Studies of Asymmetric Styrene Cyclopropanation with a Rhodium(II) Metallopeptide Catalyst Developed with a High-Throughput Screen

RAMYA SAMBASIVAN, AND ZACHARY T. BALL*
Department of Chemistry MS60, Rice University, 6100 Main Street, Houston, TX 77005

ABSTRACT Dirhodium metallopeptides have been developed as selective catalysts for asymmetric cyclopropanation reactions. A selective ligand sequence has been identified by screening on-bead metallopeptide libraries in a 96-well plate format. Efficient ligand synthesis and screening allows a 200-member library to be created and assayed in less than three weeks. These metallopeptides catalyze efficient cyclopropanation of aryldiazoacetates, providing asymmetric access to cyclopropane products in high diastereoselectivity. *Chirality 25:493–497, 2013.* © 2013 Wiley Periodicals, Inc.

KEY WORDS: asymmetric catalysis; metallopeptides; cyclopropanation; rhodium; peptide library; catalyst screening

INTRODUCTION

Peptide ligands offer advantages over traditional chiral ligands for selective catalysis: they are modular and functional-group-rich sources of chirality from the chiral pool. Modern methods for automated, parallel synthesis facilitate expedient catalyst screening. In theory, a library screening approach obviates the tedious process of chiral ligand development for each and every new reaction, much as high-throughput screening approaches now routinely deliver lead compounds for biological targets. Once a few catalyst libraries have been synthesized, new reaction development can take advantage of prior efforts.[1,2] We recently reported a rhodium(II) metallopeptide catalyst for asymmetric cyclopropanation that was discovered though a peptide screening approach.[3] In this article, we discuss practical considerations for library synthesis and screening, and we present further studies on the generality of cyclopropanation with rhodium(II) catalysts containing the chiral peptide ligand, **L2.47** (where "**L2.47**" is peptide 47/96 of the second round of optimization in 96-well plates).

The use of transition metals with peptide ligands as catalysts for asymmetric reactions is surprisingly limited. It is often challenging to design well-defined coordination spheres in such a functional-group-rich environment. There have been reports of enantioselective catalysts with unnatural amino acids containing phosphine[4–6] or pyridine[7] or phenanthroline[8] side chains which serve as handles to bind to transition metals. In other cases, entire transition-metal complexes have been attached to large proteins to form a metalloprotein which can then aid asymmetric catalysis.[9] By turning to the very stable rhodium(II) carboxylate linkage, we have benefitted from the dual advantages of a stable ligand sphere using cheap, naturally available amino acids.

The idea of catalyst screening stemmed from our previous studies demonstrating the use of 9-mer peptides containing aspartic acid residues in an internal DxxxD motif (D = aspartate) as chiral ligands for dirhodium-catalyzed asymmetric Si–H insertions.[10] In that work, we individually isolated and purified catalysts of the type Rh_2(peptide)$_2$, prepared by treatment of a peptide containing aspartates with $Rh_2(tfa)_4$ (tfa = trifluoroacetate). There are two isomeric *bis*-peptide complexes formed with each peptide sequence, due to the potential for parallel or antiparallel orientation of the peptides, which are generally separated by RP-HPLC. The orientational structure can be identified via pyrene fluorescence.[11] The solution-phase catalyst screening is cumbersome because it requires multiple HPLC separations to isolate the isomeric complexes. To speed up the process, we developed an on-bead, parallel screening method in a 96-well plate format to assess peptide sequences which were tested on bead as *mono*-peptide complexes, Rh_2(peptide)$(OAc)_2$. This screen is based on the hypothesis that optimal sequences in on-bead *mono*-peptide catalysts will tend to produce better *bis*-peptide catalysts, which can only be synthesized in solution. This screening technique identified a catalyst for the asymmetric cyclopropanation of methyl α-phenyldiazoacetate ester and styrene (Fig. 1). The "lead" on-bead catalyst producing the (1*R*,2*S*)-cyclopropane product in 54% ee at rt exhibited significant enhancement in selectivity (87% ee at –50 °C) on moving to the *bis*-peptide variant, Rh_2(**L2.47**)$_2$-A (where the suffix "A" arbitrarily identifies orientational isomers).

EXPERIMENTAL

Materials and Methods

All rhodium-catalyzed reactions were carried out in 4-ml vials. Reactions carried out below 0 °C were conducted in a Neslab CB-80 cold bath. Flash chromatography was performed with 40-63-μm particle size silica gel. NMR data was acquired with Bruker Avance 400 MHz or Bruker Avance 500 MHz instrument. ^{1}H and ^{13}C NMR spectra were referenced relative to residual solvent or TMS. Chiral HPLC analyses were performed on a Shimadzu SCL-10ADVP instrument with Phenomenex Lux 5u Cellulose-1 (250 × 4.6 mm analytical) or a Chiralpak IA (250 × 2 mm ID analytical) column with a flowrate of 1.5–1.9 ml/min and the detection wavelength was 220 nm. All reagents were purchased commercially and used without further purification. All solvents were reagent grade. The synthesis of diazo substrates[10] has been previously reported. For purpose of ee determination, racemic material was generated using $Rh_2(OAc)_4$. The absolute configuration of product **2a** is assigned by comparison of the optical rotation to previous reports.[12,13] The absolute configuration of all

Contract grant sponsor: Robert A. Welch Foundation; Contract grant number: C-1680.
Contract grant sponsor: NFS CAREER award; Contract grant number: CHE-1055569.
*Correspondence to: Zachary Ball, Department of Chemistry, Rice University, 6100 Main Street, Houston, TX 77005. E-mail: zb1@rice.edu
Received for publication 16 October 2012; Accepted 16 November 2012
DOI: 10.1002/chir.22144
Published online 8 June 2013 in Wiley Online Library (wileyonlinelibrary.com).

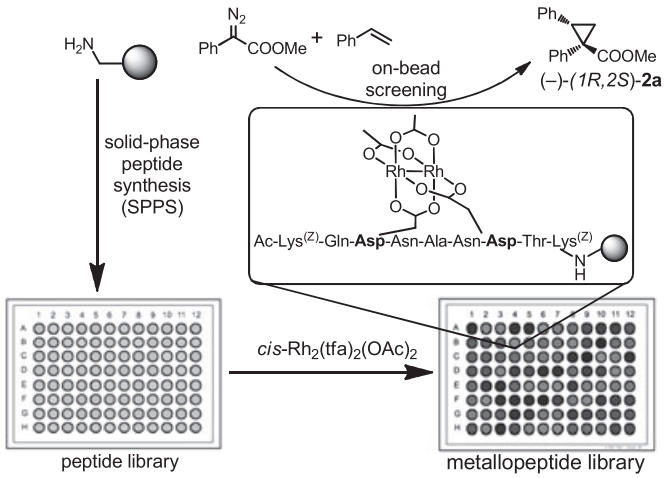


Fig. 1. On-bead screening of metallopeptide catalysts for cyclopropanation. Reaction conditions: diazo (6 μmol), styrene (60 μmol), and catalyst (~0.15 μmol), in CF_3CH_2OH. All catalysts are attached to the resin at the C-terminus of the peptides, and the peptide N-terminus is acetylated. Sequence shown is **L2.47**.

other cyclopropane products **2b–2i** is assumed by analogy. From our previously published library screening, the 'hit' peptide sequence yielding the highest enantioselectivity in cyclopropanation reaction was found to be the ligand **L2.47**, and the catalyst Rh_2(**L2.47**)$_2$-A was prepared according to reported procedures.[3] The characterization data comprising ^{1}H NMR, ^{13}C NMR, and GC-MS data have been reported for the racemic product. The chiral compounds have been characterized by TLC, HPLC, and ^{1}H NMR of the crude reaction mixture. They were all in agreement with the corresponding data obtained for the racemic product. The synthesis and characterization of products **2a** and **2b–7b** have been reported previously.[3]

General Procedure for Cyclopropanation Reactions

A solution of the catalyst Rh_2(**L2.47**)$_2$-A (0.082 mg, 0.5 mol%) in trifluoroethanol (100 μl) was stirred at –50 °C in a 4-ml vial. A mixture of methyl α-diazophenylacetate (1 mg, 0.0057 mmol) and styrene (5.92 mg, 0.057 mmol) in trifluoroethanol (100 μl) were stirred at the same temperature in another 4-ml vial. The catalyst solution was then quickly transferred to the vial containing the substrates and the reaction mixture was allowed to stir at –50 °C until the diazo compound reacted fully. The mixture was concentrated under reduced pressure and purified by flash chromatography in a glass pipette on silica gel using 1:99 diethylether/hexane to give the desired cyclopropane product.

Characterization of the Cyclopropane Products

(1*S*,2*S*)-methyl 2-phenyl-1-((*E*)-styryl) cyclopropanecarboxylate (2c). The general procedure was employed using methyl 2-((*E*)-styryl)-2-diazoacetate on a 0.005-mmol scale at –35 °C to provide the product as a white crystalline solid in 54% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.20 (m, 4H), 7.18−7.12 (m, 6H), 6.34 (d, *J* = 16 Hz, 1H), 6.13 (d, *J* = 16 Hz, 1H), 3.76 (s, 3H), 3.00 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.02 (dd, *J* = 9.0, 5.0, 1H), 1.83 (dd, *J* = 7.0, 5.0 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 174.4, 137.3, 135.7, 133.3, 129.3, 128.6, 128.2, 127.5, 127.0, 126.4, 124.3, 52.7, 35.2, 33.5, 18.8. GC-MS t_R 19.1 min (> 95%), *m/z*: $[M]^+$ calcd for $C_{19}H_{18}O_2$: 278.3; found: 278.2. Enantiomeric excess determined by HPLC; Phenomenex Lux 5u Cellulose-1 column, eluting with 99:1 hexanes/*i*-PrOH, 1.5 ml/min, (1*S*,2*S*)-enantiomer t_R 7.3 min; (1*R*,2*R*)-enantiomer t_R 5.9 min.

(*S*)-dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (2d). The general procedure was employed using dimethyl diazomalonate on a 0.006-mmol scale at rt to provide the product in 38% ee. The catalyst was dissolved in trifluoroethanol (10 μl) and this solution was added to a solution of the substrates in dichloromethane (190 μl). The reaction did not proceed at temperatures below rt and solvent insertion product of the diazo compound was observed when trifluoroethanol was exclusively used as the solvent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.18 (m, 5H), 3.78 (s, 3H), 3.35 (s, 3H), 3.23 (t, *J* = 8.6 Hz, 1H), 2.20 (dd, *J* = 8, 5.2 Hz, 1H), 1.74 (dd, *J* = 5.2, 9.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.4, 167.2, 134.7, 128.6, 128.4, 127.6, 53.0 52.4, 37.4, 32.7, 19.3. GC-MS t_R 13.0 min (> 95%), *m/z*: $[M]^+$ calcd for $C_{13}H_{14}O_4$: 234.3; found: 234.1. Enantiomeric excess determined by HPLC; Phenomenex Lux 5u Cellulose-1 column, eluting with 99:1 hexanes/*i*-PrOH, 1.5 ml/min, (*S*)-enantiomer t_R 6.1 min; (*R*)-enantiomer t_R 5.7 min.

(1*R*,2*S*)-methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate (2e). The general procedure was employed using methyl 2-(2-naphthyl)-2-diazoacetate on a 0.004 mmol scale at –50 °C to provide the product in 82% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–6.65 (m, 2H), 7.61 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.42–7.40 (m, 2H), 7.05 – 7.00 (m, 4H), 6.82 – 6.79 (m, 2H), 3.65 (s, 3H), 3.19 (dd, *J* = 7.4, 9.2, 1H), 2.22 (dd, *J* = 4.8, 9.2 Hz, 1H), 2.02 (dd, *J* = 4.8, 7.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.6, 136.4, 133.2, 132.8, 132.7, 130.7, 130.3, 128.3, 128.0, 127.8, 127.3, 126.6, 126.0, 125.9, 52.9, 37.7, 33.5, 20.9. GC-MS t_R 17.6 min (> 95%), *m/z*: $[M]^+$ calcd for $C_{21}H_{18}O_2$: 302.3; found: 302.1. Enantiomeric excess determined by HPLC; Phenomenex Lux 5u Cellulose-1 column, eluting with 99.5:0.5 hexanes/*i*-PrOH, 1.5 ml/min, (1*R*,2*S*)-enantiomer t_R 9.7 min; (1*S*,2*R*)-enantiomer t_R = 8.8 min.

(1*R*,2*S*)-methyl 1-(3-(trifluoromethyl)phenyl)-2-phenyl-cyclopropanecarboxylate (2f). The general procedure was employed using methyl 2-phenyl-(3-trifluoromethyl)-2-diazoacetate on a 0.004-mmol scale at –50 °C to provide the product in 73% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 1H), 7.27–7.16 (m, 3H), 7.07–7.05 (m, 3H), 6.77–6.75 (m, 2H), 3.68 (s, 3H), 3.17 (dd, *J* = 7.6, 9.2, 1H), 2.19 (dd, *J* = 4.8, 9.2 Hz, 1H), 1.91 (dd, *J* = 4.8, 7.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.8, 136.2, 135.8, 135.7, 130.8–129.8 (q, *J* = 128 Hz), 130.1–122.9 (q, *J* = 1080 Hz), 129.9 (q, *J* = 16), 128.3, 128.2, 128.1, 126.9, 124.1 (q, *J* = 16 Hz), 53.0, 37.2, 33.5, 20.3. GC-MS t_R 17.6 min (> 95%), *m/z*: $[M]^+$ calcd for $C_{18}H_{15}F_3O_2$: 320.3; found: 320.1. Enantiomeric excess determined by HPLC; Phenomenex Lux 5u Cellulose-1 column, eluting with 99.75:0.25 hexanes/*i*-PrOH, 1.5 ml/min, (1*R*,2*S*)-enantiomer t_R 9.9 min; (1*S*,2*R*)-enantiomer t_R 12.8 min.

(1*R*,2*S*)-methyl 1-(2-methoxyphenyl)-2-phenylcyclopropanecarboxylate (2g). The general procedure was employed using methyl 2-methoxyphenyl-2-diazoacetate on a 0.005-mmol scale at –50 °C to provide the product in 49% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.11 (m, 2H), 7.01– 6.98 (m, 3H), 6.85–6.76 (m, 3H), 6.53 (d, *J* = 8 Hz, 1H), 3.64 (s, 3H), 3.35 (s, 3H), 3.22 (dd, *J* = 7.6, 9.2, 1H), 1.97 (dd, *J* = 5.2, 9.2 Hz, 1H), 1.85 (dd, *J* = 5.2, 7.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.7, 159.2, 137.0, 131.8, 128.9, 127.9, 127.3, 126.1, 124.1, 120.0, 110.4, 55.2, 52.7, 34.3, 32.6, 20.8. GC-MS t_R 16.4 min (> 95%), *m/z*: $[M]^+$ calcd for $C_{18}H_{18}O_3$: 282.3; found: 282.1. Enantiomeric excess determined by HPLC; Phenomenex Lux 5u Cellulose-1 column, eluting with 99.5:0.5 hexanes/*i*-PrOH, 1.5 ml/min, *(1R,2S)*-enantiomer t_R 11.3 min; (1*S*,2*R*)-enantiomer t_R 10.4 min.

(1*R*,2*S*)-methyl 1-(3-bromophenyl)-2-phenylcyclopropanecarboxylate (2h). The general procedure was employed using methyl 3-bromophenyl-2-diazoacetate on a 0.004-mmol scale at –50 °C to provide the product in 86% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 2H), 7.11–7.08 (m, 3H), 6.98–6.94 (m, 1H), 6.90–6.87 (m, 1H), 6.80–6.77 (m, 2H), 3.67 (s, 3H), 3.12 (dd, *J* = 7.6, 9.2, 1H), 2.14 (dd, *J* = 5.2, 9.2 Hz, 1H), 1.86 (dd, *J* = 5.2, 7.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.9, 137.4, 135.9, 135.0, 131.0, 130.4, 129.3, 128.2, 128.1, 126.8, 121.8, 53.0, 37.1, 33.4, 20.5. GC-MS t_R 17.7 min (> 95%), *m/z*: $[M]^+$ calcd for $C_{17}H_{15}BrO_2$: 331.2; found: 331.1. Enantiomeric excess determined by HPLC; Phenomenex Lux 5u Cellulose-1 column, eluting with 99.75:0.25 hexanes/*i*-PrOH, 1.5 ml/min, (1*R*,2*S*)-enantiomer t_R 11.5 min; (1*S*,2*R*)-enantiomer t_R 12.6 min.

(1*R*,2*S*)-methyl 1-(4-phenylphenyl)-2-phenylcyclopropanecarboxylate (2i). The general procedure was employed using methyl 4-phenylphenyl-2-diazoacetate on a 0.004-mmol scale at –50 °C to provide the product in >85% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.37–7.28 (m, 5H), 7.10–7.05 (m, 5H), 6.82–6.79 (m, 2H), 3.69 (s, 3H), 3.13 (dd, *J* = 7.2, 9.2, 1H), 2.17 (dd, *J* = 4.8, 9.2 Hz, 1H), 1.91 (dd, *J* = 4.8, 7.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.5, 140.9, 136.5, 132.5, 131.0, 128.9, 128.3, 128.0, 127.8, 127.6 127.4, 127.2, 126.6, 52.9, 37.3, 33.5, 20.8. GC-MS t_R 14.1 min (> 95%), *m/z*: $[M\text{-}OMe]^+$ calcd for $C_{22}H_{18}O_1$: 298.3; found: 298.1. Enantiomeric excess determined by HPLC; Phenomenex Lux 5u Cellulose-1 column, eluting with 97:3 hexanes/*i*-PrOH, 1.5 ml/min, (1*R*,2*S*)-enantiomer t_R 3.8 min; (1*S*,2*R*)-enantiomer t_R 4.0 min.

RESULTS AND DISCUSSION

Optimization of Resin Type and Loading

Our first-generation solution-phase screening process involved synthesis of the peptides using standard FMOC protocols, cleavage from the resin, peptide purification, complexation of the purified peptides with $Rh_2(tfa)_4$, and RP-HPLC isolation of the isomeric *bis*-peptide catalysts.[10] This entire screening process was somewhat tedious in that it took weeks to screen a total of six sequences (i.e., 12 metallopeptide catalysts). To screen more efficiently, we required a new approach and resorted to an on-bead catalyst screening technique.

In the second-generation catalyst screening, the rhodium (II) metallopeptide catalysts were prepared from peptide libraries in which the peptides remain attached to the resin bead. This would eliminate the need for HPLC purification of the peptides and the metallopeptide catalysts. We decided to synthesize peptide libraries in 96-well plates and then subject the peptides to dirhodium complexation. However, we envisaged that complexation with $Rh_2(tfa)_4$ would be detrimental to the effort of identifying a selective catalyst since we again would face the problem of separating and isolating the isomeric on-bead *bis*-peptide complexes. To circumvent this issue, we decided to complex the on-bead peptides with *cis*-$Rh_2(tfa)_2(OAc)_2$ to form the *mono*-peptide catalysts and hypothesized that a selective *mono*-peptide catalyst would exhibit enhanced selectivity when prepared as a *bis*-peptide catalyst in solution. Our first goal was to identify the optimal resin on which we could synthesize the peptide libraries. From our solution-phase library screening,[10] we had identified **L21** (peptide sequence: K^ZNDAAIDAK^Z) as one of the most selective ligands for the insertion of methyl α-phenyldiazoacetate into the Si–H bond of phenyl dimethyl silane (Table 1).

We then decided to synthesize this same **L21** sequence on four different types of resins with varying resin loading in order to narrow down an optimal resin type. Also, we first established that our catalyst system could be synthesized on a solid support and that it exhibited reactivity. Similar to our solution-phase protocol, we complexed the *bis*-aspartate containing peptides on the resin bead with *cis*-$Rh_2(tfa)_2(OAc)_2$ in the presence of *N*,*N*-diisopropylethylamine using trifluoroethanol as solvent. The most important factor among several resins tested was resin loading (see Table 1 for details). The Novasyn TG amino resin had lower loadings (0.17–0.29 mmol/g) and yielded product enantioselectivity (81% at –35 °C) in the model reaction that was similar to solution-phase catalysts (Table 1). This on-bead catalyst could be used up to three times without affecting selectivity.

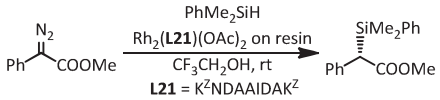
Library Screening Strategies

After identifying a suitable resin to synthesize our 96-well plate peptide library, we then explored various techniques to make the library. For the optimization of the techniques, rink amide resin was used to allow peptide cleavage and purity analysis.

Initial efforts at library synthesis.

a. *Kitchen microwave*: We initially attempted to take advantage of the benefits of microwave heating[14] by conducting the synthesis using irradiation from a simple kitchen microwave. We loaded 18 random wells

TABLE 1. Optimization of resin type and loading



Entry	Resin	Description	Loading (mmol/g)	ee (%)
1	AAPPTec RAZ001	aminomethyl polystyrene	1.12	3
2	AAPPTec RAZ051	"surface active" aminomethyl	0.76	3
3	NovaGel 855037	hydrazinobenzoyl "safety catch"	0.49	51
4	NovaSyn 855073	TG amino resin	0.29	66(81[a])

[a]Reaction at –35 °C.

in the 96-well plate with Rink amide resin and attempted peptide synthesis on a 5.4-μmol scale. Each deprotection step was carried out for 4 min and each coupling was carried out for 6 min. We varied the power setting and monitored the temperature after the heating with a laser thermometer. Unfortunately, large variations in temperatures (55–70 °C) were observed, and MALDI analysis indicated the presence of point-deletion impurities. Attempts to improve the situation by stirring within the microwave were unsuccessful, largely for technical reasons.

b. *Shaker*: We were also unsuccessful using an orbiting incubator for agitation. On MALDI analysis, the peptides synthesized in most wells had an asparagine deletion, and so we decided not to pursue using the manual shaker.

Manual peptide synthesis with magnetic stirring. A small magnetic stir bar was added to each well of the 96-well plate; the resin was distributed and the peptide synthesis was carried out using standard FMOC protocols. MALDI and RP-HPLC analysis of the peptides obtained from each well indicated the formation of >95% pure peptide in each well.

Encouraged by the purity of the peptides obtained in the above-mentioned strategy, we synthesized the peptide library for catalyst screening using the Novasyn TG amino resin and then subjected the peptides to rhodium(II) complexation. After metalation with *cis*-$Rh(OAc)_2(tfa)_2$, the 96-well plate was screened successfully against a target cyclopropanation reaction (Fig. 1). After the reaction, the reaction wells were concentrated in vacuo to remove excess styrene and then assayed directly by chiral HPLC. Reaction yields, which are generally quite high for these reactions, were not measured due to the small scale used for screening (1 mg diazo).

Employing this latter library synthesis method, a screen uncovered the "hit" sequence, **L2.47** (Fig. 2), the details of which have been previously reported.[3] The use of the Rh_2(**L2.47**)$_2$-A catalyst yielded the product cyclopropane in 92% ee for the *tert*-butyl phenyl diazoacetate (Table 2). This class of catalysts produces cyclopropane products with complete selectivity for the trans diastereomer.

Variation of Diazo Substrates in Cyclopropanation Reactions. In general, *tert*-butyl diazoesters yield better enantioselectivity than their methyl ester equivalents (Table 2; entries 1–6). The improvement was most pronounced in the case of α-methyl styrene (Table 2; entry 3).

The rhodium(II) metallopeptide catalyst Rh_2(**L2.47**)$_2$-A afforded good enantioselectivities in the cyclopropanation reaction of α-phenyldiazoacetate with a variety of olefins. We then wanted to assess the selectivity of the same catalyst with other diazo variants and subjected the catalyst to cyclopropanation reactions of styrene with a number of diazo substrates. The enantioselectivities are as shown in Table 3. In most of these reactions, the cyclopropane was obtained as the major product. A small amount (<15%) of the solvent insertion product with trifluoroethanol was formed as observed from NMR of the crude reaction mixture.

Many aryldiazoacetates gave good enantioselectivities similar to the parent compound, methyl α-phenyldiazoacetate. The naphthyl-, 3-bromo- and 4-phenyl- substrate gave selectivites of >80% (Table 3; entries 4,7,8). Chemoselective cyclopropanation of a styryldiazo substrate was also possible,

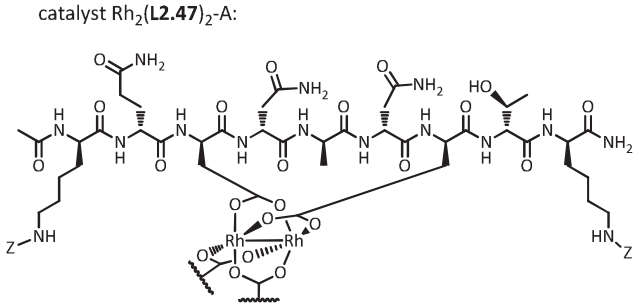
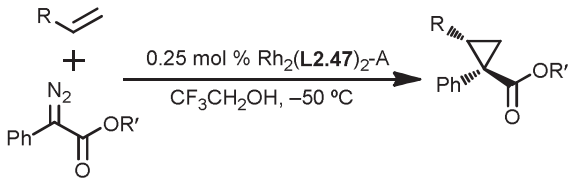
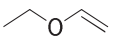
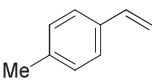
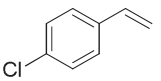


Fig. 2. Optimized ligand structure. Z = benzyloxycarbonyl.

affording product **2c** with a modest 54% ee. As observed in silane insertion, an *ortho*-substituted diazo substrate gave product with significantly decreased selectivity (49% ee, Table 3; entry 6). A non-aryl diazo substrate (dimethyl diazomalonate) undergoes cyclopropanation only at room temperature, resulting in product with 38% ee (entry 4). The lack of complete

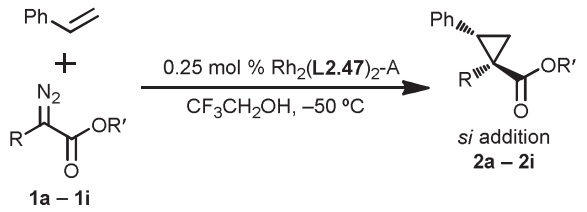
TABLE 2. Asymmetric cyclopropanation with α-diazophenylacetate[a]

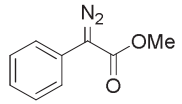
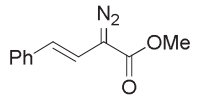
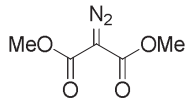
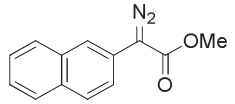
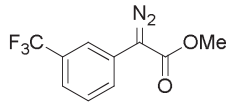
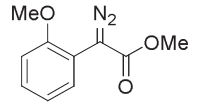
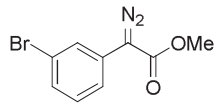
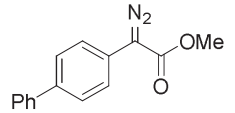


Entry	Alkene	% ee R′ = Me	% ee R′ = *t*-Bu
1		87 (**2a**)[b]	92 (**2b**)
2		8687 (**3a**)[c]	92 (**3b**)
3		6987 (**4a**)[c]	95 (**4b**)
4		9087 (**5a**)[c]	97 (**5b**)
5		9087 (**6a**)[c]	95 (**6b**)
6		72 (**7a**)[c]	80(**7b**)[d]

[a]Entries in the right column have been previously reported.[3]
[b]The absolute configuration for entry 1 was established by comparison to published data; that of other products is assumed by analogy.
[c]Reaction at –35 °C.
[d]Reaction at –25 °C.

TABLE 3. Asymmetric cyclopropanation with styrene



Entry	Starting material	Product	ee[a] (%)
1		**2a**	87
2		**2c**	54
3		**2d**	38[b]
4		**2e**	82
5		**2f**	73
6		**2g**	49
7		**2h**	86
8		**2i**	85[c]

[a]The absolute configuration of **2a** was established by comparison to published data. Other products are assumed by analogy.
[b]Reaction at rt in trifluoroethanol/CH_2Cl_2 (1:19).
[c]Enantiomeric peaks slightly overlapping in the chiral HPLC trace. This measure may underestimate the selectivity of this substrate.

substrate generality observed here is a common feature of chiral catalysts generally, and provides motivation for efficient ligand discovery approaches to address new problematic substrates as they arise.

CONCLUSIONS

Thus, on-bead catalyst screening has a number of advantages: facile ligand screening, parallel synthesis of hundreds of catalysts, and easy catalyst removal by filtration. Employing this screening technique, over 100 catalysts can be screened and a "hit" catalyst identified in a matter of days. We have established concepts for chiral ligand discovery using peptides as a general and efficient path to address the challenging problem of catalyst development for asymmetric synthesis, and we believe these ideas will be applicable to important reactions of other transition metals.

ACKNOWLEDGMENTS

We acknowledge financial support from the Robert A. Welch Foundation research grant C-1680 and from an NSF CAREER award (CHE-1055569).

LITERATURE CITED

1. Wee AGH. Rhodium(II)-catalyzed reaction of diazocompounds in the service of organic synthesis of natural and non-natural products. Curr Org Synth 2006;3:499–555.
2. Evans PA. Modern rhodium-catalyzed organic reactions, Weinheim: Wiley-VCH; 2005.
3. Sambasivan R, Ball ZT. Screening rhodium metallopeptide libraries "on bead": asymmetric cyclopropanation and a solution to the enantiomer problem. Angew Chem Int Ed 2012;51:8568–8572.
4. Gilbertson SR, Wang XF, Hoge GS, Klug CA, Schaefer J. Synthesis of phosphine-rhodium complexes attached to a standard peptide synthesis resin. Organometallics 1996;15:4678–4680.
5. Gilbertson SR, Wang XF. The parallel synthesis of peptide based phosphine ligands. Tetrahedron 1999;55:11609–11618.
6. Gilbertson SR, Wang XF. The combinatorial synthesis of chiral phosphine ligands. Tetrahedron Lett 1996;37:6475–6478.
7. Coquière D, Bos J, Beld J, Roelfes G. Enantioselective artificial metalloenzymes based on a bovine pancreatic polypeptide scaffold. Angew Chem Int Ed 2009;48:5159–5162.
8. Bos J, Fusetti F, Driessen AJM, Roelfes G. Enantioselective artificial metalloenzymes by creation of a novel active site at the protein dimer interface. Angew Chem Int Ed 2012;51: 7472–7475.
9. Thomas CM, Ward TR. Artificial metalloenzymes: proteins as hosts for enantioselective catalysis. Chem Soc Rev 2005;34: 337–346.
10. Sambasivan R, Ball ZT. Metallopeptides for asymmetric dirhodium catalysis. J Am Chem Soc 2010;132:9289–9291.
11. Sambasivan R, Ball ZT. Determination of orientational isomerism in rhodium(ii) metallopeptides by pyrene fluorescence. Org Biomol Chem 2012;10:8203–8206.
12. Davies HML, Lee GH. Dirhodium(II) tetra(*N*-(dodecylbenzenesulfonyl) prolinate) catalyzed enantioselective cyclopropenation of alkynes. Org Lett 2004;6:1233–1236.
13. Bruzinski PR. Novel chiral rhodium(II) carboxylates as catalysts in asymmetric cyclopropanations. Ph.D. Thesis (9801276). SUNY at Buffalo, Buffalo, NY, 1997.
14. Murray JK, Gellman SH. Parallel synthesis of peptide libraries using microwave irradiation. Nat Protoc 2007;2:624–631.