Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2016, 7, 6940

Enantioselective dearomatization of isoquinolines by anion-binding catalysis en route to cyclic α-aminophosphonates†

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Received 4th June 2016
Accepted 18th August 2016

DOI: 10.1039/c6sc02466a

www.rsc.org/chemicalscience

An enantioselective dearomatization of isoquinolines has been developed using chiral anion-binding catalysis. This transformation, catalyzed by a simple and easy to prepare *tert*-leucine-based thiourea derivative, makes use of silyl phosphite as a nucleophile and generates cyclic α-aminophosphonates. This is the first time asymmetric anion-binding catalysis has been applied to the synthesis of α-aminophosphonates.

Introduction

α-Aminophosphonates and the related α-aminophosphonic acid derivatives are used extensively in medicinal and pharmaceutical sciences as surrogates for α-amino acids.[1] The strong correlation between the biological activities of compounds containing α-aminophosphonic acids and their absolute configuration[2] renders the enantioselective synthesis of α-aminophosphonates imperative to such studies. Considerable advancement has taken place in the catalytic enantioselective synthesis of acyclic α-aminophosphonates using various strategies.[3,4] In contrast, enantioselective synthesis of cyclic α-aminophosphonates remains elusive,[5] despite their prominent abundance in biologically active molecules (Fig. 1).[6]

Among various methods to produce enantioenriched α-aminophosphonates, possibly the most straightforward approach involves the catalytic asymmetric addition of dialkylphosphites to imines (Scheme 1A).[7] In fact, the first example of a catalytic enantioselective synthesis of cyclic α-aminophosphonates consisted of an asymmetric hydrophosphonylation of cyclic imines, catalyzed by chiral heterobimetallic lanthanoid complexes.[8,9]

Regardless of the popularity of dialkylphosphites as a nucleophile, the unfavorable equilibrium of unreactive phosphonate over reactive phosphite[10] (Scheme 1B) often causes these reactions to be overly dependent on base activation.

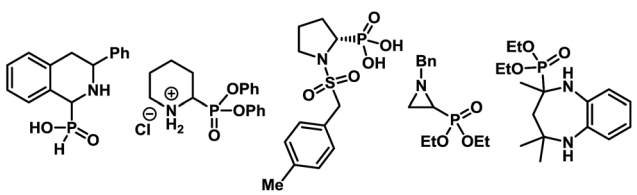
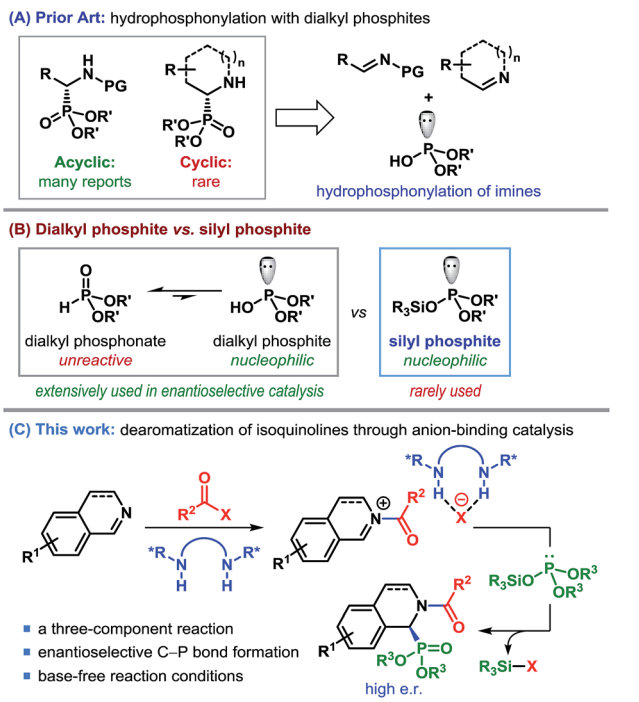


Fig. 1 Biologically relevant cyclic α-aminophosphonic acids and their derivatives.



Scheme 1 Catalytic enantioselective routes to cyclic α-aminophosphonic acids.

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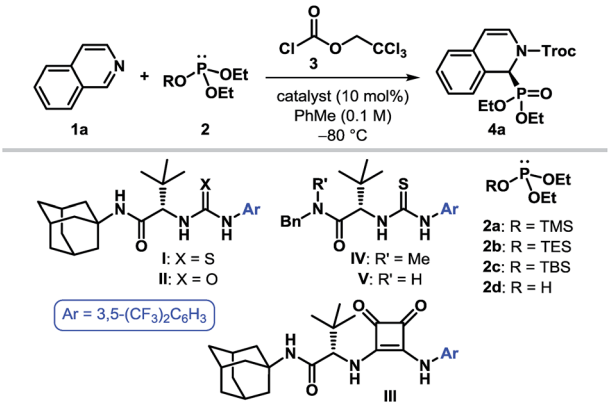
† Electronic supplementary information (ESI) available: Experimental details, characterization and analytical data. CCDC 1476699 (**4w**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc02466a

Silyl esters of dialkyl phosphonate (silyl phosphites), originally introduced by Abramov,[11] on the other hand, are free from such limitations and display excellent reactivity.[12] Nevertheless, the use of this class of highly nucleophilic silyl phosphites in enantioselective catalysis remained missing until the recent report by List and co-workers.[13]

In our effort to devise a catalytic enantioselective synthesis of cyclic α-aminophosphonates, we became interested in the addition of silyl phosphites to isoquinolines and their derivatives. Catalytic asymmetric dearomatization has emerged as a remarkably efficient strategy to synthesize a wide range of structurally and functionally important compounds.[14] The pioneering works of Reissert have paved the way for decorating nitrogeneous heterocycles through acyl activation followed by nucleophilic addition, commonly known as Reissert-type reactions.[15] We realized that the enantioface-selective addition to acyl-activated isoquinolines could be achieved through anion-binding catalysis – a concept, pioneered by Jacobsen *et al.* (Scheme 1C).[16,17] However, despite the emergence of a number of anion-binding catalyst motifs, the asymmetric dearomatization of isoquinolines driven by anion-binding catalysis has so far been restricted mostly to using silyl ketene acetals as the nucleophilic partner.[17,18] Rather surprisingly, to date no other silyl nucleophile has been employed in such reactions.

The use of silyl phosphites as a nucleophile in the dearomatization of isoquinolines appears to be tailor-made, in view of the fact that besides being a powerful nucleophile, the silyl group would also act as a sink for the counteranion ($X^{\ominus}$ in Scheme 1C) and regenerate the catalyst. This three-component reaction would, in principle, represent a general and enantioselective route to cyclic α-aminophosphonates. The successful implementation of this strategy is presented in this article.

Table 1 Catalyst identification and reaction conditions optimization[a]



Entry	Catalyst	2	t [h]	Conv.[b] [%]	er[c]
1[d]	None	**2a**	1	>95	—
2	None	**2a**	72	<5	—
3	**I**	**2a**	72	>95	94.5 : 5.5
4	**II**	**2a**	72	>95	78 : 22
5	**III**	**2a**	72	>95	60 : 40
6	**IV**	**2a**	72	>95	96 : 4
7	**V**	**2a**	72	>95	91.5 : 8.5
8	**IV**	**2b**	72	>95	96 : 4
9	**IV**	**2c**	72	>95	94.5 : 5.5
10	**IV**	**2d**	72	<5	n.d.

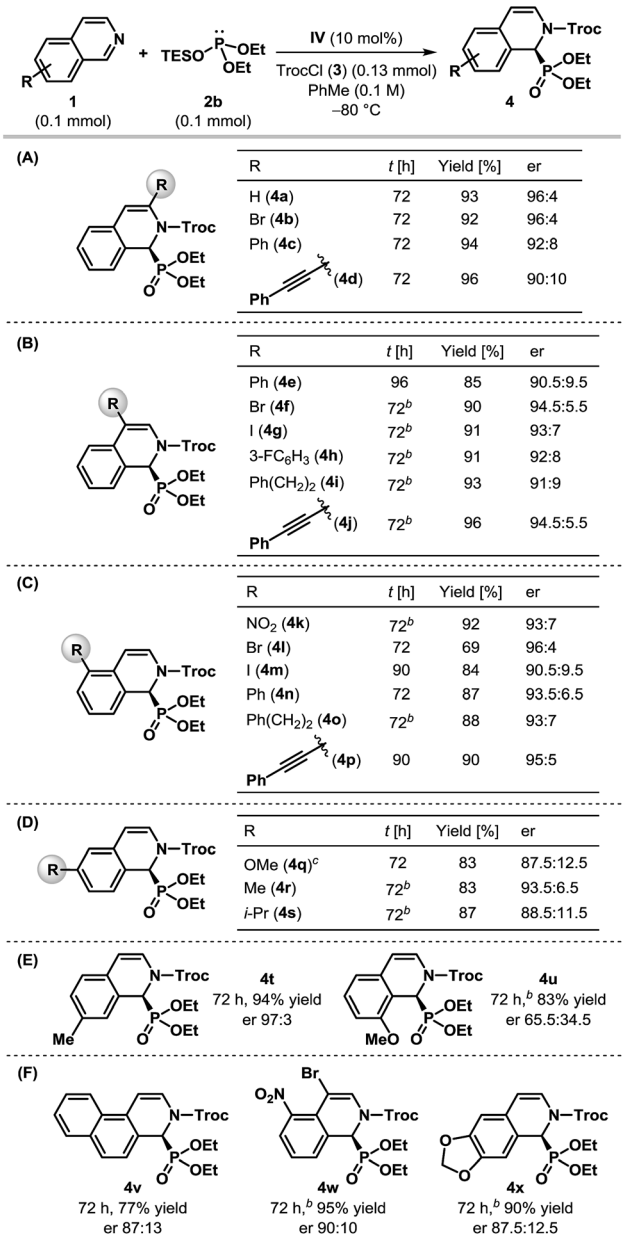
[a] Reactions were carried out on a 0.1 mmol scale using 1.0 equiv. of **1a**, 1.0 equiv. of **2** and 1.3 equiv. of **3**. [b] Conversion as determined by ^{1}H NMR of crude reaction mixture. [c] Enantiomeric ratio (er) was determined *via* HPLC analysis using a stationary phase chiral column. [d] Reaction at 25 °C. n.d. = not determined.

Results and discussion

To put our hypothesis into practice, we began our investigation with an equimolar amount of isoquinoline (**1a**) and diethyl trimethylsilyl phosphite (**2a**) in the presence of a slight excess of 2,2,2-trichloroethyl chloroformate (TrocCl, **3**) (Table 1). The reaction was indeed found to proceed efficiently to generate the desired cyclic *N*-acyl α-aminophosphonate **4a** under the influence of 10 mol% of various hydrogen bond donors. Among the different H-bonding motifs studied (entries 3–5), thiourea proved to be the best anion-binding catalyst.[19] Further optimization led to the identification of a simple and easy to prepare *tert*-leucine-derived thiourea **IV**,[20] which provided **4a** with an enantiomeric ratio (er) of 96 : 4 (entry 6). While the same level of enantioselectivity was observed when diethyl triethylsilyl phosphite (**2b**) was used as the nucleophile (entry 8), bulkier silyl phosphite **2c** furnished the product with a diminished er (entry 9). It must be noted that no conversion to the desired product occurred with diethyl phosphite (**2d**) as the nucleophile under otherwise identical reaction conditions (entry 10), thereby highlighting the superior nucleophilicity of silyl phosphites. Attempts to optimize the reaction by using different acylating agents or by changing the reaction medium and other parameters failed to provide any improvement in the optical yield.[19]

Having optimized the catalyst and the reaction conditions, we sought to test the scope and limitations of this enantioselective dearomatization reaction with respect to other isoquinoline derivatives. Even though identical results were obtained with both silyl phosphites **2a** and **2b** (Table 1, entries 6 and 8), the enantioselectivity observed for **2a** did not appear to be general for other substrates. Therefore, we decided to use diethyl triethylsilyl phosphite **2b** for the subsequent studies. The results compiled in Table 2 indicate that our protocol is generally applicable to monosubstituted isoquinolines bearing substituents at nearly every position (Table 2A–E) and even for disubstituted isoquinolines (Table 2F). In all of the cases, the products were obtained in good to excellent yields. Various 3- and 4-substituted isoquinolines were found to be effective substrates and the products were achieved with good to high enantioselectivity (Table 2A and B), although the reaction had to be carried out at −50 °C for most of the 4-substituted isoquinolines. Different substituents at the 5-position of isoquinoline were also tolerated and the desired α-aminophosphonates were generated with good enantioselectivity (Table 2C). Particularly noteworthy is the

Table 2 Scope of dearomatization with respect to isoquinolines[a]



[a] Yields correspond to the isolated yield. er determined *via* HPLC analysis using a stationary phase chiral column. [b] Reaction was performed at −50 °C. [c] Silyl phosphite **2a** was used instead of **2b**.

enantioselectivity observed for 5-nitroisoquinoline (**1k**), as the nitro group itself is capable of H-bonding with thiourea[21] and could potentially upset the anion-binding activation mode of the catalyst. The dearomatization reaction worked well with 6-substituted isoquinolines, although the products were returned with reduced enantioselectivity (Table 2D). While the α-aminophosphonate (**4t**) derived from 7-methyl isoquinoline was formed with excellent enantioselectivity, the poor er obtained in the case of 8-methoxyisoquinoline **1u** is presumably due to the steric influence of the substituent on the reaction center as a result of its proximity (Table 2E). Fused and disubstituted isoquinolines (**1v–x**) are also competent substrates for this reaction (Table 2F). However, the corresponding products (**4v–x**) were formed at most with modest enantioselectivities. Our attempts to synthesize cyclic α-aminophosphonates containing a quaternary stereogenic center by using 1-substituted isoquinolines ended in vain as no phosphonylation took place with either 1-methyl or 1-phenyl isoquinolines, even at 25 °C indicating the steric limitation of our protocol.

The absolute configuration of **4w** was determined using single crystal X-ray diffraction analysis (Fig. 2).[22] The configurations of the other products were assigned as the same, assuming that an analogous catalytic mechanism is operating.

Besides diethyl triethylsilyl phosphite **2b**, trimethylsilyl phosphites bearing different dialkyl substituents were found to be potent nucleophiles for this dearomatization reaction (Scheme 2). While a product (**6a**) with a reduced er was obtained with dimethyl phosphite (**5a**), both di(*n*-propyl) phosphite (**5b**) and diisopropyl phosphite (**5c**) rendered the reaction highly enantioselective. In fact, with **5c** as the nucleophile, the reaction on a 1.0 mmol scale using only 5 mol% of catalyst (**IV**) delivered the product (**6c**) with a comparable yield and er. Notwithstanding the longer reaction time, catalyst recovery was possible with 95% yield.[19]

The optimized catalyst and reaction conditions were found to be almost equally suitable for dihydroisoquinolines (**7**) and we were pleased to find that the corresponding α-aminophosphonates (**8**) were obtained in excellent yields (Table 3). However, the enantioselectivities observed in these reactions were generally found to be lower than those obtained for the corresponding isoquinoline derivatives.

To demonstrate the synthetic utility of the products obtained through the dearomatization of isoquinolines, we undertook the task of removing the protecting groups of cyclic *N*-Troc α-aminophosphonate **4a** (Scheme 3A). The hydrolysis of the phosphonate could be achieved easily using sodium iodide and TMSCl to obtain the N-protected cyclic α-aminophosphonic acid **9** in 65% yield without any erosion in enantioselectivity. However, an attempt to remove Troc by In/NH_4Cl[23] resulted in rearomatization to the corresponding isoquinoline derivative **10** through aerial oxidation. Such aromatization to isoquinoline derivatives, even under reductive conditions, is documented in the literature[24] and can be attributed to the inherent instability of the free secondary amine. The compounds of type **10** are known for their use as corrosion inhibitors.[25]

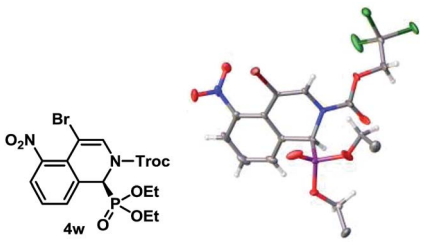
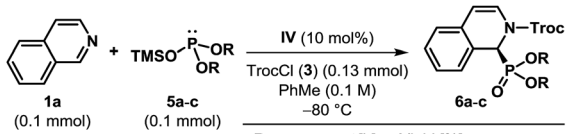


Fig. 2 Absolute configuration of **4w** and its X-ray structure.

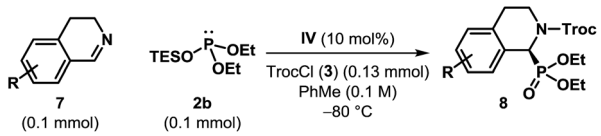


R	t [h]	Yield [%]	er
Me (**6a**)	72	92	87.5:12.5
n-Pr (**6b**)	96	96	95:5
i-Pr (**6c**)	72	96	97:3
i-Pr (**6c**)[a]	104	93	96.5:3.5

[a] The reaction on a 1.0 mmol scale with 5 mol% **IV**.

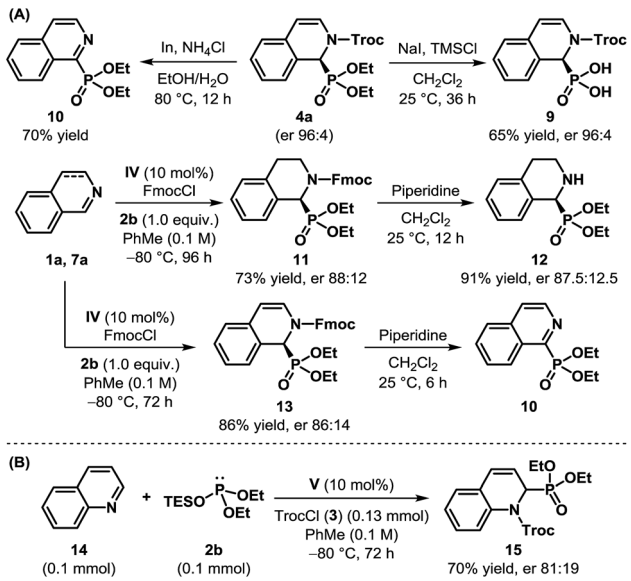
Scheme 2 Scope of dearomatization with respect to dialkyl phosphite and the reaction on a larger scale.

Table 3 Catalytic enantioselective phosphonylation of dihydroisoquinolines



Entry	R	8	t [h]	Yield[a] [%]	er[b]
1	H	**8a**	72	90	95 : 5
2	5-NO_2	**8b**	72	90	78.5 : 21.5
3	5-Ph	**8c**	72	83	81 : 19
4	7-Me	**8d**	80	96	93.5 : 6.5

[a] Yields correspond to the isolated yield. [b] er determined *via* HPLC analysis using a chiral stationary phase.

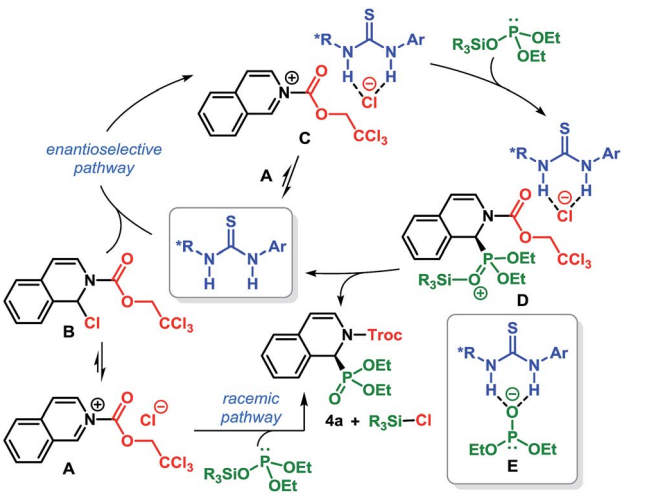


Scheme 3 (A) Removal of protecting groups, and (B) the initial results of the catalytic enantioselective dearomatization of quinoline.

Various attempts to remove the Troc group, even from **8a**, remained unsuccessful.[19] The Fmoc-protected product (**11**) derived from dihydroisoquinoline, on the other hand, when subjected to piperidine in CH_2Cl_2, cleanly resulted in cyclic α-aminophosphonate **12** in 91% yield. The reaction of Fmoc-protected dearomatized product **13**, under the same conditions, once again produced **10**, even though the free amine could be detected initially when the reaction was monitored by ^{1}H-NMR.[19]

After successfully accomplishing the enantioselective dearomatization of isoquinolines, we wondered whether our protocol could be used for quinoline (**11**).[17b] While it is more challenging to dearomatize quinoline,[26] a preliminary experiment showed that our reaction conditions were indeed suitable for this purpose. Using **V** as the catalyst, the product **12** was isolated in 70% yield with an er of 81 : 19 (Scheme 3B). Despite the modest enantioselectivity, these results clearly illustrate the potential of this approach toward the dearomatization of other nitrogenous heteroaromatics.[27]

A number of pieces of information emerged during the optimization of the reaction conditions which helped to shed light on the mechanism of this catalytic transformation. The reaction medium was found to play a crucial role in the enantioselectivity of this reaction: a homogeneous reaction mixture in CH_2Cl_2 led to the product with poor er but high enantioselectivity was observed in toluene – a solvent which results in a heterogeneous reaction mixture.[19] In addition, the silyl group of silyl phosphite exerts measurable influence on the enantioselectivity of the reaction (Table 1, entry 6 *vs.* 9). Based on these facts, a tentative mechanism is proposed as depicted in Scheme 4.[28] Isoquinoline upon treatment with TrocCl, produces the salt **A** which exists in equilibrium with its covalent form **B**. The salt **A** can readily react with silyl phosphite to furnish Troc-protected α-aminophosphonate **4a**. Its covalent form **B**, on the other hand, is unreactive toward silyl phosphite. The insolubility of **A** in toluene, especially at −80 °C, accounts for the absence of any background reaction at this temperature (Table 1, entry 2). However, the thiourea catalyst facilitates the ionization of **B** to generate salt **C**, in which the chloride ion is bound to thiourea by dual H-bonding. The direct conversion of **A** to **C** is also



Scheme 4 Proposed mechanism for the dearomatization of isoquinolines.

possible in the presence of the thiourea catalyst. The formation of **C** not only solubilizes the reactive ionic form, but at the same time owing to its proximity to the chiral thiourea-bound chloride anion, suffers an enantioface-selective attack by silyl phosphite. The resulting silylated intermediate **D** then collapses to release the product (**4a**) as well as R_3SiCl and regenerates the catalyst. The participation of silyl phosphite (as opposed to the thiourea-bound phosphite anion **E**) in nucleophilic addition accounts for the observed influence of the silyl group on the enantioselectivity of the reaction. The lower er obtained in more polar solvent is most likely due to the competing background reaction which may stem from the superior solubility of **A** in such solvents.[29] Furthermore, the superior solvation of the isoquinolinium cation and the chiral thiourea-bound chloride anion (of **C**) in more polar solvents possibly prevents the 'chiral counteranion' from being in sufficiently close proximity to the reactive center. Such proximity is necessary for the enantioface-selective attack by silyl phosphite.[16a]

Conclusions

In conclusion, we have successfully developed an enantioselective dearomatization of diversely substituted isoquinolines through the acyl activation and nucleophilic addition of silyl phosphites. Using a simple and easy to prepare *tert*-leucine derived thiourea as an anion-binding catalyst, this base-free protocol delivers cyclic α-aminophosphonates in excellent yields with moderate to high enantioselectivities. This is the first example of the use of silyl phosphites as a nucleophile in asymmetric dearomatization reactions driven by anion-binding catalysis. In fact, this is also the first time asymmetric anion-binding catalysis has been applied for the synthesis of α-aminophosphonates. A preliminary experiment with quinoline points toward the potential applicability of this strategy to other nitrogenous heteroaromatics. Efforts in this direction are currently ongoing in our laboratory.

Acknowledgements

This work is funded by DAE-BRNS [Grant No. 2013/37C/56/BRNS/2440]. A. R. C. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for the Shyama Prasad Mukherjee Fellowship. We thank Prodip Howlader (IPC, IISc, Bangalore) for his help with the X-ray structure analysis.

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