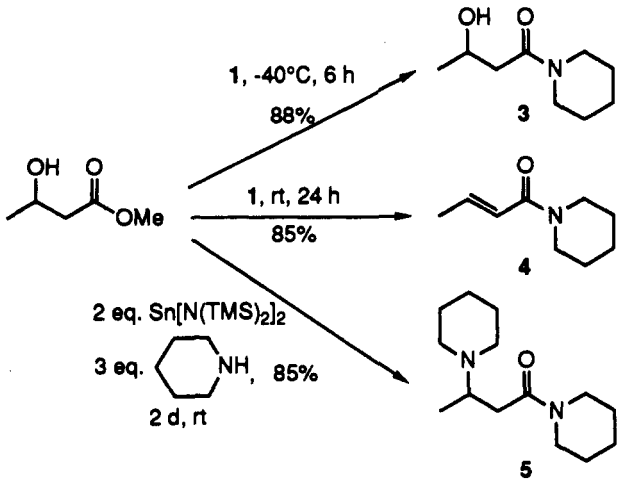
Scheme I



ferent products can be selectively prepared in high yield under judiciously chosen reaction conditions (Scheme I). Reaction of mixed tin(II) amide 1 with methyl 3-hydroxybutanoate at −40 °C yielded β-hydroxy amide 3, whereas reaction at room temperature gave α,β-unsaturated amide 4. Finally, reaction of the β-hydroxy ester with 2 equiv of $Sn[N(TMS)_2]_2$ and 3 equiv of piperidine for an extended period of time at room temperature produced β-amino amide 5.

Lastly, we found that β-keto esters could be converted to the corresponding β-keto amides, with no addition to the ketone being observed. Presumably, this is due to initial enolization of the ketone by $Sn[N(TMS)_2]_2$, to give a tin(II) alkoxy amide intermediate. As with α- and β-hydroxy esters, subsequent addition of an aliphatic amine is thought to form a new tin(II) alkoxy amide, followed by intramolecular transfer of the amino group.

Acknowledgment. We wish to thank the National Institutes of Health (GM42732) for support of this research.

Supplementary Material Available: General procedures and compound characterization data (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Enantioselective Metal Carbene Transformations with Polyethylene-Bound Soluble Recoverable Dirhodium(II) 2-Pyrrolidone-5(*S*)-carboxylates

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Summary: Ligand displacement of methyl 2-pyrrolidone-5(*S*)-carboxylate (5(*S*)-MEPYH) from Rh_2(5(*S*)-MEPY)$_4$ by a soluble polyethylene-bound 2-pyrrolidone-5(*S*)-carboxylate produced a recoverable dirhodium(II) catalyst whose effectiveness was demonstrated by high enantioselection for intramolecular cyclopropanation of 3-methyl-2-buten-1-yl diazoacetate (98% ee) and intramolecular C–H insertion of 2-methoxyethyl diazoacetate (72% ee) as well as by catalyst recovery and reuse seven times.

Dirhodium(II) carboxamides possessing chiral 2-pyrrolidone-5-carboxylate ligands are attractive catalysts for highly enantioselective metal carbene transformations.[1] Their applications extend from intermolecular cyclopropanation[2] and cyclopropenation[3] reactions to intramolecular cyclopropanation[4] and carbon–hydrogen insertion[5] reactions, and enantiomeric excesses greater than 90% have been realized. Constructed with four enantiomerically pure methyl 2-pyrrolidone-5-carboxylate (MEPYH) ligands so that each rhodium possesses two adjacent Rh–N bonds, Rh_2(5(*S*)-MEPY)$_4$ and its enantiomeric form, Rh_2(5(*R*)-MEPY)$_4$, are prepared by ligand displacement of acetate from $Rh_2(OAc)_4$ in refluxing chlorobenzene.[6] Normally used in amounts of 0.5–1.0 mol %, these catalysts are rarely recovered from experimental small-scale reactions, and there has as yet been no reliable estimate of their reuse and turnover potentials.

The recent development of anionic polyethylene carboxylates for attachment of dirhodium(II), and the successful demonstration that rhodium(II) carboxylates of terminally functionalized polyethylene carboxylic acids are effective and reusable cyclopropanation catalysts,[7] prompted our joint inquiry into the development of similarly reusable dirhodium(II) catalysts that possess chiral ligands. Consequently, polyethylene oligomers with M_n of 1500–2000 were prepared by anionic oligomerization of ethylene, carboxylated with carbon dioxide at −78 °C,[8] reduced by $Me_2S{\cdot}BH_3$ in toluene at 110 °C, and then esterified with 2-pyrrolidone-5(*S*)-carboxylic acid (eq 1). The oligomer-bound dirhodium(II) 2-pyrrolidone-5(*S*)-

(1) Doyle, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305.
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(3) Protopopova, M. N.; Doyle, M. P.; Müller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755.
(4) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423.
(5) Doyle, M. P.; van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982.
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(7) Bergbreiter, D. E.; Morvant, M.; Chen, B. *Tetrahedron Lett.* **1991**, *32*, 2731.
(8) Bergbreiter, D. E.; Blanton, J. R.; Chandran, R.; Hein, M. D.; Huang, K.-J.; Treadwell, D. R.; Walker, S. A. *J. Polym. Sci., Part A, Polym. Chem.* **1989**, *27*, 4205.

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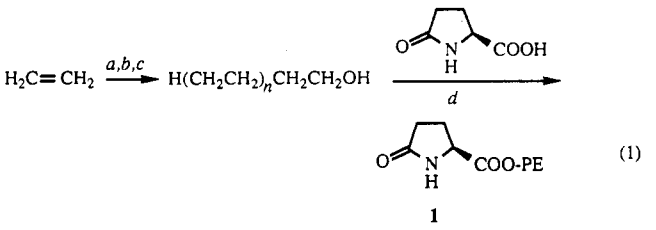
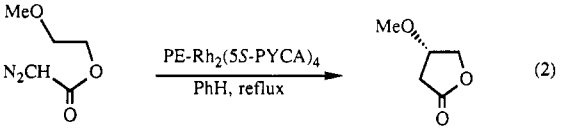


(1)

1

carboxylate catalysts, PE-Rh_2(5(*S*)-PYCA)$_4$, was prepared by ligand exchange of Rh_2(5(*S*)-MEPY)$_4$ with 1 in refluxing toluene. In this way, 25 mg (0.032 mmol) of Rh_2(5(*S*)-MEPY)$_4$ in 5 mL of ethanol was combined with 213 mg of 1 in 20 mL of toluene. After removal of ethanol by distillation, the toluene solution was refluxed for 4–6 h. The solution was then cooled, the treated polymer was filtered, and this residue was washed 5–7 times with hot ethanol (10 mL) to remove any unbound Rh_2(5(*S*)-MEPY)$_4$. The bright violet residue (200 mg) was dried in a vacuum oven (40 °C, 0.2 Torr) for 6 h before use.

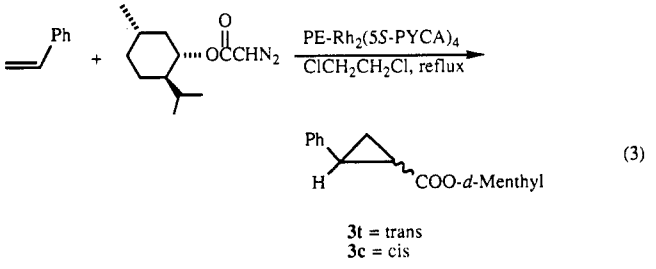
Initial uses of PE-Rh_2(PYCA)$_4$ were disappointing. For C–H insertion of the carbene derived from 2-methoxyethyl diazoacetate (eq 2), PE-Rh_2(5(*S*)-PYCA)$_4$ at 1.0 mol % in



(2)

2

refluxing benzene was a poorer catalyst (47% yield, 69% ee) than 1.0 mol % of Rh_2(5(*S*)-MEPY)$_4$ in refluxing CH_2Cl_2 (62% yield, 91% ee).[5] Reuse of the oligomer-bound catalyst[9] in four subsequent runs led to decreasing yields (51 → 22%) and enantioselection (65 → 24%). Styrene cyclopropanation with menthyl-*d* diazoacetate (eq 3) likewise proceeded with variable decreasing yields (79



(3)

3t = trans
3c = cis

→ 37% from runs 2 → 4) and diastereoselection (50 → 9% for **3t** from runs 1 → 4; 54 → 18% for **3c** from runs 1 → 4).[10]

Assuming that the cause of these decreases in yield and selectivity was due to the displacement of chiral ligand from the oligomer-bound catalyst, methyl 2-pyrrolidone-5(*S*)-carboxylate (5(*S*)-MEPYH) in an amount equal to 2.4–2.7 mol % of the diazo compound employed was added to the reaction solution with the catalyst, and the reaction sequence was repeated. Results from the C–H insertion reaction sequence with 2-methoxyethyl diazoacetate (eq 2) are shown in Figure 1. Reported product yields are those following distillation on a 0.5 mmol scale; enantiomeric excesses were obtained from capillary GC analyses with base-line separation on a γ-cyclodextrin–TFA column. The reaction sequence was terminated with the eighth run

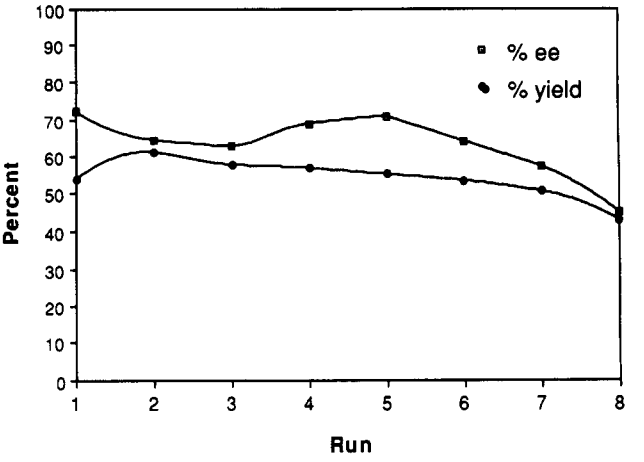
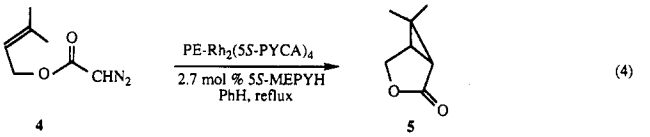


Figure 1. Enantiomeric excess and yields for 4-methoxydihydro-2(3*H*)-furanone (2) from the sequential use of recovered PE-Rh_2(5(*S*)-PYCA)$_4$ in the presence of 2.5–2.8 mol % 5(*S*)-MEPYH for the decomposition of 2-methoxyethyl diazoacetate in refluxing benzene.

when the tube containing the reaction mixture broke in the centrifuge.

A similar sequence of recations was performed with 3-methyl-2-buten-1-yl diazoacetate (4) for which intramolecular cyclopropanation (eq 4) was previously reported to occur with 92% ee.[11] Beginning with 100 mg of PE-



(4)

4 5

Rh_2(5(*S*)-PYCA)$_4$ and 1.8 mol % of 5(*S*)-MEPYH, 1.5 mmol scale reactions of **4** in refluxing benzene afforded (1*R*,5*S*)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (**5**) in 98% ee (58% yield following distillation). This exceptionally high level of enantioselection was maintained with the same catalyst in run 2 (98% ee) but fell off to 83% ee in run 3 and slowly degraded to 61% ee by run 7.[12] Isolated yields following distillation were 55 ± 3% throughout. Enantiomeric excesses were obtained by capillary GC analyses with base-line separation on a β-cyclodextrin–PH (permethylated hydroxypropyl) column.

Intermolecular cyclopropanation of styrene with menthyl-*d* diazoacetate in refluxing benzene (eq 3), performed in the same manner as with the previous examples, also provided considerable improvement through five runs. Diastereomeric excesses from the first to fifth run were 53 → 27% (trans isomer) and 59 → 41% (cis isomer) with the major decrease in % de (46 → 33 for **3t** and 54 → 46 for **3c**) occurring after run 2. The trans/cis product ratio remained at 1.7 ± 0.1 after run 2 (**3t**/**3c** = 2.1 for runs 1 and 2).

The viability of dirhodium(II) catalysts for highly enantioselective metal carbene reactions is clearly demonstrated by these results. With mechanical losses in the oligomer-bound catalyst of about 7 mg per run in these 100-mg small-scale reactions, the amount of catalyst actually employed decreases from 1.0 mol % in the first run to about 0.5% for the fifth run. When only 2–3 mol % of 5(*S*)-MEPYH was added to the reaction solution, the effectiveness of the catalyst for highly enantioselective

(9) PE-Rh_2(5(*S*)-PYCA)$_4$ precipitates upon cooling. After centrifugation, the reaction mixture was decanted from the catalyst, and the catalyst was washed twice with 2–3-mL portions of benzene.

(10) In refluxing dichloromethane with 1.0 mol % Rh_2(5(*S*)-MEPY)$_4$, **3** was obtained in 74% yield with 31% de for **3a** and 88% de for **3b** in a ratio, **3a**/**3b**, of 1.3.

(11) Although the reported (ref 4) % ee for **5** is 92%, with purified ligand and refinements in catalyst preparation 98.6% ee was achieved in refluxing dichloromethane using Rh_2(5(*S*)-MEPY)$_4$.

(12) With Rh_2(5(*S*)-MEPY)$_4$ (1.0 mol %) in refluxing benzene, **5** was formed in 83% isolated yield with 77% ee.

transformations was not markedly diminished, and the catalyst could still be recovered and reused seven times. Further optimization can be expected.

Although lower enantioselectivities result from C–H insertion reactions of 2-methoxyethyl diazoacetate in refluxing benzene with PE-Rh_2(5(*S*)-PYCA)$_4$ than in refluxing dichloromethane with Rh_2(5(*S*)-MEPY)$_4$, the same is not true for the intramolecular cyclopropanation of 3-methyl-2-buten-1-yl diazoacetate. The maintenance of such high enantioselectivity in this latter case demonstrates that carbene dissociation from dirhodium(II) does not take place at the elevated temperatures used in this study.

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Remote Asymmetric Induction Based on Carbonyl–Ene Reactions with Bishomoallylic Silyl Ethers: Dramatic Changeover of Regioselectivity by the Remarkable Siloxy Effect

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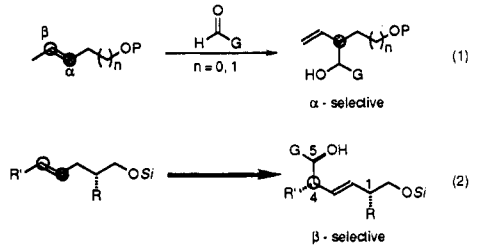
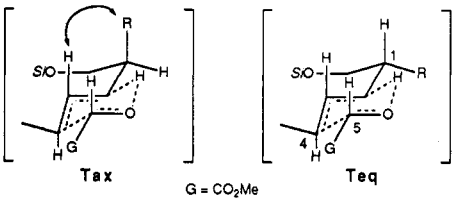
Summary: A new approach to remote asymmetric induction is described for not only a 1,4- but also a 1,5-relationship, which is based on the carbonyl–ene reactions with chiral bishomoallylic silyl ethers. Silyl ethers, rather than alkyl ethers, exhibit β-regiospecificity. Remarkably high levels of remote asymmetric induction can then be established with chiral bishomoallylic ethers to provide eventually a simple and efficient method for asymmetric induction.

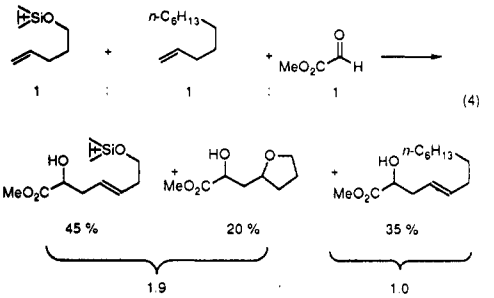
A number of methods have been devised for generating adjacent stereogenic centers (1,2-relationships) in an acyclic system with a high level of relative asymmetric induction.[1,2] However, approaches to control remote relationships by efficient relative 1,>3-asymmetric induction are rare,[3] and hence remote stereocontrol has been a challenging problem in organic synthesis. We report here a unique approach to not only 1,4- but also 1,5-remote asymmetric induction by carbonyl–ene reactions with chiral bishomoallylic silyl ethers (eq 2) which show the dramatic changeover of regioselectivity from (homo)allylic ethers (eq 1).[4]



The glyoxylate–ene reactions with (*E*)-4-hexenyl ethers **1a** were found to provide selectively the β-regioisomers **3a** (eq 3), in sharp contrast to the α-regioselectivity observed with (homo)allylic ethers[4] (Table I). Benzyl, methyl, and acetyl groups gave, however, a low level of regioselectivity (entries 1–3). Surprisingly,[3] silyl ethers led specifically to the β-regioisomer (entries 4–7). Sterically-demanding silyl groups such as *tert*-butyldiphenylsilyl were the best choice, giving the β-ene product regioselectively in good yield with exclusive *E*- and anti-selectivity (entry 7).[5] Thus, the dramatic changeover of regioselectivity implies the O-5 orbital interaction by the siloxy groups to increase the olefinic reactivity regiospecifically at the β-carbon via the folded conformation (T: R = H).[6] In fact, 4-pentenyl silyl



ether was twice as reactive as 1-undecene without siloxy group in the Lewis acid-promoted reaction (eq 4).



In view of the cyclic model, 1,4-remote stereocontrol is highly predictable. In the reaction of a chiral (*E*)-bishomoallylic ether (T: R≠H), the axial conformer T_{ax}

(1) Reviews: (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(2) For the definition of internal or relative asymmetric induction, see ref 1b.

(3) Chelation control has been, so far, of singular importance for predictable remote stereocontrol. For leading recent references, see: Molander, G. A.; Haar, J. P., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 3608. Molander has, however, proposed the neighboring-group participation in the stereocontrol of 1,4-diols. In his case, alkoxy groups such as methoxy and benzyloxy provide the higher level of diastereoselectivity than that obtained with siloxy groups to lead to 1:1 diastereomeric mixtures.

(4) (a) Mikami, K.; Shimizu, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 2952. (b) Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 464.

(5) For the physical data of ene products, see the supplementary material.

(6) Simple neighboring-group participation seems to be unlikely as a controlling element in view of the low regio- and diastereoselectivity with methoxy and benzyloxy groups. Another possibility was suggested by the reviewers: "alkoxy substituents might be less influential in controlling regio- and stereochemistry because they were complexed more effectively with the Lewis acid."

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