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Enantioselective synthesis of quaternary α-aminophosphonates by Pd-catalyzed arylation of cyclic α-ketiminophosphonates with arylboronic acids†

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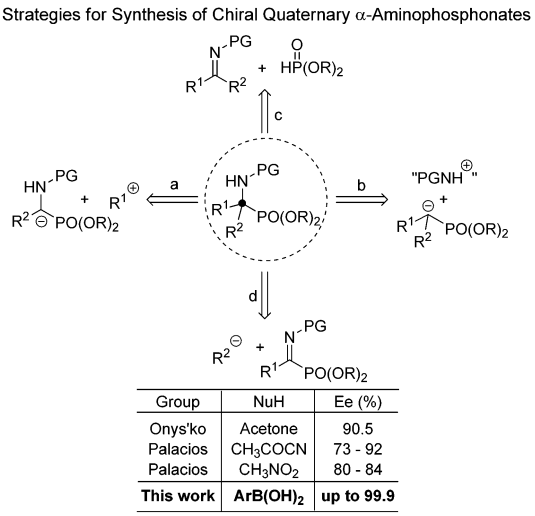
A highly enantioselective addition of arylboronic acids to cyclic α-ketiminophosphonates is reported using a chiral palladium phosphinooxazoline catalyst, providing an efficient and facile route to quaternary α-aminophosphonates in high yields and up to 99.9% enantioselectivity.

α-Aminophosphonic acids are found in a broad range of natural and biologically active molecules.[1] Their antifungal,[2] antibacterial[3] and antiviral[4] properties distinguish them as an attractive class of compounds in medicinal chemistry. Not surprisingly, considerable attention has been given to the development of elegant methodologies for their synthesis,[5] but a limited number for quaternary ones. Although facing crucial challenges, the construction of chiral quaternary centers in chemical synthesis is of great significance. To date, some strategies have been realized by several groups for the preparation of quaternary α-aminophosphonic acids and their derivatives.[6–9] One strategy involves asymmetric addition of carbon or nitrogen electrophiles to phosphonates (Scheme 1, paths a and b).[7] Direct enantioselective allylation and amination of β-keto phosphonates were reported by the groups of Ito and Jørgensen, respectively.[7b,e] More generally, asymmetric addition of phosphites to ketimines is an efficient method for the construction of quaternary α-aminophosphonates (Scheme 1, path c).[8] In addition, another straightforward protocol involves enantioselective addition of nucleophiles to α-ketiminophosphonates.[9] Significant progress is limited to asymmetric addition of a small number of nucleophiles, such as acetone,[9a] pyruvonitrile,[9b] and nitromethane[9c] (path d, Scheme 1). Notably, asymmetric addition of aryl nucleophiles to α-ketiminophosphonates is rare. To satisfy the increasing demand for diverse chiral quaternary α-aminophosphonates, developing facile and efficient strategies is still highly desirable.



Scheme 1 Catalytic synthesis of chiral quaternary α-aminophosphonates.

For the construction of chiral α-tertiary amine compounds, transition-metal-catalyzed asymmetric addition of organometallic reagents to ketimines represents one of the most straightforward methods.[10] Thanks to the pioneering work by Hayashi, rhodium-catalyzed asymmetric addition of arylboron reagents to ketimines has become an attractive research focus.[11] Noteworthily, palladium-based catalytic systems are also suitable for the same reaction and seem to be more attractive because of their lower cost than rhodium catalysts.[12] However, only a few reports concern the palladium-catalyzed addition of arylboron reagents to ketimines and the substrate scope is relatively narrow.[13] Recently, our group has been involved in the synthesis of simple α-aminophosphonates *via* a palladium-catalyzed asymmetric hydrogenation strategy.[5a] Considering the active α-ketiminophosphonates might be suitable for the addition reaction of arylboron nucleophiles, herein, we present the catalytic asymmetric arylation of cyclic α-ketiminophosphonates catalyzed

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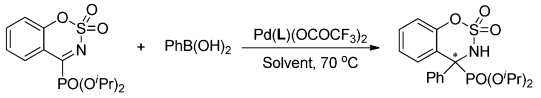
by a palladium phosphinooxazoline complex,[14] giving the chiral quaternary α-aminophosphonates in high yields and up to 99.9% enantioselectivities (Scheme 1).

At the outset, using six-membered cyclic α-ketiminophosphonates **1a** as model substrates, reaction conditions for the palladium-catalyzed arylation of **1a** with phenylboronic acid were investigated. Employing $Pd(OCOCF_3)_2$/(*R*)-^{t}Bu-Pyrox as the initial catalyst, we began our investigation by testing a variety of solvents. Fortunately, the reaction proceeded smoothly in TFE with 92% yield and 98.5% ee (Table 1, entry 4), which might be ascribed to TFE's beneficial effect on the rate of the transmetalation and protonation steps of the catalytic cycle.[13a,15] However, this reaction didn't proceed in toluene, $ClCH_2CH_2Cl$ and when using MeOH as the solvent, the phosphate group in **1a** was replaced by a methoxy group (Table 1, entries 1–3). Encouraged by the results, we further tested some other chiral ligands. No reactivity was observed when using the bisphosphine ligand (*R*)-DifluoroPhos (Table 1, entry 5). Palladium phosphinooxazoline complexes worked well with excellent enantioselectivities (99.9%) (Table 1, entries 6 and 7). Concerning the reactivity, (*S*)-^{t}Bu-Phox was chosen as the optimal chiral ligand. Importantly, the catalyst loading could be lowered to 1.0 mol% with retained enantioselectivity and slightly low activity. Therefore, the optimal reaction conditions were established: $Pd(OCOCF_3)_2$/(*S*)-^{t}Bu-Phox as the catalyst, TFE as the solvent and reaction temperature 70 °C. Moreover, the absolute configuration of the addition product (+)-**2a** was determined to be *S* by X-ray crystallographic analysis.[16]

Having identified the optimal reaction conditions, we then investigated the substrate scope and the results are shown in Table 2. Gratifyingly, most of the substrates afforded excellent enantioselectivities (>99%) and high yields (81–97%). For different phosphonate substituents, the isopropyl group afforded a slightly higher ee value than the ethyl group (Table 2, entries 1 and 2). When electron-rich groups like the methyl or methoxyl group were introduced into the phenyl ring of substrate **1**, the reactivity slightly decreased but enantioselectivities were maintained (Table 2, entries 3–6). Notably, the steric effect of the aryl substituents of substrate **1** rarely influenced the reaction (Table 2, entries 4–6). Substrates with different halogen groups were also tolerated, although the reactivity obviously decreased when the bromo group was introduced, and high enantioselectivity could be achieved (Table 2, entries 7–9). Furthermore, the arylboronic acid scope was also investigated. Electron-deficient and electron-rich arylboronic acids had a little effect on enantioselectivity (Table 2, entries 10–18). However, electron-withdrawing groups like fluoro and chloro on the arylboronic acids decreased the reactivity. After a prolonged reaction time, satisfactory yields could be still achieved (Table 2, entries 15 and 16). Additionally, the steric effect of arylboronic acids is obvious. For *o*-tolylboronic acid, no reactivity was observed. When *m*-tolylboronic acid was used, it would take 3 days to realize 81% yield, but enantioselectivity was still high (Table 2, entry 12).

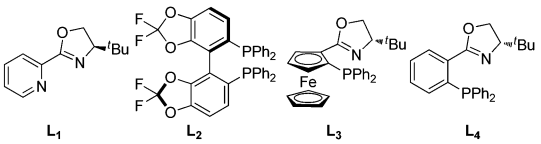
To further demonstrate the versatility of our method, the five-membered cyclic α-ketiminophosphonates **3** were chosen as the substrates for the palladium-catalyzed addition reaction (Table 3). Pleasingly, excellent yields and enantioselectivities were also achieved under the standard conditions. The electronic properties of the substituents at the *para* position of arylboronic acids rarely affected the enantioselectivity. Only when a methoxyl group was introduced at the *para* position, the ee value slightly decreased to 98.5%. The substrate with a methyl group at the 5-position of substrate **3e** was also converted to the target product with

Table 1 Optimization of reaction parameters[a]



1a 2a

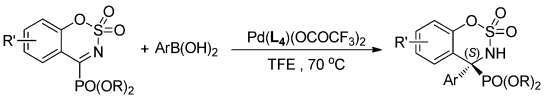
Entry	L	Solvent	Yield[b] (%)	ee[c] (%)
1	L_1	Toluene	NR	NA
2	L_1	$ClCH_2CH_2Cl$	NR	NA
3	L_1	MeOH	NR	NA
4	L_1	TFE	92	98.5 (*R*)
5	L_2	TFE	NR	NA
6	L_3	TFE	87	99.9 (*S*)
7	L_4	TFE	99	99.9 (*S*)
8[d]	L_4	TFE	95	99.9 (*S*)



L_1 L_2 L_3 L_4

[a] Reaction conditions: $Pd(L)(OCOCF_3)_2$ (5.0 mol%), **1a** (0.10 mmol), $PhB(OH)_2$ (0.20 mmol), TFE (2.0 mL), 70 °C, 4–12 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reaction conditions: $Pd(L_4)(OCOCF_3)_2$ (1.0 mol%), **1a** (0.20 mmol), $PhB(OH)_2$ (0.40 mmol), TFE (4.0 mL), 70 °C, 11 h. NR: no reaction. NA: no analysis.

Table 2 Substrate scope: six-membered cyclic α-ketiminophosphonates **1**[a]

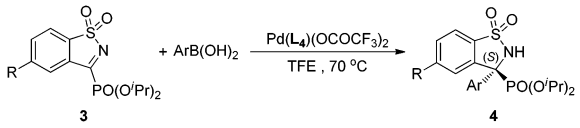


1 2

Entry	R′	Ar	*t* (h)	Yield[b] (%)	ee[c] (%)
1	H	Ph	11	95 (**2a**)	99.9
2[d]	H	Ph	8	97 (**2b**)	99.8
3	7-Me	Ph	8	89 (**2c**)	99.9
4	8-MeO	Ph	20	89 (**2d**)	99.9
5	7-MeO	Ph	24	91 (**2e**)	99.9
6	6-MeO	Ph	16	86 (**2f**)	99.5
7	6-F	Ph	11	92 (**2g**)	99.9
8	6-Cl	Ph	11	89 (**2h**)	99.9
9[e]	6-Br	Ph	48	73 (**2i**)	99.9
10	H	4-MeC_6H_4	6	89 (**2j**)	99.0
11	H	4-$MeOC_6H_4$	8	90 (**2k**)	99.7
12	H	3-MeC_6H_4	72	81 (**2l**)	99.9
13	H	3-$MeOC_6H_4$	24	92 (**2m**)	99.9
14	H	3,5-$Me_2C_6H_3$	17	90 (**2n**)	99.6
15[e]	H	4-FC_6H_4	24	96 (**2o**)	99.9
16	H	4-ClC_6H_4	72	86 (**2p**)	99.9
17	H	4-BrC_6H_4	24	91 (**2q**)	99.9
18	H	4-PhC_6H_4	7	95 (**2r**)	99.2

[a] Unless otherwise mentioned, R = ^{i}Pr, all reactions were carried out with $Pd(L_4)(OCOCF_3)_2$ (1.0 mol%), **1** (0.20 mmol), $ArB(OH)_2$ (0.40 mmol), TFE (4.0 mL), 70 °C. [b] Isolated yields. [c] Determined by HPLC. [d] R = Et. [e] Using 5.0 mol% $Pd(L_4)(OCOCF_3)_2$.

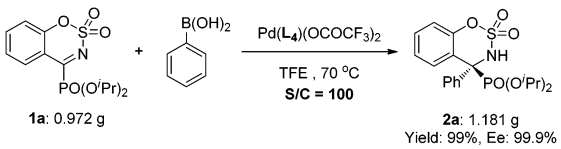
Table 3 Substrate scope: five-membered cyclic α-ketiminophosphonates **3**[a]



3 4

Entry	R	Ar	*t* (h)	Yield[b] (%)	ee[c] (%)
1	H	Ph	14	98 (**4a**)	99.0
2	H	4-MeC_6H_4	22	98 (**4b**)	99.4
3	H	4-MeOC_6H_4	22	97 (**4c**)	98.5
4	H	4-BrC_6H_4	22	95 (**4d**)	99.5
5	Me	Ph	12	95 (**4e**)	99.4

[a] Reaction conditions: Pd(**L4**)$(OCOCF_3)_2$ (1.0 mol%), **3** (0.20 mmol), $ArB(OH)_2$ (0.40 mmol), TFE (4.0 mL), 70 °C. [b] Isolated yields. [c] Determined by HPLC.



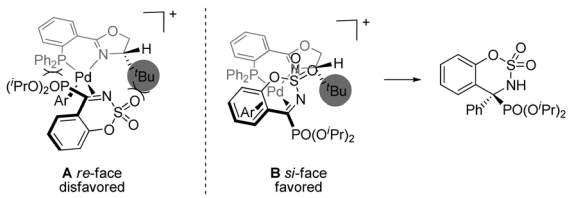
Scheme 2 Gram scale experiment.

excellent results. Moreover, the gram scale reaction proceeded smoothly with 1 mol% catalyst loading without loss of reactivity and enantioselectivity, and the excellent results further demonstrate the practicality of the above strategy (Scheme 2).

The stereochemical outcome can be explained using a transition state model. The ketimine bound to the Pd center is *trans* to the diphenylphosphine group of (*S*)-^{t}Bu-Phox and the nucleophilic aryl group is *cis* to the diphenylphosphine group. The sterically favored transition state **B**, avoiding the steric interaction between the sulfonyl moiety of the ketimine substrate and the tertiary butyl group of (*S*)-^{t}Bu-Phox, leads to the *S* product that we obtained (Scheme 3).

Notably, for simple acyclic α-ketiminophosphonates such as diethyl (phenyl(tosylimino)methyl)phosphonate, no reactivity was observed under the above standard conditions, which might be ascribed to relatively big steric hindrance and lower reactivity than the cyclic substrates.

The ring opening experiments of products have been conducted in our laboratory. For example, ring opening occurring with cleavage of the O–S bond of benzosulfamidates reduced by $LiAlH_4$ has been reported,[17] but the phosphate group cannot be retained under this condition. In addition, Ni-catalyzed coupling of benzosulfamidates with phenylboronic acid and a nickel catalysis using alkylmagnesium reagents have been reported,[18]



Scheme 3 Stereochemical model.

but the above catalytic systems are still not applicable to the benzosulfamidates bearing quaternary carbon centers. Further improvement has been achieved by Nishimura's group;[11k] the reductive cleavage of the C–O bond by using diethylzinc reagents in the presence of $NiCl_2$(dippe) affords linear α,α-diaryl-α-amino acid derivatives, but the reaction is sluggish under the standard conditions. In general, the weak C–P bond and the active phosphonate group restrained the transformations conducted under harsh conditions. Also, the steric hindrance of the quaternary α-carbon of the amino group played a negative role. Mild and effective strategies for transformations of the cyclic aminophosphonates are still to be developed in the future.

In summary, we have successfully realized the palladium-catalyzed enantioselective addition of arylboronic acids to both six- and five-membered cyclic α-ketiminophosphonates, providing an efficient and elegant access to chiral quaternary α-aminophosphonates with high yields and excellent ee values. The highlights of this method include mild reaction conditions, low catalyst loading and a wide substrate scope. Studies to extend the strategy to other functionalized α-ketiminophosphonates are ongoing in our laboratory.

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