# Enantioselective palladium catalyzed allylic substitution with chiral thioether derivatives of ferrocenyl-oxazoline and the role of planar chirality in this reaction

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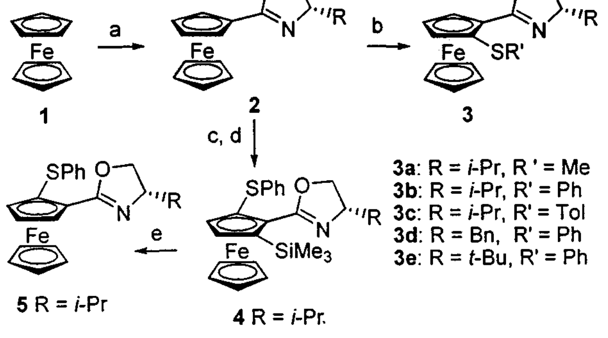
**A series of chiral thioether dervatives of ferrocenyl-oxazolines, prepared with diastereoselectivities > 95 : 5, have been shown to be highly efficient catalysts for a palladium catalyzed allylic substitution reaction, with enantioselectivity of 81–98% ee, and the role of planar chirality in these ligands was also discussed.**

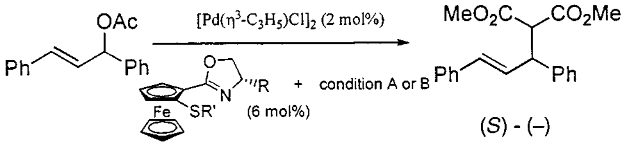
In the past few years, palladium catalyzed allylic substitutions[1] have been used extensively in asymmetric carbon–carbon bond formation to provide chemo-, regio-, diastereo-, and enantioselectivity.[2] A variety of chiral ligands have been studied. In addition to the widely used phosphine or phosphite ligands, sulfur–nitrogen ligands have recently been proved to be successful.[3] For example, Williams explored thioether of phenyloxazoline ligands for the palladium catalyzed allylic substitution,[13a,b] good to excellent enantioselectivities were obtained. Other groups also showed the high enantioselectivity obtained with this type of N,S-bidentate ligand. Recently, planar chiral bidentate ligands have been successfully applied in many asymmetric reactions. The work of Fu and coworkers showed that the single planar chiral bidentate ligands were highly efficient catalysts for several asymmetric reactions.[4] In conjunction with our group's interest on asymmetric sulfonium ylide reaction[5] and transfer hydrogenation with planar chiral ferrocene derivatives[6] as ligands, we disclose a preliminary result of our studies on the synthesis of chiral thioether derivatives of ferrocenyl-oxazoline and application in palladium catalyzed allylic substitution. The role of planar chirality in this reaction was also studied.

Recently, Ahn *et al.* have reported an efficient diastereoselective synthesis of chiral oxazolinylferrocene compounds.[7] According to Ahn's method and our own experience, a series of chiral thioether derivatives of ferrocenyl-oxazoline were synthesized as follows: oxazolinylferrocene **2** was treated with *n*-BuLi and equimolar amount of TMEDA in $Et_2O$ at −78 °C for 2 h (Scheme 1), the resulting mixture quenched with electrophiles ($Me_3SiCl$, $PhSO_2SR'$ or R'SSR'), then usual work-up to give the pure products. The diastereoselectivities of **3** and **5** determined by 300 MHz $^1H$ NMR were > 95 : 5.



**Scheme 1** *Reagents and conditions*: a, See refs. 7–9; b, (1) *n*-BuLi, TMEDA, $Et_2O$ −78 °C, 2 h; (2) $PhSO_2SMe$ or R'SSR' 67–91%; c, (1) *n*-BuLi, TMEDA, $Et_2O$, −78 °C, 2 h; (2) TMSCl 93%; d, (1) *n*-BuLi, $Et_2O$, −78 °C, 2 h; (2) PhSSPh 70%; e, TBAF, THF, reflux, 6 h 88%.

To assay the effectiveness of ligands and other factors in palladium catalyzed alylic substitution, we chose the usual test reaction, the reaction of 1,3-diphenylprop-2-enyl acetate with the nucleophile derived from dimethyl malonate. Conditions A [$NaCH(CO_2Me)_2$, THF, r.t.] or B [$CH_2(CO_2Me)_2$, BSA, LiOAc, DCM, r.t.] were used in the reaction (Scheme 2).



**Scheme 2** Condition A: $NaCH(CO_2Me)_2$, THF, r.t. Condition B; $CH_2(CO_2Me)_2$, BSA [*N,O*-Bis(trimethyl)acetamide], LiOAc, $CH_2Cl_2$, r.t.

First, we investigated the effect of different salts on reaction yields and enantioselectivies under condition B with the catalyst derived from **3c** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. The results are summarized in Table 1, and it was found that ee values did not change in the presence of the salts listed in Table 1 (88.1–89.9%), but that the reaction time varied significantly (3–48 h). In view of the reaction time, yield and ee value, the lithium acetate (Table 1, entry 4) was used throughout this work.

Using the above conditions, a variety of ligands and conditions in the palladium catalyzed asymmetric allylic substitutions are summarized in Table 2. The sense of enantioinduction was determined by HPLC and confirmed by specific rotation of the product methyl-2-carbomethoxy-3,5-diphenylpent-4-enolate[10] and was found to be *S* in all cases. Comparing conditions A and B, we obtained higher enantioselectivities with the latter, which is consistent with most literature reports.[1,2] From entries 1–6 we found that ligands **3b** and **3c** are superior to **3a**. The chiral thioether of ferrocenyl-oxazolines derived from different amino alcohols show different effectiveness for enantioselectivities. The results showed that R = *t*-Bu (entries 9,10) is superior to R = *i*-Pr (entries 3,4) or Bn (entries 7,8). Entry 11 showed that the palladium complex with ligand **4** could mediate the allylic substitution reaction

**Table 1** Asymmetric palladium catalyzed allylic substitution with different salts under condition B[a]

| Entry | Salt | *t*/h | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | None | 5 | 98 | 88.4 (*S*) |
| 2 | KOAc | 48 | 96 | 88.1 (*S*) |
| 3 | NaOAc | 48 | 85 | 88.2 (*S*) |
| 4 | LiOAc | 3 | 98 | 89.9 (*S*) |
| 5 | $Cs_2CO_3$ | 5 | 98 | 89.4 (*S*) |

[a] Reaction conditions: 2 mol% $[Pd(\eta^3\text{–}C_3H_5)Cl]_2$, 6 mol% **3c**, 3 mol% salt, 300 mol% $CH_2(CO_2Me)_2$, 300 mol% BSA. [b] Isolated yield based on the 1,3-diphenylprop-2-enyl acetate. [c] Determined by HPLC (chiralcel OJ column). [d] Absolute configuration of product was assigned through comparison of the sign of specific rotations with the literature data.[10]

**Table 2** Asymmetric palladium catalyzed allylic substitution with different ligands

| Entry | Ligand | Reaction condition | $t$/h | Yield (%)$^a$ | Ee (%)$^b$ |
|---|---|---|---|---|---|
| 1 | **3a** | A | 1 | 98 | 73.9 (*S*) |
| 2 | **3a** | B | 3 | 98 | 81.9 (*S*) |
| 3 | **3b** | A | 2 | 98 | 84.0 (*S*) |
| 4 | **3b** | B | 3 | 98 | 89.4(*S*) |
| 5 | **3c** | A | 2 | 98 | 83.9 (*S*) |
| 6 | **3c** | B | 3 | 98 | 89.9 (*S*) |
| 7 | **3d** | A | 2 | 98 | 81.1 (*S*) |
| 8 | **3d** | B | 5 | 98 | 87.8 (*S*) |
| 9 | **3e** | A | 12 | 98 | 95.6(*S*) |
| 10 | **3e** | B | 10 | 98 | 98.0 (*S*) |
| 11 | **4** | B | 3 | 98 | 75.3 (*S*) |
| 12 | **5** | B | 3 | 98 | 90.4 (*S*) |

$^a$ Isolated yield based on the 1,3-diphenylprop-2-enyl acetate. $^b$ Determined by HPLC (chiralcel OJ column). $^c$ Absolute configuration of product was assigned through comparison of the sign of specific rotations with the literautre data.[10]

smoothly, while the bulkier trimethylsilyl group may decrease the enantioselectivity of the product.

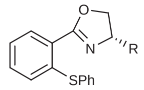
Compared with the palladium complexes of chiral thioethers of phenyloxazoline ligands reported by Williams,[3a] the palladium complexes with chiral thioethers of ferrocenyl–oxazolines are more efficient. The allylic substitution reaction catalyzed by the latter under our conditions is much faster and gives almost quantitative yields.

In order to investigate the effect of planar chirality on the absolute configuration and enantioselectivity of this reaction, diastereoisomer **5** was also synthesized, and subjected to palladium catalyzed allylic substitution. Under essentially similar conditions (condition B), a similar enantioselectivity (89.4% in entry 4 *vs.* 90.4% in entry 12, Table 2) and the same absolute configuration was obtained. It seems that the absolute configuration is governed mainly by the central chirality of the oxazoline ring. (It seems that planar chirality plays a much less important role in palladium catalyzed allylic substitution.) This phenomenon was also found in our previous work on ruthenium-catalyzed asymmetric transfer hydrogenation with ferrocene derived catalysts.[6]

**Table 3** Asymmetric palladium catalyzed allylic substitution with **3** and **9**

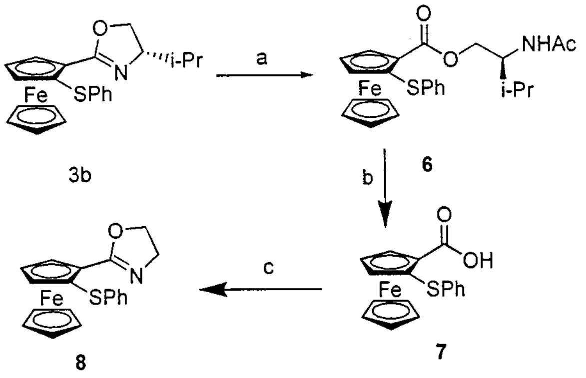
| Entry | Ligand | Condition$^b$ | $t$/h | Yield (%) | Ee (%)$^c$ |
|---|---|---|---|---|---|
| 1 | **9a**$^a$ | A' | 36 | 91 | 78 |
| 2 | **3b** | A | 2 | 98 | 84.0 |
| 3 | **9a**$^a$ | B' | 36 | 96 | 90 |
| 4 | **3b** | B | 3 | 98 | 89.4 |
| 5 | **9b**$^a$ | B' | 96 | 92 | 96 |
| 6 | **3e** | B | 12 | 98 | 98.0 |

$^a$



**9a**: R = *i*-Pr; **9b**: R = *t*-Bu. $^b$ Condition A': $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), 9 (10 mol%), $NaCH(CO_2Me)_2$, THF, 20 °C. Condition B': $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), 9 (10 mol%), KOAc (3 mol%), BSA, $CH_2(CO_2Me)_2$,$CH_2Cl_2$, 20 °C. $^c$ Absolute configuration of product was *S* for all cases.

In order to further clarify the role of the planar chirality in this reaction, we may remove the central chirality on the oxazoline ring. For this purpose, the single planar chiral thioether of ferrocenyl-oxazoline (**8**) was designed and synthesized[11] (Scheme 3). Ligand **8** was subjected to palladium catalyzed allylic substitution under essential similar conditions as above (condition B) but only 8.5% ee was obtained and the absolute configuration is *R*. This result can explain why diastereosiomer **5** achieved only a little higher ee than ligand **3b** (90.4% entry 12 *vs.* 89.4% entry 4 in Table 2); the planar chirality matched the central chirality in **5** for the oxazoline ring whereas they are mismatched in ligand **3**. The ee obtained with ligand **8** was low but did have an influence in this asymmetric allylic substitution reaction. Furthermore, it is noteworthy to compare the reaction rate of the reaction catalyzed by **3** with the counterpart of the thioether of phenyloxazoline **9** (Table 3). For all the reactions catalyzed by **9**, the rates are much slower than those of the ferrocene derivatives.[12]



**Scheme 3** *Reagents and conditions*: a, (1) TFA, $H_2O$, $Na_2SO_4$, THF; (2) $Ac_2O$, Py, $CH_2Cl_2$, 88%; b, (1) 2.5 M NaOH (aq), THF, 55 °C (2) $H_3O^+$, 85%; c, (1) $(ClCO)_2$, $NH_2(CH_2)_2OH$, $Et_3N$, $CH_2Cl_2$, (2) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 63%.

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## Notes and references

1 Reviews: C. G. Frost, J. Howarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089; B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; G. Consiglio and R. M. Waymouth, *Chem. Rev.*, 1989, **89**, 257; S. A. Godleski, in *Comprehensive Organic Synthesis*, ed. B. H. Trost, Pergamon Press, Oxford, 1991, vol. 4, p. 585.

2 Recent examples: B. M. Trost and R. C. Bunt, *Angew. Chem. Int. Ed. Engl*, 1996, **35**, 99; B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1998, **120**, 815; B. M. Trost and D. E. Patterson, *J. Org. Chem.*, 1998, **63**, 1339.

3 (*a*) G. J. Dawson, C. G. Frost, C. J. Martin and J. M. J. Williams, *Tetrahedron Lett.*, 1993, **34**, 7793; (*b*) J. V. Allen, J. F. Bower and J. M. J. Williams, *Tetrahedron Asymmetry*, 1994, **5**, 1895; (*c*) J. V. Allen, S. J. Coote, G. J. Dawson, C. G. Frost, C. J. Martin and J. M. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2065; (*d*) K. Boogwick, P. S. Pregosin and G. Trabesinger, *Organometallics*, 1998, **17**, 3254 (*e*) B. Koning, A. Meetsma and R. M. Kellogg, *J. Org. Chem.*, 1998, **63**, 5533, and references therein.

4 J. C. Ruble, J. Tweddell and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 2794; S. Qiao and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 4168.

5 A. H. Li, L. X. Dai, X. L. Hou, Y. Z. Huang and F. W. Li, *J. Org. Chem.*, 1996, **61**, 489; A. H. Li, Y. G. Zhou, L. X. Dai, X. L. Hou, L. J. Xia and L. Lin, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1317.

6 X.-D. Du, L.-X. Dai, X.-L. Hou, L.-J. Xia and M.-H. Tang, *Chin. J. Chem.*, 1998, **16**, 90.

7 K. H. Ahn, C.-W. Cho, H.-H. Beak, J. Park and S. Lee, *J. Org. Chem.*, 1996, **61**, 4937.

8 C. J. Richards, T. Damalidia, D. E. Habbis and M. B. Hursthouse, *Synlett.*, 1995, 74.

9 P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson and G. M. Whitman, *J. Am. Chem. Soc.*, 1957, **79**, 3416.

10 P. Wimmer and M. Widhalm, *Tetrahedron: Asymmetry*, 1995, **6**, 657.

11 A. M. Warshawsky and A. I. Meyers, *J. Am. Chem. Soc.*, 1990, **112**, 8090; T. D. Nelson and A. I. Meyers, *J. Org. Chem.*, 1994, **59**, 2655; W. B. Zhang, T. Kido, Y. Nakatsuji and I. Ikeda, *Tetrahedron Lett.*, 1996, **37**, 7995.

12 We also noticed a similar rate enhancing effect in the asymmetric transfer hydrogenation of ketones catalyzed by ruthenium complexes with phosphinoferrocenyloxozolines (ref. 6).

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