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Carbene-Catalyzed [4 + 2] Cycloadditions of Vinyl Enolate and (in Situ Generated) Imines for Enantioselective Synthesis of Quaternary α-Amino Phosphonates

Jun Sun,[†,∥] Chengli Mou,[‡,∥] Zhongyao Wang,[†] Fangcheng He,[†] Jian Wu,[†] and Yonggui Robin Chi*[,†,§]

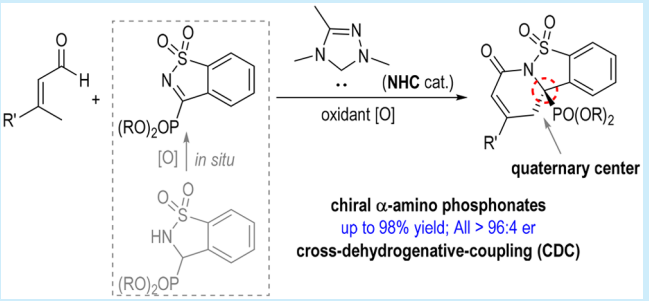
[†]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China

[‡]School of Pharmacy, Guiyang College of Traditional Chinese Medicine, Huaxi District, Guiyang 550025, China

[§]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: A carbene-catalyzed enantioselective addition of enals to five-membered cyclic imines is developed. The reaction gives chiral quaternary α-amino phosphonates bearing tetrasubstituted carbon centers with excellent enantioselectivities. The imine substrates can be generated in situ from the corresponding amines under an oxidative condition that is compatible with the carbene catalysis. Thus, a one-pot cross-dehydrogenative-coupling (CDC) reaction between enals and amines is also realized with high enantioselectivity remaining. The method provides quick enantioselective access to amino phosphonates with potential applications in medicines and pesticides.



α-Amino phosphonic acids and their esters are among the prevalent mimics of naturally existing bioactive molecules.[1] The synthesis of α-amino phosphonic acid derivatives has therefore received considerable attention.[2] Several asymmetric catalysis methods have been developed for the preparation of chiral quaternary α-amino phosphonates. For example, α-acetamido β-ketophosphonates could be allylated on their trisubstituted α-carbons via asymmetric Pd catalylsis with chiral BINAP as the ligand (Scheme 1, eq 1).[3] The C−P bond could also be formed via asymmetric organocatalytic 1,2-addition of phosphites to ketimines (Scheme 1, eq 2).[4] Che and co-workers introduced a Rh-catalyzed enantio- and diastereoselective coupling reaction of α-diazophosphonates, anilines, and electron-deficient aldehydes to prepare α-amino-β-hydroxyphosphonates (Scheme 1, eq 3).[5] An arylation reaction of cyclic α-ketiminophosphonates was recently developed by Zhou and co-workers via asymmetric Pd catalysis (Scheme 1, eq 4).[6] Despite the impressive progress, it remains challenging to synthesize quaternary α-amino phosphonates bearing tetrasubstituted α-carbon centers, especially in enantioselective fashion.[7] Additionally, catalytic methods for access to α-amino phosphonate compounds bearing multiple heterocyclic units are not available.

We are interested in the construction of chiral functional molecules with proven or potential biological activities using N-hetereocyclic carbenes (abbreviated as NHCs or carbenes) as the organic catalyst. Here we disclose a carbene-catalyzed addition of enals to five-membered cyclic imines for the quick enantioselective access to fused multicyclic isothiazolo-pyridines bearing quaternary α-amino phosphonate units (Scheme 1, eq 5). Mechanistically, the enal substrate **1** is converted to a vinyl enolate intermediate **I** with a nucleophilic γ-carbon in the presence of an NHC catalyst and an oxidant.[8] Enantioselective addition of the vinyl enolate **I** to the cyclic α-ketiminophosphonate substrate **2** gives the chiral intermediate **II**, which eventually leads to the quaternary α-amino phosphonate **3** in good yield and excellent enantioselectivity. We also found that the imine[9] substrate **2** can be generated via in situ oxidation of the corresponding amines. In such a case, the cross-dehydrogenative-coupling (CDC) reaction[10] between enals and amines is also realized with high enantioselectivity remaining.

The reaction conditions of our proposed asymmetric [4 + 2] cycloaddition were first evaluated using cyclic α-ketiminophosphonate **2a** as the electrophile (Table 1). β-Methyl-α,β-unsaturated aldehyde **1a** was chosen as the acylazolium precursor to react with α-ketiminophosphonate **2a** through an NHC-catalyzed oxidative process. With diquinone **4** as the oxidant,[11] triazolium NHC catalysts bearing *N*-mesityl substituents were examined for the formation of the α-amino phosphonate product **3a**.

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Scheme 1. Construction of Quaternary α-Amino Phosphonates through Asymmetric Catalysis

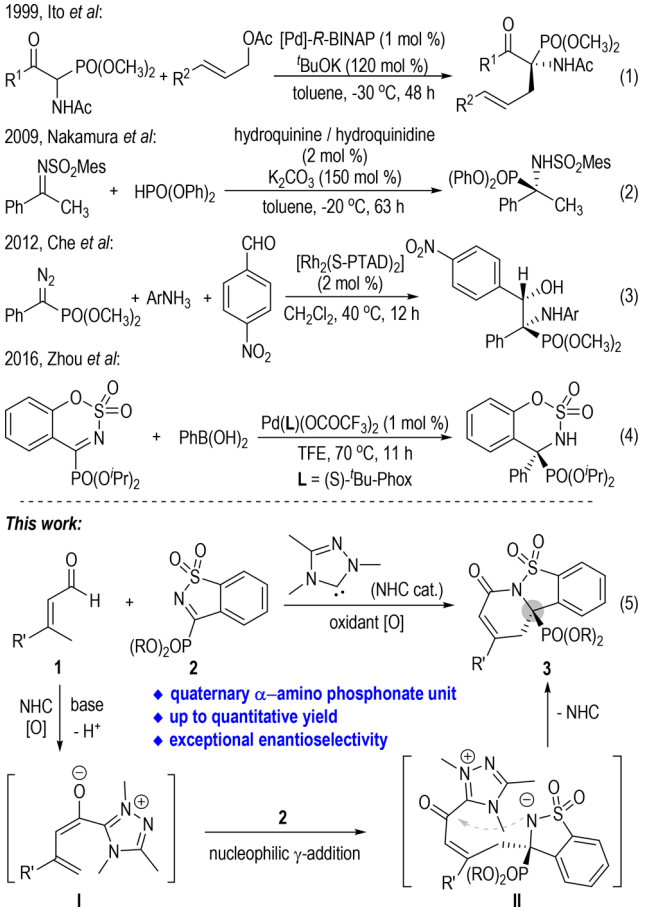
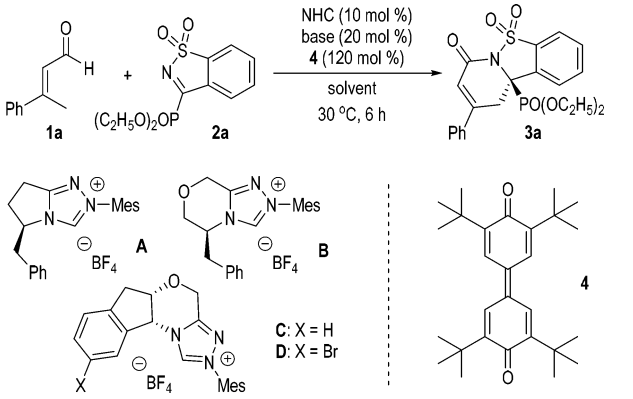


Table 1. Optimization of Reaction Conditions[a]



entry	NHC	base	solvent	yield[b]	er[c]
1	**A**	NaOAc	THF	<5	-
2	**B**	NaOAc	THF	28	8:92
3	**C**	NaOAc	THF	97	96:4
4	**D**	NaOAc	THF	98	>99:1
5	**D**	Cs_2CO_3	THF	85	>99:1
6	**D**	DBU	THF	72	>99:1
7	**D**	Et_3N	THF	40	>99:1
8	**D**	NaOAc	CH_2Cl_2	65	99:1
9	**D**	NaOAc	toluene	<10	--
10[d]	**D**	NaOAc	THF	98	>99:1[e]

[a]General conditions (unless otherwise specified): **1a** (0.06 mmol), **2a** (0.05 mmol), NHC (0.005 mmol), base (0.01 mmol), **4** (0.06 mmol), solvent (1.0 mL), 30 °C, 6 h. [b]Isolated yield of **3a**. [c]er was determined via HPLC on a chiral stationary phase. [d]**1a** (0.12 mmol), **2a** (0.10 mmol), NHC (0.005 mmol), NaOAc (0.02 mmol), **4** (0.12 mmol), THF (2.0 mL), 30 °C, 12 h. [e]The absolute configuration of **3a** was determined via X-ray analysis on its single crystals.

Pyrrolotriazolium-derived NHC catalyst **A**[12] was not efficient in this process, while the tetrahydropyridotriazolium NHC **B**[13] could furnish the product in promising yields and enantioselectivities (Table 1, entries 1−2). To our great delight, the yield of the desired product **3a** could be dramatically improved when the amino-indanol-derived NHC **C**[14] was applied as the reaction catalyst (entry 3). Moreover, the er value of **3a** could be further increased to >99:1 with NHC **D**[15] (entry 4). A variety of organic or inorganic bases could facilitate the product formation with excellent yields and er values (entries 5−7). This catalytic process could also be smoothly carried out in various solvents without obvious erosion of the reaction outcome (entries 8−9). Interestingly, the catalyst loading of this reaction could even be decreased to 5 mol %, with the desired product **3a** being afforded in almost quantitive yield with exceptional enantioselectivity after an extended reaction time (entry 10).

With the optimized reaction conditions in hand (Table 1, entry 10), we next examined the scope of enals **1** with different substitution patterns (Scheme 2). Both the electron-donating and the electron-withdrawing substituents could be installed on the *β*-benzene group of the enal substrate **1a**, with all the corresponding products obtained in excellent yields and enantioselectivities (**3a** to **3k**). The *β*-benzene group on the enal **1a** could also be heteroaromatic with retention of the product yields and er values (**3l**−**3o**). It is worth noting that aliphatic enals bearing two *β*-alkyl groups could also give the desired products in excellent optical purities with little erosion of the isolated yields (**3p**−**3q**). However, when switching the *β*-methyl group on the enal substrate **1a** into a benzyl group, no desired product could be observed.

α-Ketiminophosphonates **2** bearing electron-donating substituents on the benzene rings could facilitate the product formation in excellent yields and enantioselectivities (e.g., Scheme 3, **3r**), while electron-withdrawing substituents only gave the corresponding products in moderate yields (e.g., **3s**). Substrates **2** bearing different phosphonate units also worked smoothly in this catalytic process, with all of the products being isolated in excellent yields and er values (**3t**−**3x**).

Having successfully synthesized a variety of chiral quaternary *α*-amino phosphonates, we then sought to further shrink the synthetic routes in order to improve the overall chemical efficiencies. *α*-Sulfonamidophosphonates **5** are late precursors of the *α*-ketiminophosphonate substrates **2**.[16] After investigation into the reaction conditions, we were able to merge the oxidation process for the preparation of **2** from substrates **5** with the NHC-catalyzed asymmetric oxidative [4 + 2] reaction in one pot. The cross-dehydrogenative-coupling (CDC) reaction was then developed for the asymmetric synthesis of quaternary *α*-amino phosphonates from the saturated *α*-aminiodophosphonates **5**, with a formal $C(sp^3)$−$C(sp^3)$ coupling process involved as the key step. The chiral quaternary *α*-amino phosphonates with different substitution patterns could be so afforded in moderate yields with excellent enantioselectivities through this NHC-catalyzed CDC process (Scheme 4).

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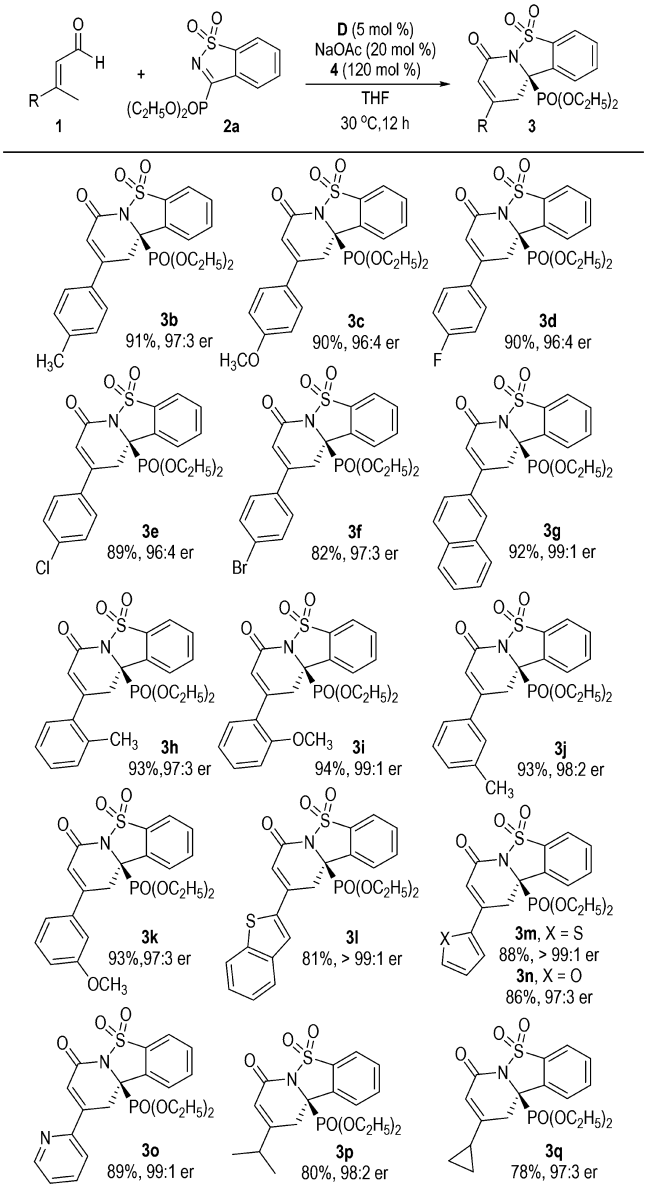
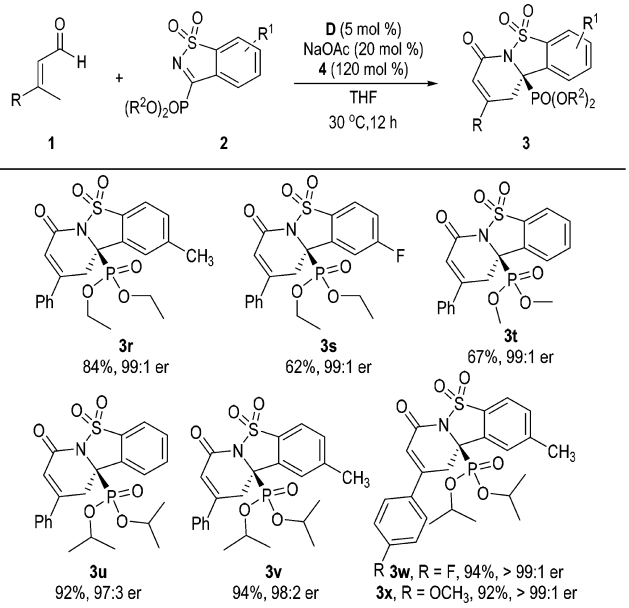
Scheme 2. Scope of Enals[a]



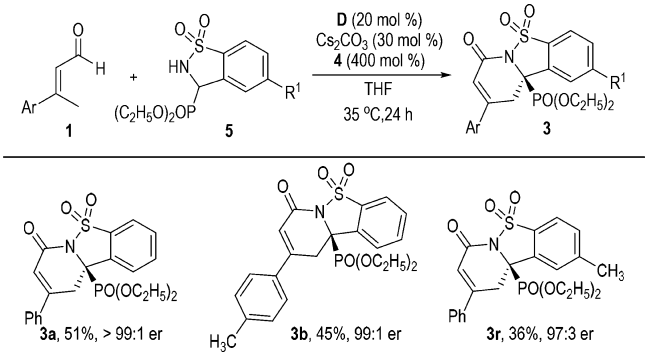
[a]Reaction conditions as stated in Table 1, entry 10. Yields are isolated yields after purification via SiO_2 column chromatography. er values were determined via HPLC on chiral stationary phase.

Scheme 3. Scope of α-Ketiminophosphonates[a]



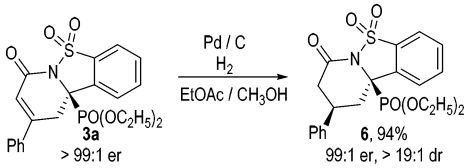
[a]Reaction conditions as stated in Table 1, entry 10. Yields are isolated yields after purification via SiO_2 column chromatography. Er values were determined via HPLC on chiral stationary phase.

Scheme 4. NHC-Catalyzed Asymmetric CDC Reaction[a]



[a]Reaction conditions: **5** (0.10 mmol), **2** (0.20 mmol), NHC (0.02 mmol), Cs_2CO_3 (0.03 mmol), **4** (0.40 mmol), THF (2.0 mL), 35 °C, 24 h. er values were determined via HPLC on a chiral stationary phase.

Scheme 5. Synthetic Transformations of 3a[a]



[a]The absolute configuration of **6** was determined via X-ray analysis on its single crystals.

The chiral multicyclic isothiazolopyridinephosphonate product **3a** obtained from this methodology could be reduced through a stereoselective hydrogenation process to give compound **6** in excellent yield with retention of the optical purity as a single diastereomer (Scheme 5).

In summary, we have developed an NHC-catalyzed asymmetric oxidative [4 + 2] reaction for the synthesis of optically pure quaternary α-amino phosphonates. Multicyclic isothiazolopyridine compounds bearing quaternary α-amino phosphonate units with various substitution patterns have been prepared in good to excellent yields with excellent enantioselectivities. An NHC-catalyzed enantioselective CDC process was also developed for quick access to the desired quaternary α-amino phosphonates. Further investigations into efficient catalytic approaches for the preparations of chiral sophisticated functional molecules are currently in progress in our laboratories.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02707.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1854450 and 1859307 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: robinchi@ntu.edu.sg.

ORCID

Yonggui Robin Chi: 0000-0003-0573-257X

Author Contributions

‖J.S. and C.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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