Catalytic Asymmetric C–C Bond Formation: Asymmetric Synthesis of *cis*-Decalin Derivatives by Palladium-Catalyzed Cyclization of Prochiral Alkenyl Iodides

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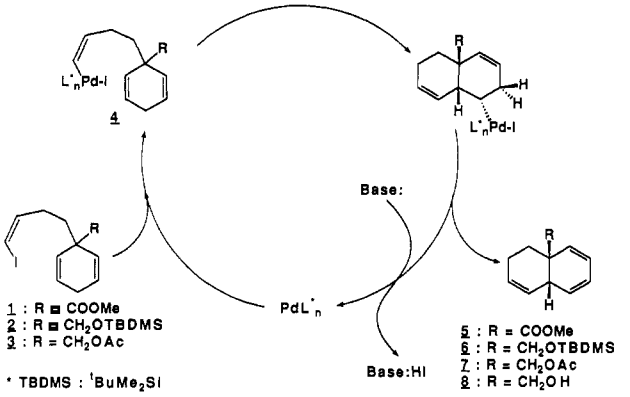
Summary: A catalytic asymmetric synthesis by the use of a Heck-type reaction has been realized for the first time, giving the *cis*-decalin derivative **5** in up to 46% ee.

Sir: The synthesis of optically active compounds is an extremely important undertaking and a formidable challenge to the synthetic chemist, because enantiomer recognition plays an important role in biological activity. Of the various ways to induce enantioselectivity in chemical reactions, the most efficient is by means of a chiral catalyst, where a small amount of chiral material can transmit chirality information to a large amount of substrate. Although a lot of successful studies on catalytic asymmetric epoxidation,[1] hydrogenation,[2] and their synthetic application have been reported, there are only a few excellent catalytic asymmetric C–C bond-forming reactions.[3] Here we report the first example of a catalytic asymmetric synthesis via Heck-type reaction,[4] giving the *cis*-decalin derivative **5** having a chiral quarternary carbon in up to 46% ee. This *cis*-decalin derivative should be a useful chiral building block for the synthesis of many biologically active substances.[5] Our basic strategy involves enantiotopic group selective ring closure of the prochiral monocyclic compounds **1**, **2**, and **3** catalyzed by palladium catalyst with chiral ligand as shown in Scheme I. No definite mechanistic information on the Heck reaction, concerning whether or not partial dissociation of ligands occurs at the stage of olefin coordination to an alkenylpalladium iodide, is available. Therefore, application of Heck reaction to a catalytic asymmetric synthesis is a quite challenging research field.

First of all, we examined the Heck-type reaction[7] of the alkenyl iodide **1**, easily prepared as shown in Scheme II. With the aim of application to asymmetric synthesis, the reaction utilizing $Pd(OAc)_2$ as a catalyst and (diphenylphosphino)ethane (DIPHOS) as a ligand was carefully investigated. When *N*,*N*-diisopropylethylamine or sodium acetate was used as a base, the reactions were very slow in all the solvents examined even at 100 °C, providing the cyclized product as a mixture of some regio- and/or stereoisomers in low yields. On the other hand, the use of Ag_2CO_3 according to Overman's procedure[7d,f] afforded the cyclized product **5** in 68% yield as a single isomer (60 °C,

Scheme I



Scheme II

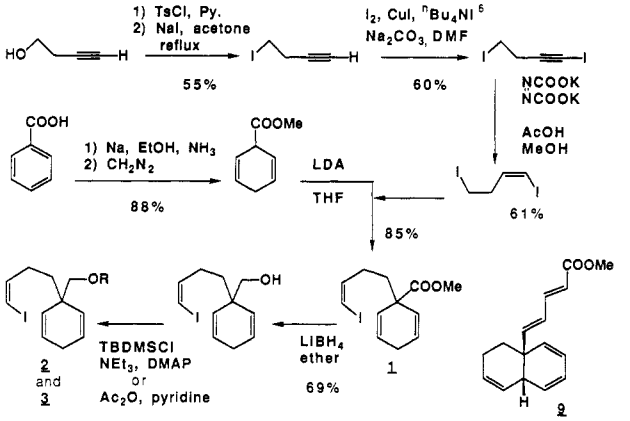
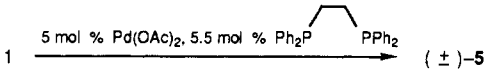


Table I. Synthesis of (±)-5 by $Pd(OAc)_2$ and (Diphenylphosphino)ethane (DIPHOS)



run	base	solvent	temp, °C	time, h	recov S.M.,[d] %	yield, %
1	$^{i}Pr_2EtN$	DMF	70–100	164	56	16[a]
2	$^{i}Pr_2EtN$	THF	reflux	65	66	16[a]
3	$^{i}Pr_2EtN$	CH_3CN	reflux	117	62	11[a]
4	$^{i}Pr_2EtN$	toluene	100	66	45	37[a]
5	AcONa	toluene	100	94	34	12[a,b]
6	Ag_2CO_3	CH_3CN	60	5	3	68[c]

[a] Obtained as a mixture of some regio- and/or stereoisomers (based on ^{1}NMR). [b] Methyl benzoate was formed in 45% yield. [c] (±)-**5** was obtained as a single isomer. [d] S.M. = starting material.

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Table II. Catalytic Asymmetric Synthesis of the *cis*-Decalin Derivatives 5, 6, and 7 Using (*R*)-BINAP in 1-Methyl-2-pyrrolidinone[a]

run	substr	temp, °C	time, h	yield, %	$[\alpha]_D$ ($CHCl_3$), deg	ee, %
1[b]	1	60	12	54	+116	33
2[c]	1	60	37.5	74	+167	46
3[c]	2	40	44	70	+152	44
4[c]	3	40	88	66	+131	36

[a] 1-Methyl-2-pyrrolidinone (10 mL) was utilized for the substrate (1 mmol). [b] The alkenyl iodide was treated with $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (5.5 mol %), and Ag_2CO_3 (2 molar equiv) in 1-methyl-2-pyrrolidinone. [c] The $LnPd^0$ catalyst (3 mol %) was first generated in situ by reaction of $Pd(OAc)_2$ with 2 molar equiv of cyclohexene and 3 molar equiv of (*R*)-BINAP per Pd in the presence of Ag_2CO_3 (2 molar equiv) (1-methyl-2-pyrrolidinone solvent, 60 °C, 3 h), and then the alkenyl iodide was added.

5 h) (Table I). The structure of **5** was unequivocally determined from the ^{1}NMR spectrum (NOE) of the silyl ether **6** derived from **5** via a two-step sequence of reactions (i. $LiAlH_4$ in ether, ii. TBDMSCl and imidazole in DMF). Formation of the *cis*-decalin derivative **5** is well explained as follows. Oxidative addition of **1** to Pd(0) gives the alkenylpalladium iodide **4** and subsequent cyclization from the same face as an alkenyl side chain followed by syn-β-hydrogen elimination affords **5**.

Having established an intramolecular Heck-type reaction yielding the *cis*-decalin derivative **5** in a stereo- and regiocontrolled manner, we next turned our attention to application to a catalytic asymmetric synthesis utilizing the alkenyl iodide **1**, $Pd(OAc)_2$, and optically active bidentate ligands in the presence of Ag_2CO_3. In the first place, a catalytic asymmetric synthesis utilizing either (*S*,*R*)-BPPFA[8] or (*S*,*S*)-BPPM[8] as a chiral ligand was investigated under the various reaction conditions, giving only low enantiomeric excess, respectively (e.g. (*S*,*R*)-BPPFA in DMF → 3%, (*S*,*S*)-BPPM in DMF → 1%). However, we were pleased to find that the use of (*R*)-BINAP[8] in DMF resulted in the formation of (+)-**5** in 19% ee (69% yield). Encouraged by this interesting result, solvent effects were carefully examined to give 8% ee (CH_3CN), 1% ee (DMSO), 2% ee (THF), 20% ee (HMPA), 19% ee (1,1,3,3-tetramethylurea), and 23% ee (*N*,*N*'-(dimethylpropylene)urea), and finally we have found that the use of 1-methyl-2-pyrrolidinone gives 33% ee[9] (Table II). The various reaction conditions were further investigated in order to obtain higher ee, giving the highest ee as follows. The $LnPd^0$ catalyst (3 mol %) was generated in situ by reaction of $Pd(OAc)_2$ with 2 molar equiv of cyclohexene and 3 molar equiv of (*R*)-BINAP per Pd in the presence of Ag_2CO_3 (1-methyl-2-pyrrolidinone solvent, 60 °C, 3 h). Addition of the alkenyl iodide **1** in 1-methyl-2-pyrrolidinone and heating at 60 °C for 37.5 h afforded the cyclized product **5** in 46% ee (74%). Likewise, the alkenyl iodides **2** and **3** were also transformed into the optically active *cis*-decalin derivatives **6** and **7** in the range of 36–44% ee as shown in Table II. The enantiomeric excess (ee) was unequivocally determined by the HPLC analysis (DAICEL CHIRACEL OJ, hexane–2-propanol, 9:1) of **8** obtainable from either **5**, **6**, or **7**,[10] and assignment of the absolute configuration was achieved by application of the CD exiton chirality method to **9**.[11,12]

In conclusion, a catalytic asymmetric synthesis utilizing a Heck-type reaction has been realized for the first time. Although the enantioselectivity is still not excellent, the present result paves the way for further improvements. Further studies along this line are in progress.

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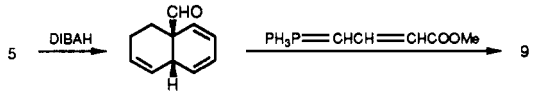
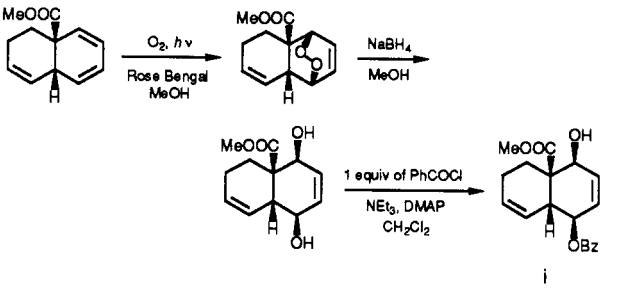
(9) Under the same reaction conditions, the use of 3 molar equiv of (*R*)-BINAP did not improve the enantiomeric excess.

(10) The cyclized products **5** and **7** were converted to **8** by treatment with $LiAlH_4$ in ether at 0 °C, while **6** was transformed into **8** on exposure to HF in aqueous CH_3CN at −30 °C.

(11) The conjugated ester **9** was synthesized as follows.



(12) The cyclized product **5** has been already converted to the highly functionalized compound i as shown below.



Preparation of Activated Imines and Their Condensation with Allylstannanes: Stereoselective Synthesis of 1,2-Amino Alcohols

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Summary: A modified Wadsworth–Emmons reaction affords hitherto inaccessible imines derived from aliphatic aldehydes and aromatic amines. Such highly activated imines condense rapidly and stereoselectively with oxygenated allylstannanes, at −78° C, under the influence of BF_3OEt_2. Analogous reactions may be induced with activated imines derived from aromatic aldehydes. A stereoselective preparation of *erythro* 1,2-amino alcohols has been developed based on the new chemistry.

Sir: We recently became interested in the synthesis of 1,2-amino alcohols[1] via Lewis acid promoted condensation

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