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New chiral ligands, pyrrolidinyl- and 2-azanorbornyl-phosphinooxazolidines for palladium-catalyzed asymmetric allylation

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Abstract

Pyrrolidinyl- **2** and 2-azanorbornylphosphinooxazolidines **3**, a new type of optically active ligands, were synthesized easily and their abilities as ligands were examined in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. Enantiomeric excesses of up to 96% have been obtained using 1 mol% of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2.1 mol% of **2**.

1. Introduction

Catalytic asymmetric synthesis has been a challenging subject in organic synthesis. The development of efficient enantioselective catalysts applicable to a wide range of carbon–carbon bond forming reactions represents a pivotal challenge to the synthetic community. Among the ligands, chiral oxazolines have proved to be extremely efficient ligands in some catalytic reactions.[1] Recently, chiral phosphinooxazolidine **1** has been shown to be an effective ligand in Pd-catalyzed asymmetric allylic substitutions[2] similarly to phosphinooxazolines. To the best of our knowledge, there is only one system **1**. We wish to report the synthesis of two kinds of new chiral ligands, pyrrolidine-based phosphinooxazolidine **2** and 2-azanorbornane-based phosphinooxazolidine **3**, followed by the application to Pd-catalyzed allylic alkylation. This allylation[3] has been widely employed as an efficient and convenient tool for carbon–carbon and carbon–heteroatom bond formation in the field of organic synthesis.

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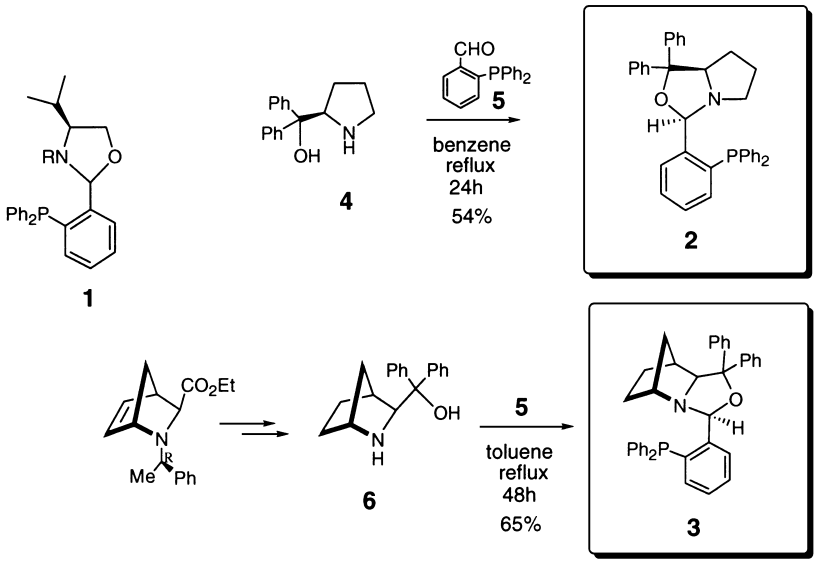
2. Results and discussion

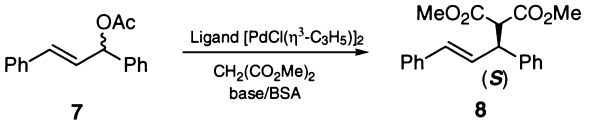
Preparations of the chiral ligands **2** and **3** are described in Scheme 1. The chiral pyrrolidinylphosphinooxazolidine **2** was readily synthesized by the condensation of commercially available (*R*)-pyrrolidinylmethanol **4** with 2-(diphenylphosphino)benzaldehyde **5** in refluxing benzene using a Dean–Stark apparatus. More sterically constrained 2-azanorbornylphosphinooxazolidine **3** was obtained from **6**, reported by our group,[4] with **5** in refluxing toluene. The stereochemistries of the newly created stereogenic center at the 2-position of the 1,3-oxazolidine ring for **2** and **3** were determined by the NOE measurement of ^{1}H NMR spectra, respectively. Thus, the NOE experiments for **2** and **3** confirmed an interaction between the hydrogen at the 2-position and at the 4-position, respectively.



Scheme 1.

In order to examine the effectiveness of the ligands, the enantioselective allylic alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate was tried in the presence of π-allylpalladium chloride dimer. The results are summarized in Table 1. The reaction was tried under the BSA standard conditions (entries 1–7). Using 2.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 10 mol% ligands (**2** and **3**), similarly to Jin's report,[2] good results were not obtained, although both ligands **2** and **3** worked to give the alkylation product **8** (entries 1 and 2). The excellent result (98 and 96% ee) (entry 3)[5] was achieved by using 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2.1 mol% ligand **2**. However, 2-azanorbornane-based phosphinooxazolidine **3** was also less effective (53%, 43% ee) under these reaction conditions (entry 4). Furthermore, this reaction was carried out under other reaction conditions using ligand **2** (entries 5–10). The reduction of the temperature to 0 or 10°C decreased the enantiomeric excesses (entries 5 and 6). When THF was used as a solvent, high enantiomeric excess (95% ee) was confirmed similarly to the case of entry 3 (entry 7). The reaction in acetonitrile did not give a good result (entry 8). The conditions using tetrabutylammonium fluoride (TBAF) gave 85 and 87% ee (entry 9). However, reduction of the temperature decreased the enantiomeric excess (73% ee) (entry 10).

Table 1
Asymmetric Pd-catalyzed allylation of 1,3-diphenyl-2-propenyl acetate



7 8

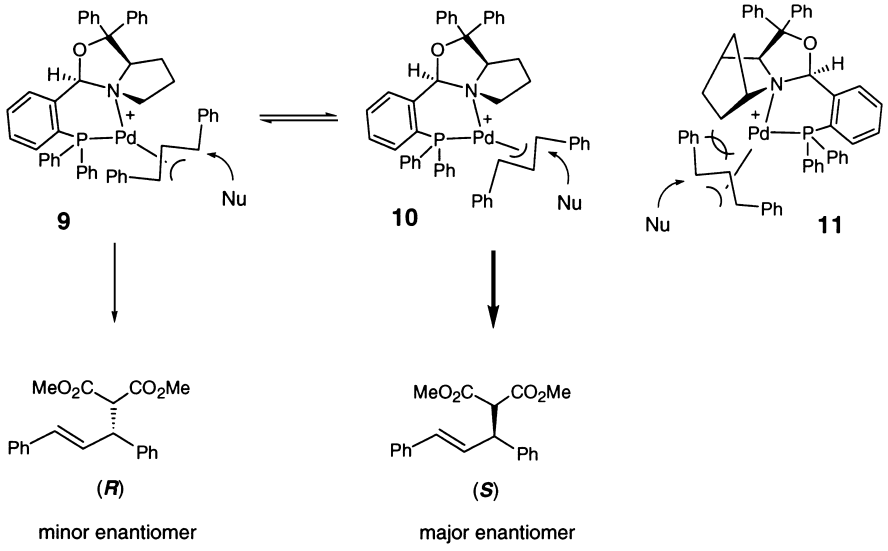
Entry	Ligand	Ligand (mol%)	Temp. (°C)	Solvent	Base	Time (h)	Yield[d] (%)	E.e.[e,f] (%)
1[a]	**2**	10	r.t.	CH_2Cl_2	CH_3COOK	6	77	86
2	**3**	10	r.t.	CH_2Cl_2	CH_3COOK	6	54	46
3[b]	**2**	2.1	r.t.	CH_2Cl_2	CH_3COOK	3	98	96
4	**3**	2.1	r.t.	CH_2Cl_2	CH_3COOK	5	53	43
5	**2**	2.1	10	CH_2Cl_2	CH_3COOK	9	86	83
6	**2**	2.1	0	CH_2Cl_2	CH_3COOK	9	84	71
7	**2**	2.1	r.t.	THF	CH_3COOK	6	90	95
8	**2**	2.1	r.t.	CH_3CN	CH_3COOK	3	83	81
9[c]	**2**	2.1	r.t.	CH_3CN	TBAF	3	85	87
10	**2**	2.1	10	CH_2Cl_2	TBAF	9	79	73

a) Molar ratio for entries 1,2 : $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.025 equiv.), dimethyl malonate (3 equiv.), *N,O*-bis- (trimethylsilyl)acetoamide (BSA) (3 equiv.), potassium acetate (0.03 equiv.) . b) Molar ratio for entries 3-8: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.01 equiv.), dimethyl malonate (3 equiv.), *N,O*-bis(trimethylsilyl)acetoamide (BSA) (3 equiv.), potassium acetate (0.02 equiv.). c) Molar ratio for entries 9-10: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.01 equiv.), dimethyl malonate (3 equiv.), *N,O*-bis(trimethylsilyl)acetoamide (BSA) (3 equiv.), tetrabutylammonium fluoride (TBAF) (3 equiv.). d) Isolated yields. e) Determined by HPLC analysis using a DAICEL chiralcel OD-H column. f) S-Configuration based on the specific rotation with literature data, [3a,b] $[\alpha]_D^{23} = 23.57$ (c 1.4, $CHCl_3$)(96% ee)

Unfortunately, better results were not found under these conditions. From the above results, phosphinooxazoline **2** is an excellent ligand in this allylation under the reaction conditions of entry 3.

It is considered that the enantioselective step in Pd-catalyzed allylation is the substitution of π-allyl complexes with nucleophiles and nucleophilic attack occurs predominantly at the allyl terminus from *trans* to the better π-acceptor (P≫N).[6] Since the (*S*)-product was obtained as the major enantiomer, the reaction probably proceeds through an M-type **10** rather than a W-type **9** intermediate.[6] In addition, the differentiation of chemical yields and enantiomeric excesses for the ligands **2** and **3** may be explained by steric inferences. Thus, the 2-azanorbornane skeleton, which

is more bulky than the pyrrolidine skeleton, obstructs the construction of the π-allyl palladium complex **11** (Scheme 2).



Scheme 2.

3. Conclusions

We have prepared two kinds of new chiral ligands **2** and **3**. These worked as ligands for allylic substitution reactions. In particular **2** was a good and effective ligand and gave an excellent chemical yield and enantiomeric excess. It is expected that **2** and **3** would act as good ligands in other catalytic asymmetric reactions. Further applications and modifications of the ligand **2** are in progress.

4. Experimental

4.1. General

IR spectra were measured with a Perkin–Elmer 1725X spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX 270 and a JEOL JNM-LA 400 spectrometer with TMS as an internal standard. MS were taken on Hitachi RMG-6MG and JEOL-JNM-DX 303 spectrometers. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Thin layer chromatography was performed with Merck F-254 silica gel plates. Preparative thin layer chromatography was carried out on Merck PSC-Fertirplatten Kieselgel 60 F254 plates.

4.2. (2R,5R)-1-Aza-2-(2-diphenylphosphino)phenyl-3-oxa-4,4-diphenylbicyclo[3.3.0]octane 2

(*R*)-(+)-α,α-Diphenyl-2-pyrrolidinemethanol **4** (100 mg, 0.4 mmol), 2-(diphenylphosphino)-benzaldehyde **5** (128 mg, 0.44 mmol), *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol)

and benzene (8 ml) were placed in a flask equipped with a Dean–Stark trap. The mixture was refluxed overnight. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (hexane:ether = 6:1) to give pure **2** (112 mg) in 54% yield. Mp 52–54°C, $[\alpha]_D^{23} = +95.0$ (c 1.0, $CHCl_3$). IR (film) cm^{-1}: 746, 697. ^1H NMR ($CDCl_3$) δ 7.62 (m, 1H), 7.11–7.38 (m, 22H), 6.88 (m, 1H), 6.36 (d, $J = 6.3$ Hz, 1H), 4.31 (t, $J = 7.0$ Hz, 1H), 2.93 (m, 1H), 2.75 (m, 1H), 1.43–1.70 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 137.18, 133.99, 133.81, 133.70, 133.52, 133.28, 128.83, 128.26, 128.21, 128.15, 128.10, 128.00, 127.77, 127.69, 127.63, 127.50, 126.47, 126.39, 126.18, 126.04, 94.78, 94.45, 73.34, 50.52, 27.82, 24.43. Anal. calcd for $C_{36}H_{32}NOP$: C, 82.26; H, 6.14; N, 2.66. Found: C, 81.98; H, 6.10; N, 2.46. MS m/z: 525 (M^+).

4.3. (1R,3S,6S,7S)-2-Aza-3-(2-diphenylphosphino)phenyl-4-oxa-5,5-diphenyltricyclo[5.2.1.0^{2,6}]-decane ***3***

Compound **6** (200 mg, 0.72 mmol), 2-(diphenylphosphino)benzaldehyde **5** (240 mg, 0.81 mmol) and toluene (20 ml) were placed in a flask equipped with a Dean–Stark trap. The mixture was refluxed for 48 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (hexane:ether = 5:1) to give pure **3** (230 mg) in 65% yield. Mp 230–232°C, $[\alpha]_D^{23} = -45.3$ (c 1.7, $CHCl_3$). IR (film) cm^{-1}: 748, 697. ^1H NMR ($CDCl_3$) δ 8.14 (m, 1H), 7.05–7.69 (m, 23H), 6.06 (d, $J = 5.3$ Hz, 1H), 4.11 (s, 1H), 2.56 (s, 1H), 1.89 (br s, 1H), 1.51 (d, $J = 9.5$ Hz), 1.16–1.26 (m, 2H), 0.82 (m, 1H), 0.65 (m, 1H), 0.53 (d, $J = 9.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 138.40, 138.32, 137.62, 137.55, 135.88, 135.65, 134.90, 134.89, 134.43, 134.23, 133.43, 133.24, 129.06, 128.86, 128.52, 128.50, 128.43, 128.01, 127.99, 127.94, 127.60, 125.90, 125.85, 115.95, 112.12, 81.41, 81.58, 60.39, 53.01, 51.54, 51.51, 27.92, 23.75. Anal. calcd for $C_{38}H_{34}NOP$: C, 82.73; H, 6.21; N, 2.54. Found: C, 82.84; H, 6.18; N, 2.45. MS m/z: 551 (M^+).

4.4. General procedure [method A (entries 1–8), method B (entries 9–10)] for the Pd-catalyzed allylic substitutions of rac-*1,3-diphenyl-2-propenyl acetate with dimethyl malonate using* ***2*** *and* ***3*** *as chiral ligands*

Method A: a mixture of ligand **2** (entries 1–2: 0.04 mmol; entries 3–8: 0.008 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (entries 1–2: 0.01 mmol; entries 3–8: 0.004 mmol) in dry solvent (1 ml) indicated in Table 1 was stirred at room temperature for 1 h and the resulting yellow solution was added to a mixture of acetate **7** (0.4 mmol) and base [entries 1–8: potassium acetate (entries 1–2: 0.012 mmol; entries 3–8: 0.008 mmol)] in dry solvent (1 ml) using a syringe followed by the addition of dimethyl malonate (1.2 mmol) and BSA (1.2 mmol). Method B: a mixture of ligand **2** (0.008 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.004 mmol) in dry solvent (1 ml) was stirred at room temperature for 1 h and the resulting yellow solution was added to a solution of acetate **7** (0.4 mmol) in dry solvent (1 ml) using a syringe followed by the addition of a mixture of dimethyl malonate (1.2 mmol), TBAF (1.2 mmol) and BSA (1.2 mmol). The reactions of methods A and B were carried out at ambient temperature and the reaction mixtures were diluted with ether and were quenched with satd NH_4Cl. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (hexane:ether = 5:1) to give a pure product **8**. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, 0.5 ml/min, hexane:2-propanol = 98:2). The absolute configuration was determined by specific rotation.[3a,b]

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