Organocatalysis Hot Paper

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Enantioselective Synthesis of Piperidines through the Formation of Chiral Mixed Phosphoric Acid Acetals: Experimental and Theoretical Studies**

Zhankui Sun, Grace A. Winschel, Paul M. Zimmerman, and Pavel Nagorny**

Abstract: *An enantioselective intramolecular chiral phosphoric acid-catalyzed cyclization of unsaturated acetals has been utilized for the synthesis of functionalized chiral piperidines. The chiral enol ether products of these cyclizations undergo subsequent in situ enantioenrichment through acetalization of the minor enantiomer. A new computational reaction exploration method was utilized to elucidate the mechanism and stereoselectivity of this transformation. Rather than confirming the originally postulated cyclization proceeding directly through a vinyl oxocarbenium ion, simulations identified an alternative two-step mechanism involving the formation of a mixed chiral phosphate acetal, which undergoes a concerted, asynchronous S_N2'-like displacement to yield the product with stereoselectivity in agreement with experimental observations.*

Since the realization that Lewis and Brønsted acids could enhance the reactivity of conjugated carbonyls,[1] a variety of catalytic asymmetric methods for the activation and functionalization of α,β-unsaturated carbonyl-containing organic compounds have emerged in the scientific literature.[2] Typically, existing protocols are based on LUMO activation of pendent olefin functionalities and could be achieved through the formation of chiral carbonyl-bound complexes (i.e., **3** or **4**; Figure 1) or iminium ions. It is noteworthy that **3** and **4** are cationic in nature and could be viewed as oxocarbenium ions with reactivities similar to those of unsaturated acetal-derived oxocarbenium ions (**2**). While indeed a number of synthetically useful transformations involving the generation of **2** from **1** are known,[3] the existing asymmetric methods typically rely on the use of chiral auxiliaries[4,5] and only one recent report from our group[7a] suggests that such transformations are amenable to asymmetric catalysis.

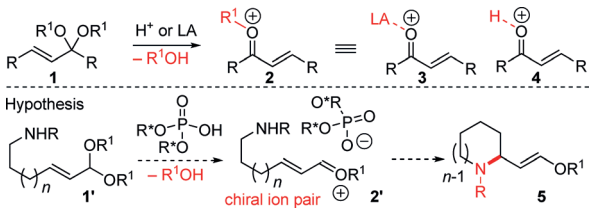

Figure 1. Proposed phosphate-directed aza-Michael reaction of unsaturated acetals.

Our group has long-standing interests in understanding and exploring the chemistry of reactions which proceed through oxocarbenium/chiral phosphate intermediates. Although a number of selective transformations which presumably proceed through such ion pairs have been described,[6] a better mechanistic understanding of these phenomena is often required. Recently, we became interested in exploring the unique reactivities of the unsaturated oxocarbenium **2**, which can be formed by protonation of the unsaturated acetals **1** (Figure 1).[7] Ionic [2+4] cycloadditions are perhaps the most well-known transformations associated with the intermediacy of **2**.[3] However, less common reactions such as aza-Michael reactions, proceeding through **2′**, could be envisioned once the analogy between **2** and the species **3** and **4** is drawn. Although intramolecular catalytic aza-Michael reactions involving unsaturated aldehydes are known,[8] the cyclizations of **1′** leading to **5** remain unprecedented.

This report describes the first example of a highly enantioselective cyclization of the unsaturated acetals **1′** leading to functionalized chiral piperidines **5** as proposed in Figure 1. Detailed computational studies employing a new methodology were conducted to elucidate the mechanism of this transformation, and to demonstrate the utility of this simulation method in highly complex settings. Remarkably, these computational studies identified a new transacetalization/S_N2'-like pathway as the more energetically feasible mechanism.

The cyclization of the unsaturated acetal **1a** leading to the piperidine **5a** was investigated first (Table 1). The selectivity and yield of this cyclization were found to be highly dependent on the polarity of the solvent, with highly nonpolar hydrocarbon-based solvents providing the best yields and enantioselectivities. Careful evaluation of solvents and chiral phosphoric acids (CPAs) as the catalysts (see Table S1 in the Supporting Information) led to the selection of carbon tetrachloride as the solvent and the CPA **6** as the catalyst of choice, and **5a** was obtained in 89% yield and 57% *ee* along with about 5% of the acetal **7** (entry 1). As expected, lowering the reaction temperature to −20°C resulted in improved selectivity (entry 2). The enantioselectivity was also found to be sensitive to the catalyst loading and the levels of *E*/*Z*-isomer purity of **1a** (entries 3 and 4). Additionally,

[*] Dr. Z. Sun, G. A. Winschel, Prof. Dr. P. M. Zimmerman, Prof. Dr. P. Nagorny
Department of Chemistry, University of Michigan
Ann Arbor, MI 48109 (USA)
E-mail: paulzim@umich.edu
nagorny@umich.edu

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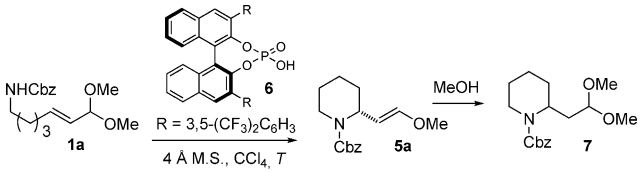
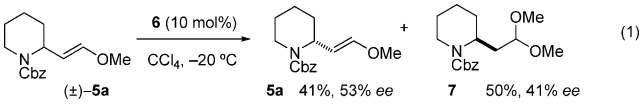
Table 1: Initial screen and reaction optimization.



Entry	**6** (mol%)	**1a** *E*/*Z*	*t* [h]	*T* [°C]	**5a** Yield [%]	**5a** *ee* [%]
1	5	20:1	14	RT	89	57
2	5	20:1	14	−20	86	71
3	10	20:1	14	−20	88	75
4	10	10:1	14	−20	83	63
5[b]	10	20:1	14	−20	81	84
6[b]	10	20:1	24	−20	81	84
7[b]	10	20:1	30	−20	75	87
8[b]	15	20:1	24	−20	74	88
9[b]	15	20:1	48	−20	62	95

[a] All reactions were performed on a 0.1 mmol scale (0.02 M solution) of **1a** (*E*/*Z* > 20:1) with 200 mg 4 Å M.S. [b] Reaction run with 100 mg 4 Å M.S. Cbz = benzyloxycarbonyl, M.S. = molecular sieves.

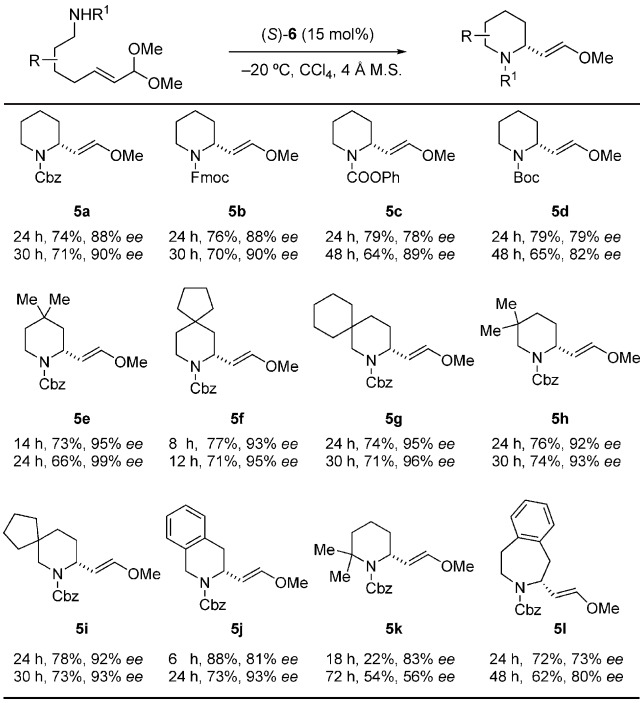
a remarkable dependence of enantioselectivity on reaction time was discovered when reduced amounts of molecular sieves were used (entries 5–9). Thus, longer reaction times lead to improved enantioselectivities and decreased yields, and formation of **5a** in 87% *ee* with 75% yield was observed if the reaction time was extended to 30 hours (entry 7). Interestingly, increased amounts of **7** (ca. 14–16%) were observed in this experiment. Based on this observation, we surmized that the CPA **6** catalyzed the reaction of the minor enantiomer of **5a** with the methanol by-product generated in this reaction, thus resulting in the enantioenrichment of **5a**. Indeed, the reaction of racemic **5a** and methanol catalyzed by **6** led to kinetic resolution, thus yielding enantioenriched **5a** and **7** [Eq. (1)]. To speed up this process (i.e., resolution leading to **7**) 15 mol% of **6** was employed (entries 8 and 9). Consequently, running a reaction under the optimized reaction conditions resulted in 74% yield and 88% *ee* of **5a** after 24 hours (entry 8), and 95% *ee* and 62% yield of **5a** after 48 hours (entry 9).



(1)

An investigation of the reaction scope was executed next (Table 2). The reaction yields and enantioselectivities were monitored at two different times. The cyclization reaction was found to be tolerant to the changes in the protecting groups and good to excellent enantioselectivities were observed for Fmoc-, carbophenoxy-, and Boc-protecting groups. Importantly, the three products **5b–d** underwent enantioenrichment, with the carbophenoxy-protected substrate **5c** showing the most dramatic improvement in *ee* value (i.e., 11%) over the course of 24 hours. The cyclizations were further found to be tolerant to C4 substitution on the piperidine ring. Thus, highly enantioselective cyclizations led to the formation of the C4-substituted piperidines **5e** and **5f**. Similarly, substitution

Table 2: Reaction scope.[a]

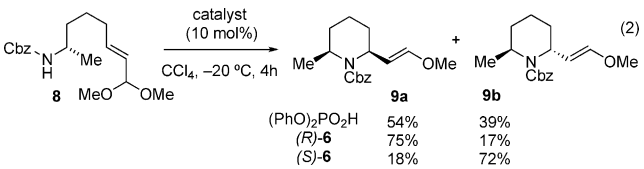


[a] All reactions were performed on 0.1 mmol scale (0.02 M solution) with 100 mg 4 Å M.S. Acetals derived from **5** were the major side products in each case. **5l** was run at 0 °C. Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl.

on the C5-position of the ring also had a beneficial effect on the selectivity of the reaction and highly enantioselective formation of **5g**, **5h**, and **5i** was observed. This methodology can also be applied to the synthesis of chiral tetrahydroisoquinolines. Remarkably, significant enantioenrichment of **5j** (from 81% *ee* after 6 h to 93% *ee* after 24 h) was observed over the course of the cyclization.

The effect of the C6 substitution was also evaluated. Formation of **5k** proceeded with significantly slower rates, and the enantioselectivity for the formation of **5k** dropped with the progression of the reaction. Finally, the possibility of forming seven-membered heterocycles was investigated, and the formation of **5l** proceeded with enantioselectivity and enantioenrichment similar to that observed for the six-membered ring systems (**5a–5k**).

Next, cyclization of the chiral substrate **8** was tested [Eq. (2)]. Typically, heteroconjugate additions lead to the

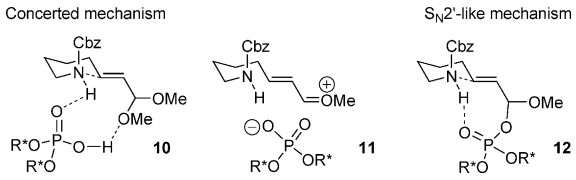


(2)

formation of thermodynamically (and kinetically) more stable *cis* products (i.e., **9a**).[9] The use of chiral catalysts offers a chance to override the course of such cyclizations and favor the formation of the less stable *trans* products (i.e., **9b**).[10] Exposure of **8** to achiral acids such as $(PhO)_2PO_2H$, resulted in almost unselective formation of both the diaste-

reomers **9a** (54%) and **9b** (39%). At the same time, use of (*R*)-**6** under the optimized reaction conditions resulted in enhanced formation of the *cis*-product **9a** (75%) and only 17% of **9b** was formed. Additionally, the use of (*S*)-**6** yielded the desired selectivity switch and the *trans*-product **9b** was obtained as the major product (72%) and only 18% of **9a** was produced.

Our original mechanistic proposal was based on an ionic mechanism operating directly via the oxocarbenium intermediate **11** (Scheme 1) to give the cyclized product.[12] Also



Scheme 1. Potential reaction mechanisms.

under consideration was synchronous variation (**10**), utilizing the bifunctional nature of the catalyst, thus promoting cyclization upon simultaneous protonation of the methoxy group and deprotonation of the nitrogen atom. To identify a plausible reaction mechanism, a computational study was employed and utilized the automated discovery of chemical reaction steps methodology developed in the Zimmerman group.[13] This approach explores a variety of chemically reasonable elementary steps and identifies the most kinetically and thermodynamically likely steps, thus producing minimum-energy reaction paths and transition state structures. By performing this search over a combinatorial set of possible reactions, this approach avoids over-reliance on chemical intuition, which could inadvertently bias the mechanistic outcome by causing key reaction intermediates to be overlooked.

Indeed, our full system simulations based on the aforementioned methods and conducted on the Cbz-protected substrate **5a** and (*S*)-**6** as the catalyst (see the Supporting Information) ruled that the highly organized, synchronous mechanism proceeding via **10** (Scheme 1) has a barrier which is too high (> 30 kcal mol^{-1}) to be consistent with the reaction conditions. At the same time, computational investigations identified an unexpected lower-barrier S$_N$2′-like cyclization mechanism, operating through the chiral phosphate acetal **12**.

The results of the computational studies as well as the proposed reaction mechanism are summarized in Figure 2. Activation barriers for each elementary step were determined using the growing string method with an exact transition-state search using B3LYP and a 6-31G** basis set.[13c] The important reaction intermediates and transition states were then subject to single-point energy calculations to compute the Gibbs free energies, including CCl_4 solvent corrections, using a dispersion-corrected ωB97X-D exchange-correlation functional with a 6-311 + G(d,p) basis set.[13,14]

This computational analysis identified the lowest energy path as proceeding by protonation of the methoxy group nearest to the acidic proton of the phosphoric acid to give **14** as a transitory structure, after which methanol departs through transition state **TS-I** (Figure 2). The activation energy for **TS-I** was computed to be 16.9 kcal mol^{-1}. As the methanol is liberated, rather than proceeding in a concerted fashion through cyclization (via **11**), the reactive species is trapped by the phosphate to yield the energetically favorable intermediate **13**. This is downhill from **TS-I** by 12.7 kcal mol^{-1}, thus relieving the system of the high-energy reorganization process to continue through to the cyclization event. Notably, the ion pair did not prove to be stable at structures near **TS-I**

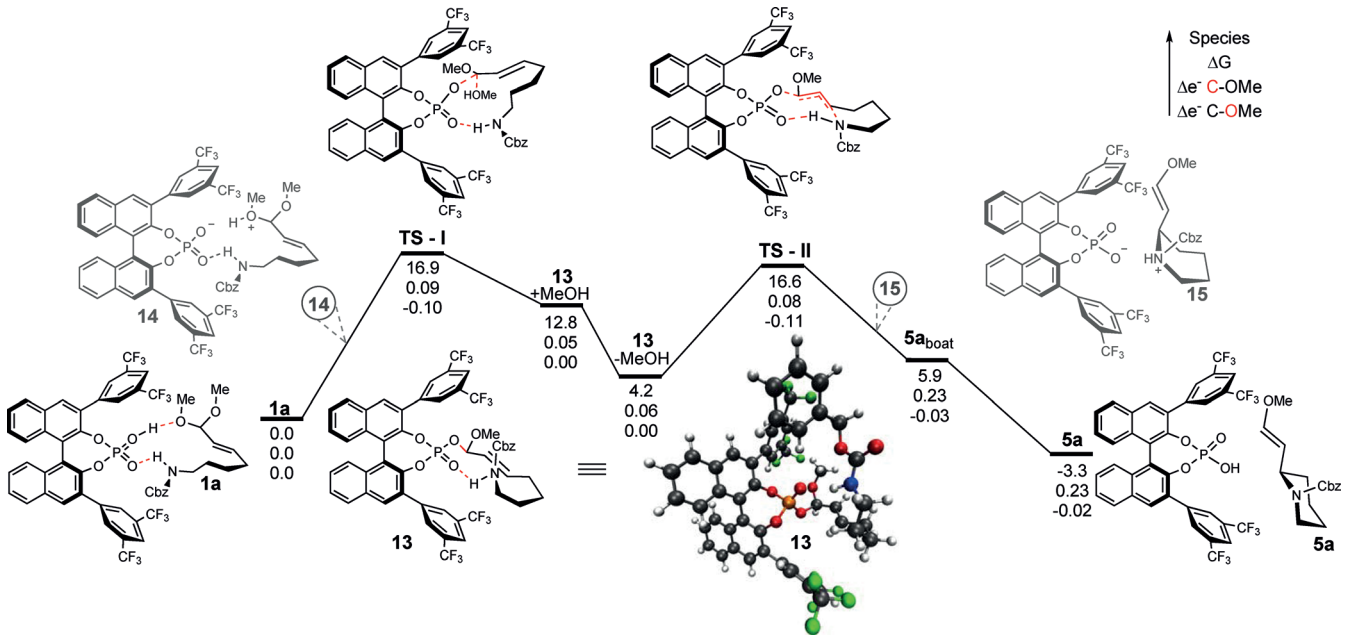


Figure 2. Most favored reaction pathway from calculations.[11] Change in electron density for the methoxy oxygen atom, which remains bound to the substrate and the carbon atom to which it is attached, illustrate no significant charge build-up over the course of the reaction.

for methanol detachment.[11] From **13**, **TS-II** forms with a free-energy barrier at 16.6 kcal mol^{-1} above the starting species. This reaction step consists of a concerted, but asynchronous detachment of the phosphate, ring closure, and deprotonation of the transitory **15** to yield **5a**$_{boat}$, which relaxes to **5a**. The slight downhill nature of the reaction is further consistent with the observed chiral resolution.

The change in electron density of the methoxy oxygen atom and the carbon atom, to which it is attached, show no notable change in electron density (Figure 2) with the largest Δe^- observed for oxygen in **TS-II**, at $-0.11\,e^-$, and is consistent with a non-ionic transition state. While the existence of stable carbenium/chiral phosphate intermediates has been evoked in several instances, covalently linked binol-derived phosphates are rarely proposed to be viable intermediates in CPA-catalyzed reactions.[6] Although structurally similar carbohydrate-derived anomeric phosphates are well known, **13** is energetically uphill from the starting species. As an unstable intermediate, **13** did not prove to be substantially isolable and we could not identify it directly by NMR spectroscopy. It is noteworthy that the proposed mechanism is in line with the studies by Toste and co-workers,[15] who demonstrate that dithiophosphoric acid-catalyzed asymmetric additions to dienes proceeded through a covalent intermediate similar to **13**.

Additionally, a similar reaction path leading to the minor stereoisomer was investigated. In support of experimental observations, the reaction pathway to form the minor enantiomer is 3.2 kcal mol^{-1} higher in energy than that of the observed major stereoisomer shown in Figure 2 (see Scheme SI–SIII). This selectivity stems from the ability of **1a** to form a hydrogen bond between the N-H and a phosphate oxygen atom of (*S*)-**6** in **TS-II**. Following formation of phosphate acetal **13**, the complex leading to the major enantiomer is aligned for hydrogen-bond formation, while this is not the case for the minor enantiomer.

In conclusion, a highly enantioselective intramolecular chiral phosphoric acid-catalyzed cyclization of unsaturated acetals has been utilized for the synthesis of functionalized chiral piperidines. The chiral enol ether products of these cyclizations were found to undergo subsequent in situ enantioenrichment as a result of the acetalization of the minor enantiomer, which resulted in enhanced enantioselectivities. New computational methods were applied to understand the mechanism of this transformation.[13] Rather than confirming the originally postulated cyclization proceeding directly through a vinyl oxocarbenium ion, our simulations identified an alternative two-step mechanism proceeding through the formation of a mixed chiral phosphate acetal which undergoes a concerted asynchronous S_N2'-like displacement leading to the product.

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[11] Note that the protonated **14** and **15** are not identified as stable structures. Optimization of the structures **14** and **15** led to **1a** and **5a**, respectively, thus indicating these are not stationary points on the PES. For the potential energy surface for the formation of the minor enantiomer refer to Schemes SI–SIII.
[12] The transition-states **11** and **12** could be distinguished by the change in the charge distribution as well as by the PO-C distances. Refer to the Supporting Information (p. 21) for a more detailed discussion.
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