Solid-Phase Synthesis of Recyclable Diphosphine Ligands

Frank J. L. Heutz,a Michiel C. Samuelsa and Paul C. J. Kamer*a

An efficient solid-phase synthetic approach towards diphosphine ligands is demonstrated. This modular method offers facile access to this important class of ligands, in quantitative yield, providing huge potential for ligand fine-tuning. These supported ligands can be efficiently applied in asymmetric catalysis. Moreover, the immobilized catalysts can successfully be recycled multiple times addressing several synthetic and work-up challenges in the field of catalytic chemistry.

Introduction

Homogeneous asymmetric catalysis has developed as a powerful tool towards enantiomerically pure compounds and has huge potential, especially for the fine-chemical industry.[1] Still, in spite of decades of research, only a handful of so-called privileged ligands are known which are highly active and selective in a wide range of reactions.[2] It still remains an enormous challenge to develop new catalysts for specific reactions purely based on rational design. The selectivity is heavily dependent on very subtle ligand effects and consequently the discovery of new high-performance catalysts is still reliant on trial-and-error, which makes it necessary to screen large families of ligands.[3]

Yet, there is still a lack of efficient combinatorial methodologies which enable the synthesis and screening of vast ligand libraries. This especially applies to bidentate phosphorus ligands whereas these systems have shown to be highly successful in asymmetric transition-metal catalysis.[4] This can mainly be attributed to the intrinsically more difficult synthesis of these type of ligands and their sensitivity towards moisture and air.[5] Consequently, combinatorial methods for phosphine ligands have focused mainly on incorporating phosphines in peptides[6] or on parallel solution phase modification of functional group containing phosphines.[7]

Solid-phase synthesis (SPS) is widely employed in combinatorial chemistry for the generation of large compound libraries.[8] The main advantage of employing a solid support in the synthesis of ligands is the ease of purification, often by a simple filtration or decantation step. As a consequence large excesses of reagents can be used to drive reactions to completion.[9] In contrast to monodentate ligands, there have been only scarce reports on SPS of bidentate phosphorus ligands, for example by the groups of Li,[10] Portnoy,[11] and Kamer.[12] These all have focused on aminophosphane-based bidentate ligands, but a modular approach for diphosphines directly on a support however remains elusive. This is mainly due to compatibility issues arising when employing common organolithium and Grignard reagents in solid-phase synthesis.

An additional advantage when employing solid-phase synthesis is the potential ease of catalyst recovery and recycling. Product and catalyst separation often presents a large problem in homogeneous catalysis[13] and there are numerous reports of individual polymer-supported ligands applied in homogeneous catalysis.[14] However, the combination of SPS of large structural diverse ligand libraries and subsequently employing them in catalyst recycling is rare. Direct parallel SPS synthesis of diphosphines would facilitate the fast and efficient preparation of a series of structurally diverse immobilized catalysts. Herein we report a successful solid-phase synthetic approach towards libraries of recyclable resin-bound diphosphine ligands.

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Scheme 1 Solid-phase synthesis of supported diphosphines $4a$-$k$(BH$_3$)$_2$, all reactions were performed in THF at room temperature (except step V, 4f-j at 50 °C).

Results and Discussion

Solid-phase synthesis of supported diphosphines

Following the solid-phase synthetic approach shown in scheme 1, a series of 11 supported diphosphine ligands was synthesized. A commercially available resin, JandaJel-Cl™ (JJ) was chosen as support. Moreover, it was possible to directly translate the developed method to a similar support i.e. Merrifield resin (MF). The synthesized ligands, of which the general structure is shown in table 1, possess three points of diversity, namely the two phosphorus moieties and the ligand backbone. By varying the substituents ($R_1$ and $R_2$) and the backbone length ($n$), it is possible to quickly synthesize large ligand libraries showing great structural diversity.

Table 1 Synthesized supported diphosphine ligands $4a$-$k$.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Resin</th>
<th>$R_1$</th>
<th>$n$</th>
<th>$R_2$</th>
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<tbody>
<tr>
<td>4a</td>
<td>JJ</td>
<td>phenyl</td>
<td>1</td>
<td>phenyl</td>
</tr>
<tr>
<td>4b</td>
<td>JJ</td>
<td>cyclohexyl</td>
<td>1</td>
<td>phenyl</td>
</tr>
<tr>
<td>4c</td>
<td>JJ</td>
<td>phenyl</td>
<td>2</td>
<td>phenyl</td>
</tr>
<tr>
<td>4d</td>
<td>JJ</td>
<td>phenyl</td>
<td>2</td>
<td>$R_1R_2$</td>
</tr>
<tr>
<td>4e</td>
<td>JJ</td>
<td>cyclohexyl</td>
<td>2</td>
<td>phenyl</td>
</tr>
<tr>
<td>4f</td>
<td>JJ</td>
<td>cyclohexyl</td>
<td>1</td>
<td>$o$-tolyl</td>
</tr>
<tr>
<td>4g</td>
<td>JJ</td>
<td>phenyl</td>
<td>2</td>
<td>$o$-tolyl</td>
</tr>
<tr>
<td>4h</td>
<td>JJ</td>
<td>cyclohexyl</td>
<td>2</td>
<td>$o$-tolyl</td>
</tr>
<tr>
<td>4i</td>
<td>JJ</td>
<td>phenyl</td>
<td>2</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>4j</td>
<td>JJ</td>
<td>cyclohexyl</td>
<td>2</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>4k</td>
<td>MF</td>
<td>phenyl</td>
<td>2</td>
<td>$R_1R_2$</td>
</tr>
</tbody>
</table>

The ligands were synthesized under mild conditions and obtained in high purity. Between reaction steps only a simple purification, filtration and washing of the resin was required, making it possible to use an excess of reagents. The whole synthesis was readily followed with gel-phase $^{31}$P NMR as can be seen in figure 1. Each step proceeded quantitatively, demonstrating the power of this solid-phase synthetic approach. In contrast, the overall yields for the solution-phase synthesis of similar ligands generally lie around 35-50% but can be as low as 10% for diphosphines bearing different substituents on both phosphorus moieties.

The first step of the synthesis consists of reacting a commercially available chloromethyl functionalized resin with a primary lithium phosphide (scheme 1, step I). Subsequently, the supported phosphine was protected by treatment with BH$_3$·SMe$_2$. The formation of the desired products and progress of the reaction could be monitored by $^{31}$P NMR (fig. 1).

In the next step, the chiral ligand backbone was introduced, after lithiation of the supported phosphine-boranes ($1a$-$c$(BH)$_3$). Lithium disopropylamide (LDA) was chosen as preferred lithiation reagent as $n$-BuLi had shown to be too basic and led to the deprotonation at the benzylic position. Subsequent ring opening of cyclic sulfates $2a$-$c$, with full inversion at the stereogenic center, led to the formation of the supported Li-salts of phosphine sulfates $3a$-$f$(BH)$_3$. This reaction was also monitored using $^{31}$P NMR and formation of the lithium sulfate group could be confirmed using FTIR spectroscopy and $^7$Li NMR.

![Figure 1](https://example.com/figure1.png)

**Fig. 1** Solid-phase synthesis of representative diphosphine $4e$(BH)$_3$ monitored by gel-phase $^{31}$P NMR.

Next, analogous to the first step, the second phosphorus moiety was introduced by reaction with various secondary lithium phosphides. When compared to the first step this...
reaction proceeded less readily. A large excess of reagents and in some cases, elevated temperatures up to 50 °C (4f- jBH$_4$) were necessary. The disappearance of the lithium sulfate group could be monitored using $^7$Li NMR and FTIR and the formation of a second phosphorus moiety in a 1:1 ratio was observed using $^{31}$P NMR (figure 1, V). Lastly, the diphosphines were protected by treatment with BH$_3$SMe$_2$ providing the supported ligands 4a-k(BH$_3$)$_2$ in high purity.

**Rh-catalyzed asymmetric hydrogenation**

The series of resin-bound ligands was employed in the Rh-catalyzed asymmetric hydrogenation of several benchmark substrates (table 2). Firstly, the protecting borane groups were removed by treating the ligands with an excess of amine, in this case DABCO (10 eq.). Next, the resin-bound ligands were suspended in DCM in the presence of [Rh(COD)$_2$]BF$_4$ (COD = 1.5-cyclooctadiene; 1.1 eq.) and subsequently washed and filtered off. *In situ* $^{31}$P NMR experiments have been performed to confirm full consumption of non-complexed ligand upon addition of [Rh(COD)$_2$]BF$_4$. The resulting very broad NMR signals confirmed chelating coordination of the bidentate ligands over the full course of the reaction. Similar broad signals have been observed by Landis et al. in comparable systems and representative examples are provided in the ESI.

The obtained orange supported catalysts were employed in the asymmetric hydrogenation of methyl α-acetamidoacrylate (I), α-acetamidocinnamic acid (II) and its methyl ester (III).

As can be seen in table 2, the observed conversions ranged from 26 to >99% while the enantiomeric excess varied between 2 and 83%. It was observed that small changes in ligand structure can have a profound effect on the activity and selectivity, once more confirming the importance of screening large ligand libraries and the necessity for facile combinatorial methods to synthesize these ligands.

Even though the supported ligands are present as a mixture of two epimers at the first phosphorus moiety, high enantioselectivities were observed for some of the ligands. This in accordance with Deerenberg et al. who found that for similar bidentate phosphorus ligands the enantioselectivity is mainly determined by the chiral backbone of the ligand and not the P-stereogenic center. Upon changing the stereocenters in the backbone, the opposite enantiomer was obtained as can be seen for ligand 4c versus 4d while exhibiting similar activity and selectivity (entries 3 and 4). The small difference in ee observed for substrate I can most likely be attributed to a small matched/mismatched effect of the P-stereogenic phosphorus center.

Having different substituents however, did have a pronounced effect. Bulky substituents like cyclohexyl groups seemed to have a detrimental influence on both activity and selectivity (entries 9 and 10). Lastly, the influence of the support on the asymmetric hydrogenation was investigated.

**Table 2 Results of Rh-catalyzed asymmetric hydrogenation.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate I</th>
<th>Substrate II</th>
<th>Substrate III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conv.</td>
<td>ee</td>
<td>Conv.</td>
</tr>
<tr>
<td>1</td>
<td>4a</td>
<td>&gt;99</td>
<td>17 (S)</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>&gt;99</td>
<td>13 (S)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>&gt;99</td>
<td>49 (S)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>&gt;99</td>
<td>40 (R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>&gt;99</td>
<td>60 (S)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>&gt;99</td>
<td>3 (S)</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>&gt;99</td>
<td>63 (S)</td>
<td>40</td>
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<tr>
<td>8</td>
<td>4h</td>
<td>&gt;99</td>
<td>29 (S)</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>&gt;99</td>
<td>4 (R)</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>4j</td>
<td>&gt;99</td>
<td>2 (R)</td>
<td>29</td>
</tr>
<tr>
<td>11</td>
<td>4k</td>
<td>&gt;99</td>
<td>21 (R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>12</td>
<td>BDPP</td>
<td>&gt;99$^{[a]}$</td>
<td>40 (S)</td>
<td>&gt;99$^{[a]}$</td>
</tr>
</tbody>
</table>

* Reaction conditions: In a stainless steel autoclave, Rh/substrate = 1:30, p(H$_2$) = 1.2 bar, T = 25 °C, t = 16 h, 0.5 mL of THF, all runs were performed in duplicate and deviations were within 1%. * Percentage conversion determined by GC. * Enantiomeric excess of product determined by chiral GC (absolute configuration drawn in parenthesis). * Data taken from Ref. 20; reaction performed at p(H$_2$) = 5 bar in MeOH. * Data taken from Ref. 21. * Data taken from Ref. 22. n.d. = not determined.
When comparing ligand 4d on JandaJeI™ with the same ligand but supported on Merrifield resin 4k it can be seen that the former exhibits higher enantioselectivity (entries 4 and 11). This might possibly be attributed to the better swelling properties and more solution-like behavior of JandaJeI™. This clearly shows that also the choice of support can have a strong influence on the actual catalytic performance.

Compared to a solution-phase analogue of the immobilized ligands, in this case (S,S)-2,4-bis(diphenylphosphino)pentane [(S,S)-BDPP, entry 12], several of the supported ligands achieved similar and in some cases even higher enantioselectivities. For substrate I the best performing ligand were 4c and 4g (entries 5 and 7). No direct solution analogues have been reported in literature but these ligands outperformed (S,S)-BDPP (entry 12). For substrate II the solution ligand (S,S)-BDPP shows a slightly higher ee than the best performing supported ligand from our library (4c). For substrate III however, supported ligand 4e outperforms its homogenous counterpart exhibiting higher enantioselectivity (entry 5).

**Supported catalyst recycling**

The recyclability of these immobilized homogeneous catalysts was investigated. JJ-supported ligand 4c was employed in the asymmetric hydrogenation of substrate II examining its recycling capabilities. For the recycling experiments it was decided to go to a shorter reaction time (30 min) as the effects of catalyst degradation are more pronounced at lower conversion which leads to a fairer assessment of the recyclability of supported catalysts.

When performing initial recycling experiments it was found that the active catalyst was sensitive to both moisture and air. Moreover, both the presence of H_{2} and substrate were necessary to ensure catalyst stability. Because of this it was decided to change the reaction set-up and perform the recycling experiments in a Schlenk vessel under a flow of H_{2} instead of in an autoclave. In this way the resin work-up, e.g. washing the resin with stock solution, could be performed while maintaining a H_{2} atmosphere excluding exposure to moisture and air.

The results of the recycling of ligand 4c are depicted in table 3 and show that this ligand could be used up to 3 times without loss of activity and up to 7 times with only a slight drop in conversion. Moreover, the enantioselectivity did not appear to go down.

Next, the same ligand supported on Merrifield resin was investigated to study the effect of the support on the recycling capabilities. From figure 2 it can be concluded that MF-supported ligand 4k seemed to be more stable and performs better than its JJ-supported counterpart. Supported ligand 4k could be used up to 6 times without any loss of activity. Moreover, the selectivity did not drop over over 11 reaction cycles.

![Fig. 2 Catalyst recycling of supported ligand 4k in the Rh-catalyzed asymmetric hydrogenation of substrate II, cycle 1-11: same conditions as table 3, cycle 12: same conditions as table 2.](image)

Interestingly, the enantioselectivity under recycling conditions seemed to be significantly higher compared to the optimized conditions in an autoclave (table 2, entry 11). After 11 reaction cycles the same supported catalyst was tested under the above mentioned conditions, still achieving full conversion overnight and exhibiting similar selectivity when compared to 4k in table 2 (entry 11). These promising results indicate that these immobilized catalysts have potential for application in a continuous flow reactor configuration.

Lastly, the amount of rhodium leaching was determined by ICP-OES analysis of the reaction solution after each recycle. For supported ligand 4k an initial rhodium leaching of 4.5 ppm was observed after the first cycle. After 5 cycles the Rh-leaching remained constant and dropped below 1 ppm, corresponding in total to less than 0.2% of the initial rhodium content. The higher initial Rh-leaching might be attributed to physically bounded, non-coordinated rhodium residues present in the pores of the resin. This seems to be in accordance with the observation that the ee steadily increases over subsequent recycles as the rhodium residues, which can reduce the selectivity, are washed out. The fact that leaching is minimal but the activity still drops after 6 cycles seems to indicate that other processes play a role in catalyst deactivation. Possibly traces of air or moisture were introduced during the catalyst work-up between reaction cycles leading to catalyst

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**Table 3 Results for recycling of ligand 4c in asymmetric hydrogenation.**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Conv.</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4c</td>
<td>II</td>
<td>34</td>
<td>84 (S)</td>
</tr>
<tr>
<td>2</td>
<td>4c</td>
<td>II</td>
<td>38</td>
<td>85 (S)</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>II</td>
<td>36</td>
<td>86 (S)</td>
</tr>
<tr>
<td>4</td>
<td>4c</td>
<td>II</td>
<td>31</td>
<td>86 (S)</td>
</tr>
<tr>
<td>5</td>
<td>4c</td>
<td>II</td>
<td>30</td>
<td>86 (S)</td>
</tr>
<tr>
<td>6</td>
<td>4c</td>
<td>II</td>
<td>27</td>
<td>87 (S)</td>
</tr>
<tr>
<td>7</td>
<td>4c</td>
<td>II</td>
<td>28</td>
<td>87 (S)</td>
</tr>
</tbody>
</table>

* Reaction conditions: In a Schlenk vessel under H_{2} atmosphere, Rh/substrate = 1:30, p(H_{2}) = 1 atm, T = 25 °C, t = 30 min, 1.5 mL of THF, all runs were performed in duplicate and deviations were within 1%. * Percentage conversion determined by GC. * Enantiomeric excess of product determined by chiral GC (absolute configuration drawn in parenthesis).
deactivation. This observation, combined with the low levels of Rh-leaching and the fact that the presence of both substrate and H₂ are necessary for catalyst stability, might make this system ideally suited for catalysis under flow conditions.

Conclusion

In summary we have demonstrated the first modular solid-phase synthetic procedure providing more facile access to libraries of diphosphine ligands compared to traditional solution phase synthetic techniques. Using this efficient approach, requiring only a simple work-up in between each step, the supported diphosphines were obtained in high purity and in quantitative yield. Subsequently, these bidentate phosphine ligands were screened in the Rh-catalyzed asymmetric hydrogenation of several benchmark substrates. Some members of the ligand series displayed high activity and selectivity, demonstrating that small changes in ligand structure can have a profound effect on the actual catalysis. This once again stresses the importance of trial-and-error in ligand discovery and the necessity of facile combinatorial methods towards large ligand libraries. Lastly, the recyclability of these supported ligands was investigated. Ligand 4k, immobilized on Merrifield resin, could be used up to 6 times without any drop in conversion. Moreover, the enantioselectivity did not decrease over 11 reaction cycles. These promising results show high potential for the application of this system in continuous flow catalysis.

Experimental

General considerations

All reactions and manipulations were carried out under inert conditions using standard Schlenk techniques or in an MBraun glovebox unless stated otherwise. All glassware was dried prior to use to remove traces of water. All chemicals were obtained from commercial suppliers and used as received unless otherwise stated. Toluene was distilled from sodium, diethyl ether and THF were distilled from sodium/benzophenone and triethylamine, dichloromethane and acetonitrile were distilled from calcium hydride. JandaJel-C™ (50-100 mesh, 0.96 mmol g⁻¹, 2% cross-linked) was obtained from Sigma-Aldrich. Novabiochem™ Merrifield resin (100-200 mesh, 1.3 mmol g⁻¹, 1% cross-linked) was obtained from EMD Millipore.

Synthesis of supported phosphine-borane sulfates (3a-fBH₃)

Step 1
A chloromethyl functionalized resin was swollen in THF and cooled to −78 °C. A freshly prepared primary lithium phosphide solution (1.2 eq.), also cooled to −78 °C was added under gentle stirring to avoid mechanical abrasion of the resin. The reaction mixture was allowed to warm up to room temperature and was left overnight without stirring. The supernatant solution was removed and the resin was washed subsequently with three portions of THF followed by three portions of Et₂O. The product was directly used in the next step without additional purification.

Step 2
A resin-bound phosphine, synthesized in the previous step, was swollen in THF. Next, BH₃SMε₃ (10 eq.) was added under gentle stirring to avoid mechanical abrasion of the resin. Upon addition the resin colored white and the reaction was stopped when no gas evolution could be observed anymore. Next, the supernatant solution was removed and the resin was washed subsequently three portions of THF and Et₂O. The product was dried in vacuo yielding a white resin-bound phosphine-borane.

Synthesis of supported phosphine-borane sulfates (3a-fBH₃)

Step 1
A resin-bound phosphine-borane was swollen in THF. Next, LDA (10 eq.) was added under gentle stirring to avoid mechanical abrasion of the resin. Upon addition the resin colored dark brown and was allowed to react for 3 hours. Next, the supernatant solution was removed and the resin was washed subsequently with three portions of THF. The product was used in the next step without additional purification.

Step 2
A lithiated resin-bound phosphine-borane synthesized in the previous step was swollen in THF. A cyclic sulfate (1.2 eq.) was azeotropically dried with toluene (3 times), dissolved in THF and subsequently added to the resin under gentle stirring to avoid mechanical abrasion. Upon addition the resin turned from dark brown to yellow and was allowed to react overnight. Next, the supernatant solution was removed and the resin was washed subsequently with three portions of THF followed by three portions of Et₂O. The product was dried in vacuo yielding a light yellow resin.

Synthesis of supported diphosphine-boranes (4a-k(BH₃))

Step 1
A resin-bound phosphine-borane sulfate was swollen in THF and cooled to −78 °C. A freshly prepared secondary lithium phosphide solution (10 eq.), also cooled to −78 °C was added under gentle stirring to avoid mechanical abrasion of the resin. The reaction mixture was allowed to warm up to room temperature and was left overnight without stirring. The supernatant solution was removed and the resin was washed subsequently with three portions of THF followed by three portions of Et₂O. The product was dried in vacuo yielding a light yellow/orange resin-bound diphosphine. The product was used directly in the next step without further purification.
A resin-bound diphosphine, synthesized in the previous step, was swollen in THF. Next, BH$_3$·SMc$_3$ (10 eq.) was added under gentle stirring to avoid mechanical abrasion of the resin. Upon addition the resin colored white and the reaction was stopped when no gas evolution could be observed anymore. Next, the supernatant solution was removed and the resin was washed subsequently with three portions of THF followed by three portions of Et$_2$O. The product was dried in vacuo yielding a white resin–bound diphosphine–borane.

**Rh-catalyzed asymmetric hydrogenation**

The hydrogenation experiments were performed in a stainless steel autoclave charged with an insert suitable for 10 reaction vessels including Teflon mini stirring bars. In a typical experiment, a reaction vessel was charged with a deprotected resin-bound diphosphine (3.0 μmol) and a solution of [Rh(COD)$_2$]BF$_4$ (3.0 μmol) in CH$_2$Cl$_2$ (1 mL) and the heterogeneous mixture was allowed to stir gently for 4 h. The supernatant solution was removed and the resulting orange resin was washed subsequently with three 1 mL portions of THF followed by three 1 mL portions of Et$_2$O. Next, a solution of substrate (0.5 mL, 0.18 M, 30 eq.) in THF was added to the reaction vessel. Subsequently, the autoclave was purged three times with 5 bar of H$_2$ and then pressurized to 1.2 bar. The reaction mixtures were gently stirred at 25 °C. After 16 h, the autoclave was depressurized and the reaction mixtures were filtered over a plug of silica. Prior to GC measurements substrate II and its products were derivatized using (trimethylsilyl)diazomethane (2 M in diethyl ether). The conversion and the enantiomeric excess were determined by chiral GC. See supplementary information for columns and conditions.

**Acknowledgements**

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**Notes and References**


Graphical Abstract

The first efficient solid-phase synthetic approach towards diphosphine ligands is demonstrated. This modular method offers facile access to a class of ligands providing huge potential for ligand fine-tuning.

Diagram:

$\bullet$ = Solid support  
$P$ = phosphane moiety  
$B = \text{(chiral) ligand backbone}$  
$X = \text{functional group}$