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Highly Regio- and Enantioselective Heck Reaction of *N*-Methoxycarbonyl-2-pyrroline with Planar Chiral Diphosphine-oxazoline Ferrocenyl Ligands

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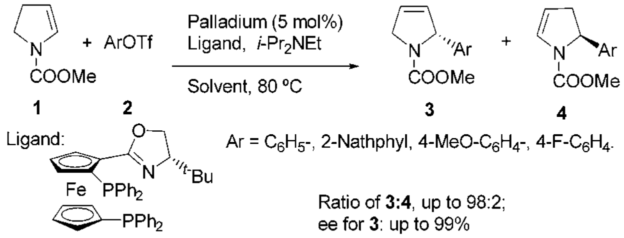
ABSTRACT



A series of planar chiral diphosphine-oxazoline ferrocene ligands were effectively applied in the asymmetric arylation of *N*-methoxycarbonyl-2-pyrroline, and up to 99% ee was observed for the product 3. The regioselectivity of this reaction was strongly affected by the different precursors of the palladium species and the polarity of the solvent.

Heck reaction is one of the most powerful tools in contemporary organic synthesis.[1] The intermolecular asymmetric Heck reaction has been devised mainly for use with dihydrofuran as a substrate,[2] which was first reported by Hayashi and co-workers in 1991.[3] Much research has been devoted to expanding the scope of the substrates and to increasing the chemical selectivity. Dihydropyrrole derivatives are suitable substrates and more useful in organic synthesis; their asymmetric Heck reactions had been reported by Hayashi,[4] Tietze,[5] and Pfaltz.[6] When BINAP and BITIANP were applied in this reaction, double-bond-isomerized product **4a** was obtained as the major product,[4,5] up to 93% ee was found when BITIANP was used as the ligand.[5] However, the report on the reaction to give the product **3a** (2,5-dihydropyrrole) in high regio- and enantioselectivity is rather limited. Only when PHOX was applied in this reaction, product **3a** was the single product, obtained with 85% ee value (Scheme 1).[6] During the course of synthesis of planar chiral ferrocene

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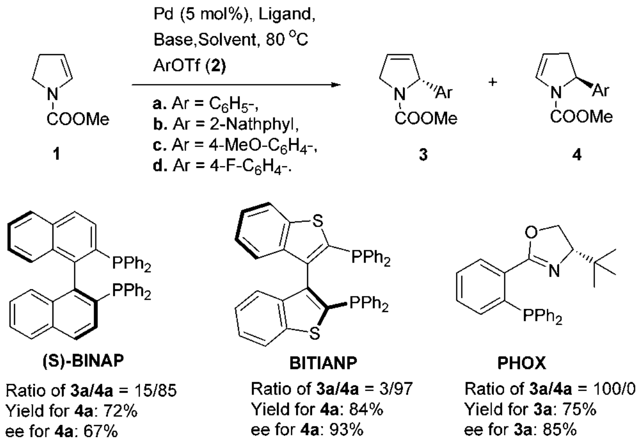
Scheme 1. Intermolecular Heck Reaction of *N*-Methoxy-carbonyl-2-pyrroline



ligands and their applications in asymmetric catalysis,[7] we found that diphosphine-oxazoline ferrocenyl ligands are effective in the asymmetric arylation of 2,3-dihydrofuran.[8] Herein, we would like to show that these ligands are also useful in the arylation of *N*-methoxycarbonyl-2-pyrroline and that high regio- and enantioselectivity were obtained.

Initially, the asymmetric Heck reactions of *N*-methoxycarbonyl-2-pyrroline (**1**) in the presence of ligand (*S*,*S*p)-**5a**−**d** were performed in toluene at 80 °C using 5 mol % Pd(OAc)$_2$ as a catalyst with a Pd/ligand ratio of 1:2 and *i*-Pr$_2$NEt as a base.[9] The best enantioselectivity (98% ee) for 2,5-dihydropyrrole **3a** with high regioselectivity (ratio of **3a**:**4a** was 93:7) was observed with *tert*-butyloxazoline ligand (*S*,*S*p)-**5c**. A similar result (ratio of **3a**:**4a** was 91:9 and 97.7% ee for **3a**) was also found with benzyl ligand (*S*,*S*p)-**5b**. However, when the substituent on the oxazoline ring was an isopropyl or phenyl group, the ee value of product **3a** decreased to 78 and 62%, respectively, but a good regioselectivity still remained (96:4 and 94:6 for **3a**:**4a**, respectively). Then, when a ligand with (*R*p)- planar chirality, (*S*,*R*p)-**5a**, was applied in this reaction, the ee value decreased significantly (40% ee for **3a**); however, the configuration of product was still (*R*)- with high conversion, and the regioselectivity was also diminished (80:20), because the planar (*R*p)- and central (*S*)- chiralities of the ligand were not matched in this case.[8b,10,11]

With these results in hand, the other aryl triflates were applied in this reaction to examine the generality of the ligand system. When 2-naphthyl triflate was applied, with ligands (*S*,*S*p)-**5b** or (*S*,*S*p)-**5c** and Pd(OAc)$_2$ as catalysts in toluene, naphthylation product **3b** was provided with better regio- and enantioselectivity (ratio of **3b**:**4b** was 85:15, 66% ee for **3b**) with (*S*,*S*p)-**5c** (Table 1, entries 1 and 2). Even better regio- and enantioselectivity was found (90:10, 79% ee) when benzene was used instead of toluene, the difference being more obvious than in phenylation (Table 2, entry 2 vs 3). When 4-methoxyl-phenyl triflate and 4-fuloro-phenyl triflate were applied in this reaction, higher regioselectivity (98:2) was observed in these two cases either with an electron-

Table 1. Enantioselective and Regioselective Heck Reaction of *N*-Methoxycarbonyl-2-pyrroline with Different Aryl Triflate[a]

	ligand	solvent	Ar	conversion[b] (%)	ratio[b] of **3**:**4**	yield (%) of **3**	ee[c] (%) of **3** (*R*)[d]
1	(*S*,*S*p)-**5b**	toluene	2-naphthyl	60	75:25	39	53
2	(*S*,*S*p)-**5c**	toluene	2-naphthyl	84	85:15	67	66
3	(*S*,Sp)-**5c**	benzene	2-naphthyl	76	90:10	62	79
4	(*S*,Sp)-**5c**	benzene	4-MeO-C$_6$H$_4$	75	98:2	68	90
5	(*S*,Sp)-**5c**	benzene	4-F-C$_6$H$_4$	85	98:2	76	97

[a] Reactions were carried out in the presence of ligand and Pd(OAc)$_2$ at 80 °C under an argon atmosphere. [b] Conversions and the ratio of **3**/**4** were determined by GC with *n*-tridecane as an internal standard based on aryl triflate (**2**). [c] Determined by HPLC. [d] Absolute configuration of products was assigned according to the literature method.[4]

Table 2. Effect of Solvent and Palladium Precursors on the Regioselectivity of Asymmetric Phenylation of *N*-Methoxycarbonyl-2-pyrroline[a]

	palladium	solvent	conversion[b] (%)	ratio[b] of **3a**:**4a**	**3a** (*R*)[c]		**4a** (*S*)	
					ee[d] (%)	yield (%)	ee[d] (%)	yield (%)
1	Pd(OAc)$_2$	benzene	78	95:5	98	68	nd	
2	Pd(OAc)$_2$	toluene	75	93:7	98	63	nd	
3	[Pd$_2$(dba)$_3$·dba]	benzene	93	31:69	nd		11	60
4	Pd(OAc)$_2$	DMF	92	75:25	99	52	nd	
5	Pd(OAc)$_2$	(CH$_2$Cl)$_2$	93	42:58	nd		29	47
6[e]	[Pd$_2$(dba)$_3$·dba]	(CH$_2$Cl)$_2$	85	34:66	nd		18	53

[a] Reactions were carried out in the presentce of 5 mol % catalyst (palladium precursor and (*S*,*S*p)-**5c**) at 80 °C for 3 days under an argon atmosphere. [b] Conversions and ratio of **3a**/**4a** were determined by GC with *n*-tridecane as an internal standard based on phenyl triflate (**2a**). [c] Absolute configuration of products was assigned through comparison of the sign of specific rotations with literature data.[4] [d] Determined by HPLC on a Chiralcel OG-H column. [e] Carried out at 80 °C for 2 days.

donating MeO− group or with an electron-withdrawing F group (Table 1, entries 4 and 5).

When planar ferrocene diphosphinooxazoline ligands were applied in the asymmetric Heck reaction of 2,3-dihydrofuran, dramatic change of regioselectivity were found with different palladium precursors and solvents.[8] This change also holds in the case of pyrroline derivatives. When [$Pd_2(dba)_3$•dba] was applied with ligand (*S*,*S*p)-**5c** as a catalyst in the phenylation in benzene, the regioselectivity changed from 95:5 to 31:69 (Table 2, entry 3 vs entries 1 and 2). This change is like that in the arylation of 2,3-dihydrofuran: [$Pd_2(dba)_3$•dba] favors the formation of isomerized product **4a**, while $Pd(OAc)_2$ favors the formation of **3a**.[8] When a more polar solvent such as DMF was used with $Pd(OAc)_2$ and ligand (*S*,*S*p)-**5c** was used as a catalyst, the regioselectivity (75:25) was lower than that in benzene and toluene, but the ee value of isomer **3a** was still high. In the case of 1,2-dichloroethane, the regioselectivity favored the formation of the isomerized product.

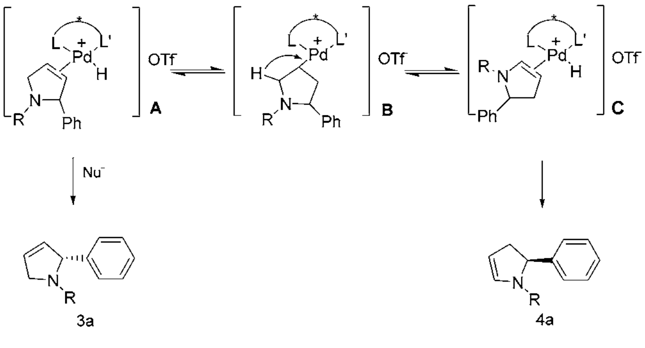
This has been rationalized by the assumption that acetate anion in the reaction system should possess sufficient nucleophilicity toward the cationic palladium center in the hydride−olefin complex **A** to cause the dissociation to give product **3a** (Scheme 3). However, when [$Pd_2(dba)_3$•dba] was used, a similar nucleophile attack could not occur, so palladium would re-insert into the olefin to give complex **C**; a subsequent β-hydride elimination therefore proceeded more easily to give **4a**. Furthermore, the nucleophilicity of an acetate anion should be more pronounced in a nonpolar medium such as benzene.[12,13]

Scheme 2. Diphosphine-oxazoline Ferrocenyl Ligands

(S,Sp)-5a R = *i*-Pr
(S,Sp)-5b R = Bn
(S,Sp)-5c R = *t*-Bu
(S,Sp)-5d R = Ph

(S,Rp)-5a R = *i*-Pr

Scheme 3. Possible Mechanism of Influence on the Path toward **3a** or **4a**



R = COOMe

In summary, a series of planar ferrocene diphosphine-oxazoline ligands were successfully applied in the asymmetric arylation of *N*-methoxycarbonyl-2-pyrroline, and high regio- and enantioselectivity were realized. The properties of solvents and the palladium species have a great impact on the regioselectivity of the reaction.

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Supporting Information Available: General experimental procedure and analytical data for ligands **5** and products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] **Geneal Experimental Procedure.** Palladium species (50 μmol), diphosphine-oxazoline ferrocenyl ligand (0.1 *m*mol), and solvent (5 mL) were placed under Ar in a Schlenk tube with a magnetic stirring bar. After 30 min of reaction, aryl triflate (1 mmol) and *n*-tridecane (20 mg) (as an internal GC standard) were added, followed by the addition of *N*-methoxycarbonyl-2-pyrroline **1** (638 mg, 5 mmol) and *i*-Pr_2NEt (2 mmol). The mixture was stirred at 80 °C under Ar until the reaction was complete according to GC analysis. The reaction mixture was diluted with additional EtOAc (20 mL), and the resulting red suspension was extracted with saturated Na_2CO_3 (3 × 10 mL) solution. The organic solution was dried with Na_2SO_4 and then concentrated to give a red oil, which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to afford **3** and **4** as a colorless oil.

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