halides, the reduction of ozonides, and the isomerization of α,β-acetylenic esters and in the Staudinger reaction. In general, filtration of the resin from the reaction mixtures and evaporation gave the corresponding products in high yield and purity.

Immobilized reagents, catalysts, and scavenger reagents combine the advantages of simple purification, in that only filtration and washing are required to remove large excesses of reagents, with the ease of reaction monitoring associated with classical solution phase methodologies. It is therefore not surprising that the use of solid-supported reagents has become the subject of considerable emphasis within the past few years. A range of such reagents has been developed, of which most are either based on polystyrene beads or inorganic supports.[1] Recent efforts have improved their loading and physical properties, resulting in highly versatile reagents. Nonetheless, there is need to simplify the elaboration and costs of solid-supported reagents and to further improve their properties. In these terms, the use of polymers derived from ring-opening metathesis (ROM) has the advantage that ruthenium carbenes can convert readily available and highly functionalized monomers to well-defined supported reagents (ROMPgels).[2] The resulting polymers have high loadings and undergo significant swelling in various solvents. A range of ROMPgel-supported reagents have been prepared and used in parallel synthesis.[3]

Due to the many transformations involving triphenylphosphine and the difficulties encountered in subsequent workup, this reagent was among the first to be made available on a polymer support.[4] To further explore the scope of the ROMP methodology, we herein report the synthesis and utilization of ROMPgel-supported triphenylphosphine **4**.

4-Bromoiodobenzene (**1**) was coupled to norbornadiene via a palladium-catalyzed *exo*-hydroarylation reaction to afford the bromide **2** (80%). Bromide **2** was allowed to react with butyllithium and chlorodiphenylphosphine to produce the phosphine monomer **3** in 92% yield (Scheme 1).

(1) (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *23*, 3815. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 651.

(2) (a) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565. (b) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903.

(3) (a) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **1999**, *1*, 579. (b) Barrett, A. G. M.; Cramp, S. M.; Hennessy, A. J.; Procopiou, P. A.; Roberts, R. S. *Org. Lett.* **2001**, *3*, 271. (c) Arnauld, T.; Barrett, A. G. M.; Seifried, R. *Tetrahedron Lett.* **2001**, *42*, 7899. (d) Arnauld, T.; Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 2663.

(4) McKinley, S. V.; Rakshys, J. W. *J. Chem. Soc., Chem. Commun.* **1972**, 134. For a recent example of the use of this reagent, see: Lizarzaburu, M. E.; Shuttleworth, S. J. *Tetrahedron Lett.* **2002**, *43*, 2157 and references therein.

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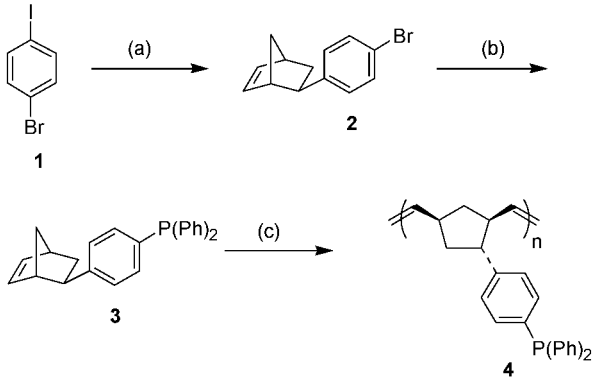
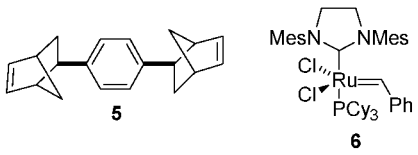
Scheme 1[a]

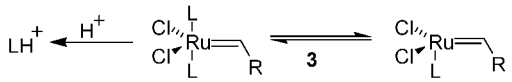


Reagents and conditions: (a) $Pd(Ph_3)_2(OAc)_2$, norbornadiene, piperidine, HCO_2H, DMF, 80%; (b) n-BuLi, THF, -78°C, PPh_2Cl, 92%; (c) i. 0.5-1 mol% **6**, 15 mol% **5**, CH_2Cl_2, 40°C, 91%; ii. $EtOCH{=}CH_2$, 100%.



Attempted polymerization of alkene **3** using the ruthenium carbene **7** was unsuccessful presumably due to competitive inhibition of the catalytic cycle by the phosphine residue (Scheme 2). However, addition of trifluoroacetic acid to

Scheme 2



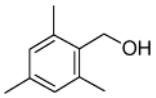
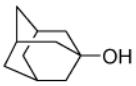
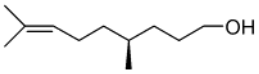
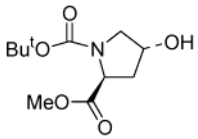
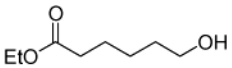
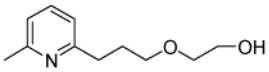
7 L=PCy_3, R=Ph

phosphine **3** counterbalances inhibition by protonation of the residues. Polymerization of the resultant trifluoroacetate salt derived from phosphine **3** in the presence of the cross linker **5**[5] (15 mol %) and neutralization gave the ROMPgel **4** (87%).

The most appealing approach to ROMPgel **4** is to use the ruthenium catalyst **6**, which provides the polymer **4** without the need for the acidification and neutralization steps. The reason for this is the lower affinity of the ruthenium catalyst **6** for triphenylphosphine, caused by its electron rich heterocyclic carbene ligand. When a solution of monomer **3**, cross linker **5** (15 mol %), and catalyst **6** (0.5−1-mol %) in dichloromethane was heated to 40 °C for 1 h, an insoluble polymer was obtained in 91% yield (Scheme 1). After termination of the polymerization with ethyl vinyl ether, the polymer was ground up, filtered, washed repeatedly with THF and diethyl ether, and dried. The resulting ROMPgel **4** has a high loading (2.5 mmol/g) and good swelling properties in dichloromethane, THF, and toluene. It has successfully been applied to the conversion of alcohols into halides, the reduction of ozonides, and the isomerization of α,β-acetylenic esters and in the Staudinger reaction.

The conversion of alcohols into halides was carried out by heating a mixture of the substrate and ROMPgel **4** (2 equiv) in dichloromethane and carbon tetrachloride (95:5) at reflux (Table 1). Subsequent filtration of the resin and

Table 1. Conversion of Alcohols into Halides

alcohol	halide	time/temp	yield[a]
	Cl	6h/45°C	89%
	Br	7h/20°C	71%
	I	2h/20°C	74%
	Cl	18h/45°C	91%
	Cl	microwave 15min/120°C	89%
	Cl	3h/45°C	100%
	Cl	1.5h/45°C	100%
	Cl	3h/45°C	100%
	Cl	3h/45°C	100%

[a] Yields refer to the isolated products. Purities, as judged by ^1H and ^{13}C NMR spectra, IR and GC-MS, were >95% in every case.

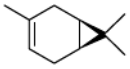
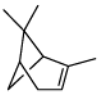
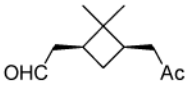
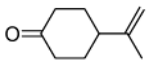
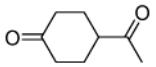
washing with THF and diethyl ether afforded the corresponding chlorides in excellent yields (89−100%) and high levels of purity (>95%). It was found that the reaction time could be reduced dramatically be heating the reaction mixture in a microwave oven. In a similar fashion, using either carbon tetrabromide (1.5 equiv) or I_2 (1.8 equiv) as the halogen source, bromides and iodides were produced albeit in slightly lower yields. Prior to workup, excess carbon tetrabromide was converted to bromoform (bp_{760} 150 °C) by the addition of methanol.

Triphenylphosphine is a valuable reagent for the reduction of ozonides, but removal of triphenylphosphine oxide from the products usually requires chromatography. In contrast, the use of ROMPgel **4** greatly simplifies the purification. Three ozonides were prepared by bubbling ozone through a solution of the parent alkene in dichloromethane and 2-propanol (3:1) at −78 °C until a blue color persisted. Excess ozone was removed by passing a stream of nitrogen through the solution when reduction of the ozonides was accomplished by adding ROMPgel **4** (1.5 equiv) to the mixture

(5) Arnauld, T.; Barrett, A. G. M.; Hopkins, B. T.; Zecri, F. J. *Tetrahedron Lett.* **2001**, *42*, 8215.

and shaking it at ambient temperature for 2 h. Subsequent filtration of the resin furnished the corresponding keto aldehydes or ketones in 96−100% yield and >95% purity (Table 2).

Table 2. Reduction of Ozonides

alkene	product	yield[a]
		99%
		96%
		100%

[a] Yields refer to the isolated products. Purities, as judged by ^{1}H and ^{13}C NMR spectra, IR and GC-MS, were >95% in every case.

Triphenylphosphine is known to catalyze the isomerization of α,β-acetylenic esters to produce $\Delta^{2,4}$-dienoates.[6] The latter are common flavor constituents and important building blocks for complex target molecules.

This important transformation was readily carried out by heating a mixture of ethyl 2-hexynanoate, **4** (0.4 equiv), and acetic acid (0.5 equiv) in toluene (Scheme 3). The use of

Scheme 3[a]

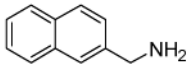
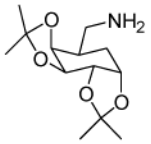
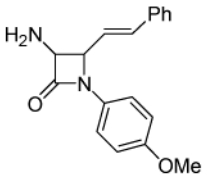
[a] Reagents and conditions: 0.4 equiv of **4**, 0.5 equiv of AcOH, PhMe, 110 °C, 18 h, 97% (90% purity).

supported phosphine in this reaction is particularly attractive as the reagent can be recovered simply by filtration and reused.

Finally, ROMPgel-supported triphenylphosphine has been employed in the Staudinger reaction.[7] Typically, a mixture of the azide, **4** (2 equiv), and THF was heated to reflux until the substrate no longer could be detected in solution (2−5 h). The reaction mixture was cooled to room temperature, and aqueous ammonia (35%) was added.

When the evolution of gas ceased, the mixture was heated to reflux for another 1−3 h. Subsequent filtration of the resin afforded the amino derivatives in high yield (87−100%) and purity (90−98%) (Table 3).

Table 3. Conversion of Azides to Amines

product	yield (purity)[a]
	87% (90%)
	100% (90%)
	100% (98%)
	100% (98%)

[a] Yields refer to the isolated products. Purities as judged by ^{1}H and ^{13}C NMR spectra, IR and GC-MS.

In conclusion, ROMPgel-supported triphenylphosphine shows high reactivity in various transformations, including the conversion of alcohols to halides, the reduction of ozonides, the isomerization of α,β-acetylenic esters to $\Delta^{2,4}$-dienoates, and in the Staudinger reaction. The reagent is easy to handle and, as opposed to the polystyrene based reagent, it is straightforward to synthesize without the use of specialized equipment or in depth knowledge of polymer synthesis.

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OL026008Q

(6) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933.

(7) (a) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (b) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763.