Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1495–1500

TETRAHEDRON: *ASYMMETRY*

Synthesis of planar chiral selenide derivatives of ferrocenyl-oxazoline and their application in enantioselective palladium catalyzed allylic substitution reaction

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Received 22 January 2000; accepted 22 February 2000

Abstract

A series of chiral selenide derivatives of ferrocenyl-oxazolines was synthesized and applied in a palladium catalyzed allylic reaction, with high enantioselectivity and moderate yield: the role of planar chirality in this reaction was also studied.

1. Introduction

Asymmetric catalysis plays a vital role in organic synthesis, in which the chiral ligand is a key point. How to design and develop efficient chiral ligands for transition metal catalyzed reactions has become one of the most intense areas of investigation. In the past few years, attention has been directed to non C_2-symmetric bidentate ligands, which have been successfully applied in various asymmetric catalyzed reactions. The bidentate ligands used usually contain nitrogen, oxygen, phosphine or sulfur functionalities.[1] Comparatively, little attention has been paid to selenium-containing ligands.[2]

In our previous work,[3] chiral thioether derivatives of ferrocenyl-oxazoline were synthesized and used in enantioselective palladium catalyzed allylic substitutions.[4] In a model reaction of 1,3-diphenylprop-2-enyl acetate with the nucleophile derived from dimethylmalonate, the highest ee of the product reached 98% when ligand **1** was used. We also synthesized ligand **2** containing only planar chirality to check the role of the planar chirality in this reaction. Selenium, which lies in the same group as sulfur in the periodic table, has similar coordination abilities as palladium. So we envisage that ligand **3** containing selenium and a similar skeleton to **1** should be successfully applied in the palladium catalyzed allylic substitution reaction. In this paper, we report the

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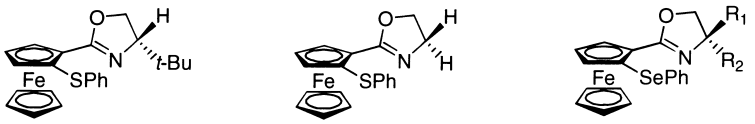
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00078-1

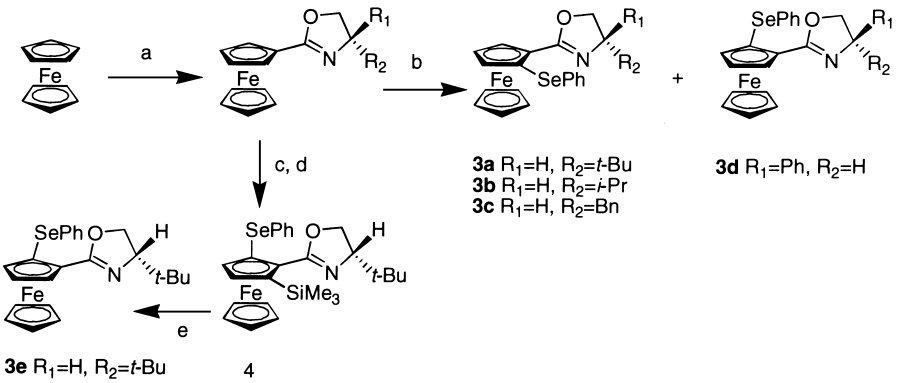
synthesis of selenide derivatives of ferrocenyl-oxazoline and their applications as chiral ligands in palladium catalyzed asymmetric allylic substitutions.



1 2 3

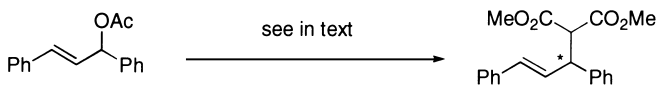
2. Results and discussion

By analogy to the chiral thioether derivatives of ferrocenyl-oxazoline, the chiral selenide derivatives of ferrocenyl-oxazoline were also synthesized. From commercially available ferrocene and enantiomerically pure aminoalcohol, ferrocenyl-oxazolines were prepared easily according to the literature protocols.[5,6] The ferrocenyl-oxazolines containing different R-substitutuents were treated with *n*-BuLi and an equimolar amount of TMEDA in Et_2O at –78°C for 2 h, the resulting mixture quenched with PhSeSePh, then usual work-up gave the products with diastereoselectivities of >95:5 determined by 300 ^1H NMR (Scheme 1).



Scheme 1. Reagents and conditions: (a) see Ref. 5a; (b) (i) *n*-BuLi, TMEDA, Et_2O, –78°C, 2 h; (ii) PhSeSePh, 62–93%; (c) (i) *n*-BuLi, TMEDA, Et_2O, –78°C, 2 h; (ii) TMSCl; (d) (i) *n*-BuLi, TMEDA, Et_2O, rt, 1 h; (ii) PhSeSePh, 93%; (e) TBAF, THF, reflux, 81%

To examine the catalytic efficiencies of **3** as chiral ligands in palladium catalyzed allylic substitutions, the usual model reaction of 1,3-diphenylprop-2-enyl acetate with the nucleophile derived from dimethylmalonate was chosen (Scheme 2) and the results are summarized in Table 1.



Scheme 2.

Table 1
Asymmetric palladium catalyzed allylic substitution with *rac*-1,3-diphenyl-2-propenyl acetate and dimethylmalonate using **3** as ligands[a]

Entry	ligand	solvent	Time	Yield%[b]	Ee%[c]
1	**3a**	CH_2Cl_2	4d	80	98.3(S)[d]
2	**3a**	CH_2Cl_2	4d	71	99.3(S)
3	**3b**	CH_2Cl_2	4d	68	90.6(S)
4	**3b**	THF	4d	35	70.8(S)[e]
5	**3c**	CH_2Cl_2	4d	24	92.7(S)
6	**3d**	CH_2Cl_2	4d	17	85.9(R)
7	**3e**	CH_2Cl_2	3d	78	92.2(S)

[a] Molecular ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$,/ligand **3**/LiOAc/$CH_2(CO_2Me)_2$/BSA = 2/6/3/300/300.
[b] Isolated yield based on 1, 3- diphenyl-2-propenyl acetate.
[c] Determined by HPLC (chiracel OD column) and the absolute configuration of the product was assigned through comparison of the sign of specific rotations with the literature data.[7]
[d] 3mol% KOAc was used instead of LiOAc.
[e] Reaction with the $NaCH(CO_2Me)_2$ prepared in situ in THF.

In our previous work,[3] it was found that LiOAc could accelerate the reaction of palladium catalyzed allylic substitutions with chiral thioether derivatives of ferrocenyl-oxazoline as ligands. However, with chiral selenide derivatives of ferrocenyl-oxazolines as ligands, LiOAc does not accelerate the reaction but improves the enantioselectivity slightly (entries 1 and 2). When THF was used as solvent and sodium malonate as nucleophile was applied, both the yield and enantioselectivity decreased (entries 3 and 4).

Due to the special structure of ferrocenyl derivatives, we examined the roles of central chirality and planar chirality. To investigate the effect of the central chirality, different R-substituents were introduced into the oxazolinyl ring of the ligands. From the data in Table 1, ligand **3a** with *tert*-butyl as the substituent achieved the best yield and enantioselectivity. When R was the ^{i}Pr group only moderate yields and good enantioselectivities were observed. Ligand **3c** and **3d** with phenyl and benzyl as substituents, respectively, showed good enantioselectivity but poor catalytic reactivity. In order to examine the role of planar chirality in this reaction,[3,8,9] ligands **3a** and **3e** were compared. Ligand **3e** has the same central chirality but opposite planar chirality than ligand **3a**. The results showed that better enantioselectivity was achieved by using **3a** compared with **3e** under the same reaction conditions. That is, the two types of chirality in **3a** are matched in this reaction. From Table 1 it can also be concluded that the central chirality is probably a more decisive factor in controlling the configuration of the product as the products with the same configuration were obtained when **3a**–**c** and **3e** were used and they have the same central chiral configuration, while the product with (*R*) configuration was afforded using **3d** as ligand and its central chiral configuration differs from that of **3a**–**c** and **3e**.

3. Conclusion

A series of chiral selenide derivatives of ferrocenyl-oxazolines have been successfully synthesized with high diastereoselectives, and their catalytic efficiency in palladium catalyzed allylic substitutions of *rac*-1,3-diphenyl-2-propenyl acetate has been examined. Both central chirality and planar chirality have been investigated. The high enantioselectivity achieved with the N, Se bidentate ligands here should encourage further studies of chiral ligands containing selenium atom.

4. Experimental

4.1. General methods

All reactions were performed under an atmosphere of either argon or nitrogen using oven-dried glassware. Solvents were treated prior to use according to standard methods. The commercially available reagents were used as received without further purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in $CDCl_3$ at room temperature. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter with a thermally jacketed 10 cm cell at 25°C (concentration c given as g/100 mL). IR spectra were measured in cm^{-1}, using a Shimadzu IR-440 infrared spectrophotometer. Mass spectra and high-resolution mass spectra were taken using HP5989A and Finnigan MAT mass spectrometers, respectively. Elemental analyses were performed on a Foss-Heraeus Vario EL instrument. Enantiomeric excess values were determined by chiral HPLC on a Chiralcel OD column.

4.2. (S,S)-2-(Phenylseleno)-1-(4-tert-butyloxazolinyl)ferrocene **3a**

To a solution of [4-(*S*)-*tert*-butyl-2-oxazolinyl]ferrocene (311 mg, 1 mmol) in dry ether (15 mL) was added TMEDA (0.2 mL, 1.3 mmol) at 25°C. The resulting mixture was cooled to –78°C and *n*-BuLi (0.8 mL, 1.6 M in hexane) was added dropwise and stirred for 2 h at this temperature. The mixture was treated with PhSeSePh (453 mg, 1.5 mmol) and stirred for another 1 h at room temperature. The reaction mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was extracted twice with Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the crude product, which was subsequently purified by column chromatography (EtOAc:petroleum ether = 1:10) to give **3a** (419 mg, 90%). ^{1}H NMR δ 7.65–7.62 (m, 2H), 7.32–7.26 (m, 3H), 4.74 (br, 1H), 4.29–4.21 (m, 2H), 4.20 (s, 5H), 4.20–4.16 (m, 1H), 4.05 (m, 1H), 3.98 (m, 1H), 0.99 (s, 9H); MS (EI) *m*/*z* 467 (M+1, 100), 409 (30), 253 (40), 121 (22); IR (KBr, cm^{-1}) 2951 (m), 1655 (s), 1457 (w), 1140 (m), 980 (s); $[\alpha]_D^{20} = -627$ (c 0.30, $CHCl_3$); mp 97–98°C. Anal. calcd for $C_{23}H_{25}FeNOSe$: C, 59.25; H, 5.40; N, 3.10. Found: C, 59.17; H, 5.19; N, 2.85.

4.3. (S,S)-2-(Phenylseleno)-1-(4-iso-propyloxazolinyl)ferrocene **3b**

A similar procedure as for **3a** gave **3b** in 93% yield (1 mmol scale). ^{1}H NMR δ 7.58–7.55 (m, 2H), 7.29–7.25 (m, 3H), 4.81 (s, 1H), 4.36–4.28 (m, 2H), 4.20 (s, 5H), 4.13 (m, 1H), 4.10–4.02 (m, 2H), 1.85 (m, 1H), 1.03 (d, 3H, J = 6.72 Hz), 0.95 (d, 3H, J = 6.67 Hz); MS (EI) *m*/*z* 453 (M+1, 100), 452 (M^+, 21), 210 (27), 121 (22); IR (KBr, cm^{-1}) 2967 (w), 1659 (s), 1459 (w), 1141 (m), 981 (s); $[\alpha]_D^{20} = -475$ (c 0.29, $CHCl_3$); mp 101–102°C. Anal. calcd for $C_{22}H_{23}FeNOSe$: C, 58.43; H, 5.13; N, 3.10. Found: C, 58.03; H, 5.00; N, 2.90.

4.4. (S,S)-2-(Phenylseleno)-1-(4′-benzyloxazolinyl)ferrocene **3c**

A similar procedure as for **3a** gave **3c** in 62% yield (1 mmol scale). ^{1}H NMR δ 7.56–7.52 (m, 2H), 7.33–7.22 (m, 8H), 4.79 (m, 1H), 4.46 (m, 1H), 4.31–4.24 (m, 2H), 4.16–4.18 (m, 1H), 4.17 (s,

5H), 4.04 (dd, 1H, $J_1 = 7.51$ Hz, $J_2 = 8.18$ Hz), 3.17 (dd, 1H, $J_1 = 4.90$ Hz, $J_2 = 13.70$ Hz), 2.72 (dd, 1H, $J_1 = 8.41$ Hz, $J_2 = 13.69$ Hz); MS (EI) *m/z* 501 (M+1, 44), 500 (M^+, 16), 253 (27), 121 (33), 91 (100), 56 (27); IR (KBr, cm^{-1}) 3050 (w), 2924 (m), 1654 (s), 1476 (m), 1137 (m), 978 (s); $[\alpha]_D^{20} = -281$ (c 0.85, $CHCl_3$). Anal. calcd for $C_{26}H_{23}FeNOSe$: C, 62.45; H, 4.60; N, 2.80. Found: C, 62.54; H, 4.86; N, 2.76.

4.5. (R,R)-2-(Phenylseleno)-1-(4′-phenyloxazolinyl)ferrocene **3d**

A similar procedure as for **3a** gave **3d** in 62% yield (1 mmol scale). ^1H NMR δ 7.56–7.53 (m, 2H), 7.34–7.25 (m, 8H), 5.28 (dd, 1H, $J_1 = 7.73$ Hz, $J_2 = 9.86$ Hz), 4.87 (m, 1H), 4.71 (dd, $J_1 = 8.27$ Hz, $J_2 = 9.92$ Hz), 4.35 (dd, 1H, $J_1 = 2.07$ Hz, $J_2 = 5.17$ Hz), 4.26–4.23 (m, 1H), 4.25 (s, 5H), 4.14 (t, 1H, $J_1 = J_2 = 8.00$ Hz); MS (EI) *m/z* 487 (M+1, 46), 486 (M^+, 17), 210 (36), 121 (100), 91 (37), 56 (67); IR (KBr, cm^{-1}) 3057 (w), 2924 (w), 1650 (s), 1476 (m), 1136 (m), 981 (s); $[\alpha]_D^{20} = +303$ (c 0.43, $CHCl_3$). Anal. calcd for $C_{25}H_{21}FeNOSe$: C, 61.78; H, 4.32; N, 2.88. Found: C, 61.68; H, 4.55; N, 2.90.

4.6. (S)-2-(R)-(Phenylseleno)-5-(S)-(trimethylsilyl)-1-(4′-tert-butyloxazolinyl)ferrocene **4**

To a solution of 2-(*S*)-(trimethylsilyl)-1-(4′-*tert*-butyloxazolinyl)ferrocene (383 mg, 1 mmol) in dry ether (15 mL) at 25°C was added *n*-BuLi (0.8 mL, 1.6 M in hexane). The reaction mixture was stirred at the same temperature for 1 h before treating with PhSeSePh (450 mg, 1.5 mmol). After usual workup and column chromatography (EtOAc:petroleum ether = 1:10) compound **4** was obtained (495 mg, 92%) as an orange solid. ^1H NMR δ 7.62–7.59 (m, 2H), 7.30–7.26 (m, 3H), 4.25 (m, 3H), 4.18 (s, 5H), 4.14 (t, 1H, $J_1 = J_2 = 8.00$ Hz), 3.97 (dd, 1H, $J_1 = 7.38$ Hz, $J_2 = 9.99$ Hz), 0.92 (s, 9H), 0.28 (s, 9H); MS (EI) *m/z* 539 (M+1, 100), 325 (36), 230 (31), 73 (37); IR (KBr, cm^{-1}) 2954 (s), 1649 (s), 1477 (w), 1260 (m), 958 (w); $[\alpha]_D^{20} = +415$ (c 0.34, $CHCl_3$); mp 76–77°C. Anal. calcd for $C_{26}H_{33}FeNOSeSi$: C, 58.05; H, 6.18; N, 2.60. Found: C, 58.16; H, 6.16; N, 2.43.

4.7. (S,R)-2-(Phenylseleno)-1-(4′-tert-butyloxazolinyl)ferrocene **3e**

To a solution of **4** (480 mg, 0.9 mmol) in THF (4.5 mL) at 25°C was added tetrabutylammonium fluoride (4.5 mL, 1 M in THF). Then the resulting reaction mixture was heated to reflux for 3 h. After usual workup and column chromatography (EtOAc:petroleum ether = 1:10) ligand **3e** was afforded (340 mg, 81%). ^1H NMR δ 7.55–7.42 (m, 2H), 7.26–7.13 (m, 3H), 4.88 (br, 1H), 4.43–4.42 (m, 1H), 4.36–4.33 (m, 2H), 4.27–4.18 (m, 1H), 4.23 (s, 5H), 3.95 (m, 1H), 0.90 (s, 9H); MS (EI) *m/z* 467 (M+1, 48), 466 (M^+, 16), 253 (31), 121 (41), 56 (49); IR (KBr, cm^{-1}) 3075 (w), 2953 (m), 1656 (s), 1477 (s), 1137 (m), 976 (s); $[\alpha]_D^{20} = -126$ (c 0.54, $CHCl_3$). Anal. calcd for $C_{23}H_{25}FeNOSe$: C, 59.25; H, 5.40; N, 3.10. Found: C, 59.22; H, 5.51; N, 3.00.

4.8. General procedure for the palladium catalyzed allylic substitutions of rac-1,3-diphenyl-2-propenyl acetate

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3.7 mg, 0.01 mmol) and ligand **3** (0.03 mmol) were dissolved in dry CH_2Cl_2 (2 mL), and then stirred for 30 min at room temperature under an atmosphere of argon. To this solution were successively added *rac*-1,3-diphenyl-2-propenyl acetate (126 mg, 0.5 mmol), dimethylmalonate (0.17 mL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (0.37 mL, 1.5 mmol), and

lithium acetate (1 mg, 0.015 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed twice with ice-cold saturated aqueous ammonium chloride. The organic phase was dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc:petroleum ether = 1:15) to give the pure product. The enantiomeric purities were determined by HPLC (Chiralcel OD column).

Acknowledgements

This research was financially supported by the National Natural Science Foundation of China (29790127 and 29872045), Chinese Academy of Sciences and Shanghai Committee of Science and Technology.

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