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Pd-catalyzed enantioselective synthesis of quaternary α-amino acid derivatives using a phenylalanine-derived P-chirogenic diaminophosphine oxide

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Abstract—A Pd-catalyzed enantioselective synthesis of quaternary α-amino acid derivatives using a phenylalanine-derived P-chirogenic diaminophosphine oxide is described. Asymmetric allylic substitution using acyclic β-keto esters with a nitrogen functional group at the α-carbon as prochiral nucleophiles proceeded in the presence of 5 mol % of Pd catalyst, 10 mol % of chiral diaminophosphine oxide **1j**, BSA, and appropriate additives, affording the corresponding quaternary α-amino acid derivatives in excellent yield and in up to 92% ee.

The incorporation of quaternary α-amino acids in peptide chains is one of the most commonly utilized methods for developing peptidomimetics.[1] Such modifications provide higher stability against metabolic degradation, and influence the conformational rigidity and lipophilicity of peptidic compounds, which often allow for higher selectivity toward receptors. In addition to these biological aspects, unnatural quaternary α-amino acids serve as valuable chiral building blocks in organic synthesis.[2] Therefore, asymmetric synthesis of quaternary α-amino acid derivatives has attracted considerable attention, and various catalytic asymmetric synthetic methods have been reported to date.[3,4]

Pd-catalyzed asymmetric allylic substitution using β-keto esters with a nitrogen functional group at the α-carbon as the prochiral nucleophiles is one of the most straightforward approaches for synthesizing chiral quaternary α-amino acid derivatives. Although several types of Pd-catalyzed asymmetric allylic substitutions using prochiral nucleophiles have been investigated since 1980s,[5] there are only a few reports of asymmetric synthesis of such tetrasubstituted carbons using this strategy.[6,7] The catalyst system using a chiral BINAP-Pd complex, developed by Ito et al., is the state of the art for this type of reaction, affording *N*-acetyl quaternary α-amino acid derivatives with up to 95% ee.[6a] We recently reported that aspartic acid-derived P-chirogenic diaminophosphine oxides function as effective chiral ligands in transition metal catalysis in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA).[8,9] These chiral diaminophosphine oxides were successfully applied to enantioselective construction of quaternary carbons through Pd-catalyzed asymmetric allylic substitution using β-keto esters as prochiral nucleophiles.[8a–c] Products possessing an all-carbon quaternary stereocenter were obtained with up to 95% ee using cyclic β-keto esters as the prochiral nucleophiles. In contrast, enantioselectivity was moderate when acyclic β-keto esters with an acetamido group at the α-carbon were used as the prochiral nucleophiles (e.g., Table 1, entry 1). We hoped to overcome this drawback by tuning the reaction conditions. Herein, we report a Pd-catalyzed enantioselective synthesis of quaternary α-amino acid derivatives using a phenylalanine-derived P-chirogenic diaminophosphine oxide.

We first examined the effect of the structure of chiral diaminophosphine oxide using asymmetric allylic substitution of cinnamyl acetate **2** with **3a** (Fig. 1 and Table 1). When 5 mol % of Pd catalyst and 10 mol % of (S,R_P)-**1a** were used as the catalyst, the reaction proceeded at 4 °C to provide the corresponding product (*R*)-**4a** in 90% yield with 78% ee (entry 1). Although the same reaction was performed using other structurally modified

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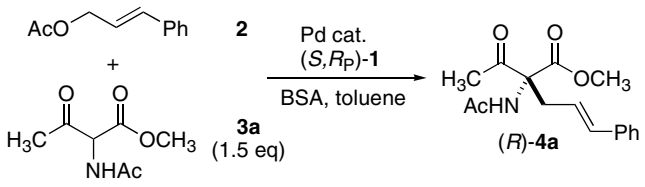
Table 1. Effect of the structure of chiral diaminophosphine oxide[a]



Entry	(S,R_P)-**1**	Time (h)	Yield[b] (%)	ee[c] (% ee)
1	**1a**	48	90	78
2	**1b**	60	23	51
3	**1c**	48	94	78
4	**1d**	48	90	79
5	**1e**	48	49	77
6	**1f**	20	99	69
7	**1g**	48	36	79
8	**1h**	48	95	88
9	**1i**	60	60	78
10	**1j**	24	98	92

[a] Reaction conditions: **2** (0.2 mmol scale), (η^3-$C_3H_5PdCl)_2$ (2.5 mol %), **1** (10 mol %), **3a** (1.5 equiv), BSA (4 equiv), toluene (0.15 M), 4 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.

preligands (S,R_P)-**1a**–**g**, there was no increase in the enantioselectivity (entries 2–7). Further studies revealed that enantioselectivity was improved when the reaction was performed using P-chirogenic diaminophosphine oxides prepared from other amino acids. Finally, (S,R_P)-**1j**, prepared from (*S*)-phenylalanine, was best for asymmetric induction, affording (*R*)-**4a** in 98% yield with 92% ee (entry 10).

We next examined the scope and limitations of other nucleophiles. When the developed conditions were employed for methyl ketone-type substrates **3a**,**b**, ethyl ketone-type substrate **3d**, and benzamido-type substrate **3i**, the corresponding quaternary α-amino acid derivatives were obtained in excellent yield with high enantioselectivity. There was, however, a remarkable decrease in the reactivity when other substrates were used (Table 2, left column). To improve the reactivity, we investigated the effect of the addition of acetate salt to the reaction. Detailed screening revealed that 10 mol % of KOAc dramatically increased the reactivity.[10] Asymmetric allylic substitutions using *N*-acyl-protected alkyl ketone-type substrates **3a**–**g**, **3i**, and **3j** proceeded smoothly in the presence of KOAc, affording the corresponding quaternary α-amino acid derivatives in excellent yield with high enantioselectivity (86–92% ee) (Table 2, right column).[11,12] The reaction adducts were highly crystalline compounds and the optical purity was efficiently enriched by a single recrystallization (entry 1). The present reaction conditions were also effective in asymmetric allylic substitution using carbamate-type substrates **3k** and **3l**. The corresponding products **4k** and **4l** were obtained in excellent yield with high enantioselectivity (entries 11–12).

In striking contrast to alkyl ketone-type substrates, no reaction occurred when phenyl ketone-type substrate **3h** was used as the prochiral nucleophile (Table 2, entry 8). This unsatisfactory result led us to focus on the asymmetric allylic substitution of **2** using **3h** as the nucleophile (Table 3). The effect of the addition of other potassium salts using **3h** was examined, revealing that the counter anion of the potassium salt dramatically affected the catalytic activity. When 10 mol % of KCl was used as the additive, the corresponding product **4h** was obtained in 99% yield with 82% ee (entry 4). There was a remarkable increase in the reactivity when both KCl (10 mol %) and KOAc (10 mol %) were used as the additive, affording the corresponding products without significant loss of the enantiomeric excess (entry 7). When the reaction was performed using 20 mol % of KCl, there was a decrease in both the yield and enantioselectivity (entry 8). This result indicates that KCl and KOAc would function independently in this reaction system. Asymmetric allylic substitution of γ-alkyl-substituted allylic alcohol derivatives was also examined (Scheme 1). Although asymmetric allylic substitution of acetate derivative **5a** with **3a** was performed using 5 mol % of the catalyst, the reaction did not proceed to completion in the presence of KOAc (72 h, 49% yield, 70% ee), or in the presence of both KCl and KOAc (72 h, 60% yield, 81% ee). There was a significant increase in the reactivity when methyl carbonate derivative **5b** was used as the electrophile, affording **6** in 99% yield and in 82% ee.

Transformation of the reaction adduct into the corresponding quaternary α-amino acid was also examined using **4k** as the substrate (Scheme 2). *syn*-Selective reduction of the ketone using L-Selectride® gave *syn*-β-hydroxy α-amino ester **7** in 93% yield as a single diastereomer.[6a] This compound was transformed into the corresponding quaternary α-amino acid **8** by treatment with LiOH in THF–H_2O (95% yield).

In conclusion, we succeeded in the Pd-catalyzed enantioselective synthesis of quaternary α-amino acid

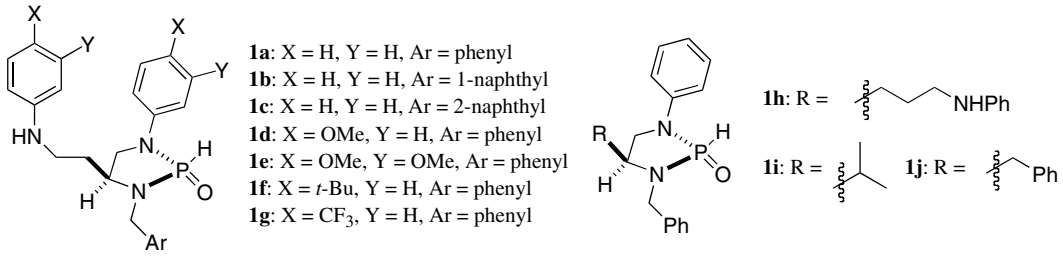
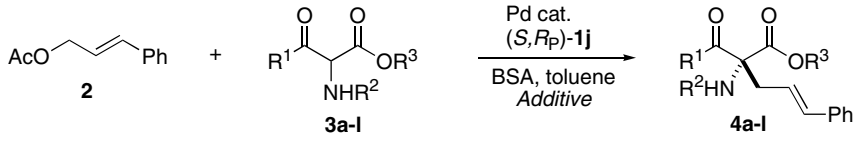


Figure 1. Chiral diaminophosphine oxides (S,R_P)-**1a**–**j**.

Table 2. Scope and limitations[a]



3a, 4a: $R^1 = CH_3$, R^2 = Ac, $R^3 = CH_3$
3b, 4b: $R^1 = CH_3$, R^2 = Ac, $R^3 = CH_2CH_3$
3c, 4c: $R^1 = CH_3$, R^2 = Ac, $R^3 = CH_2Ph$
3d, 4d: $R^1 = CH_2CH_3$, R^2 = Ac, $R^3 = CH_3$
3e, 4e: $R^1 = CH_2CH_2Ph$, R^2 = Ac, $R^3 = CH_3$
3f, 4f: R^1 = *i*-Pr, R^2 = Ac, $R^3 = CH_3$
3g, 4g: R^1 = cHex, R^2 = Ac, $R^3 = CH_3$
3h, 4h: R^1 = Ph, R^2 = Ac, $R^3 = CH_3$
3i, 4i: $R^1 = CH_3$, R^2 = benzoyl, $R^3 = CH_3$
3j, 4j: $R^1 = CH_3$, R^2 = crotonoyl, $R^3 = CH_3$
3k, 4k: $R^1 = CH_3$, R^2 = COOMe, $R^3 = CH_3$
3l, 4l: $R^1 = CH_3$, R^2 = COOBn, $R^3 = CH_3$

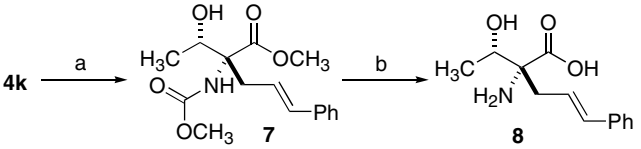
Entry	Nucleophile	Additive free			Additive: KOAc (10 mol %)		
		Time (h)	Yield[b] (%)	ee[c] (% ee)	Time (h)	Yield[b] (%)	ee[c] (% ee)
1	**3a**	24	98	92 (*R*)	12	99 (70)[d]	90 (99)[e] (*R*)
2	**3b**	24	99	92	16	99	92
3	**3c**	48	52	91	48	99	89
4	**3d**	48	96	86	24	98	87
5	**3e**	24	No reaction	—	24	99	89
6	**3f**	72	38	89	48	99	90
7	**3g**	72	32	83	48	99	86
8	**3h**	24	No reaction	—	24	No reaction	—
9	**3i**	30	99	92	20	99	92
10	**3j**	24	No reaction	—	24	99	90
11	**3k**	48	No reaction	—	60 (24)[f]	73 (99)[f]	89 (90)[f]
12	**3l**	48	No reaction	—	60	99	89

[a] Reaction conditions: **2**, $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol %), (*S*,R_P)-**1j** (10 mol %), **3a–l** (1.5 equiv), BSA (4 equiv), toluene (0.15 M), KOAc (0 mol % or 10 mol %), 4 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Yield of recrystallization from EtOH.
[e] Enantiomeric excess after single recrystallization from EtOH.
[f] 10 mol % of KOAc and 10 mol % of KCl were used as the additive.

Table 3. Asymmetric allylic substitution of **2** with **3h**[a]

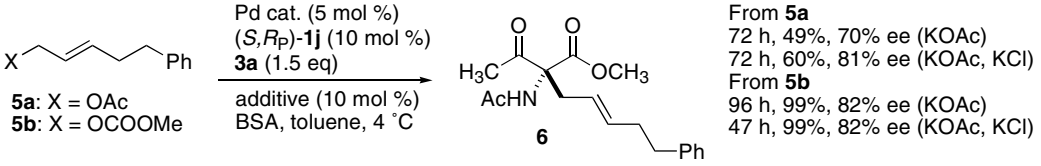
Entry	Additive	Time (h)	Yield[b] (%)	ee[c] (% ee)
1	—	72	No reaction	—
2	KOAc (10 mol %)	72	No reaction	—
3	KF (10 mol %)	72	Trace	—
4	KCl (10 mol %)	96	99	82
5	KBF_4 (10 mol %)	72	99	76
6	KPF_6 (10 mol %)	96	81	73
7	KOAc (10 mol %) KCl (10 mol %)	46	99	80
8	KCl (20 mol %)	46	89	73

[a] Reaction conditions: **2**, $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol %), (*S*,R_P)-**1j** (10 mol %), **3h** (1.5 equiv), BSA (4 equiv), toluene (0.15 M), additive, 4 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.



Scheme 2. Conversion of **4k** into quaternary α-amino acid **8**. Reagents and conditions. (a) L-Selectride®, THF, −78 °C, 93%, *syn*/*anti* = >99:1. (b) LiOH, THF/H_2O, rt, 95%.

derivatives using a phenylalanine-derived P-chirogenic diaminophosphine oxide. Asymmetric allylic substitution using various types of β-keto esters with a nitrogen functional group at the α-position proceeded in the presence of the appropriate additives, providing the corresponding quaternary α-amino acid derivatives in up to 92% ee. Application to asymmetric synthesis of



Scheme 1. Asymmetric allylic substitution of **5**.

biologically active compounds, as well as mechanistic investigation into the role of additives, is currently in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.020.

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10. See Supplementary data for details.
11. For the general procedure, see Supplementary data.
12. Although the role of additives in the present catalytic asymmetric reaction is unknown, NMR experiments indicated that KOAc might be related to the generation of active nucleophiles. For experimental data, see Supplementary data.