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Interesting and Effective P,N-Chelation of Tetrasubstituted Ferrocene Ligands for Palladium-Catalyzed Asymmetric Allylic Substitution

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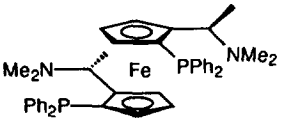
Abstract: The complexation of 1,1'-bis(diphenylphosphino)-2,2'-bis(oxazolinyl)-ferrocene with palladium(II) in solution was studied and with this kind of P,N-chelating tetrasubstituted ferrocene compounds as chiral ligands, up to 99% ee was given to the palladium-catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate.

Hayashi and coworkers reported a very interesting C_2-symmetric tetrasubstituted ferrocene ligand **1** with which an excellent enantiomeric excess was given to the coupling reaction of vinyl bromide and 1-phenylethylzinc chloride.[1] For the purpose of developing more effective and more readily available chiral ligands,



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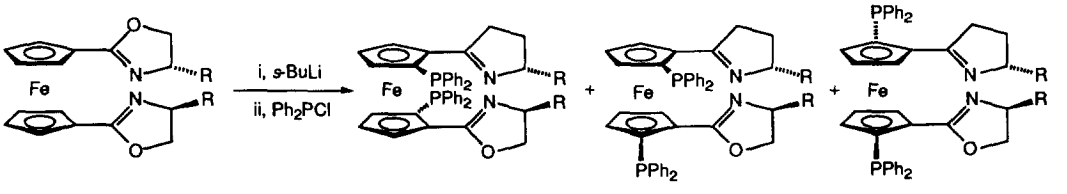
we recently reported the highly diastereoselective ortho-lithiation of 1,1'-bis(oxazolinyl)ferrocenes **2**, by which novel C_2-symmetric tetrasubstituted ferrocene compound **3** as a major product and asymmetric compound **4** as a minor product were prepared with ease, but the C_2-symmetric tetrasubstituted ferrocene compound **5** was not detected (Scheme 1).[2] Here we report the interesting complexation behavior of these products with palladium(II) and their high ability for the palladium-catalyzed asymmetric allylic substitution.

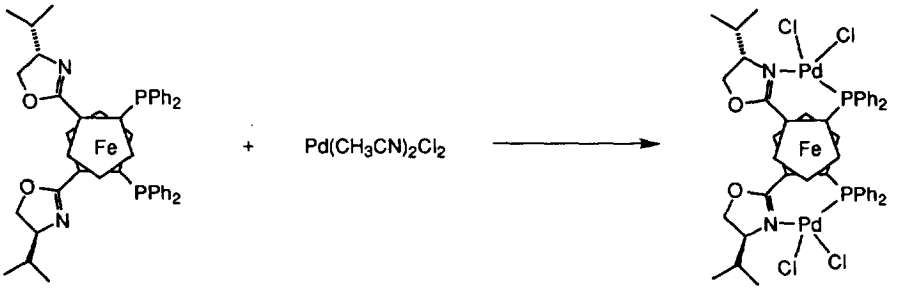


2 (a,b) **3 (a,b)** **4 (a,b)** **5 (a,b)**

Scheme 1 (**a**, R = *i*Pr; **b**, R = *t*Bu)

The complexation behavior of **3** with palladium(II) in solution was different from that of **1**, which gave a 1:1 P,P-chelate upon treatment with dichlorobis(acetonitrile)palladium(II).[1] When **3a** was mixed with 1 equiv. of dichlorobis(acetonitrile)palladium(II) in acetonitrile, a P,P-chelate was not detected. But a C_2-symmetric 1:2 P,N-chelate **6** was formed upon using 2 equiv. of dichlorobis(acetonitrile)palladium(II) (Scheme 2).[3] The

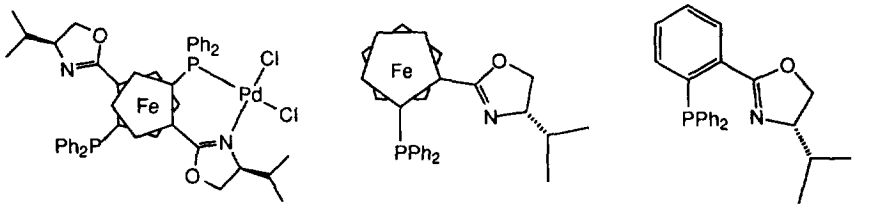
difference in the complexation behaviors of **1** and **3** may be due to their structural features, that is, the oxazolinyl group of **3** having a C=N double bond has stronger coordination ability towards Pd(II) than the dimethyl amino group of **1**.



3a **6**

Scheme 2

As Park and coworkers reported, the complexation property of asymmetric product **4**, which was prepared by them as a main product *via* the ortho-lithiation of 1,1'-bisoxazolinylferrocene **2** with *t*-butyllithium is very interesting. As **4a** was treated with 1 equiv. of dichlorobis(acetonitrile)palladium(II), a 1:1 P,N-chelate **7** was generated, but **7** did not react with additional dichlorobis(acetonitrile)palladium(II) to give a 1:2 P,N-chelate. The P,N-chelating Cp ring of **7** has a (*R*)-planar configuration around the ferrocene axis and the substituent on the chelating oxazolinyl ring has an *anti* orientation with respect to the ferrocenyl iron atom.[4] This chelating fashion is opposite to that of **6** in which both of the P,N-chelating Cp rings have an (*S*)-planar configuration around the ferrocene axis and the substituents on the oxazolinyl rings have a *syn* orientation with respect to the ferrocenyl iron atom. The reason why the 1:1 P,N-chelate with the (S)-planar Cp ring of **4** and the 1:2 P,N-chelate with **4** could not be formed is due to the steric hindrance. Thus, the substituent on the oxazolinyl group of the (*S*)-planar Cp ring should be placed near the diphenylphosphino group of the (*R*)-planar Cp ring, causing a great steric interaction between the isopropyl and the phenyl groups if these chelates were formed. But in complex **6**, the substituent on the oxazolinyl group of one Cp ring is located far from the diphenylphosphino group of another Cp ring, and there is little steric interaction between them.



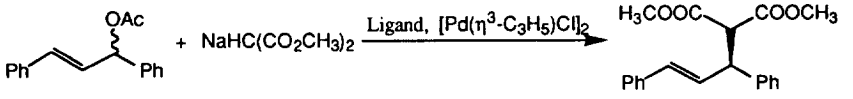
7 **8** **9**

Nishibayashi[5a] and Richards[5b] prepared compound **8** with which as a chiral ligand a 60% ee was given to the rhodium-catalyzed asymmetric hydrosilylation of acetophenone.[5a] We confirmed that a P,N-chelate with Pd(II)[6] was formed, which should have the same chelating fashion as **6** but opposite to **7**, upon treating **8** with 1 equiv. of dichlorobis(acetonitrile)palladium(II) in acetonitrile.

The palladium-catalyzed asymmetric allylic substitution, one of the most important asymmetric reactions, has been studied with many kinds of chiral ligands.[7,8] Recently, Helmchen,[8a] Pfalts[8b] and Williams[8c] independently developed the phosphorus-containing oxazoline ligand **9** with which an excellent enantiomeric

excess was given to the substitution of *rac*-1,3-diphenyl-2-propenyl acetate. With compounds **3**, **4** and **8** as chiral ligands, we also carried out this reaction as a preliminary experiment. Since these compounds possess some additional structural features compared with compound **9**, they may help us to understand the steric and the electronic effects of ligands and to find more effective ligands for asymmetric catalytic reactions.

As we expected, all of these ligands showed high efficiency for the palladium-catalysed asymmetric allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate **10** to **11** (Scheme 3, Table 1).



10 **11**

Scheme 3

Table 1. Allylic substitution of 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate[a]

Ligand (L*)	*Catalyst*[c]	*Solvent*	ee (%)[d]	*Enantiomer*[e]
3a	2.5mol% Pd; 1.5mol% L*	THF	94	(S)-(-)
3a	2.5mol% Pd; 3.0mol% L*	THF	96	(S)-(-)
3a	2.5mol% Pd; 5.0mol% L*	THF	96	(S)-(-)
3a[b]	2.5mol% Pd; 3.0mol% L*	THF	66	(S)-(-)
3a	2.5mol% Pd; 3.0mol% L*	CH_2Cl_2	96	(S)-(-)
3b	2.5mol% Pd; 3.0mol% L*	THF	99	(S)-(-)
4a	2.5mol% Pd; 3.0mol% L*	THF	96	(S)-(-)
8	2.5mol% Pd; 3.0mol% L*	THF	93	(S)-(-)
8	2.5mol% Pd; 6.0mol% L*	THF	93	(S)-(-)
8[b]	2.5mol% Pd; 3.0mol% L*	THF	58	(S)-(-)

a) Reactions were conducted with 1 mmol of **10** and 3 mmol $NaHC(CO_2Me)_2$ in 3 ml of solvent at 20 ℃ under argon and were completed within 6 hours. All the reactions gave above 90% isolated chemical yields. b) These reactions were run using 3 mmol of $H_2C(CO_2Me)_2$, 3 mmol of BSA and 20 μmol of CH_3CO_2K in place of $NaHC(CO_2Me)_2$. c) The catalyst was prepared by treating $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with **3a**, **3b**, **4a** or **8** in 1 ml of solvent at 20 ℃ for 1 hour before use. d) The enantiomeric excess was determined by the ^{1}H-NMR analysis in the presence of the shift reagent Eu(hfc)$_3$.[9] e) The absolute stereochemistry of the product was determined by comparison of the optical rotation with literature values.[9]

It was shown that when sodium dimethyl malonate was used as a nucleophile, all of the ligands **3**, **4**, and **8** gave above 93% ee with more than 90% isolated chemical yields. The substituent R on the oxazolinyl ring affected the ee results and a bulkier group gave a better ee. Thus, when **3b** having *tert*-butyl groups was used as a chiral ligand, up to 99% ee was given to the allylic substitution. This is one of the best results reported so far for the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with carbon nucleophiles.[7e] However, it was surprising that the asymmetric ligand **4a** having an opposite planar configuration of the P,N-chelating Cp ring to that of C_2-symmetric ligand **3a** gave the same enantiomorphicity of product and the same extent of ee as ligand **3a**. Thus, it was proved that for the allylic substitution, the planar chirality of this kind of ferrocene ligands did not affect the reaction, and product enantiomorphicity was determined only by the chirality of the substituent on the oxazolinyl ring. Also, the ferrocenyl ring played an important role only as an effective connector of diphenylphosphino and oxazolinyl groups in the structure of ligands. Therefore, it was clear from this result that the mixture of **3** and **4** derived from **2** should also have high enantioselectivity for the palladium-catalyzed allylic substitution of **10** to **11**, and there is no need to separate them when used as the ligand for this

substitution reaction.

In many cases, the best ee for the allylic substitution was obtained using dimethyl malonate / *N,O*-bis(trimethylsilyl)acetamide (BSA), sometimes in the presence of added acetate ion.[7e] However, in our case, excellent results were achieved with sodium dimethyl malonate as a nucleophile. When dimethyl malonate / BSA was used in place of sodium dimethyl malonate, the ee was largely depressed and only a moderate ee was obtained with **3** or **8** as the chiral ligand.

In addition, changing the solvent from THF to an apolar solvent, such as CH_2Cl_2, did not have a significant effect on both reaction rate and enantioselectivity.

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3. **6**: ^{1}H-NMR (600 MHz, CD_3CN): δ 1.06 (12H, d, *J* 6.9 Hz, CH_3), 2.90 (2H, m, Me_2CH), 3.29 (2H, brs, FcH), 4.07 (2H, brs, FcH), 4.48 (2H, t, *J* 9.6 Hz, OCH), 4.66 (2H, dd, *J* 4.2, 9.6 Hz, OCH), 4.97 (2H, brs, FcH), 5.18 (2H, m, NCH), 7.16 (4H, m, PhH), 7.32 (4H, m, PhH), 7.49 (2H, m, PhH), 7.64 (2H, m, PhH), 7.70 (4H, m, PhH), 8.13 (4H, m, PhH). FAB-MS (m/e) : 1097 $(M\text{-}Cl)^+$.
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6. **[8]** $PdCl_2$: ^{1}H-NMR (600 MHz, CD_3CN): δ 1.02 (3H, d, *J* 7.1 Hz, CH_3), 1.03 (3H, d, *J* 7.1 Hz, CH_3), 2.91 (1H, m, Me_2CH), 3.81 (5H, s, FcH), 4.44 (1H, t, *J* 9.4 Hz, OCH), 4.58 (1H, dd, *J* 4.7, 9.4 Hz, OCH), 4.64 (1H, brs, FcH), 4.87 (1H, t, *J* 2.6 Hz, FcH), 5.17 (1H, brs, FcH), 5.20 (1H, m, NCH), 7.34 (4H, m, PhH), 7.48 (1H, m, PhH), 7.72 (3H, m, PhH), 8.38 (2H, m, PhH). For comparison with **[8]** $PdCl_2$, the ^{1}H-NMR data of **8** is as follows: ^{1}H-NMR (600 MHz, CD_3CN): δ 0.87 (3H, d, *J* 7.0 Hz, CH_3), 0.93 (3H, d, *J* 6.5 Hz, CH_3), 1.64 (1H, m, Me_2CH), 3.63 (1H, brs, FcH), 3.75 (1H, m, NCH), 3.91 (1H, dd, *J* 7.0, 8.2 Hz, OCH), 4.15 (5H, s, FcH), 4.18 (1H, dd, *J* 8.2, 9.4 Hz, OCH), 4.42 (1H, brs, FcH), 4.88 (1H, brs, FcH), 7.13 (2H, m, PhH), 7.24 (3H, m, PhH), 7.40 (3H, m, PhH), 7.48 (2H, m, PhH).
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