Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1835–1841

TETRAHEDRON: *ASYMMETRY*

Transition metal-catalyzed asymmetric cycloaddition reactions of a chiral (β-sulfinyl)vinylcyclopropane derivative: asymmetric synthesis of a cyclopentane derivative using a chiral sulfinyl functionality as the chiral source

Kunio Hiroi* and Akio Yamada

Department of Synthetic Organic Chemistry, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981-8558, Japan

Received 6 March 2000; accepted 27 March 2000

Abstract

Asymmetric synthesis of a cyclopentane derivative using a chiral sulfinyl functionality as the chiral source has been successfully executed by a transition metal-catalyzed asymmetric cycloaddition reaction of a chiral (β-sulfinyl)vinylcyclopropane derivative with acrylonitrile. The effects of the catalysts, ligands, and solvent were examined. The degree of the asymmetric induction and the chemical yield were highly dependent on the catalyst and, especially, the ligand used. A plausible mechanism of the asymmetric induction is proposed.

1. Introduction

Much attention has been devoted to organic synthesis with transition metal catalysts in recent years.[1] We have taken much interest in stereochemically advantageous synthetic reactions using the characteristics of transition metal catalysts, especially quite recently in asymmetric synthesis with these catalysts.[2] We have developed novel methodologies for asymmetric carbon–carbon bond formation using chiral allyl esters,[3] chiral enamines,[4] imines, and hydrazones bearing phosphine groups,[5] intramolecular metallo-type ene reactions of chiral allylic sulfones[6] and transition metal-catalyzed asymmetric vinylcyclopropane–cyclopentene rearrangements via chiral π-allyl transition metal complexes bearing chiral sulfinyl groups.[7] We have focused, furthermore, on the chemistry of chiral π-allyl transition metal complexes bearing a chiral sulfinyl functionality[8] originated from cyclopropane derivatives,[9] and the asymmetric induction via the chiral intermediary complexes.

* Corresponding author.

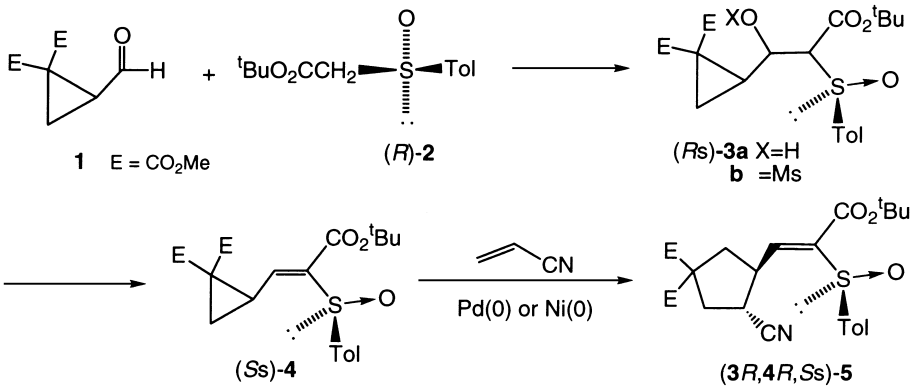
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00120-8

We wish to communicate herein the asymmetric synthesis of a cyclopentane derivative by transition metal-catalyzed asymmetric cycloaddition reaction of a chiral (β-sulfinyl)vinylcyclopropane derivative with an electrophilic olefin. Much attention has been paid to the synthesis of cyclopentane derivatives,[10] owing to the usefulness of the skeletons in organic synthesis and the inaccessibility of the structures. In particular, an asymmetric synthesis of cyclopentane compounds has received much attention; however, few reports have been published on [3+2] asymmetric cycloaddition reactions.[11]

2. Results and discussion

2.1. The transition metal-catalyzed asymmetric cycloaddition reactions

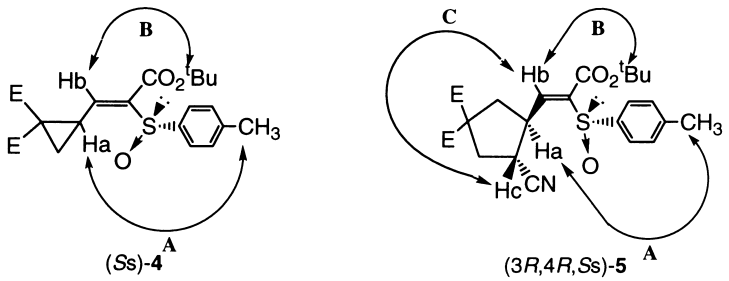
A model compound, chiral (β-sulfinyl)vinylcyclopropane derivative (*S*s)-**4**, was prepared by the addition of lithium ester enolate of *t*-butyl (*R*)-*p*-toluenesulfinylacetate **2** (treated with LDA) to aldehyde **1** (in THF at –78°C for 4 h) followed by the mesylation of the alcohol (*R*s)-**3a** (with MsCl–Et_3N in CH_2Cl_2 at 0°C for 1 h) and the dehydromesylation of the mesylate (*R*s)-**3b** (with DBU in THF at –20°C for 28 h). The asymmetric carbon center on the cyclopropane ring of (*S*s)-**4** obtained above was confirmed as racemic by HPLC analysis. The structure of (*S*s)-**4** was determined by the NMR spectral analysis with NOE measurements. The geometry of the olefin bond in **4** was confirmed as (*Z*)-configuration between the *p*-toluenesulfinyl group and the cyclopropane ring by the observation of strong NOE between the methyl in the tolyl group and the hydrogen (Ha) on the cyclopropane ring (A), and between the *t*-butyl group in the ester and the olefinic hydrogen (Hb) (B) in the NMR spectral analysis (Scheme 1).



Scheme 1.

The asymmetric cycloaddition reactions of (*S*s)-**4** with acrylonitrile were carried out under heating in THF, DME, CH_3CN, or DMSO in the presence of a palladium catalyst (0.1 equiv.) such as $Pd(PPh_3)_4$, $Pd(dba)_2$, or $Pd_2(dba)_3{\cdot}CHCl_3$, and a phosphine ligand (0.2 equiv.) such as PPh_3, bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), or 1,4-bis(diphenylphosphino)butane (dppb), to give stereoselectively an optically active cyclopentane derivative (3*R*,4*R*,*S*s)-**5** (Scheme 2). The results obtained are summarized in Table 1. The highest

chemical yield of the product (3*R*,4*R*,*S*s)-**5** was obtained on the use of $Pd(PPh_3)_4$ as the catalyst and PPh_3 as the ligand, whereas the use of other bidentate-phosphine ligands resulted in poor yields of (3*R*,4*R*,*S*s)-**5**. It should be noted that the degree of the asymmetric induction was especially dependent on the phosphine ligand used. Use of PPh_3 as a ligand with $Pd(PPh_3)_4$, $Pd(dba)_2$, or $Pd_2(dba)_3{\cdot}CHCl_3$ afforded rather enantiomeric excess (66, 70, and 56%, respectively) of the product (3*R*,4*R*,*S*s)-**5**. The nickel-catalyzed asymmetric cycloaddition of (*S*s)-**4** with acrylonitrile was carried out under heating in THF, DME, or CH_3CN in the presence of $Ni(COD)_2$ (0.1 equiv.) and PPh_3 (0.2 equiv.). The highest chemical yield and diastereoselectivity of (3*R*,4*R*,*S*s)-**5** were obtained under reflux in THF for 3 h in the $Ni(COD)_2$-catalyzed reaction, as shown in Table 2. The stereochemistry of the product obtained by the nickel-catalyzed reactions was the same as that by the palladium-catalyzed reactions. The diastereomeric excess (d.e.) of the product (3*R*,4*R*,*S*s)-**5** was determined by HPLC analysis.



Scheme 2.

Table 1
The palladium-catalyzed asymmetric cycloaddition reactions of (*S*s)-**4**[a]

Catalyst	Ligand	Solvent	Reaction temp. (°C)	Reaction time (h)	Yield (%) of (3*R*,4*R*,*S*s)-**5**	d.e. (%) of (3*R*,4*R*,*S*s)-**5**[b]
$Pd(PPh_3)_4$	PPh_3	THF	66	3	51	66
$Pd(PPh_3)_4$	PPh_3	DME	60	3	22	25
$Pd(PPh_3)_4$	PPh_3	CH_3CN	60	3	18	44
$Pd(PPh_3)_4$	PPh_3	DMSO	80	3	10	43
$Pd(PPh_3)_4$	dppm	THF	66	3	8	30
$Pd(PPh_3)_4$	dppe	THF	66	3	14	21
$Pd(PPh_3)_4$	dppb	THF	66	3	17	6
$Pd(dba)_2$	PPh_3	THF	66	3	12	70
$Pd(dba)_2$	PPh_3	CH_3CN	60	5	6	43
$Pd_2(dba)_3{\bullet}CHCl_3$	PPh_3	THF	66	4	11	56

a) The vinylcyclopropane derivative (*S*s)-**4** was treated with acrylonitrile (20 equiv.) in the presence of a catalyst (0.1 equiv.) and a ligand (0.2 equiv.).
b) The diastereomeric excess (d.e.) of (3R,4R,Ss)-**5** was determined by the HPLC analysis with CHIRALPAK AS.

The stereochemistry of the product **5** was confirmed by NMR spectral analysis with NOE measurements. The *trans* configuration between the olefinic group and the cyano group was assigned by the observation of a strong NOE (C) between the olefinic hydrogen (Hb) and

Table 2
The nickel-catalyzed asymmetric cycloaddition reactions of (*Ss*)-**4**[a]

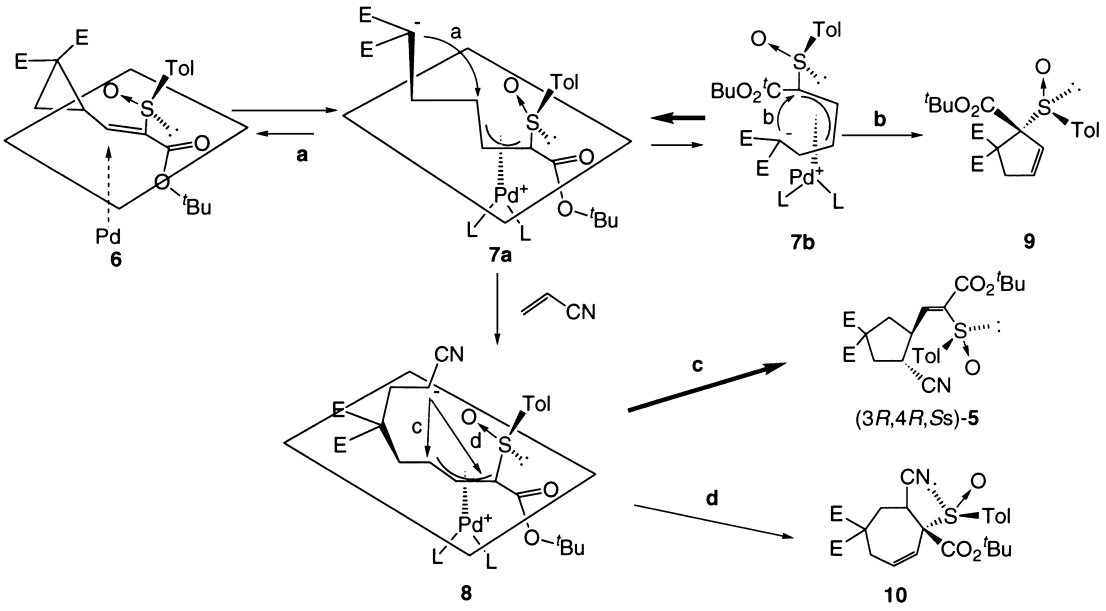
Solvent	Reaction temp. (°C)	Yield (%) of (3*R*,4*R*,*Ss*)-**5**	d.e. (%) of (3*R*,4*R*,*Ss*)-**5**[b]
THF	66	35	53
CH_3CN	60	5	33
DME	60	7	17

a) The vinylcyclopropane derivative (*Ss*)-**4** was treated with acrylonitrile (20 equiv.) for 3 h in the presence of $Ni(COD)_2$ (0.1 equiv.) and PPh_3 (0.2 equiv.).
b) The diastereomeric excess (d.e.) of (3R,4R,Ss)-**5** was determined by the HPLC analysis with CHIRALPAK AS.

the α-hydrogen (Hc) to the cyano group. The (*Z*)-configuration between the *p*-toluenesulfinyl group and the cyclopentyl group was confirmed by the observation of strong NOE between the methyl substituent in the *p*-toluenesulfinyl group and the hydrogen (Ha) on the cyclopentyl group (A), and between the *t*-butyl group in the ester and the olefinic hydrogen (Hb) (B). The absolute configuration of the product was deduced on the basis of the mechanism of the asymmetric induction mentioned below.

2.2. The mechanism of the asymmetric reaction

A possible mechanism of this asymmetric cycloaddition reaction is proposed as follows. It was confirmed by the HPLC analysis of the starting (*Ss*)-**4** recovered before completion of the reaction that the asymmetric carbon center on the cyclopropane ring of (*Ss*)-**4** used still remained racemic. This means that this asymmetric cyclization reaction would not result from kinetic resolution. Therefore, an intermediary π-allylpalladium complex would be formed by the effect of



Scheme 3.

the chiral sulfinyl goup, without steric control by the racemic carbon center. The palladium catalyst would react from the sterically less crowded downward direction on the same side as the sterically smallest lone pair side of the chiral sulfinyl group in the conformationally most stable conformer (as shown in **6**) having coplanarity between the olefinic bond and the sulfur–oxygen bond of the sulfinyl group,[12] affording a chiral π-allylpalladium complex **7** possessing a chiral sulfinyl group at the α site. The intermediary π-allylpalladium complex **7a** would be preferred to **7b** in the equilibrium of π-allyl intermediates due to the steric effect in **7b**. Therefore, the carbanion formed would undergo a conjugate addition to acrylonitrile in preference to the intramolecular substitution reaction via **7b** (giving **9**), to form **8**. The α carbanion to the cyano group would react from the back side of the palladium catalyst at the sterically less crowded γ site in the π-allylpalladium system via path c to afford (3*R*,4*R*,*S*s)-**5**. The reaction at the sterically crowded α site via path d (giving **10**) was not observed (Scheme 3).

Thus, this novel method is characterized by the transition metal-catalyzed asymmetric cycloaddition utilizing chiral sulfinyl groups as chiral sources, and is advantageous for the highly stereoselective asymmetric synthesis of cyclopentane derivatives.

3. Experimental

Infrared (IR) spectra were obtained in the indicated state with a JASCO DR-81 Fourier-transform IR spectrometer. NMR spectra were determined in the indicated solvent with a JEOL EX-270 (^{1}H NMR; 270 MHz) high-resolution NMR spectrometer; chemical shifts are given in ppm from tetramethylsilane as an internal standard. Splitting patterns are designated as s, singlet; m, multiplet. Mass spectra were taken on a JEOL JMS-DX 303/JMA-DA 5000 system. High performance liquid chromatography (HPLC) was performed with a Tosoh UV-8010 CCPM (column: Daicel Chiralpak AS, hexane:*i*-PrOH 1:20, 0.5 ml/min, 254 nm). Optical rotations were measured with a JASCO DIP-370 polarimeter. Thin layer or thick layer plates (preparative TLC) were made of Merck silica gel 60PF-254 activated by drying at 140°C for 3.5 h.

*3.1. Dimethyl (*Rs*)-2-[1-hydroxy-2-(*tert*-butoxycarbonyl)-2-(*p*-toluenesulfinyl)ethyl]cyclopropane-1,1-dicarboxylate **3a***

A solution of *tert*-butyl (*R*)-*p*-toluenesulfinylacetate **2** (500 mg, 1.97 mmol) in THF (5 ml) was added at –78°C to a solution of lithium diisopropylamide in THF (5 ml) [generated from diisopropylamine (238 mg, 2.36 mmol) and a 1.7N *n*-hexane solution of *n*-butyllithium (1.38 ml, 2.36 mmol)], and the solution was stirred for 1.5 h. Then, a solution of dimethyl 2-formylcyclopropane-1,1-dicarboxylate **1** (439 mg, 2.36 mmol) in THF (5 ml) was added to the above solution and the reaction mixture was stirred at –78°C for 4 h. The reaction solution was diluted with ether, then washed successively with a 10% aqueous HCl solution, an aqueous saturated $NaHCO_3$ solution and an aqueous saturated NaCl solution, and dried over anhydrous Na_2SO_4. The filtrate was evaporated in vacuo and the crude product was submitted to preparative TLC over silica gel (ether:*n*-hexane 8:1) to give (*R*s)-**3a** (869 mg, yield 70%). IR ν_{max}^{film} cm^{-1}: 3480 (OH), 1730 (ester), 1600 (aromatic), 1035 (SO). ^{1}H NMR (270 MHz) ($CDCl_3$) δ: 1.19–1.38 (m, 9H, $C(CH_3)_3$), 1.39–1.58 (m, 3H, CH_2 and OH), 1.62–1.69 (m, 1H, CH_2CH), 2.41 (s, 3H, $C_6H_4CH_3$), 3.30–3.55 (m, 2H, SCHCH), 3.65, 3.83 (s, s, 6H, $(CO_2CH_3)_2$), 7.25–7.62 (m, 4H, C_6H_4). *m*/*z*: 440 (M^+). Exact mass determination: 440.1422 (calcd $C_{21}H_{28}O_8S$: 440.1505).

3.2. Dimethyl (Ss)-2-[2-(tert-butoxycarbonyl)-2-(p-toluenesulfinyl)vinyl]cycloropane-1,1-dicarboxylate **4**

Methanesulfonyl chloride (0.07 ml, 0.92 mmol) was added at 0°C to a mixture of (*R*s)-**3a** (200 mg, 0.44 mmol) obtained above and triethylamine (0.19 ml, 1.36 mmol) in dichloromethane (10 ml), and the reaction mixture was stirred at 0°C for 1 h. The mixture was diluted with ether, filtered by Celite, and evaporated in vacuo. The crude mesylate (*R*s)-**3b** obtained was submitted to dehydromesylation. 1,8-Diazabicyclo[5.4.0]undecene-7 (208 mg, 1.36 mmol) was added at 0°C to a solution of (*R*s)-**3b** obtained above in THF (5 ml) and the reaction mixture was stirred at –20°C for 28 h. The reaction mixture was diluted with chloroform, then washed successively with a 10% aqueous HCl solution, an aqueous saturated $NaHCO_3$ solution and an aqueous saturated NaCl solution, and dried over anhydrous Na_2SO_4. The filtrate was evaporated in vacuo and the crude product was submitted to preparative TLC over silica gel (ether:*n*-hexane 5:1) to give (*S*s)-**4** (190 mg, yield 99%). $[\alpha]_D$ +231.4 ($c=1.8$, MeOH). IR ν_{max}^{film} cm^{-1}: 1730 (ester), 1630 (olefin), 1600 (aromatic), 1035 (SO). ^1H NMR (270 MHz) ($CDCl_3$): 1.35 (s, 9H, $C(CH_3)_3$), 1.39–1.58 (m, 2H, CH_2), 2.41 (s, 3H, $C_6H_4CH_3$), 2.61–2.74 (m, 1H, CH_2CH), 3.65, 3.83 (s, s, 6H, $(CO_2CH_3)_2$), 6.39–6.47 (m, 1H, C=CH), 7.25–7.62 (m, 4H, C_6H_4). *m*/*z*: 422 (M^+). Exact mass determination: 422.1095 (calcd $C_{21}H_{26}O_7S$: 422.1824).

3.3. Dimethyl (3R,4R,Ss)-3-cyano-4-[2-(tert-butoxycarbonyl)-2-(p-toluenesulfinyl)vinyl]cyclopentane-1,1-dicarboxylate **5**

3.3.1. A general procedure

A 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing tetrakis(triphenylphosphine)palladium (13.7 mg, 0.012 mmol) and triphenylphosphine (6.2 mg, 0.024 mmol), was flushed with nitrogen and maintained under a positive pressure of nitrogen, and then THF (1 ml) was added to the above flask. A solution of (*Ss*)-**4** (50 mg, 0.12 mmol) in THF (1 ml) and a solution of acrylonitrile (0.1 ml, 2.36 mmol) in THF (1 ml) were successively added to the above mixture. The reaction mixture was refluxed for 3 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The crude product was submitted to preparative TLC over silica gel (ether:*n*-hexane 8:1) to give (3*R*,4*R*,*Ss*)-**5** (29 mg, yield 51%). The results obtained under other reaction conditions using a palladium or nickel catalyst are summarized in Tables 1 and 2. (3*R*,4*R*,*Ss*)-**5**: $[\alpha]_D$ +100.0 ($c=0.6$, MeOH). IR ν_{max}^{film} cm^{-1}: 2249 (nitrile), 1735 (ester), 1635 (olefin), 1600 (aromatic), 1035 (SO). ^1H NMR (270 MHz) ($CDCl_3$): 1.33 (s, 9H, $C(CH_3)_3$), 1.40–1.58 (m, 4H, CH_2CCH_2), 1.88–1.98 (m, 2H, CHCHCN), 2.38 (s, 3H, $C_6H_4CH_3$), 3.77, 3.83 (s, s, 6H, $(CO_2CH_3)_2$), 6.41–6.50 (m, 1H, CH=C), 7.35–7.80 (m, 4H, C_6H_4). *m*/*z*: 475 (M^+). Exact mass determination: 475.1190 (calcd $C_{24}H_{29}NO_7S$: 475.1665).

References

1. Tsuji, J. *Tetrahedron* **1986**, *42*, 4361–4401.
2. Brunner, H. *Synthesis* **1988**, 645–654; Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257–276; Blystone, S. L. *ibid.* **1989**, *89*, 1663–1679; Sawamura, M.; Ito, Y. *ibid.* **1992**, *92*, 857–871.
3. Hiroi, K.; Abe, J.; Suya, K.; Sato, S.; Koyama, T. *J. Org. Chem.* **1994**, *95*, 203–213.
4. Hiroi, K.; Abe, J. *Tetrahedron Lett.* **1990**, *31*, 3623–3626.
5. Hiroi, K.; Haraguchi, M.; Masuda, Y.; Abe, J. *Chem. Lett.* **1992**, 2409–2412.

6. Hiroi, K.; Hirasawa, K. *Chem. Pharm. Bull.* **1994**, *42*, 1036–1040.
7. Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153–156.
8. Hiroi, K.; Onuma, H.; Arinaga, Y. *Chem. Lett.* **1995**, 1099–1100.
9. Hiroi, K.; Yoshida, Y.; Kaneko, Y. *Tetrahedron Lett.* **1999**, *40*, 3431–3434.
10. Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119.
11. Krohn, K. *Organic Synthesis Highlights*; VCH: Weinheim, 1991; pp. 96–104; Welker, M. E. *Chem. Rev.* **1992**, *92*, 97–112.
12. Marino, J. P.; Laborde, E. *J. Am. Chem. Soc.* **1988**, *110*, 966–968.