mismatch are shown in Table 2. Little or no fluorescence changes were observed in binding of the pyrene probe to RNA possessing a mismatch facing the modified nucleoside. Similarly, the mismatch at the 5′-site near the pyrene modification in the target RNA affected the duplex fluorescence. In contrast, an RNA mismatch at the site separated more than three bases from the pyrene did not show significant effect on the duplex fluorescence. These observations strongly suggest that the base pairings at the neighboring positions of the modification are important for rearrangements of the local structural elements to yield a strongly emitting pyrene moiety in the duplex.

The structural basis for the different fluorescence properties between pyrene-modified RNA/RNA and pyrene-modifed DNA/DNA duplexes requires further investigation. With high quantum efficiency, sequence specificity, and binding affinity, RNA oligonucleotides labeled by a pyrenylmethyl group at the 2′-sugar residue provide a useful tool for monitoring RNA hybridization. The present labeling method should be applicable to investigation of RNA structures.[32]

Experimental Section

Synthesis of Pyrene-Modified RNA. Pyrene-modified oligoribonucleotides were synthesized by standard phosphoramidite chemistry using 5′-DMT-2′-(1-pyrenylmethyl)uridine phosphoramidite (DMT = 4,4′-dimethoxytrityl).[22] After removal of base and phosphate protective groups, the oligomers were purified with 20% denaturing polyacrylamide gel electrophoresis. The final deprotection of the 2′-blocking group (Fpmp = [1-(2-Fluorophenyl)-4-methoxypiperidinyl]) was done with HCl (0.1 M) treatment. After neutralization, the solution was passed through a Sep-Pak C18 cartridge giving the desired oligonucleotides (8–10 O.D.; absorbance at 260 nm). The integrity of the purified oligonucleotides was verified with ion-spray mass-spectral analysis.

Physical Measurements. All measurements were carried out in Na_3PO_4 (10 mM) and NaCl (100 mM), adjusted to pH 7.0. Duplex melting curves were obtained at a common total strand concentration (4.3×10^{-5} M) containing a 1:1 molar ratio of oligonucleotides. Fluorescence spectra were obtained at an excitation wavelength of 338 nm. Fluorescence quantum yields were estimated at 23 °C on the basis of quinine sulfate in sulfuric acid (1.0 N) as a standard.

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Versatile Approaches to the Polymer-Supported Synthesis of Bidentate Phosphorus-Containing Ligands

George Y. Li,* Paul J. Fagan, and Patricia L. Watson

In recent years, combinatorial chemistry has been developed and applied by the pharmaceutical industry to rapidly synthesize and screen thousands of compounds in libraries for drug discovery and optimization.[1, 2] Combinatorial approaches have also led to the discovery of more efficient superconducting,[3] photoluminescent,[4] magnetoresistive,[5] dielectric,[6] and polymeric[7] materials, and the development of heterogeneous catalysts.[8] Moreover, promising results in the application of combinatorial methods to homogeneous

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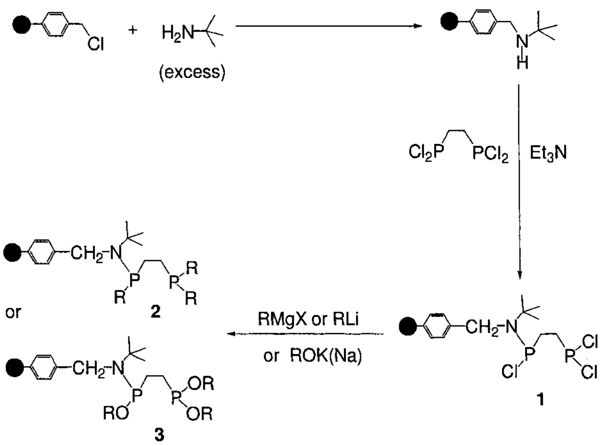
catalysis spurred innovation in efficient synthetic and screening methods.[9, 10] One potentially valuable approach is the combinatorial synthesis of homogeneous ligands using solid-supported methods.[11] Bidentate phosphorus-containing ligands are especially important owing to the major role these ligands have played in the development of homogeneous catalysis.[12] We report here the facile and rapid polymer-supported synthesis of novel diphosphane, phosphane–phosphinite, phosphane–thiophosphane, and phosphane–chlorophosphane ligands[13] (abbreviated P–P ligands) to access a variety of ligand architectures for the combinatorial preparation of homogeneous catalysts.

The polymer-supported phosphane–aminophosphanes (substrates of Table 1) were straightforwardly synthesized (Scheme 1) by treating Merrifield's resin with excess *tert*-butylamine to form the polymer-supported secondary amine. This resin reacts with 1,2-bis(dichlorophosphanyl)ethane in the presence of triethylamine to give the polymer-supported precursor **1**. Only one phosphorus atom of bis(dichlorophosphanyl)ethane is linked to the resin probably due to steric impediments of the *tert*-butyl groups and the excess of diphosphane used. Reaction of the precursor **1** with a variety of organomagnesium halides, organolithium reagents, and metal alkoxides in THF at room temperatures led to complete substitution of P–Cl bonds. After filtration and washing with THF, H_2O, and hexane, the resins **2** and **3** with cleavable diphosphane or diphosphinite ligands were obtained. The formation of **1**–**3** was conveniently monitored by routine ^{31}P NMR spectroscopy (Figure 1) and was judged complete based on the cleaved products (Table 1).



Scheme 1. Synthesis of polymer-supported cleavable P–P ligands.

Cleavage of the P–P ligands from resin **2** proceeds selectively with PCl_3 at room temperature and with a variety of alcohols and thioalcohols[14] in refluxing THF to generate the corresponding phosphane–chlorophosphanes (compounds **5** in Eq. (1)), phosphane–phosphinites,[15] and phosphane–thiophosphanes (compounds **4** in Eq. (1)). Yields in Table 1 refer to products isolated by simple filtration, followed by removing solvents and excess cleavage reagent under vacuum and are referenced to the initial loading of the Merrifield resin. In all cases, the crude cleaved products were obtained with a high degree of purity ($\geq 95\,\%$) as ascertained by $^1H/^{31}P$ NMR spectroscopy (see Figure 1) and GC/MS. Known products were identified by comparison with $^1H/^{13}C/^{31}P$ NMR spectral data from literature and/or with data from authentic samples. New compounds were characterized by one- and two-dimensional $^1H/^{13}C/^{31}P$ NMR spectroscopy, high-resolution mass spectrometry, and other standard techniques.[16]

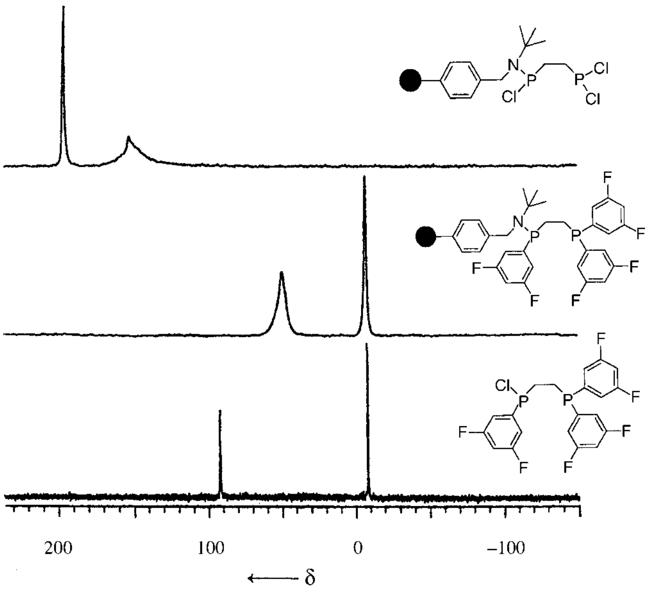
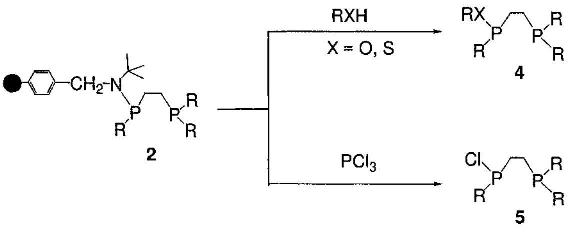


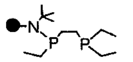
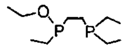
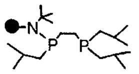
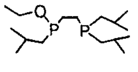
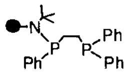
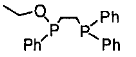
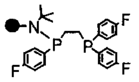
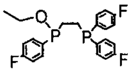
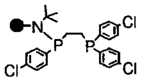
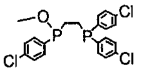
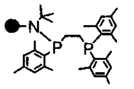
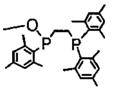
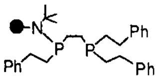
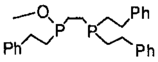
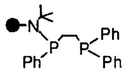
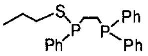
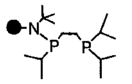
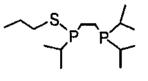
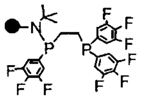
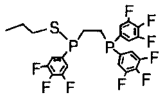
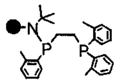
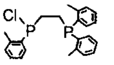
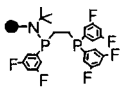
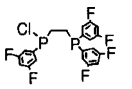
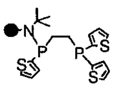
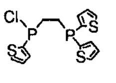
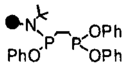
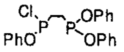
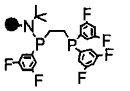
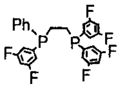
Figure 1. Routine 121-MHz ^{31}P NMR spectra of a resin-supported P–P ligand precursor (top), the resin-supported diphosphane ligand (middle), and the cleaved phosphane–chlorophosphane (bottom).

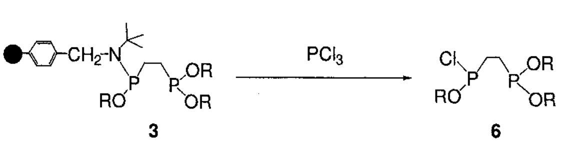


(1)

Entries 1, 2, 7, and 9 in Table 1 illustrate substitutions with aliphatic Grignard compounds to obtain electron-rich P–P ligands, and entries 3–6 and 10–13 demonstrate formation of aromatic P–P ligands including compounds with electron-withdrawing substituents. Entry 14 shows clean and complete replacement of chloride by alkoxy groups in the presence of the alcohol and an inorganic or organic base. The cleavage of **2** furnishes the novel C_1 symmetric ligands in moderate yields. These kinds of ligands are difficult to prepare by standard solution chemistry.[13] Examples for cleavage by RSH reagents are entries 8–10. Entries 11–13 further illustrate that polymer-supported ligands **2** can be employed to generate a phosphane–chlorophosphane which can be further modified with a variety of RMgX (the product of entry 12 is used for the reaction shown as entry 15), ROH, and amines.[17] Interestingly, with P–N and P–O bonds present, PCl_3 regiospecifically cleaves the P–N bond to afford phosphinite–chlorophosphinites **6** [Eq. (2)] (Table 1, entry 14), presumably due to the greater reactivity of the P–N bond. Cleavages of **2** on 13.6-g and 6.0-g scales (entries 3 and 12) generated 2.17 g (59 %) and

Table 1. Polymer-supported synthesis of P–P ligands.

Entry	Substrates **2**, **3**	$\delta(^{31}P)$	Product **4**–**6**	$\delta(^{31}P)$	Yield [%] (isolated)
1		52.2, –17.8		135.8, –18.2	51
2		45.5, –35.0		132.5, –33.5	24
3		47.1, –11.4		120.4, –11.6	59
4		46.2, –14.3		119.2, –14.0	27
5		45.4, –13.6		124.7, –13.4	30
6		48.3, –17.8		131.5, –17.7	30
7		48.3, –23.8		138.5, –23.0	26
8		47.1, –11.4		30.0, –11.8	31
9		63.4, 9.4		51.5, 9.9	53
10		47.6, –7.5		31.2, –9.0	71
11		31.9, –33.7		89.5, –33.0	75
12		49.2, –7.3		91.4, –8.7	74
13		33.0, –38.0		76.7, –38.3	57
14		182.1, 137.0		199.3, 178.9	56
15		49.2, –7.3		–8.4, –10.3	59

 (2)

3 **6**

1.58 g (74%) of the cleaved phosphane–phosphinite and phosphane–chlorophosphane, respectively, illustrating the practicability of the present process.

The procedures reported here allow not only the synthesis of polymer-supported P–P ligands, but also their cleavage from the resin, thus making them available in solution. All separation and purification steps are simple filtrations and, given the ready availability of original reagents, the process is amenable to library synthesis. Thus the cleavable compounds **1**–**3** are ideally suited for the rapid and regioselective synthesis of a variety of novel C_1-symmetric P–P ligands. Applications of the resin-supported P–P ligands as well as of the cleaved ligands in catalysis will be reported later.

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Enantioselective Reduction of Ketones Catalyzed by Polymer-Supported Sulfonamide Using NaBH$_4$/Me$_3$SiCl (or BF$_3\cdot$OEt$_2$) as Reducing Agent[**]

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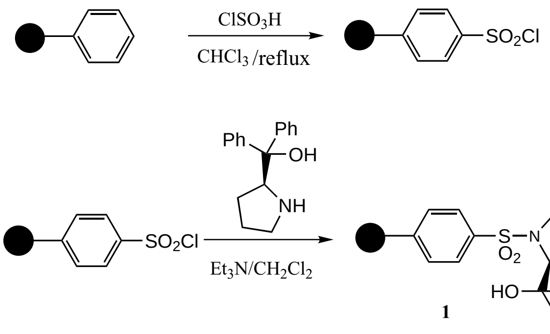
The enantioselective reduction of ketones to form optically active secondary alcohols is a major area of research in organic chemistry, and a large number of reducing agents and chiral catalysts have been developed that facilitate this reaction under a wide range of conditions.[1] One of the most successful reduction reactions involves the use of borane in the presence of homogeneous catalysts derived from chiral amino alcohols.[2] These catalysts often provide higher enantioselectivities than heterogeneous catalysts, but the development of efficient heterogeneous catalysts is still a challenging target, because workup of the reaction and the recovery of heterogeneous catalysts are more convenient than those of homogeneous catalysts. In the past decade, various groups have reported the preparation and application of heterogeneous catalysts for the enantioselective reduction of ketones,[3] and several reducing agents were used: BH$_3$,[4] NaBH$_4$,[5] and LiAlH$_4$.[6] Of these reducing agents, BH$_3$ was most widely applied and gave the best results in the presence of polymer-supported chiral amino alcohols. However, only a few of the reducing agents displayed high reactivity and enantioselectivity owing to the diffusion limitations caused by the polymer matrix. Furthermore, the use of BH$_3$ as a reducing agent requires a lot of precautions because of its toxicity. It is therefore necessary to develop new reducing systems that can easily be employed and that give high enantiomeric excesses.

It has been reported that diborane can be generated by treating NaBH$_4$ with Me$_3$SiCl[7] or BF$_3\cdot$OEt$_2$.[8] Herein, to the best of our knowledge, we report the first asymmetric reduction of ketones by employing NaBH$_4$/Me$_3$SiCl (or BF$_3\cdot$OEt$_2$) as reducing agents, and polymer-supported chiral sulfonamide **1** as the catalyst (Scheme 1).

The two-step synthetic route to **1** is outlined in Scheme 1. In the first step, the polymer beads of polystyrene resin (2% divinylbenzene, 200–400 mesh) were treated with excess chlorosulfonic acid in refluxing chloroform to give the chlorosulfonylated polymer according to a literature procedure.[9] This polymer was synthesized several times; the yield was typically 96%, and the degree of chlorosulfonylation determined by elemental analysis was 4.72 mmol Cl and 4.73 mmol S per gram of polymer. In the second step, (*S*)-diphenylprolinol was grafted onto the chlorosulfonylated polymer in the presence of Et$_3$N at room temperature over four days. After the reaction was complete, the insoluble chiral polymer **1** was isolated from the reaction mixture by filtration, and then thoroughly washed with water and methanol. Chiral polymer **1** was characterized by IR spectroscopy, which revealed the characteristic absorptions of the SO$_2$ group at 1154 and 1359 cm^{-1}, and by elemental analysis, which showed that the N content was 2.29 mmol per gram of **1**.



Scheme 1.

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