Effective Chiral Thiophene Diamine Derivatives in Pd-Catalyzed Enantioselective Allylic Alkylation

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Received November 18, 2003

Key Words : Allylic alkylation, Pd-catalyzed, Thiophene diamines

Enantioselective allylic alkylations have been widely employed as efficient and convenient tools for carbon-carbon bond formation in the field of organic synthesis.[1] During the last decade, various chiral ligands have been developed for Pd-catalyzed enantioselective allylic alkylation.[2] In particular, high levels of asymmetric induction have been achieved using the palladium complexes of phosphine-oxazoline hybrid ligands,[3] amidine,[4] Tetradentate bisphosphinobioxazolines ligands,[5] sulfur-imine type chiral ligands,[6] various S, N ligands[7] containing oxazoline moiety are also known to afford a high enantioselectivity. However, tetradentate sulfur-nitrogen ligands such as chiral thiophene diamine derivatives, have never been examined as ligands in

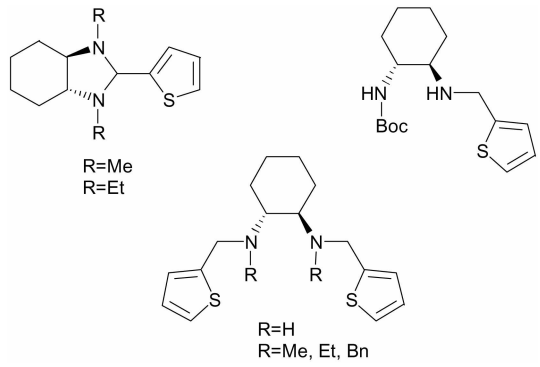
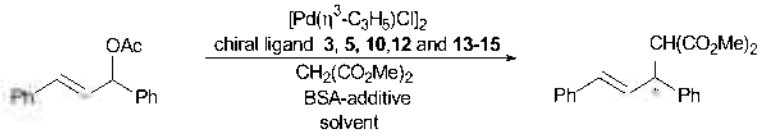


Table 1. Pd-catalyzed enantioselective allylic alkylation of 1,3-diphenyl-2-propenyl acetate using the chiral ligands **3**, **5**, **10**, **12** and **13-15**



Entry	Ligand (mol %)	L*/Pd	Temp. (°C)	Solvent	Additive	Time (h)	Conversion (%)[a]	ee (%)[b] (Config.[c])
1	**3**(10)	4/1	20	THF	LiOAc	22	65	60(S)
2	**5**(10)	4/1	20	THF	LiOAc	22	70	70.8(S)
3	**5**(10)	4/1	20	THF	KOAc	22	80	61(S)
4	**10**(10)	4/1	20	THF	KOAc	22	70	80(R)
5	**12**(10)	4/1	20	THF	KOAc	22	83	94.8(R)
6	**12**(10)	4/1	20	CH_2Cl_2	KOAc	12	65	88.0(R)
7	**12**(10)	1/1	20	THF	KOAc	48	50	88.5(R)
8	**12**(10)	4/1	20	THF	LiOAc	12	74	88.3(R)
9	**12**(10)	4/1	20	CH_2Cl_2	LiOAc	12	30	78.6(R)
10	**12**(10)	4/1	0	CH_2Cl_2	KOAc	48	98	90(R)
11	**12**(10)	2.5/1	20	THF	KOAc	22	85	90(R)
12	**13**(10)	4/1	20	CH_2Cl_2	KOAc	12	99	65(R)
13	**13**(10)	4/1	20	THF	KOAc	12	88	66(R)
14	**13**(10)	4/1	20	CH_2Cl_2	LiOAc	12	99	93.7(R)
15	**13**(10)	4/1	20	THF	LiOAc	22	80	98(R)
16	**13**(10)	4/1	0	CH_2Cl_2	LiOAc	18	20	93.7(R)
17	**13**(10)	4/1	0	THF	LiOAc	18	30	94.5(R)
18	**14**(10)	4/1	20	THF	KOAc	18	15	25(R)
19	**14**(10)	4/1	20	CH_2Cl_2	KOAc	22	20	35(R)
20	**15**(10)	4/1	20	CH_2Cl_2	KOAc	20	18	33(R)
21	**15**(10)	4/1	20	CH_2Cl_2	LiOAc	20	23	42(R)

[a]The conversion was determined by GC analysis. [b]The enantiomeric excess was determined by HPLC with chiralcel OD column (25 cm × 0.46 cm): 1% 2-propanol in hexane, flow rate 0.5 mL/min. [c]Absolute configuration was assigned by the elution order from a Daicel chiralcel column.

this reaction to date. Here in, we wish to report palladium-catalyzed enantioselective allylic alkylation using chiral thiophene diamine derivatives which were prepared from enantiomerically pure (*R,R*)-1,2-diaminocyclohexane.

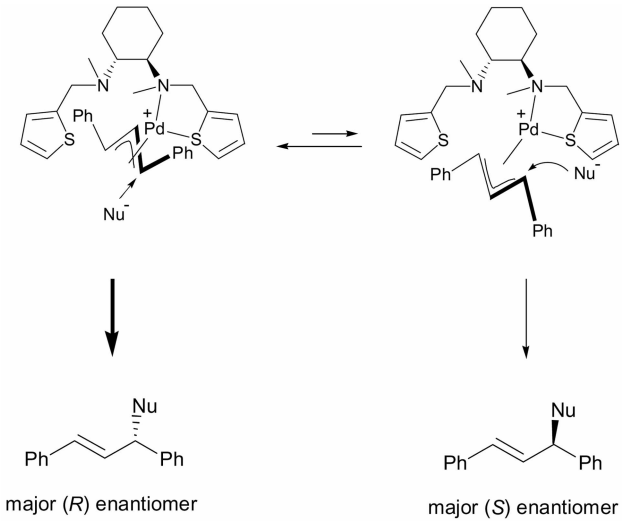
To examine the effectiveness of the thiophene diamine derivatives as chiral ligands in palladium-catalyzed enantioselective allylic alkylation, the reaction between rac-1,3-diphenyl-2-propenyl acetate and dimethyl malonate has been investigated under standard conditions in the presence of N,O-bis(trimethylsilyl) acetamide (BSA) and KOAc or LiOAc as base.[8]

The results are summarized in Table 1. As shown in Table 1, the enantioselectivity is strongly dependant on the structure of thiophene diamine derivatives.

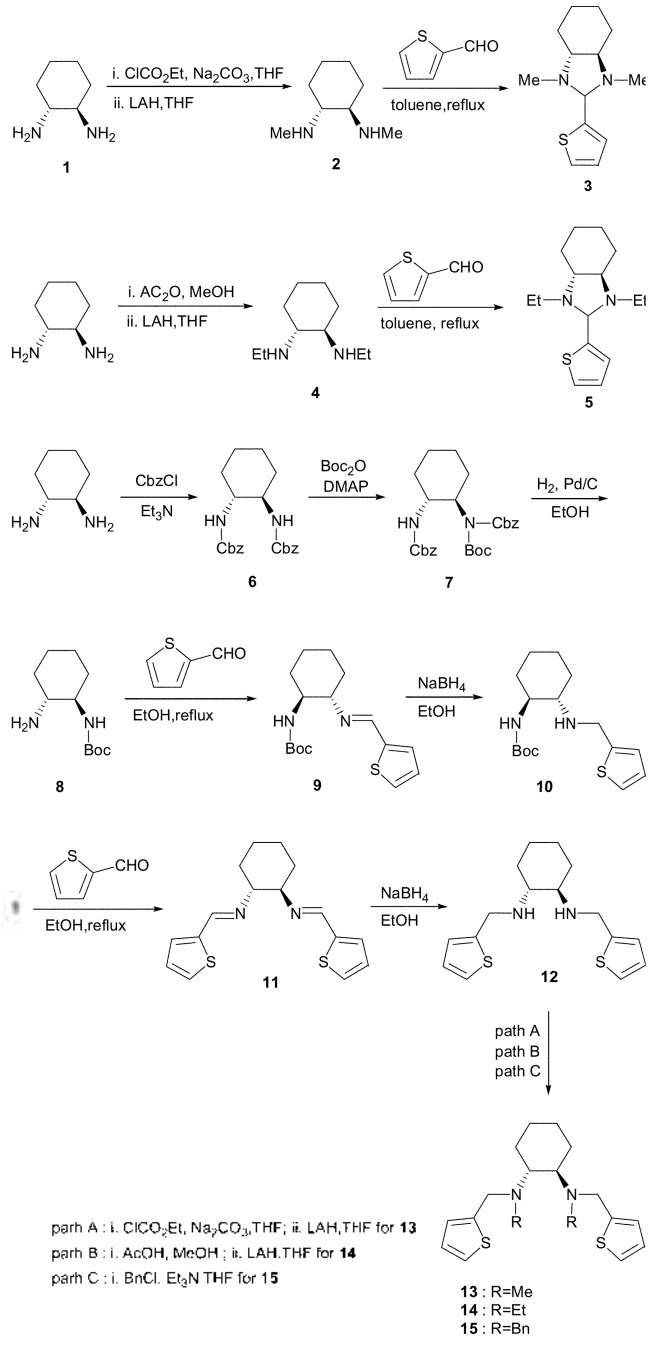
The tetradentate thiophene diamine derivatives **12** and **13** are proved to be very efficient in terms of enantioselectivity in the reaction. In particular, *N,N*-dimethyl derivative **13** affords the alkylation product with up to 98% ee. The results are comparable to those to phosphinooxazolines.[9] In case of ligand 12, use of THF as solvent is more desirable than CH_2Cl_2. The reduction of temperature to 0 °C seems to have little effect on the enantiomeric excess. BSA-KOAc as additive source gave somewhat better enantioselectivity. And then, in case of ligand **13**, solvent exchange and reduction of temperature didn't play a key role in the enantioselectivity. Surprisingly, however, additive sources showed great difference in the enantioselectivity. BSA-LiOAc gave much better enantioselectivity. Moreover, we investigated the influence of the ratio of ligand versus palladium on the enantiomeric excess, and observed an increase in the ee value with the amount of ligand introduced. The best result in enantioselectivity was obtained when the ratio of ligand/palladium was 4/1. It has been found that poor results were obtained in terms of enantioselective and reactivity in case of ligand **14** and **15**. In contrast, bidentate thiophene diamine derivatives **3** and **5** gave moderate asymmetric induction and modest reactivity.

Although the chelation mode of ligand with Pd metal is not clear, asymmetric induction by ligand **13** can be explained as follows. Probably, a nucleophilic attack to π-allyl-palladium complex proceeds predominantly at the allyl terminus trans to the better -acceptor. Thus, the nucleophile addition could proceed through the complex having a W-shaped allyl part as a major path that which led to (*R*)-configuration as illustrated in Scheme 1.

In conclusion, we have developed the effective of chiral ligands, bi-, tri- and tetradentate thiophene diamine derivatives, for the Pd-catalyzed enantioselective allylic alkylation. These chiral ligands could be applied successfully and the high enantioselectivities were attainable in this enantioselective allylic alkylation.



Scheme 1



Scheme 2

Experimental Section

Generals: NMR spectra were recorded at 400 MHz (^{1}H and ^{13}C) using a Varian Unity INOVA400 Spectrometer. FT-IR spectra were obtained on BRUKER IFS 48 spectrometer. CH_2Cl_2 was distilled from CaH_2. Tetrahydrofuran was refluxed over sodium at least for 5h under nitrogen atmosphere. (*R,R*)-1,2-diaminocyclohexane was purchased from Aldrich. All experiments were conducted under an atmosphere of nitrogen. Optical rotations were measured on a Perkin Elmer 241 polarimeter and were reported using 1-dm cell along with the solvent and concentration in g/100 mL. Flash chromatography was carried out using Merck silica gel 60 (230 to 400 mesh). The enantiomeric excesses of the product were determined by HPLC (Daicel chiralcel OD-H column, 25 cm × 0.46 cm, λ 254 nm, 1% 2-propanol in hexane, 0.5 mL/min.).

Scheme 2 shows the method to synthesize the bidentate chiral thiophene diamine derivatives (**3** and **5**), tri- and tetradentate thiophene diamine derivatives (**10**, **12** and **13**-**15**). These chiral ligands can be readily derived from enantiomerically pure (*R,R*)-1,2-diaminocyclohexane **1** and 2-thiophenecarboxaldehyde. The chiral ligand **12** can be readily synthesized by condensation of enantiomerically pure (*R,R*)-1,2-diaminocyclohexane **1** and 2-thiophenecarboxadehyde in the refluxing ethanol, followed by reduction with $NaBH_4$ at room temperature for 6h. The chiral ligand **13**[10] was synthesized by the reaction of (*R,R*)-1,2-diamino cyclohexane derivative **12** with ethyl chloroformate in the H_2O, followed by lithium aluminum hydride (LAH) reduction in anhydrous THF. The chiral ligand **14** and **15** were prepared through methylation and benzylation as described in Scheme 2. The compound **8** was synthesized by the method with similar yield.[11]

Acknowledgment. This research was supported by the Institute of Clean Technology, Inha University.

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10. Selected data: for NMR ($CDCl_3$, 298 K): δ_H (400 MHz) 1.25 (m, 4H), 1.68 (m, 4H), 2.29 (s, 6H), 2.66 (m, 2H), 3.98 (dd, *J* 2.8, 4H) 6.92-7.2 (m, 6H); δ_C (400 MHz) 22.5, 25.9, 27.3, 36.1, 54.7, 63.4, 124.6, 126.3 and 126.6.; $[\alpha]_D$ = -22.98 (c = 1.0, $CHCl_3$); IR (KBr) 3300, 2930, 2790, 1450, 1340, 825 and 690.
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