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Palladium-catalyzed asymmetric allylic amination: enantioselective synthesis of chiral α-methylene substituted β-aminophosphonates†

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Spiroketal backbone based diphosphine ligands (SKP) were disclosed to be highly efficient and enantioselective (94 → 99% ee) in the palladium catalyzed asymmetric allylic amination of 2-diethylphosphonate-substituted allylic acetates, affording a series of chiral β-aminophosphonates bearing an α-methylene functionality in high yields with excellent regioselectivities.

Amino phosphonic acids[1] are phosphorus analogues of the corresponding amino acids, in which the planar and less bulky carboxylic acid group is replaced by a tetrahedral phosphonic acid functionality. In this context, β-amino phosphonic acids and their derivatives, as the isosteres of β-amino acids, have been revealed to possess a diverse range of medicinal properties including anti-bacterial,[2] enzyme inhibitors,[3] antibiotics,[4] anti-HIV,[5] and anti-inflammatory[6] activities (Fig. 1). Given their growing importance in pharmaceutical applications, it is not surprising to see that the synthesis of β-amino phosphonic acid derivatives has attracted considerable interest of the synthetic community.[7] Whereas a number of useful methods have been developed in general, there remains a dearth of efficient and versatile methodologies for the asymmetric synthesis of optically active β-amino phosphonic acid derivatives.[8] Since the initial reports on the catalytic asymmetric synthesis of β-amino phosphonates *via* the amino hydroxylation of unsaturated phosphonates in the late 1990s,[9] several types of catalytic systems have been documented to date, including the catalytic asymmetric hydrogenation of β-amidovinylphosphonates,[10] asymmetric Mannich reactions,[11] and the desymmetrization of aziridines by phosphites.[12] Alternatively, optically enriched β-amino phosphonates have also been obtained indirectly *via* catalytic asymmetric nitroaldol[13] or phospha-Michael additions[14] followed by reduction of the resulting β-nitroethylphosphonates. Despite these notable advances, catalytic stereoselective protocols that can provide an efficient direct access to chiral β-aminophosphonic acid derivatives are still scarce. Herein, we report a highly enantioselective catalytic asymmetric amination of 2-(diethylphosphonyl)-substituted allylic acetates, to afford a range of α-methylene-β-aminophosphonates in excellent optical purities.

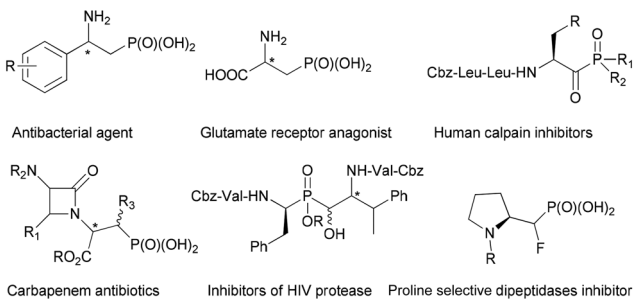

Fig. 1 Selected examples of bioactive β-aminophosphonic acid derivatives.

Recently, our group has reported the development of spiroketal-based chiral diphosphine ligands (SKP),[15] a new class of diphosphines with sterically well-defined spiro backbones.[16] The SKP ligands were found to be highly efficient in the Pd catalyzed asymmetric allylic amination[17] of racemic ethyl 2-(acetoxy(phenyl)methyl)acrylates, a type of Morita–Baylis–Hillman (MBH) adduct,[18] to give the corresponding β-arylamino acid esters with high regio- and enantioselectivities.[19] Kinetic and mechanistic studies indicated that the unusual long distance of the two P atoms in the SKP ligand allows for its unique role in the reaction, *i.e.* the ligand adopts an organo- and organometallic bifunctional mode in the cooperative catalysis.[20] Encouraged by these results, we sought to extend the catalytic system to the asymmetric allylic amination of 2-(diethylphosphonyl)-substituted allylic acetates. The

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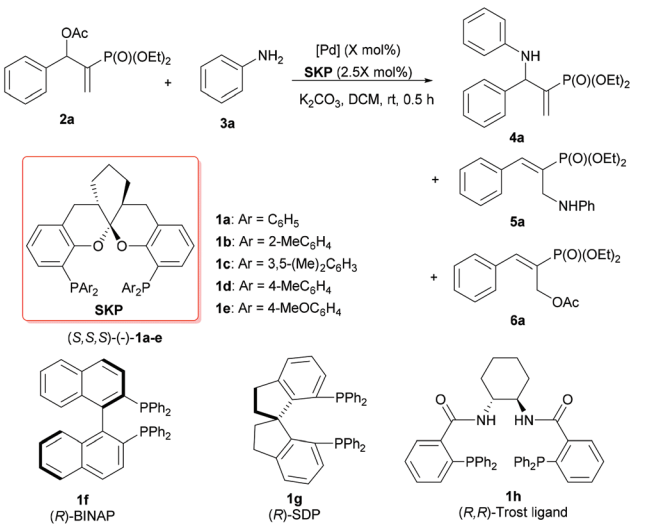
expected amination products would be enantioenriched β-aminophosphoric acid derivatives which can be viewed as the bioisosteres of α-methylene-β-amino acids that have very recently been found to be a key unnatural amino acid unit in a new class of endomorphin-1 analogues with potent antinociceptive activity.[21] Furthermore, the olefin functionality present in the amination products may constitute a useful handle for further synthetic manipulation, thus giving ready access to a wider array of β-amino phosphoric acid derivatives.

The study was initiated by a survey of the reaction conditions, including variations in palladium sources and SKP ligands, catalyst loadings, solvents, and bases, for the amination of 2-(diethylphosphonyl)-substituted allylic acetate (**2a**) with aniline (**3a**) as the nucleophile. The reactions were generally conducted at room temperature for 0.5 h, using the complex generated *in situ* from a SKP ligand [(*S*,*S*,*S*)-**1a–e**] and a palladium precursor as the catalyst. The effects of solvents and bases on the reaction of **2a** and **3a** were examined in the presence of the $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.0 mol%)/(*S*,*S*,*S*)-**1a** (2.5 mol%) catalyst, indicating that both parameters have a significant impact on the reactivity as well as the chemo-, regio-, and enantioselectivities (for details, see Table S1 in the ESI†). In these cases, the reaction was found to be best performed in dichloromethane in the presence of two equivalents of anhydrous K_2CO_3 as the base, to afford the chiral allylic amination product **4a** in 95% yield with excellent chemo-, regio-, and enantioselectivities (**4a**/**5a**/**6a** = >98/<2/0, >99% ee, entry 1 in Table 1). Under these optimized reaction conditions, the effects of catalyst compositions and loadings on the reaction of **2a** and **3a** were further evaluated, using SKP ligands (*S*,*S*,*S*)-**1a–e** with subtle variations in their aryl substituents at the P atoms and a couple of Pd precursors. The results are summarized in Table 1. With $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.0 mol%) as the palladium precursor, a sharp difference in catalytic behavior was observed among the SKP ligands (*S*,*S*,*S*)-**1a–e** (entries 1–5). For example, high activity and excellent regio-/enantioselectivities were obtained using ligand **1a**, **1c**, or **1e** with phenyl, 3,5-xylyl or 4-methoxyphenyl substituents, respectively, affording the targeted product **4a** in high yields (92–95%) with 98–99% ee values (entries 1, 3, and 5). In contrast, ligand **1b** possessing 2-tolyl moieties on the P atoms obviously deteriorates the reactivity and regioselectivity, leading to only very poor conversion (5%) and a modest branched/linear regioselectivity (**4a**/**5a** = 2/3) under otherwise identical conditions (entry 2). Intriguingly, 4-tolyl-bearing ligand **1d**, with structural features analogous to both **1a** and **1e**, afforded much inferior chemoselectivity albeit with a 98% ee for **4a** (entry 4), presumably as a result of incomplete amination of the isomerization product **6a** within 0.5 h. Intriguingly, the reaction results with some privileged chiral ligands,[16] *e.g.*, (*R*)-BINAP, (*R*)-SDP or (*R*,*R*)-Trost ligand, were less satisfactory under the otherwise identical conditions, affording incomplete conversions and moderate chemo-, regio- and enantioselectivities (entries 6–8). These facts clearly indicated that SKP ligands demonstrate unique performance in the catalysis of this type of asymmetric transformation. With

Table 1 Catalytic asymmetric allylic amination of **2a** with aniline **3a** catalyzed by various palladium complexes of bisphosphine ligands[a]

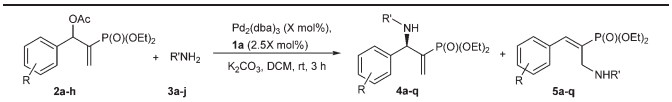


Entry	[Pd][b] (*X* mol%)	Ligand[b]	Conv.[c] (%)	**4a**/**5a**/**6a**[c]	Yield[d] (%)	ee[e] (%)
1	$[Pd(C_3H_5)Cl]_2$ (1)	**1a**	>99	>98/<2/0	95	>99
2	$[Pd(C_3H_5)Cl]_2$ (1)	**1b**	5	2/3/0	—	—
3	$[Pd(C_3H_5)Cl]_2$ (1)	**1c**	>99	93/2/5	92	>99
4	$[Pd(C_3H_5)Cl]_2$ (1)	**1d**	>99	68/2/30	63	98
5	$[Pd(C_3H_5)Cl]_2$ (1)	**1e**	>99	>98/<2/0	94	98
6	$[Pd(C_3H_5)Cl]_2$ (1)	**1f**	34	31/69/0	9	43
7	$[Pd(C_3H_5)Cl]_2$ (1)	**1g**	16	70/30/0	10	4
8	$[Pd(C_3H_5)Cl]_2$ (1)	**1h**	57	56/34/10	28	10
9	$Pd_2(dba)_3$ (1)	**1a**	>99	>98/<2/0	95	98
10[f]	$Pd(OAc)_2$ (2)	**1a**	36	36/0/64	12	88
11[f]	$Pd(CH_3CN)_2Cl_2$ (2)	**1a**	>99	44/6/50	43	95
12[g]	$[Pd(C_3H_5)Cl]_2$ (0.5)	**1a**	>99	>98/<2/0	95	98
13[g]	$[Pd(C_3H_5)Cl]_2$ (0.1)	**1a**	87	89/0/11	82	97
14[g]	$Pd_2(dba)_3$ (0.2)	**1a**	>99	>98/<2/0	95	98
15[g]	$Pd_2(dba)_3$ (0.1)	**1a**	>99	>98/<2/0	94	98
16[g]	$Pd_2(dba)_3$ (0.05)	**1a**	64	94/0/6	57	98

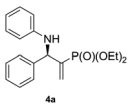
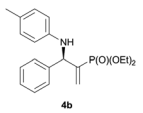
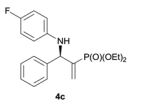
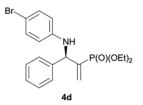
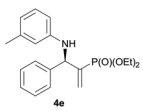
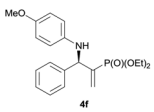
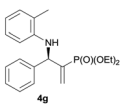
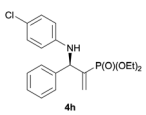
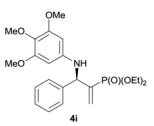
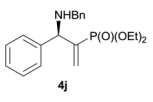
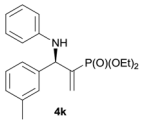
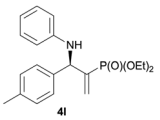
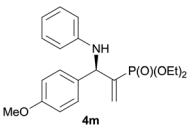
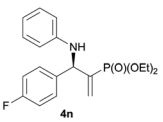
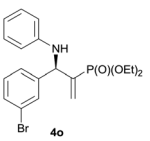
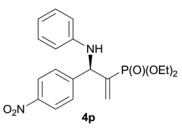
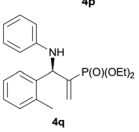
[a] Unless otherwise noted, the reaction was performed with **2a** (0.2 mmol) and **3a** (0.4 mmol), K_2CO_3 (0.4 mmol) in CH_2Cl_2 (2 mL) at rt for 0.5 h. [b] The molar percent of the Pd salt relative to that of **2a**. In each case, the loading of the SKP ligand was 1.25 equiv. relative to that of Pd. [c] Determined by ^{1}H NMR spectroscopy. [d] Yield of the isolated **4a**. [e] The ee value of **4a** was determined by chiral HPLC. [f] The loading of **1a** was 2.5 mol% relative to that of **2a**. [g] The reactions were run for 3 h.

1a as the ligand, the use of different palladium precursors also resulted in distinct catalytic activities and selectivities (entries 1 and 9–11). While the use of $Pd_2(dba)_3$ delivers excellent results nearly identical to those of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (entries 9 *vs.* 1), $Pd(OAc)_2$ or $Pd(CH_3CN)_2Cl_2$ turns out to be much less efficient, realizing only partial conversion of **2a** (entry 7) and lower yields of **4a** (entries 10 and 11), or a substantial amount of the unreacted isomerization product **6a** (entry 11). Further trials to lower the catalyst loadings were thus performed using either $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ or $Pd_2(dba)_3$ along with ligand **1a** as the catalyst, and the reaction times were prolonged to 3 h (entries 12–16). Under these conditions, the loading of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was lowered to 0.5 mol% without loss of either yield of selectivities (entry 12), whereas further decreasing the

Table 2 Catalytic asymmetric allylic amination of MBH adducts **2a–h** with various amines **3a–j** catalyzed by Pd/(*S*,*S*,*S*)-**1a**[a]



R	R'	R, R'
2a: H	**3a**: Ph	**4a**: H, Ph
2b: *m*-CH_3	**3b**: *p*-$CH_3C_6H_4$	**4b**: H, *p*-$CH_3C_6H_4$
2c: *p*-CH_3	**3c**: *p*-FC_6H_4	**4c**: H, *p*-FC_6H_4
2d: *p*-OCH_3	**3d**: *p*-BrC_6H_4	**4d**: H, *p*-BrC_6H_4
2e: *p*-F	**3e**: *m*-$CH_3C_6H_4$	**4e**: H, *m*-$CH_3C_6H_4$
2f: *m*-Br	**3f**: *p*-$OCH_3C_6H_4$	**4f**: H, R' = *p*-$OCH_3C_6H_4$
2g: *p*-NO_2	**3g**: *o*-$CH_3C_6H_4$	**4g**: H, *o*-$CH_3C_6H_4$
2h: *o*-CH_3	**3h**: *p*-ClC_6H_4	**4h**: H, *p*-ClC_6H_4
	3i: 3,4,5-$(OCH_3)_3(C_6H_2)$	**4i**: H, 3,4,5-$(OCH_3)_3(C_6H_2)$
	3j: Bn	**4j**: H, Bn
		4k: *m*-CH_3, Ph
		4l: *p*-CH_3, Ph
		4m: *p*-OCH_3, Ph
		4n: *p*-F, Ph
		4o: *m*-Br, Ph
		4p: *p*-NO_2, Ph
		4q: *o*-CH_3, Ph

Entry	4	*X*	**4**/**5**[b]	Yield[c] (%)	ee[d] (%)
1	 **4a**	0.1	>98/<2	94	98
2	 **4b**	0.1	95/5	91	95
3	 **4c**	0.1	>98/2	94	96
4	 **4d**	0.1	91/9	87	98
5	 **4e**	0.1	95/5	83	94
6	 **4f**	0.1	93/7	88	96
7	 **4g**	0.1	96/4	70	98
8	 **4h**	0.1	96/4	84	98
9	 **4i**	0.1	>98/2	89	98
10	 **4j**	0.1	90/10	84	98
11	 **4k**	0.5	93/7	75	94
12	 **4l**	0.5	96/4	92	97
13	 **4m**	0.5	94/6	80	94
14	 **4n**	0.5	92/8	70	96
15	 **4o**	0.5	97/3	84	98
16	 **4p**	0.5	98/2	75	>99
17	 **4q**	1	61/39	40	94

[a] Unless otherwise noted, the reactions were typically performed at rt with **2** (2.0 mmol) and **3** (4.0 mmol), K_2CO_3 (4.0 mmol) in CH_2Cl_2 (20 mL) for 3 h, in the presence of a specified amount of catalysts $Pd_2(dba)_3$ and (*S*,*S*,*S*)-**1a**. [b] Determined by ^1H NMR spectroscopy. [c] Yield of the isolated **4a–q**. [d] The ee values of **4a–q** were determined by chiral HPLC. The absolute configurations for **4a–q** were all determined to be *R* (see text).

loading to 0.1 mol% resulted in partial conversion and declined yield (entry 13). In this context, $Pd_2(dba)_3$ seems to be superior as the palladium precursor, and its loading can be lowered all the way to 0.1 mol% with essentially no changes in yields or ee values of **4a** (entries 14 and 15 *vs.* 9). Further lowering of the $Pd_2(dba)_3$ loading to 0.05 mol%, however, led to a significant decrease in the reactivity albeit still with a 98% ee value for **4a** (entry 16).

Subsequently, we proceeded to examine the substrate scope of the catalysis by variation in both the 2-diethylphosphonate-substituted allylic acetates (**2a–h**) and nucleophilic amines (**3a–j**). The reactions were run under the optimized conditions with a low loading of $Pd_2(dba)_3$ (0.1–0.5 mol%) and (*S*,*S*,*S*)-**1a**, and the results are summarized in Table 2. Gratifyingly, excellent enantioselectivities (94 → 99% ee) were observed in the resultant β-aminophosphonates **4a–q** (entries 1–17). Both electron-donating and electron-withdrawing groups on the phenyl rings, located whether on the aromatic amine or on the allylic acetate, are well tolerated. The regioselectivities for the amination products (**4**/**5**) are also generally high, ranging from

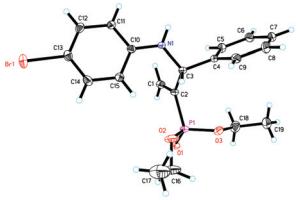


Fig. 2 X-ray single crystal structure of (*R*)-**4d**.

90/10 to >98/2 (entries 1–16). The reaction involving substrate **2h** was an exception (entry 17), however, giving a much higher content of the linear amination product (**4q**/**5q** = 61/39) and a moderate yield (40%) of **4q** even at a relatively high loading of the catalyst (1.0 mol%), probably as a result of unfavorable interaction with the Pd catalyst caused by the sterically congested *o*-tolyl group in **2h**. It is also noteworthy that the stereoelectronic properties of the aromatic amines have no obvious influence on the catalysis, as reactions of **2a** with a range of anilines (**3a–i**) gave the corresponding products **4a–i** in comparable good yields, high regioselectivities and excellent enantioselectivities (entries 1–9). The amination of **2a** also proceeded smoothly with benzylamine **3j**, an aliphatic nucleophile, to furnish β-aminophosphonate **4j** in 84% yield with a 90 : 10 branched/linear ratio and 98% ee (entry 10). Finally, the absolute configuration of **4d** was unambiguously established to be *R* by the X-ray crystal diffraction analysis (Fig. 2), while those for other products were deduced to be all *R* by comparison of their Cotton effects with that of (*R*)-(−)-**4d** as shown in the CD spectra (Fig. S2, ESI†).

Conclusions

In conclusion, we have developed an efficient asymmetric synthesis of enantioenriched β-aminophosphonates bearing an α-methylene functionality. Using the complex generated *in situ* from the SKP ligand and a palladium precursor as the catalyst, asymmetric allylic amination of 2-diethylphosphonate-substituted allylic acetates proceeded smoothly under mild conditions with various amines as the nucleophiles, affording a series of β-aminophosphoric acid derivatives in good to excellent yields, high regioselectivities, and uniformly excellent enantioselectivities (94 → 99% ee). It is noteworthy that the olefin functionality present in the chiral β-aminophosphonate products may provide a useful handle for further synthetic manipulation, and thus may stimulate future explorations to use them as intermediates to access a wider array of β-amino phosphoric acid derivatives.

Experimental

General procedures for SKP/Pd catalyzed asymmetric amination of 2-(diethylphosphonyl)-substituted allylic acetates

Into a Schlenk tube equipped with a magnetic stirring bar were added $Pd_2(dba)_3$ (1.8 mg, 0.005 mmol), (*S*,*S*,*S*)-**1a** (9.6 mg, 0.0125 mmol) and dichloromethane (5 mL) under a stream of argon. The solution was stirred for 5 min, followed by addition of **2** (0.5 mmol), K_2CO_3 (138 mg, 1.0 mmol) and **3** (1.0 mmol). The mixture was stirred for 3 h at room temperature, and then the solid residue was removed by filtration through a pad of Celite. The branched to linear ratio (**4**/**5**) of the amination products was determined by ^1H NMR analysis of an aliquot of the filtrate. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel with petroleum ether/EA (1/2) as the eluent to afford optically enriched α-methylene β-amino phosphonate ester **4**.

The method can be applied in the Gram-scale preparation of β-aminophosphonates **4a** under a reduced catalyst loading. By following the above mentioned procedure, the reaction of **2a** (4.0 mmol, 1.24 g) with **3a** (740 mg, 8.0 mmol) proceeded smoothly at rt for 8 h in dichloromethane (38 mL) in the presence of $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*S*,*S*,*S*)-**1a** (13.2 mg, 0.02 mmol), and K_2CO_3 (1.1 g, 8.0 mmol), to give branched amination product **4a** (1.17 g, 85% yield) with 98% ee.

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