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[13] A fully automated procedure for deriving and arraying stock solutions from the dihydropyrancarboxamide-containing macrobeads described herein has been developed and will be reported elsewhere; ref. [10c].

[14] After surveying several loading/ligand/metal/solvent combinations, 20 mol% of **1** in THF was found to provide the best combination of kinetics and selectivity.

[15] The configurations of the cycloadducts were assigned by analogy. See refs. [8a, c].

[16] We have ruled out isomerization of the alkenyl ether and epimerization of the acetal center as reasons for the lower selectivity.

[17] The details of this procedure and the relationship between the 108 cleaved compounds and their associated electrophoretic tags are reported in ref. [12].

[18] For 25 of the 108 samples, the molecular ion observed upon ionization corresponded to a fragment of the compound.

[19] To the best of our knowledge, this is the first report of the use of a substoichiometric amount of chiral controller to perform a carbon – carbon bond forming reaction on solid phase.

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Decoding Products of Diversity Pathways from Stock Solutions Derived from Single Polymeric Macrobeads**

Helen E. Blackwell, Lucy Pérez, and Stuart L. Schreiber*

Efficient phenotypic and proteomic screening of small molecules derived from diversity-oriented organic syntheses[1] requires a library realization platform[2] that 1) produces a sufficient quantity of compound per bead to perform many hundreds of assays[3] and 2) supports reliable compound structure identification. To facilitate the latter, solid-phase library-encoding strategies[4] have been developed that allow the identity of the compounds to be inferred postsynthesis directly from individual beads.[5] We recently adapted the chemical-encoding strategy introduced by Still and co-workers[6] to a high-capacity (1.4 mequiv $g^{-1} \approx 100$ nmol/bead), 500 – 600 μm polystyrene (PS) solid support (Scheme 1),[3] a key element of a "one-bead, one-stock-solution" technology platform.[7] We have now discovered that the stock solutions of compounds cleaved from individual beads contain sufficient tags to allow the structures of their corresponding small molecules to be inferred reliably. Two methods used for the decoding of the library of 4320 dihydropyrancarboxamides reported in the preceding Communication are described.[8]

The encoding method features structurally related chloroaromatic diazoketone "tags",[6b] which are introduced through an acylcarbene insertion into the phenyl rings of PS catalyzed by $[Rh_2(O_2CCPh_3)_4]$ (**1**) to yield cycloheptatrienes (Scheme 1).[9] To decode a library compound, the tags are cleaved oxidatively from the solid support with ceric ammonium nitrate (CAN) to yield free alcohols,[10] which are then silylated (with *N*,*O*-bis-(trimethylsilyl)acetimide, BSA) and injected directly onto a gas chromatograph equipped with electron-capture detection (GC/ECD) for analysis (each tag trimethylsilyl ether has a unique GC retention time). For low-loaded solid support (≈100 pmol/bead) it has been postulated that the carbene inserts predominantly into the support due to

[*] Prof. S. L. Schreiber, Dr. H. E. Blackwell, L. Pérez
Howard Hughes Medical Institute
Department of Chemistry and Chemical Biology and
Harvard Institute of Chemistry and Cell Biology (ICCB)
Harvard University
12 Oxford Street,
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-0751
E-mail: sls@slsiris.harvard.edu

[**] H.E.B. and L.P. contributed equally to this work. We thank the National Institute of General Medical Sciences (GM-52067) for the support of this research. We are especially grateful to Dr. Andrew Tyler for expert mass spectroscopy support. The Harvard ICCB is supported by Merck & Co., Merck KGaA, the Keck Foundation, and the National Cancer Institute. H.E.B. is supported by a postdoctoral fellowship from the Jane Coffin Childs Memorial Fund for Medical Research (sponsored by Merck & Co.). L.P. is a Research Fellow, and S.L.S. is an Investigator with the Howard Hughes Medical Institute at the Department of Chemistry and Chemical Biology, Harvard University.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

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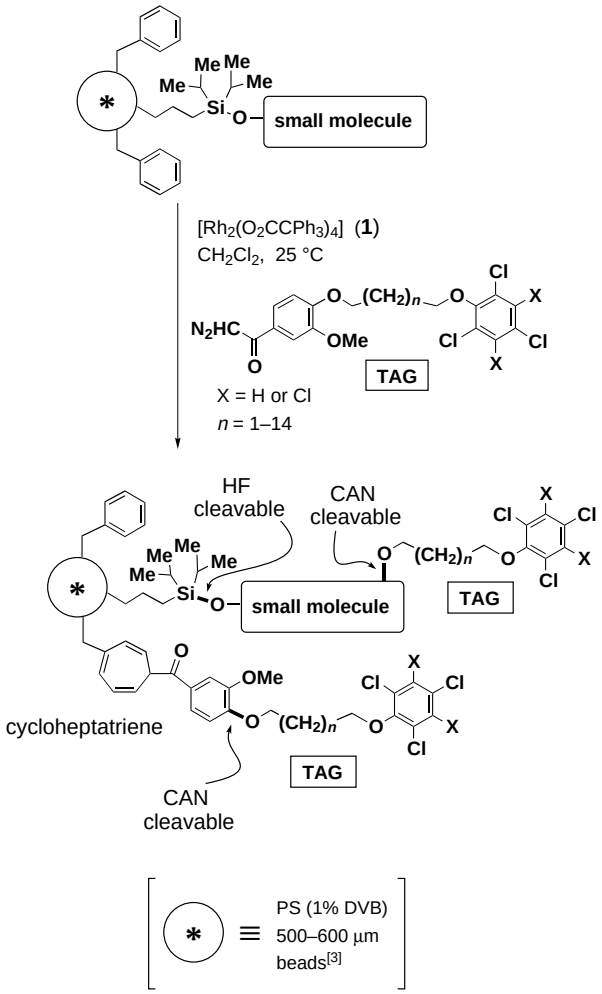
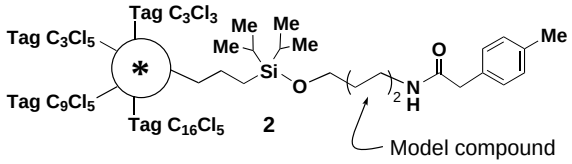


Scheme 1. General reaction protocol for encoding PS macrobeads with diazoketone chloroaromatic tags. The chemical bonds broken upon compound cleavage and tag cleavage are highlighted in bold. PS = polystyrene, DVB = divinylbenzene, HF = hydrogen fluoride, CAN = ceric ammonium nitrate.

the greater proportion of the support relative to compound.[11, 12] However, because our PS macrobead supports contain considerably more bound compound than standard solid-phase resin (that is, ≈50–100 nmol/bead),[3] and we had to use higher relative tag concentrations to encode the supports effectively,[11] we decided to investigate the amount of tag attached directly to the support-bound synthetic compounds. On one hand, we were concerned that acylcarbene insertion could cause significant compound contamination, which would defeat the goal of a "one-bead, one-compound" approach.[7] On the other hand, we were hopeful that the level of compound tagging would be sufficient to allow effective decoding without complicating analyses of the properties of the compounds (< 0.1 %).

In fact, during our optimization of the encoding/decoding procedure on PS macrobeads, we observed that the tag peaks in the GC traces for beads decoded *before* compound cleavage were dramatically stronger than those for beads decoded *after* compound cleavage.[7] Treatment of the solid support with hydrogen fluoride/pyridine (HF–py) to cleave the attached compounds from the silyl ether linker (Scheme 1) did not concurrently cleave the attached tags;[13] therefore, we surmised the difference in relative peak area could be explained by significant incorporation of the diazoketone tags into the support-bound compound. These compound-associated tags were being cleaved simultaneously with those inserted into the PS macrobead and were thus inflating the relative tag peak intensities.

To verify tag insertion into the support-bound compound during the encoding process, PS macrobeads were loaded with a model compound, *N*-(5-hydroxypentyl)-4-methylbenzamide to form **2** (Scheme 2).[14] A portion of **2** (20 mg) was treated



Scheme 2. Encoding test support **2** used in compound-decoding experiments. The macrobeads were encoded with four tags: tag C_3Cl_3 (X = H, n = 1), tag C_3Cl_5 (X = Cl, n = 1), tag C_9Cl_5 (X = Cl, n = 7), and tag $C_{16}Cl_5$ (X = Cl, n = 14). These four tags were selected because their respective trimethylsilyl (TMS) ethers had GC retention times that spanned the full time window of the GC spectrum.

with HF–py to effect cleavage of the model compound and to generate an unadulterated compound sample, before any encoding took place. Another 20 mg sample was encoded with four chloroaromatic diazoketone tags following our optimized procedure[7a] and subsequently treated with HF–py to release the attached compound. The two compound samples were characterized by ^{1}H NMR spectroscopy and liquid chromatography/mass spectrometry (LC–MS), and both techniques failed to show any detectable tag incorporation into the compound (see Supporting Information). However, these results did not preclude direct compound decoding by GC/ECD because the level of sensitivity of the EC detector (subpicomolar) is far greater than that of ^{1}H NMR spectroscopy and LC–MS detection techniques.

The solid compound obtained from a single, encoded bead was subjected to the identical decoding conditions developed for bead decoding, and GC/ECD analysis of the silylated product revealed that the tags had inserted into the compound.[15] Furthermore, the signals obtained when the compound itself was decoded were dramatically stronger (≈10^2 times) than those detected from bead decoding performed after compound cleavage. Indeed, 20 pmol of each tag were observed when the entire compound stock solution obtained from one macrobead was subjected to the optimized decoding protocol. The reason for this apparent increase in tag amount relative to standard bead decoding can be attributed, in part, to the higher efficiency of the homogeneous oxidative cleavage reaction in solution, relative to the heterogeneous reaction on polymeric support.[16] This higher efficiency observed in stock-solution decoding enables decoding times and temperatures to be reduced to 2 h and 25 °C, respectively, to obtain similar tag amount measurements. The amount of tag inserted into the compound per bead is approximately 2–3 orders of magnitude less than the amount used for encoding. We estimate that the stock solution derived from a single bead

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(20 μL of a ≈5 mM solution per bead) encoded at this level remains analytically pure (>99.9%) and anticipate that the trace impurities introduced by tag insertion should not compromise a "one-bead, one-compound" approach.

The ability to decode directly from a compound's stock solution should be advantageous in many circumstances, including those where GC signals from bead decoding are not sufficiently strong or clear to assign a chemical structure to a "hit" or if the parent bead cannot be located (a reality in solid-phase synthesis, for example, due to static electricity). As direct "stock-solution decoding" gives GC signals approximately 100 times greater than those obtained from bead alone, we postulated it should be possible to decode a compound, or "hit", by decoding only a small portion of its respective stock solution. To this end, fractions (that is, 1%, 5%, 10%, 50%, and 100%) of a stock solution of the model compound of **2** cleaved from a single encoded bead were subjected to the decoding procedure. This analysis demonstrated that submitting just 1% of the compound's stock solution was sufficient for clear and reproducible decoding, equivalent or superior to bead-decoding data (Figure 1).

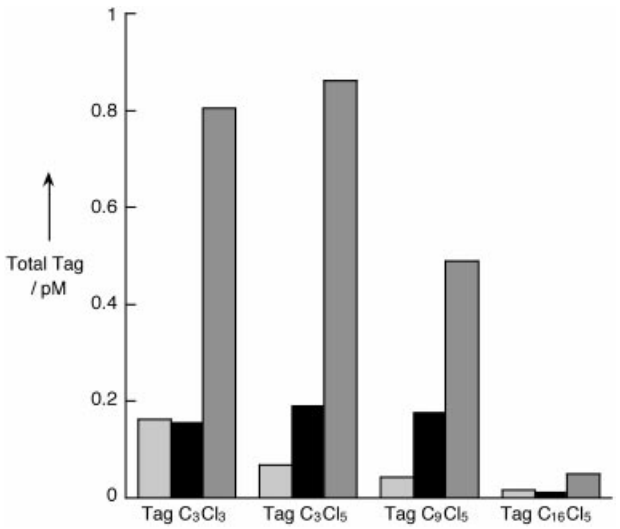

Figure 1. Graph of quantitative GC data for decoding from either an individual macrobead of test support **2** (light gray) or from 1 or 5% (black and dark gray, respectively) compound stock solutions prepared from a single macrobead of **2**. Bead and stock-solution decoding procedure: 0.25 M CAN (1:1 tetrahydrofuran/H_2O), 2 h, 25 °C, 1 min sonication, BSA:decane (1:1). See the Supporting Information for further details.

We now have three ways to determine the chemical history of a bead relying solely on encoding: the bead can be decoded either 1) before compound cleavage, 2) after compound cleavage, or 3) from a fraction of its respective compound's stock solution. To the best of our knowledge, the latter is the first example of decoding chemical tags covalently attached to compounds as a strategy for structure elucidation after split-pool synthesis.[11]

In order to test the reliability of stock-solution decoding to determine the chemical history of an actual library member, this method was applied to selected samples from the dihydropyrancarboxamide library described in the preceding paper.[8] This synthesis resulted in 54 (27×2 enantiomers) separate portions of PS support containing 4320 stereochemically and structurally distinct compounds. Two beads were taken from each of the 54 final library pools, arrayed into individual tubes, and treated with HF–py to release the compounds from the beads. Samples from each of the stock solutions for the 108 compounds (diluted to 5 μM in acetonitrile) were subjected to MS (atmospheric pressure chemical ionization, APCI) analysis, and the corresponding beads and/or aliquots of stock solution were subjected to GC/ECD decoding to compare the two results and check for agreement between mass spectral and chemical encoding data.

We were gratified to observe that, for 107 of the 108 samples, the structure assignments made by GC bead and/or stock-solution decoding were in complete agreement with the MS data. The majority of the samples could be decoded from their respective beads; however, the bead-decoding GC traces for 10 of the samples were not easily interpreted, so a fraction (≈5%) of the corresponding stock solutions was subjected to direct decoding as described above. All 10 of these samples yielded clean GC traces that decoded for a compound identical to that assigned by MS, which thus demonstrates the feasibility of direct stock-solution decoding with real library compounds. Finally, there were two cases in which the parent bead was lost, so it was necessary to resort to stock-solution decoding. Once more, stock-solution decoding agreed with the MS data for these missing beads. Of note, there was only one example of the 108 samples analyzed where the compound identity assigned by GC decoding could not be confirmed by MS: In this case, both bead and stock-solution GC decoding were identical but neither a parent molecular ion nor a compound fragment was observed in the MS spectrum which was in agreement with this structure assignment.[17] Representative GC, LC, and MS traces and chemical structure assignments, which demonstrate bead and stock-solution decoding, respectively, are shown in Figure 2 for samples 12 and 48.[18]

The successful partial decoding of the dihydropyrancarboxamide library validates not only our encoding/decoding protocol, but also the use of direct stock-solution decoding as a reliable decoding strategy. While we decoded only 2.5% of the theoretical total library members for this study, stock-solution decoding has been done on an ad hoc basis during the biological screening of this library (data not shown), and to date all of the 25 "hits" have been successfully identified. Currently, the "hits" that were difficult to decode previously from a split-pool library on PS macrobeads that used a completely different set of reactions and substrates are being decoded directly from the stock solutions with the compound-decoding approach reported herein. Preliminary results of four different diversity-oriented synthetic pathways suggest stock-solution decoding will be feasible with many different chemistries. Obtaining the chemical history of small molecules synthesized through diversity-oriented syntheses by direct stock-solution decoding should expedite compound structure elucidation, minimize storage requirements (parent beads can be discarded), and be amenable to automation with a laboratory liquid-handling robot; this will potentially make

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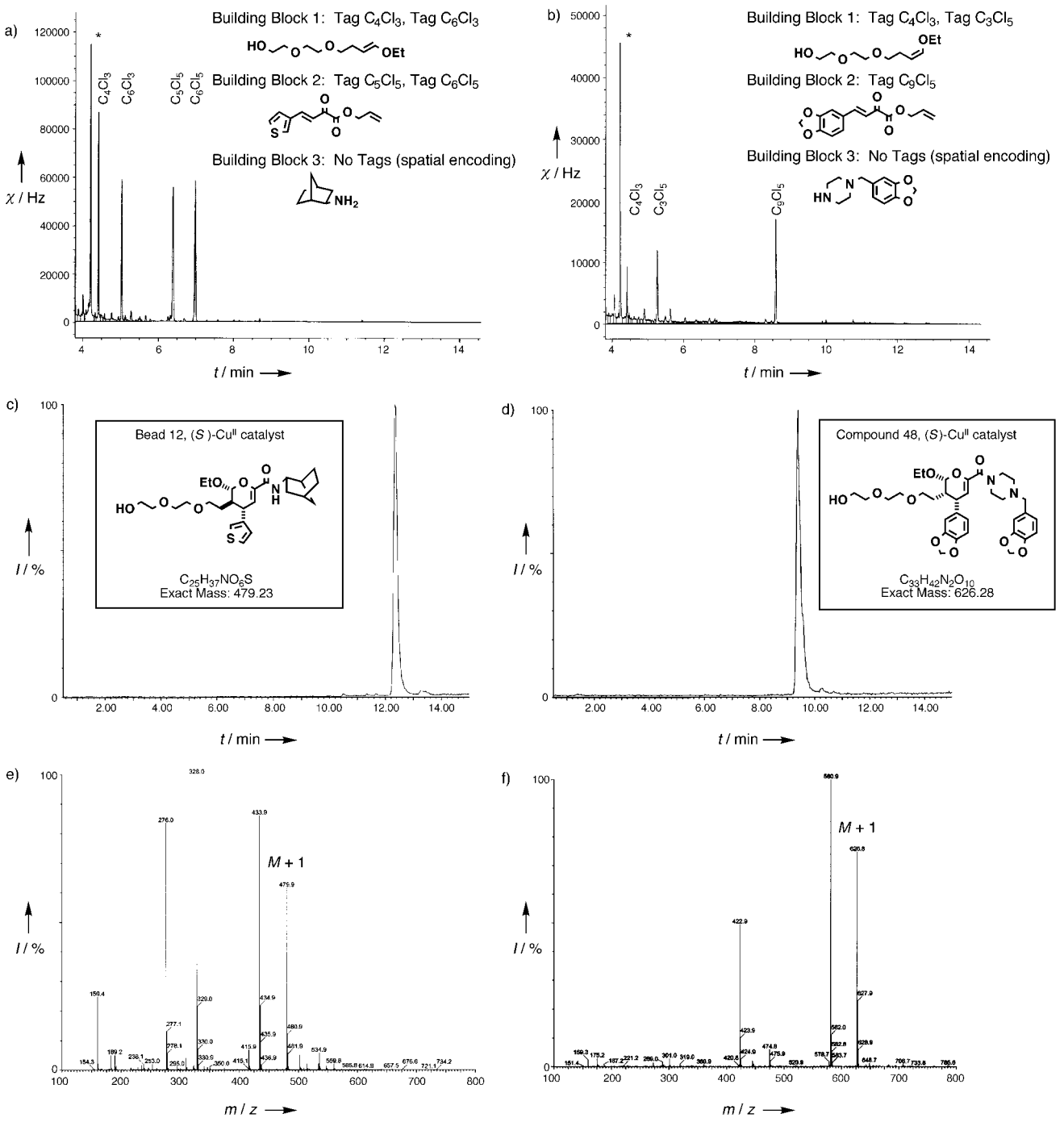

Figure 2. Representative examples of GC (a, b), LC (c, d), and MS (e, f) spectra from bead and stock-solution decoding (samples 12 and 48, respectively). The *bead-decoding* GC trace for sample 12 (a) decodes for a library compound with an exact mass identical to that obtained by MS (e) of the compound cleaved from that bead (APCI, observed mass = 479.9 [*M*+1]). The *stock-solution-decoding* GC trace for sample 48 (b) decodes for a library compound with an exact mass identical to that obtained by MS (f) of the compound stock solution (APCI, observed mass = 626.8 [*M*+1]). The single peaks in the LC spectra (c, d) correspond to these molecular ions. [The starred peak (∗) in the GC traces (a, b) is an impurity frequently present with the electrophoric tags.]

the "global" decoding of entire split-pool libraries a reality in the future.[19]

Received: June 11, 2001 [Z17257]

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[11] Still and co-workers reported tag insertion into a support-bound tetrapeptide during the encoding process, in a ratio of 1:8 with tag inserted into the support (PS bead diameter = 50 – 100 μm, loading = 100 pmol g^{-1}). The authors used substantially less diazoketone tag (1 pmol tag/bead) to encode their synthesis resin than we found to be sufficient for 500 – 600 μm PS macrobeads (20 nmol tag/bead), presumably due to a more efficient heterogeneous insertion reaction on smaller beads. See refs. [6b] and [7].
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[15] Attempts to determine the structure of the tag-inserted compound have been unsuccessful so far. However, we postulate that an aromatic-ring and/or N–H insertion reaction occurred. See ref. [12].
[16] Given the different efficiencies of the homogeneous and heterogeneous tag-cleavage reactions, we could not determine quantitatively if more tag was inserting into the compound rather than the bead, or vice versa.
[17] This discrepancy can be attributed to either unsuccessful chemical reaction in one or more of the library steps and/or poor ionization by MS, and serves as a reminder that encoding records the sequence of chemical reactions to which a bead is subjected, not the structure of the compound.
[18] The structures assigned to the 108 samples can be found in the Supporting Information.
[19] Supporting Information available: Representative encoding and decoding protocols, ^1H NMR spectroscopy, LC, and GC data, and full details of the partial library decoding.

Highly Enantioselective Hydrogenation of Acyclic Imines Catalyzed by Ir – f-Binaphane Complexes**

Denming Xiao and Xumu Zhang*

Dedicated to Professor K. Barry Sharpless on the occasion of his 60th birthday

Although great accomplishments have been achieved in the highly enantioselective hydrogenation of prochiral alkenes and ketones in the last few decades,[1] limited progress has been made in the asymmetric hydrogenation of imines.[2] A number of efficient asymmetric catalysts for the reduction of alkenes and ketones are ineffective for the hydrogenation of related imine compounds. Since chiral amines are important functionalities in many biologically active molecules, the development of practical methods for the hydrogenation of imines is extremely important in organic synthesis.

Among some notable achievements in the field, Buchwald and co-workers[3] have developed a chiral titanocene catalyst for the reduction of imines, and the system is highly effective for the hydrogenation of cyclic imines. A number of group VIII transition metal catalysts that bear chiral chelating phosphanes have been explored for the hydrogenation of imines, and these systems generally have a very limited substrate scope.[4, 5] The highly enantioselective hydrogenation of *N*-(phenylethylidene)aniline (89 % *ee*) and related imines by using an Ir – phosphaneoxazoline complex as the catalyst have been reported by Pfaltz and co-workers.[6] A significant industrial process that uses the Ir-catalyzed asymmetric hydrogenation of an *N*-arylimine (10^6 turnovers and 80 % *ee*) has been developed.[7] Despite these impressive advances, the lack of highly enantioselective and reactive catalysts with broad substrate scopes for the hydrogenation of imines is still a major problem in asymmetric catalysis. Herein we report a highly enantioselective hydrogenation of *N*-arylimines catalyzed by Ir complexes with a novel chiral ferrocene phosphane group and an important additive effect for the Ir-catalyzed asymmetric hydrogenation of imines.

Recently we made a chiral phosphane ligand, binaphane, and used it for the Rh-catalyzed highly enantioselective hydrogenation of enamides.[8] However, Rh and Ir complexes of chiral binaphane are not effective for the hydrogenation of imines. To alter the steric and electronic properties of the binaphane ligand, we envisioned that the introduction of a ferrocene backbone would be helpful. The new air-stable, chiral 1,1′-bisphosphanoferrocene (**1**; abbreviated as f-binaphane) was then prepared by using a similar route used in the synthesis of binaphane (Scheme 1).

[*] Prof. Dr. X. Zhang, D. Xiao
Department of Chemistry, The Pennsylvania State University
University Park, PA 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: xumu@chem.psu.edu

[**] This work was supported by a NIH grant and a Dreyfus Teaching-Scholar Award. We acknowledge a generous loan of precious metals from Johnson Mathey Inc. and a gift of chiral GC columns from Supelco.

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