ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2018, **5**, 1148

Received 27th December 2017,
Accepted 27th January 2018

DOI: 10.1039/c7qo01158j

rsc.li/frontiers-organic

Synthesis of chiral γ-aminophosphonates through the organocatalytic hydrophosphonylation of azadienes with phosphites†

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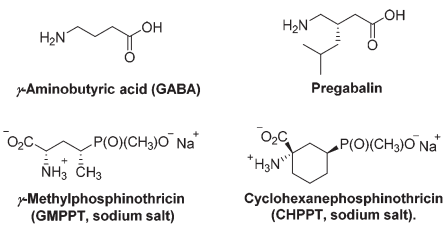
An organocatalytic enantioselective 1,4-addition of phosphites to azadienes has been successfully developed using quinine as a catalyst, providing an efficient and facile route to optically active γ-aminophosphonates with up to 94% ee.

γ-Aminobutyric acid (GABA), a four-carbon non-protein amino acid, is a significant component of the free amino acid pool and is widely present in bacteria, plants and vertebrates.[1] It has been documented as an antihypertensive and antidepressant compound in the past decade.[1b] The drug pregabalin (GABA's derivative) is indicated as a treatment for generalized anxiety disorder.[2] Being the structural analogues of γ-amino acids, γ-amino phosphonic acid derivatives also exhibit important biological activities such as the inhibition of ovine brain glutamine synthetase and *Escherichia coli* glutamine synthetase (Scheme 1).[3]

Recently, the catalytic asymmetric synthesis of optically active phosphonic acid derivatives has attracted increasing attention due to their important applications in biological and medical science.[4] The catalytic enantioselective addition of phosphorus nucleophiles is one of the most powerful synthetic methodologies for the construction of functionalized organophosphorus compounds *via* phosphorus–carbon bond formation. In particular, the catalytic asymmetric conjugate addition of appropriate phosphorus nucleophiles to α,β-unsaturated carbonyl compounds, including aldehydes,[5] ketones,[6] esters[7] and amides,[8] can provide the corresponding optically active phosphonic acid derivatives (Scheme 2a). However, the 1,4-addition of phosphorus nucleophiles to α,β-unsaturated imines has not been described. Therefore, the development of a direct, convenient and efficient methodology for the synthesis of optically active γ-amino phosphonic acid derivatives through the organocatalytic enantioselective 1,4-addition of α,β-unsaturated imines to the phosphorus nucleophiles is highly desirable.

Azadienes **1** were identified to be effective reactants for addition reactions owing to the driving force of aromatization.[9] Herein, we report an organocatalytic asymmetric hydrophosphonylation of azadienes, giving γ-aminophosphonates with high enantioselectivity (Scheme 2b).

At the outset, we initiated our investigation by screening the reaction conditions of asymmetric hydrophosphonylation



Scheme 1 Selected bioactive molecules of γ-amino (phosphonic) acid derivatives.

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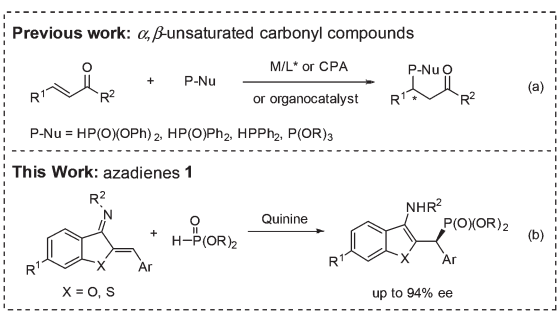
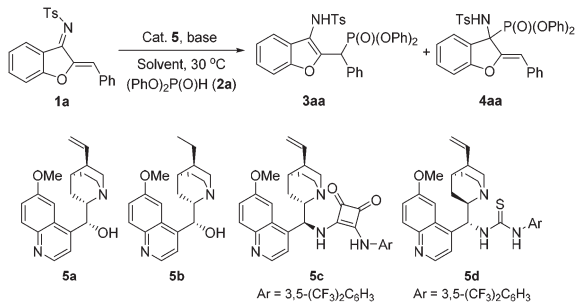
†Electronic supplementary information (ESI) available: Experimental details, compound characterization, and NMR and HPLC spectra. CCDC 1588669. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7qo01158j



Scheme 2 Asymmetric hydrophosphonylation and hydrophosphinylation of unsaturated carbonyl compounds and azadienes.

Table 1 The evaluation of reaction parameters[a]

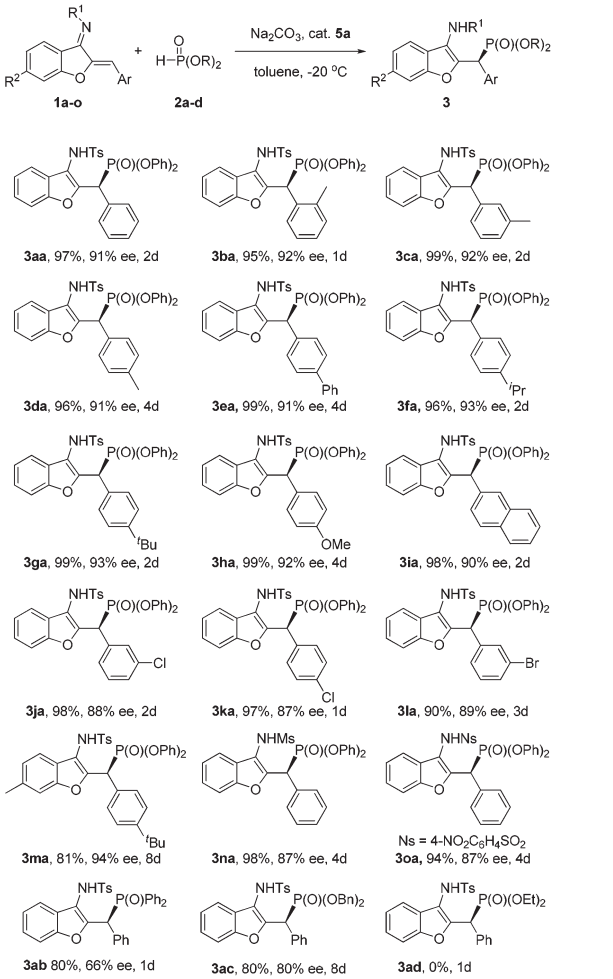


Entry	Base	Solvent	Cat.	rr[b]	Yield[c]	ee[d] (%)
1	—	Toluene	**5a**	>19 : 1	8	68 (*S*)
2	Na_2CO_3	Toluene	**5a**	>19 : 1	98	86 (*S*)
3	K_2CO_3	Toluene	**5a**	>19 : 1	91	54 (*S*)
4	NaOH	Toluene	**5a**	>19 : 1	96	45 (*S*)
5	Na_2CO_3	DCM	**5a**	>19 : 1	97	83 (*S*)
6	Na_2CO_3	THF	**5a**	>19 : 1	98	54 (*S*)
7	Na_2CO_3	DMF	**5a**	>19 : 1	91	3 (*S*)
8	Na_2CO_3	Toluene	**5b**	>19 : 1	95	83 (*S*)
9	Na_2CO_3	Toluene	**5c**	5 : 1	80	76 (*S*)
10	Na_2CO_3	Toluene	**5d**	3 : 1	74	7 (*R*)
11[e]	Na_2CO_3	Toluene	**5a**	>19 : 1	97	90 (*S*)
12[f]	Na_2CO_3	Toluene	**5a**	>19 : 1	94	92 (*S*)
13[f,g]	Na_2CO_3	Toluene	**5a**	>19 : 1	**97**	**91 (*S*)**

[a] Reaction conditions: Azadiene **1a** (0.15 mmol), **2a** (0.45 mmol), organocatalyst **5** (7.5 μmol), base (0.075 mmol), solvent (2.0 mL), 30 °C, 4 h-7 d. [b] rr (**3aa** : **4aa**) is the regioisomeric ratio and is determined by ^{1}H NMR spectroscopy. [c] Isolated yields. [d] Determined by chiral HPLC. [e] 0 °C (**2a** was added at 0 °C). [f] −20 °C (**2a** was added at −20 °C). [g] Toluene (1.0 mL).

between azadiene **1a** and diphenyl phosphite **2a** with a variety of cinchona alkaloids (Table 1). This reaction gave the desired product **3aa** in 8% yield with 68% ee within 48 h without a base (entry 1). Upon the introduction of sodium carbonate, the desired product **3aa** was delivered in 98% yield and 86% enantioselectivity (entry 2). Notably, inorganic bases played a vital role in reactivity and enantioselectivity. The screening of several other inorganic bases revealed that sodium carbonate remained superior to potassium carbonate and sodium hydroxide (entries 3 and 4). Subsequently, various solvents were extensively examined (entries 5–7). Among the different kinds of solvents, toluene proved to be the most favorable solvent in terms of yield and enantioselectivity. Next, a series of bifunctional organocatalysts were explored. In contrast to the quinine **5a**, other organocatalysts tended to give inferior results (entries 8–10). In the case of the organocatalysts **5c** and **5d**, moderate regioselectivities were observed and the ratios of the 1,2-addition product **4aa** increased. The temperature effect was also evaluated (entries 11 and 12). Improved enantioselectivity with excellent yield was obtained upon reducing the reaction temperature. It is worth noting that when the reaction was performed at −20 °C, the reaction time was prolonged to 7 days. Satisfactorily, when the solvent loading was reduced to 1.0 mL, the reaction performed very well, delivering the corresponding chiral product in excellent yield and high enantioselectivity (entry 13). Notably, the reaction time was shortened to 2 days. Therefore, the optimal reaction conditions were established: using **5a** as a catalyst, sodium carbonate as a base, and toluene as a solvent to perform the reaction at −20 °C.

With the aforementioned optimal reaction conditions, the scope and generality were next evaluated (Scheme 3). Gratifyingly, most of the substrates afforded excellent enantioselectivities and high yields. For substrates **1a–1i**, the electronic and steric properties of the substituent on the aromatic ring (Ar) had no obvious influence on the enantioselectivity and yield of the reaction. In addition, the halogen substituted substrates **1j–1l** were also favorable reaction partners, and the reaction proceeded smoothly with good enantioselectivities (87–89%) and high yields (90–98%). The substrate with a methyl group at the 6-position of the substrate **1m** was also converted to the corresponding product with 94% ee and 81% yield. Finally, we shifted our focus to various substituents on

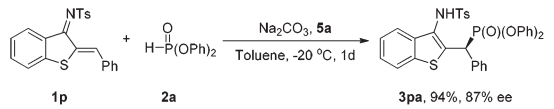


Scheme 3 Substrate scope. Reaction conditions: azadienes **1** (0.15 mmol), **2** (0.45 mmol), Na_2CO_3 (0.075 mmol), cat. **5a** (7.5 μmol), toluene (1.0 mL), −20 °C (**2a** was added at −20 °C). The rr were over 19 : 1 in all cases, unless otherwise noted.

the nitrogen in sulfonylimine, and excellent yields and good enantioselectivities could also be obtained.

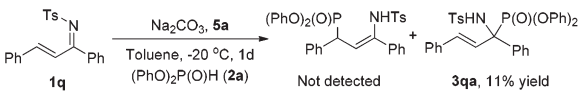
Furthermore, to demonstrate the versatility of our method, different phosphorus nucleophiles were also investigated (Scheme 3). Moderate 66% enantioselectivity and regioselectivity were observed for the diphenylphosphine oxide **2b**. For simple benzyl substituted phosphites **2c**, moderate 80% enantioselectivity was obtained under the above standard conditions. Surprisingly, no reactivity was observed for simple diethyl phosphite. The disappointing result of diethyl phosphite was also observed by Nakamura.[10] This phenomenon implies that the acidity of the proton of diethyl phosphite might play an important role. Meanwhile, Jacobsen thought that there is a correlation between the reactivity and the acidity of the phosphite proton.[11]

Delightedly, the substrate with benzothiophene **1p** was also a suitable reaction partner under the standard conditions, giving the desired product **3pa** with 94% yield and 87% ee (eqn (1)).



1p **2a** **3pa**, 94%, 87% ee (1)

In order to demonstrate the importance of the driving force of aromatization, we set out to explore the reaction of the simple acyclic azadiene substrate **1q** (eqn (2)). The reaction proceeded under the standard conditions to give only the 1,2-addition product **3qa** instead of the 1,4-addition product. It is obvious that the driving force of aromatization played a vital role in regioselectivity.



1q Not detected **3qa**, 11% yield (2)

The absolute configuration of the addition product (−)-**3aa** was unambiguously assigned to be *S* by X-ray single crystallographic analysis after a simple recrystallization with ethyl acetate and ^{n}hexane (Fig. 1).

On the basis of the above experimental results and Nakamura's work on the hydroquine-catalyzed asymmetric hydrophosphonylation of *N*-tosylimines in the presence of sodium carbonate,[10] a plausible transition state for the enantioselective hydrophosphonylation of azadienes using quinine **5a** was proposed as shown in Fig. 2. Quinine acts as a dual-activating organocatalyst; one is hydrogen bonding between the quinine hydroxyl group and the ketimine moiety, and the other is the nitrogen in quinine as a Brønsted base to activate the nucleophilicity of sodium phosphite by coordination with a sodium ion.

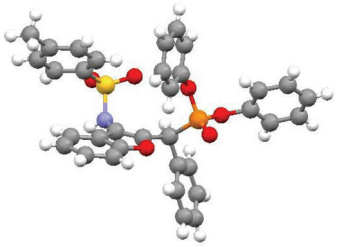


Fig. 1 X-ray crystal structure of compound (−)-**3aa**.

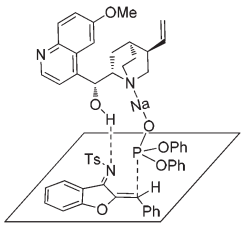


Fig. 2 A proposed transition state.

Conclusion

In summary, we have developed an efficient method for the synthesis of chiral γ-aminophosphonates through a bifunctional quinine-catalyzed asymmetric hydrophosphonylation of azadienes with phosphites in good yields with up to 94% ee. The key issue is the excellent selectivity of the 1,4-addition of azadienes, which is from the driving force of aromatization of the adducts. Further investigations of related strategies are currently ongoing in our laboratory.

Experimental

A typical procedure for the enantioselective hydrophosphonylation of azadiene 1a

To a solution of azadiene **1a** (56.3 mg, 0.15 mmol), sodium carbonate (7.9 mg, 0.075 mmol) and catalyst quinine **5a** (2.4 mg, 7.5 μmol) in toluene (1.0 mL), diphenyl phosphite **2a** (87 μl, 0.45 mmol) was added at −20 °C and stirred for 2 days. Water was added to the reaction mixture, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product, followed by column chromatography to give the product (*S*)-**3aa** as a white solid (89 mg, 97% yield, 91% ee). Enantiomeric excess was determined by HPLC (IC column, ^{n}hexane/^{i}PrOH 70/30, 0.70 mL min^{-1}, 220 nm), 30 °C, t_1 = 14.3 min, t_2 = 15.5 min (maj).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Natural Science Foundation of China (20102348), the Chinese Academy of

Sciences (QYZDJ-SSW-SLH035), Strategic Priority Research Program of the Chinese Academy of Sciences (XDB17020300), and the Dalian Bureau of Science and Technology (2016RD07) is acknowledged.

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