Asymmetric Hydrogenation of Ketones with Ruthenium Complexes of *rac*- and Enantiopure (*S*,*S*)-1,2-Bis((diphenylphosphino)methyl)cyclohexane: A Comparative Study with *rac*- and (*R*)-BINAP

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Summary: Ruthenium(II) complexes of the type trans-[$RuCl_2$-{1,2-bis((diphenylphosphino)methyl)cyclohexane}(diamine)] based on the inexpensive and easy-to-prepare rac- and (S,S)-1,2-bis-((diphenylphosphino)methyl)cyclohexane form highly active and enantioselective catalysts for the asymmetric hydrogenation of a wide range of aryl and heteroaryl ketones, in most cases giving ee's that exceed those obtained with their BINAP counterparts. Although precatalysts based on 1,2-bis((diphenylphosphino)-methyl)cyclohexane slowly isomerize in solution to afford the thermodynamically favored isomer with a cis arrangement of chlorides, catalysts generated from both isomers afford similar enantioselectivities.

Introduction

During the past decade, asymmetric catalysis has evolved into an indispensable and highly valuable tool for the synthesis of nonracemic intermediates and products.[1] The design of catalysts for asymmetric synthesis was initially guided by the premise that a rigid, conformationally restricted, enantiopure ligand was required to obtain high ee's. However, alternative strategies have now begun to emerge which involve the use of a conformationally flexible, meso, or racemic ligand to convey asymmetry in enantioselective catalysis.[2] In the last case, a chiral additive is used to selectively activate one enantiomer of a racemic catalyst, a strategy that has been successfully applied to the ruthenium-catalyzed asymmetric hydrogenation of unfunctionalized ketones.[3] Having first demonstrated that ruthenium(II) complexes of the type [$RuCl_2$(diphosphine)(diamine)], based on an enantiopure diphosphine and amine, form catalysts that are highly active and enantioselective for the asymmetric reduction of a wide range of ketones,[4] Noyori and co-workers proceeded to show that ruthenium(II) complexes of racemic BINAP derivatives could be activated by a nonracemic 1,2-diamine.[5] For example, complexes based on *rac*-2,2′-bis(ditolylphosphino)-1,1′-binaphthyl (*rac*-tolBINAP) and (*S*,*S*)-1,2-diphenylethylenediamine ((*S*,*S*)-DPEN) were found to catalyze the asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexenone to afford the corresponding alcohol in 95% ee, which was similar to the ee obtained with the (*R*)-tolBINAP/(*S*,*S*)-DPEN combination. In comparison, a catalyst based on the mismatched combination of (*S*)-tolBINAP and (*S*,*S*)-DPEN gave an ee of only 26%. In an elegant extension of these studies,[6] the same researchers substituted the conformationally flexible *tropos* diphosphine 2,2′-[(3,5-dimethylphenyl)phosphino]biphenyl (DM-BIPHEP) for the *rac*-tolBINAP ligand to afford [$RuCl_2$-(DM-BIPHEP){(*S*,*S*)-DPEN}] and revealed a marked dependence of the enantioselectivity on the diastereoisomeric ratio of the precatalyst, with the 1:1, 2:1, and 3:1 mixtures giving enantioselectivities of 63, 73, and 84%, respectively. Moreover, the catalyst generated from DM-BIPHEP gave a higher enantioselectivity than its *rac*-DMBINAP counterpart.

While a number of related reports on the use of an achiral or racemic diphosphine in the ruthenium-catalyzed asymmetric hydrogenation of ketones have appeared,[7] the vast majority of catalysts that have been developed for this transformation are based on an enantiopure diphosphine,[8] which is often either relatively expensive and/or has to be prepared via a multistep synthesis. As part of an ongoing program aimed at developing the applications of inexpensive, readily accessible, conformationally flexible and racemic ligands in asymmetric catalysis,[9] we became interested in exploring the use of *rac*- and (*S*,*S*)-1,2-bis((diphenylphosphino)methyl)cyclohexane (*rac*-**1** and (*S*,*S*)-**1**) in the ruthenium-catalyzed hydrogenation of ketones, reasoning that there was a clear and direct analogy between these diphosphines and *rac*- and (*R*)-BINAP, respectively (Chart 1). Moreover, both *rac*- and (*S*,*S*)-1,2-bis((diphenylphosphino)-methyl)cyclohexane are inexpensive and straightforward to prepare on a multigram scale from readily available starting

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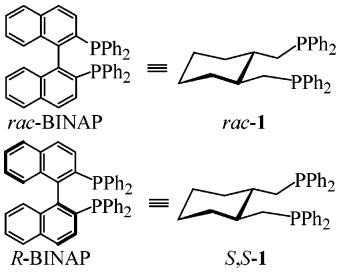
materials. Herein, we report that ruthenium complexes of these diphosphines form highly efficient catalysts for the asymmetric hydrogenation of a range of aryl and heteroaryl ketones and give ee's that either rival or exceed those obtained with their BINAP counterparts.

Chart 1



Results and Discussion

Diphosphines *rac*- and (*S*,*S*)-**1** were synthesized on a multigram scale by reaction of *rac*- or (*S*,*S*)-1,2-bis(bromomethyl)-cyclohexane with lithium diphenylphosphide, rather than from the ditosylate or mesylate as previously described.[10] In the case of (*S*,*S*)-**1,** the corresponding dibromide was prepared via the Lewis acid catalyzed diastereoselective Diels−Alder reaction between (−)-menthyl fumarate and 1,3-butadiene.[11] The enantiopurity of (*S*,*S*)-**1** was established by comparison of its $[\alpha]_D$ value with that reported in the literature.[10] Although ruthenium complexes of the type *trans*-[$RuCl_2$(diphosphine)(diamine)] are typically prepared from $[RuCl_2(benzene)]_2$, according to the procedure originally described by Noyori,[4b] we chose to use $[RuCl_2(py)_2(nbd)]$ as the precursor, following a protocol developed by Bergens[12] for the synthesis of a range of diphosphine−diamine complexes (Scheme 1). In a typical procedure, addition of (*S*,*S*)-**1** to a chloroform solution of $[RuCl_2(py)_2(nbd)]$ results in rapid and quantitative formation of *trans*-[$RuCl_2${(*S*,*S*)-1,2-bis((diphenylphosphino)methyl)cyclohexane}$(py)_2$] (**2**), which can be isolated as a deep yellow crystalline solid by diffusion of a dichloromethane solution layered with hexane or reacted directly with an enantiopure diamine to afford diphosphine−diamine complexes of the type **3**. Interestingly, upon standing in solution, **3** slowly converts into the thermodynamically favored isomer **4**, with a cis arrangement of chloride ligands. The presence of only one pair of doublets in the ^{31}P NMR spectrum of **4** is entirely consistent with a highly diastereoselective isomerization to afford one of the two possible diastereoisomers, which, in the case of *cis*-[$RuCl_2${(*S*,*S*)-**1**}-{(*R*,*R*)-DPEN}], was identified by a single-crystal X-ray study; the molecular structure is shown in Figure 1. In contrast, we found no evidence for the corresponding isomerization of *trans*-[$RuCl_2${(*R*)-BINAP}{(*R*,*R*)-DPEN}], even after standing in solution for several weeks or heating at reflux. Interestingly,

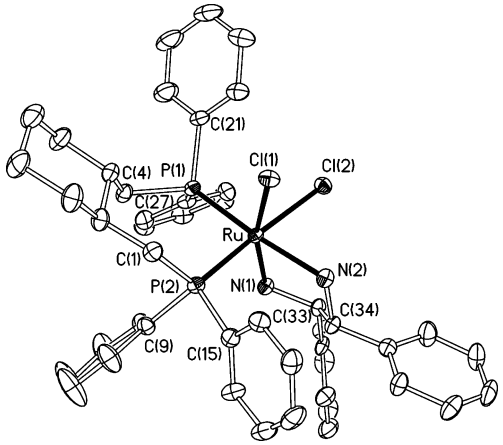
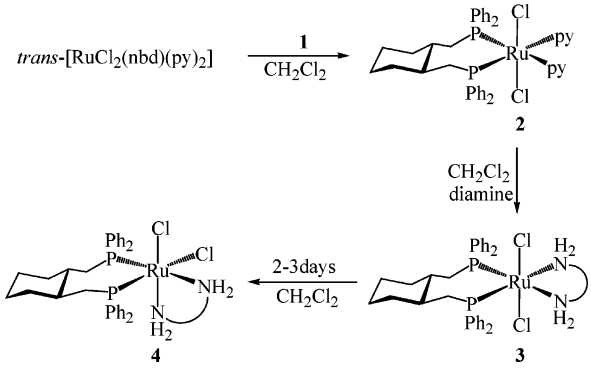


Figure 1. Molecular structure of *cis*-[$RuCl_2${(*S*,*S*)-**1**}{(*R*,*R*)-DPEN}], showing the cis arrangement of chloride ligands and the λ configuration at ruthenium. Hydrogen atoms and the dichloromethane molecule of crystallization have been omitted for clarity. Ellipsoids are at the 30% probability level. Selected bond lengths (Å) and angles (deg): Ru−P(1), 2.2794(10); Ru−P(2), 2.2634(10); Ru−N(1), 2.141(3); Ru−N(2), 2.171(3); Ru−Cl(1), 2.45289(10); Ru−Cl(2), 2.5278(10); P(1)−Ru−P(2), 92.07(3); N(1)−Ru−N(2), 79.44(11); Cl(1)−Ru−Cl(2), 89.77(4), P(1)−Ru−N(2), 172.31(8); Cl(1)−Ru−N(1), 164.25(8); P(2)−Ru−Cl(2), 176.00(3).

James and co-workers recently reported that compounds of the type [$RuCl_2$(dppf)(diimine)], based on 2,2′-bipyridine or 1,10-phenanthroline, exist exclusively as the *cis*-dichloride while those based on a diamine such as ethylenediamine or 1,3-diaminopropane have a trans arrangement of chloride ligands;[13a] In the case of [$RuCl_2$(dppb)(2,2′-bipy)], both *trans*- and *cis*-dichloro complexes are accessible and correspond to the kinetic and thermodynamic products, respectively.[13b]

Scheme 1



Reasoning that the catalytic behavior of enantiopure and racemic 1,2-bis(diphenylphosphinomethyl)cyclohexane could parallel that of enantiopure and racemic BINAP, we first undertook comparative catalyst testing with each of these diphosphines and chose acetophenone as the model substrate and *trans*-[$RuCl_2$(**1**)(diamine)] (**3**) as the precatalyst. Examination of the results in Table 1 reveals that the catalyst based on (*S*,*S*)-**1**/(*R*,*R*)-DPEN is slightly more enantioselective than the (*R*)-BINAP/(*R*,*R*)-DPEN combination, giving 1-phenylethanol in 90% and 86% ee, respectively (entries 1 and 3). Gratifyingly,

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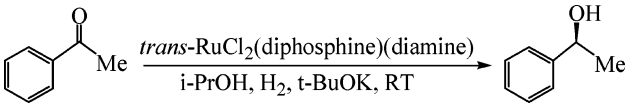
Table 1. Asymmetric Hydrogenation of Acetophenone Using *trans*-[$RuCl_2$(diphosphine)(diamine)] Precatalysts Based on (*S*,*S*)-1, *rac*-1, (*R*)-BINAP, and *rac*-BINAP[a]



entry	diphosphine	diamine	ee (%)[b]
1	(*S*,*S*)-**1**	(*R*,*R*)-DPEN	90 (*S*)
2	(*S*,*S*)-**1**	(*R*,*R*)-DACH	84 (*S*)
3	(*R*)-BINAP	(*R*,*R*)-DPEN	86 (*S*)
4	(*R*)-BINAP	(*R*,*R*)-DACH	84 (*S*)
5	*rac*-**1**	(*R*,*R*)-DPEN	86 (*S*)
6	*rac*-**1**	(*R*,*R*)-DACH	82 (*S*)
7	*rac*-BINAP	(*R*,*R*)-DPEN	48 (*S*)
8	*rac*-BINAP	(*R*,*R*)-DACH	46 (*S*)
9	(*R*,*R*)-**1**	(*R*,*R*)-DPEN	18 (*S*)
10	(*S*)-BINAP	(*R*,*R*)-DPEN	32 (*R*)

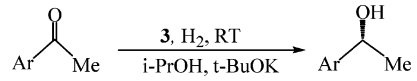
[a] Reactions were conducted with 0.17 M solutions of ketone in 2-propanol with $S/C = 1000/1$ unless otherwise noted, with added t-BuOK at 20−22 °C and 10 atm of H_2 pressure for 12 h. [b] The ee's were determined by chiral GC, and the absolute configuration was determined by comparison of the sign of the optical rotation or the retention time with literature data. Average of three runs.

the corresponding catalyst containing *rac*-**1** and (*R*,*R*)-DPEN gave a markedly higher enantioselectivity than its *rac*-BINAP/(*R*,*R*)-DPEN counterpart, with ee values of 86% and 48%, respectively (entries 5 and 7). Although the ee obtained with *rac*-BINAP was lower than anticipated, related studies have typically employed a subtituted BINAP derivative such as tolBINAP or DM-BINAP to acheive optimum enantioselectivities, which necessarily precludes a meaningful comparison with literature values. In this regard, studies are currently underway to investigate the influence of aryl substitution on catalyst performance with the aim of optimizing enantioselectivities.[4a] Further analysis of the ee values reveals that hydrogenation of acetophenone via the (*S*,*S*)-**1**/(*R*,*R*)-DPEN cycle occurs ca. 20 times faster than the (*R*,*R*)-**1**/(*R*,*R*)-DPEN cycle, whereas the relative rate for the corresponding BINAP system is ca. 2. A similar pattern of enantioselectivities was also obtained with a catalyst based on (*S*,*S*)-**1** and (*R*,*R*)-1,2-diaminocyclohexane ((*R*,*R*)-DACH). The 1-phenylethanol generated with (*S*,*S*)-**1**/(*R*,*R*)-DPEN precatalyst was shown to have an *S* absolute configuration, and in this regard (*S*,*S*)-**1** behaves in a manner similar to (*R*)-BINAP. This is not surprising, since the four-carbon tethers of (*S*,*S*)-**1** and (*R*)-BINAP both adopt a λ conformation and in combination with the λ conformation of (*R*,*R*)-DPEN will present similar chiral molecular surfaces for differentiating the enantiofaces of aromatic ketones.[14] These results clearly suggest that easy-to-prepare and inexpensive diphosphines such as **1** could prove to be practical alternatives to more expensive and synthetically demanding enantiopure ligands.

Encouraged by the enantioselectivities obtained in these preliminary studies, we next extended our investigations to include asymmetric hydrogenation of a range of aryl and heteroaryl substrates using a catalyst generated from *trans*-[$RuCl_2${(*S*,*S*)-**1**}(diamine)] (**3**). The results in Table 2 demonstrate that a range of aryl-substituted methyl ketones can be hydrogenated with good to very high enantioselectivities and that, for each substrate examined, the catalyst based on (*S*,*S*)-**1**/(*R*,*R*)-DPEN consistently outperformed its (*R*,*R*)-DACH counterpart, although both catalysts gave similar patterns of enantioselectivities across the entire range of substrates. Closer inspection of the results reveals that methyl ketone substrates containing an ortho-substituted aromatic ring gave the highest ee's. For example, *o*-chloro- and *o*-bromoacetophenone were reduced using the precatalyst [$RuCl_2${(*S*,*S*)-**1**}{(*R*,*R*)-DPEN}] in 92 and 90% ee, respectively, whereas their para-substituted counterparts were reduced in only 85 and 84% ee, respectively. An increase in the size of the nonaromatic substituent in aryl/alkyl ketones was accompanied by a reduction in enantioselectivity. While the drop in enantioselectivity between acetophenone and propiophenone was relatively small, larger substituents were less well tolerated and a significant drop in ee was observed when an isopropyl group was introduced, for both precatalysts examined (entries 17 and 18).

The combination of Ru^{II}/(*S*,*S*)-**1** with (*R*,*R*)-DPEN or (*R*,*R*)-DACH also proved effective for the hydrogenation of heterocyclic ketones, giving the corresponding alcohols in good to high enantioselectivity (81−94%). For instance, hydrogenation of 2-acetylthiophene and furan with the (*S*,*S*)-**1**/(*R*,*R*)-DPEN-based catalyst was particularly efficient and gave ee's in excess of 90%, slightly higher than the ee of 86% obtained with its DACH counterpart. In contrast, the same catalyst systems were slightly less effective for the hydrogenation of 2- and 4-acetylpyridine, which were converted to the alcohol in 84 and 81% ee, respectively. Noyori has previously reported ee's as high as 99% for the asymmetric hydrogenation of heteroaromatic ketones

Table 2. Asymmetric Hydrogenation of Ketones Using *trans*-[$RuCl_2$(diphosphine)(diamine)] (3) Precatalysts Based on (*S*,*S*)-1 and *rac*-1[a]



			diphosphine			
			(*S*,*S*)-**1**		*rac*-**1**	
entry	diamine	Ar or ketone	ee (%)[b]	conversn (%)[c]	ee (%)[b]	conversn (%)[c]
1	(*R*,*R*)-DPEN	Ph	90 (*S*)	>99	86 (*S*)	>99
2	(*R*,*R*)-DACH	Ph	84 (*S*)	>99	76 (*S*)	>99
3	(*R*,*R*)-DPEN	1-naphthyl	90 (*S*)	>99	88 (*S*)	97
4	(*R*,*R*)-DACH	1-naphthyl	85 (*S*)	99	77 (*S*)	97
5	(*R*,*R*)-DPEN	*p*-ClC_6H_4	85 (*S*)	98	80 (*S*)	>99
6	(*R*,*R*)-DACH	*p*-ClC_6H_4	83 (*S*)	92	72 (*S*)	96
7	(*R*,*R*)-DPEN	*o*-ClC_6H_4	92 (*S*)	99	88 (*S*)	96
8	(*R*,*R*)-DACH	*o*-ClC_6H_4	88 (*S*)	94	75 (*S*)	94
9	(*R*,*R*)-DPEN	*o*-BrC_6H_4	94 (*S*)	99	89 (*S*)	99
10	(*R*,*R*)-DACH	*o*-BrC_6H_4	90 (*S*)	99	80 (*S*)	99
11	(*R*,*R*)-DPEN	*p*-$CH_3C_6H_4$	88 (*S*)	99	85 (*S*)	99
12	(*R*,*R*)-DACH	*p*-$CH_3C_6H_4$	85 (*S*)	99	73 (*S*)	97
13	(*R*,*R*)-DPEN	*p*-$CH_3OC_6H_4$	88 (*S*)	>99	79 (*S*)	>99
14	(*R*,*R*)-DACH	*p*-$CH_3OC_6H_4$	85 (*S*)	>99	73 (*S*)	>99
15	(*R*,*R*)-DPEN	propiophenone	89 (*S*)	99	85 (*S*)	99
16	(*R*,*R*)-DACH	propiophenone	83 (*S*)	98	60 (*S*)	98
17	(*R*,*R*)-DPEN	isobutyrophenone	28 (*S*)	89	29 (*S*)	90
18	(*R*,*R*)-DACH	isobutyrophenone	16 (*S*)	87	15 (*S*)	90
19	(*R*,*R*)-DPEN	2-thienyl	94 (*S*)	94	90 (*S*)	>99
20	(*R*,*R*)-DACH	2-thienyl	86 (*S*)	94	76 (*S*)	95
21	(*R*,*R*)-DPEN	3-pyridyl	84 (*S*)	99	75 (*S*)	98
22	(*R*,*R*)-DACH	3-pyridyl	82 (*S*)	97	50 (*S*)	99
23	(*R*,*R*)-DPEN	4-pyridyl	81 (*S*)	99	65 (*S*)	99
24	(*R*,*R*)-DACH	4-pyridyl	80 (*S*)	96	55 (*S*)	97
25	(*R*,*R*)-DPEN	2-furyl	92 (*S*)	99	84 (*S*)	99
26	(*R*,*R*)-DACH	2-furyl	86 (*S*)	96	73 (*S*)	97

[a] Reactions were conducted in 2-propanol with $S/C = 1000/1$ unless otherwise noted, with added t-BuOK at 20−22 °C and 10 atm of H_2 pressure for 12 h. [b] The ee's were determined by chiral GC, and the absolute configurations were determined by comparison of the sign of the optical rotation or retention time with literature data. [c] Determined by GC or ^1H NMR. Average of three runs.

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using a catalyst based on (*R*)-xylylBINAP and (*R*)-DAIPEN, now widely accepted as the optimum system for a range of substrates.[15]

On the basis of the impressive enantioselectivities reported for the hydrogenation of aryl/methyl ketones with a catalyst generated from a 1:1 mixture of diastereoisomeric [$RuCl_2$(*rac*-tolBINAP){(*S*,*S*)-DPEN)}],[5] we next examined the efficacy of the corresponding catalysts based on *rac*-**1** for asymmetric hydrogenation of the same series of substrates, full details of which are presented in the last two columns of Table 2. Gratifyingly, for the majority of substrates examined, the ee's were only marginally lower than those obtained with enantiopure (*S*,*S*)-**1** and showed a similar trend in enantioselectivity across the range of substrates. Moreover, as for (*S*,*S*)-**1**, the catalyst based on *rac*-**1**/(*R*,*R*)-DPEN consistently outperformed its (*R*,*R*)-DACH counterpart.

Finally, in a comparative study with acetophenone as substrate, the performance of the catalyst generated from the cis precatalyst **4** matched that of its trans counterpart. For example, asymmetric hydrogenation of acetophenone with the catalyst generated from *cis*-[$RuCl_2${(*S*,*S*)-**1**}{(*R*,*R*)-DPEN}] gave 1-phenylethanol in 89% ee, while the catalyst generated from *cis*-[$RuCl_2$(*rac*-**1**){(*R*,*R*)-DPEN}] and *cis*-[$RuCl_2${(*S*,*S*)-**1**}/{(*S*,*S*)-DPEN}] gave ee's of 85 and 15%, respectively. Not surprisingly, the catalyst generated from a mixture of trans and cis isomers gave the same ee's as those obtained with the pure isomer.

In conclusion, ruthenium(II) complexes of inexpensive and easy-to-prepare racemic and enantiopure diphosphines based on a 1,2-bis(dimethyl)cyclohexyl tether form highly efficient and selective catalysts for the asymmetric hydrogenation of a range of ketones, giving ee's and conversions that rival or exceed those obtained with BINAP. The performance of these catalysts is quite surprising, since enantioselectivities obtained with diphosphines which form conformationally flexible seven-membered chelate rings are often significantly lower than those obtained with catalysts based on biaryl diphosphines. Interestingly, while the *trans*-dichloride precatalyst undergoes a quantitative isomerization to afford a cis arrangement of chlorides, catalysts generated from both isomers gave similar levels of stereocontrol. Once optimized, these catalysts could prove to be practical alternatives to more expensive enantiopure systems for the asymmetric hydrogenation of ketones and/or C−C and C−heteroatom bond formation via bifunctional transition-metal-based catalysis.[16]

Experimental Section

General Experimental Procedure for the Asymmetric Hydrogenation of Acetophenone. A flame-dried Schlenk flask was charged with propan-2-ol (10 mL), acetophenone (0.206 g, 1.72 mmol), and catalyst (0.00172 mmol) and the resulting mixture degassed by three successive freeze−thaw cycles. A solution of *t*-BuOK in propan-2-ol (0.026 mL, 0.0258 mmol, 1 M solution) was added and the resulting solution transferred to a 50 mL Parr stainless steel benchtop reactor. The vessel was pressurized to 10 atm with hydrogen and left to stand for 10 s before releasing the gas though an outlet valve. After this sequence was repeated six times, the reactor was pressurized to ca. 10 atm and the solution stirred vigorously at 20−22 °C for 16 h. The pressure was released, and the resulting mixture was filtered through a short silica plug, diluted with diethyl ether, and analyzed by chiral GC (Supelco Beta DEX column, 0.25 mm i.d. × 25 m, injection temperature 200 °C, column conditions 35 °C for 5 min, ramp to 115 °C at 5 °C/min, hold for 20 min, ramp to 170 °C at 5 °C/min, hold for 10 min, pressure 18.9 psi): t_R of *R* enantiomer, 26.1 min; t_R of *S* enantiomer, 27.2 min.

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Supporting Information Available: Text and figures giving experimental procedures and characterization data for all compounds and GC analysis of the reduction products and a CIF file giving crystal data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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