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Facile one-pot synthesis of *cinchona alkaloid*-based P,N ligands and their application to Pd-catalyzed asymmetric allylic alkylation

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ABSTRACT

A novel class of bidentate chiral P,N donor ligands based on *cinchona alkaloids* is described. These ligands are easily synthesized in one-pot from commercially available enantiopure 1,2-diphenyl-1,2-ethanediol and cinchona alkaloids in two steps. Their application to the palladium(II)-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate gave the corresponding products in excellent yields and up to 94% ee. The effect of ligands, substrates, nucleophiles, and temperature on the reaction was also investigated.

1. Introduction

Readily accessible *cinchona alkaloids* play a significant role in organic chemistry as chiral base catalysts, ligands, and chromatographic selectors in asymmetric synthesis.[1,2] There are already a number of papers on them. However, compared with their broad applications as organocatalysts, *cinchona alkaloids,* and their derivatives as ligands attached to transition metals have developed more slowly despite the fact that the osmium-complexed *cinchona alkaloid* derivatives designed by Sharpless et al. achieved great success in asymmetric catalysis.[3] To date, with the exception of one type of *N,N*-bidentate *cinchona alkaloid* ligand as reported by our group,[3] there have been no published reports on P,N-bidentate ligands derived from *cinchona alkaloids*. Moreover, palladium-catalyzed asymmetric allylic substitution is versatile, and widely used in organic synthesis for the enantioselective formation of C–C and C-heteroatom bonds.[4] Over the past decade, we have seen a huge advance in enantiocontrol in Pd-catalyzed allylic substitution reactions.[5] However, there still remains some drawbacks about the catalytic systems which have been reported to date.[4]

Herein, we report the synthesis of a new family of P,N-bidentate ligands which was derived from *cinchona alkaloids* and their catalytic action in asymmetric palladium-catalyzed asymmetric allylic alkylation (AAA).

2. Results and discussion

Cinchona alkaloids contain five stereogenic centers: N_1, C_3, C_4, C_8, and C_9.[6] When chiral phosphorochloridite derived from an enantiopure 1,2-diol was coupled with *cinchona alkaloids* by substituting the hydroxyl group at C_9, a family of phosphites with a retentive configuration at C_9 was achieved. Characterized by seven stereogenic centers and two donor sites (quinuclidine N atom and P atom), these *cinchona alkaloid* derivatives can provide a chelate ring when coordinated to transition metal.

The chiral ligands **2a**–**d** were easily prepared from (*S*,*S*)-1,2-diphenyl-1,2-ethane diol and *cinchona alkaloids* in 'one-pot' via two steps (Scheme 1). Initially, (*S*,*S*)-1,2-diphenyl-1,2-ethanediol was added into phosphorus trichloride in dry THF to give a phosphorochloridite intermediate. The phosphorochloridite intermediate was not isolated in its pure form but used directly in solution to react with *cinchona alkaloids* **1a**–**d** in the presence of triethylamine as an acid-binding agent. After stirring overnight at 60 °C, the heterogeneous system produced ligands **2a**–**d**. The total yields ranged from 63% to 75%.

With target ligands **2** in hand, we turned our attention to investigating their potential utilities in asymmetric catalysis. The palladium-catalyzed AAA reaction was chosen as a model reaction to test them.

The steric properties of ligands **2a**–**d** were identified to affect the activity and enantioselectivity of the AAA reaction of 1,3-diphenyl-3-acetoxyprop-1-ene. The results are shown in Table 1. Cinchonine and quindine-derived ligands **2a** and **2d** exhibited better catalytic activity and enantioselectivity than their pseudo-enantiomers **2b** and **2c** (Table 1, entries 1–4).

Moreover, the effect of nucleophiles on the reaction was also investigated. The reaction with acetylacetone in place of dimethyl malonate gave the corresponding product with an (*S*)-configuration in higher yields and moderate to excellent ees (Table 2). A similar improvement was also found in the same reaction with 3-methyl-2,4-pentanedione **4** as a nucleophile (Table 2) and (*S*)-3-acetyl-3-methyl-4,6-diphenylhex-5-en-2-one was obtained.

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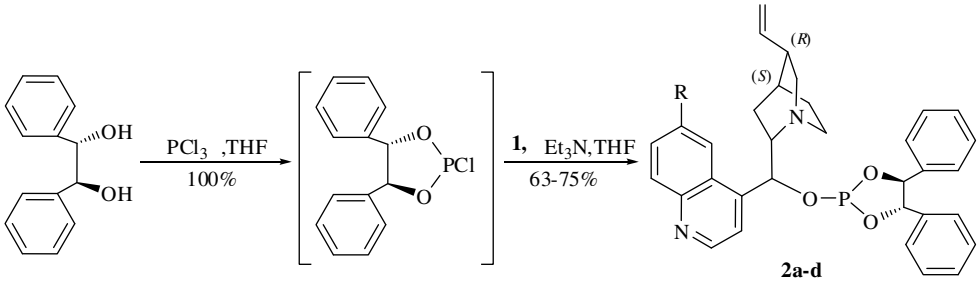
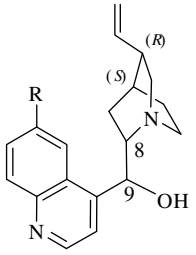
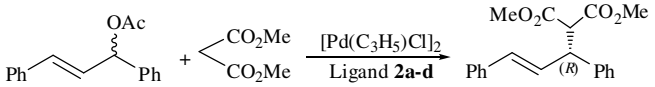




1a	R = H	cinchonine (8*R*,9*S*)
1b	R = H	cinchonidine (8*S*,9*R*)
1c	R = OMe	quinine (8*S*,9*R*)
1d	R = OMe	quinidine (8*R*,9*S*)

Scheme 1. The synthesis of ligands **2a–d**.

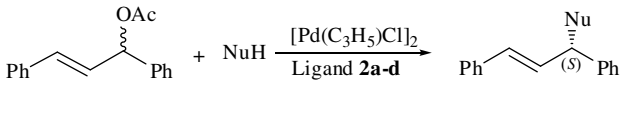
Table 1
AAA reaction with dimethyl malonate as a nucleophile catalyzed by Pd–ligand **2** complex[a]

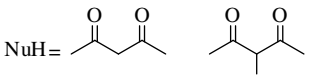


Entry	Ligand	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%) (config.[d])
1	**2a**	28	15	100	70 (*R*)
2	**2b**	28	32	65	55 (*R*)
3	**2c**	28	32	75	45 (*R*)
4	**2d**	28	24	93	62 (*R*)
5	**2a**	0	24	100	83 (*R*)
6	**2a**	−30	24	72	94 (*R*)
7	**2d**	0	48	74	75 (*R*)
8	**2d**	−30	48	45	88 (*R*)

[a] All reactions were performed using 2 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6 mol % ligand, 3 mol % KOAc, 300 mol % BSA, 300 mol % dimethyl malonate, and 1 equiv substrate in 5 mL dry CH_2Cl_2 under N_2.
[b] Isolated yield.
[c] The ee values were determined by chiral HPLC (Chiral OD-H column, *n*-hexane/*i*-propanol = 90:10, 0.5 mL/min).
[d] The absolute configuration was assigned by comparison of the sign of specific rotation with reported data.[7]

Table 2
AAA reaction catalyzed by Pd–ligand **2** complex with **3** or **4** as nucleophile[a]





3 **4**

Entry	Ligand	NuH	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%) (config.[d])
1	**2a**	**3**	28	9	100	80 (*S*)
2	**2b**	**3**	28	24	85	66 (*S*)
3	**2c**	**3**	28	18	82	66 (*S*)
4	**2d**	**3**	28	18	95	73 (*S*)
5	**2a**	**3**	0	24	80	92 (*S*)
6	**2b**	**3**	0	24	65	75 (*S*)
7	**2c**	**3**	0	24	60	77 (*S*)
8	**2d**	**3**	0	24	75	85 (*S*)
9	**2a**	**4**	28	12	100	75 (*S*)
10	**2b**	**4**	28	24	85	65 (*S*)
11	**2c**	**4**	28	12	73	59 (*S*)
12	**2d**	**4**	28	15	100	66 (*S*)
13	**2a**	**4**	0	24	75	90 (*S*)
14	**2b**	**4**	0	24	65	78 (*S*)
15	**2c**	**4**	0	24	Scarce	N.D
16	**2d**	**4**	0	24	70	85 (*S*)

[a] All reactions were performed using 2 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6 mol % ligand, 3 mol % KOAc, 300 mol % BSA, 300 mol % **3** or **4**, and 1 equiv substrate in 5 mL dry CH_2Cl_2 under N_2.
[b] Isolated yield.
[c] The ee values were determined by chiral HPLC (entries 1–8: chiral AD column, *n*-hexane/2-propanol = 99:1, 1.0 mL/min; entries 9–16: chiral OJ-H column: *n*-hexane/*i*-propanol = 90:10, 0.8 mL/min).
[d] The absolute configuration was assigned by comparison of the sign of specific rotation with reported data.[7,8]

The experiment suggested that the activity and stability of the nucleophile's carbanion had a great influence on the reaction efficiency, as 'soft nucleophiles' **3** and **4** were generally more active than dimethyl malonate under basic conditions.

Furthermore, the AAA reaction was also temperature dependent. Similar to most asymmetric catalytic reactions, the substrate conversion decreased but the enantioselectivity was improved when the temperature was lowered (Tables 1 and 2).

It is known that cinchona alkaloids **1a** and **1b** behave as pseudo-enantiomers, as do **1c** and **1d**.[2,6] When they are used to catalyze asymmetric reactions, such as asymmetric dihydroxylation and enantioselective decarboxylation, enantiomers with similar enantiomeric excesses but opposite absolute configuration are often obtained.[6,9] However, in our experiments, ligands **2a–d** always gave the same configuration of product in the AAA reaction under the same conditions. Obviously, it is not the backbone structure of cinchona alkaloid in ligands **2a–d** but that of (*S*,*S*)-1,2-diphenyl-1,2-ethanediol, which is responsible for the configuration of the products. The oppositely configured (*S*)-product was prepared when ligands derived from the (*R*,*R*)-1,2-diphenyl-1,2-ethanediol were used to catalyze the AAA reaction under the reaction conditions.

Instead of 1,3-diphenyl-3-acetoxyprop-1-ene, the asymmetric allylic alkylation of 3-acetoxy-cyclohexene was also examined

under the same conditions as shown in Table 1. However, it resulted in a low enantiomeric excess (<29% ee) and chemical yield (<45%), which were unsatisfactory.

3. Conclusion

In conclusion, we have described the first case of *cinchona alkaloid*-based P,N ligands. They were easily synthesized from *cinchona alkaloids* and optically active C_2-symmetric 1,2-diols. The application for palladium-catalyzed enantioselective allylic alkylation gave high yields and moderate to excellent ees. The effects of steric changes in the ligands, substrates, nucleophiles, and reaction temperature were investigated. Further evaluation on the applications of this novel class of P,N ligands in asymmetric catalysis is currently in progress.

4. Experimental

4.1. General remarks

All reactions were performed under a nitrogen atmosphere in freshly dried and distilled solvents. Solvents were treated prior to use according to the standard method. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR were recorded on a Bruker AMX-300 spectrometer in $CDCl_3$ at room temperature. Optical rotations were measured using a Perkin–Elmer 343 polarimeter at 25 °C. Mass spectra were performed on Waters Quattro-Premier instrument. Ee values were determined by HPLC on a chiracel OJ-H, AD, and OD-H columns. (*S,S*)-1,2-diphenyl-1,2-ethanediol was prepared as described.[10] The commercially available reagents were used without further purification.

4.2. General procedure for the preparation of ligands 2a–d

A solution of (*S,S*)-1,2-diphenyl-1,2-ethanediol (1.07 g, 5 mmol) in absolute THF was added dropwise to phosphorus trichloride (0.69 g, 5 mmol) under nitrogen. The mixture was stirred at room temperature until no starting material was detected by TLC. Subsequently, selected cinchona alkaloids (5 mmol) and triethylamine (3 mL) were added to the clear system, then the system was heated to 60 °C. After being stirred for 17 h, the suspension was filtered and the mother liquor was concentrated to give a light yellow solid. This solid was dissolved in water and extracted with degassed CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After being concentrated, light yellow crude product was obtained and purified by flash column chromatography on silica gel using *n*-hexane/acetone/triethylamine (3:3:1) as the eluent.

4.2.1. Cinchonine-9-yl phosphite (ligand 2a)

Using cinchonine, ligand **2a** was obtained as a white foam solid (75%). Mp = 37–38 °C. $[\alpha]_D^{25} = -108$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (1H), 8.19 (2H), 7.05–7.69 (13H), 6.02 (2H), 5.13 (1H), 5.08 (1H), 4.87 (2H), 3.32 (1H), 2.66–3.08 (6H), 1.09–2.03 (4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 148.1, 146.3, 139.8, 136.1, 134.3, 130.1, 128.8, 128.5, 128.3, 128.2, 128.0, 127.9, 127.5, 127.2, 127.0, 126.5, 126.4, 126.1, 125.0, 123.0, 118.8, 114.3, 86.1, 86.0, 82.9, 60.4, 49.5, 48.7, 39.5, 27.6, 25.9, 23.3; ^{31}P NMR (202 MHz, $CDCl_3$): δ 143.5; HRMS (ESI): calcd for $C_{33}H_{33}N_2O_3P$+H: 537.2, found: 537.0.

4.2.2. Cinchonidine-9-yl phosphite (ligand 2b)

Using cinchonidine, ligand **2b** was afforded as a white foam solid (68%). Mp = 39–40 °C. $[\alpha]_D^{25} = -35$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (1H), 8.19 (2H), 7.05–7.69 (13H), 6.02 (2H), 5.13 (1H), 5.08 (1H), 4.87 (2H), 3.32 (1H), 2.66– 3.08 (6H), 1.09–2.03 (4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 148.1, 146.3, 139.8, 136.1, 134.3, 130.1, 128.8, 128.5, 128.3, 128.2, 128.0, 127.9, 127.5, 127.2, 127.0, 126.5, 126.4, 126.1, 125.0, 123.0, 118.8, 114.3, 86.1, 86.0, 82.9, 60.4, 49.5, 48.7, 39.5, 27.6, 25.9, 23.3; ^{31}P NMR (202 MHz, $CDCl_3$): δ 143.5; HRMS (ESI): calcd for $C_{33}H_{33}N_2O_3P$+H: 537.2, found: 537.0.

4.2.3. Quinine-9-yl phosphite (ligand 2c)

Using quinine, ligand **2c** was obtained as a white foam solid (70%). Mp = 62–64 °C. $[\alpha]_D^{25} = -29.5$ (*c* 1, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77 (1H, d), 8.05 (1H, d), 7.13–7.51 (13H), 5.78–5.85 (2H, m), 4.85–5.09 (4H, m), 3.88 (3H, s), 1.25–3.3 (11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 147.1, 144.8, 144.3, 141.4, 136.1, 135.6, 135.5, 131.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8 126.5, 126.4, 126.3, 126.1, 121.2, 119.2, 113.9, 101.2, 86.1, 86.0, 83.3, 59.9, 56.4, 55.1, 46.1, 42.1, 39.4, 29.2, 27.5; ^{31}P NMR (202 MHz, $CDCl_3$): δ 142.8; HRMS (ESI): calcd for $C_{34}H_{35}N_2O_4P$+H: 567.2, found: 567.1.

4.2.4. Quindine-9-yl phosphite (ligand 2d)

Using quindine, ligand **2d** was prepared as a white foam solid (63%). Mp = 64–65 °C. $[\alpha]_D^{25} = -69.6$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77 (1H, d), 8.05 (1H, d), 7.13–7.51 (13H), 5.78–5.85 (2H, m), 4.85–5.09 (4H, m), 3.88 (3H, s), 1.25–3.3 (11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 147.1, 144.8, 144.3, 141.4, 136.1, 135.6, 135.5, 131.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8 126.5, 126.4, 126.3, 126.1, 121.2, 119.2, 113.9, 101.2, 86.1, 86.0, 83.3, 59.9, 56.4, 55.1, 46.1, 42.1, 39.4, 29.2, 27.5; ^{31}P NMR (202 MHz, $CDCl_3$): δ 142.8; HRMS (ESI): calcd for $C_{34}H_{35}N_2O_4P$+H: 567.2, found: 567.1.

4.3. General procedure for the palladium-catalyzed AAA reaction of *rac*-1,3-diphenyl-2-propenyl acetate

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3.7 mg, 0.01 mmol) and the appropriate ligand (0.03 mmol) were dissolved in dry CH_2Cl_2 (5 mL) and then stirred for 0.5 h at room temperature under nitrogen. *rac*-1,3-Diphenyl-2-propenyl acetate (126 mg, 0.5 mmol) was added to this solution and continuously stirred for 10 min. To the resulting solution were successively added dimethyl malonate (0.17 mL, 1.5 mmol), *N,O*-bis(trimethylsilyl) acetamide (0.37 mL, 1.5 mmol), and potassium acetate (0.015 mmol). The reaction mixture was stirred at a suitable temperature and monitored by TLC. After that, the reaction solution was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous ammonium chloride. The organic phase was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/*n*-hexane = 1:10) to give the pure product. The enantiomeric excess was determined by HPLC.

Acknowledgments

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