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Catalytic Asymmetric Aza-Darzens Reaction with a Vaulted Biphenanthrol Magnesium Phosphate Salt

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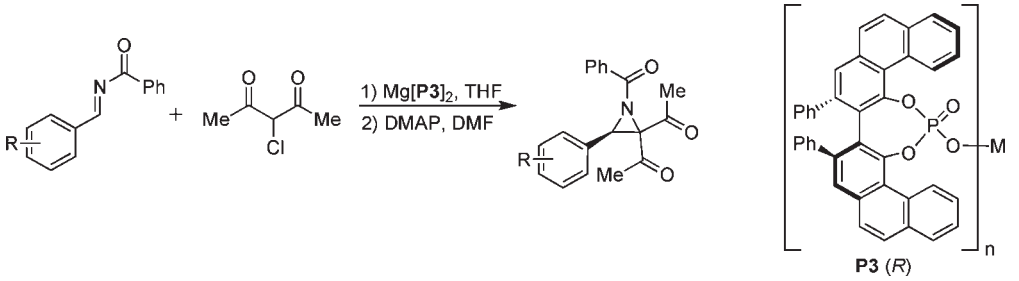
ABSTRACT



Conditions for a catalytic asymmetric aza-Darzens aziridine synthesis mediated by a vaulted biphenanthrol (VAPOL) magnesium phosphate salt is described. Using simple substrates, this methodology explores the scope and reactivity of a new magnesium catalyst for an aziridination reaction capable of building chirality and complexity simultaneously.

The Darzens aziridine synthesis, first proposed by Deyrup,[1] is a pathway to prepare complex aziridines, with considerable synthetic utility, from common synthetic building blocks. Examples where such aziridines are used as versatile intermediates are mainly through their ring-opening reactions for the preparation of chiral amines.[2] Clearly, new catalytic asymmetric methods of aziridine synthesis via the aza-Darzens reaction would be interesting due to this synthetic potential. In two reports from 1999 and 2000, a breakthrough by Wulff in the area of catalytic asymmetric aziridination of imines was reported.[3] The catalyst for this reaction, while initially believed to be a boron Lewis acid, was later proven to be a chiral Brønsted acid after intense mechanistic study.[4] Additionally, in 1999, independently both Sweeney[5] and Davis[6] reported asymmetric versions of the aza-Darzens reaction using stoichiometric amounts of chiral reagents. In other early studies, Johnston and co-workers published a triflic acid-catalyzed aza-Darzens variant.[7] More recently, a number

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of new Brønsted acid variants similar to these reactions were subsequently published, with highly enantioselective conditions described.[8] We believed that, despite the above efforts, the use of typical aza-Darzens-type nuceophiles[9] like α-halo-1,3-dicarbonyl compounds could lead to functionalized aziridines using chiral phosphoric acids as potential catalysts.[10]

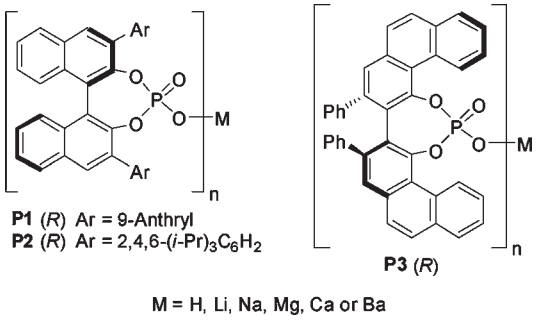
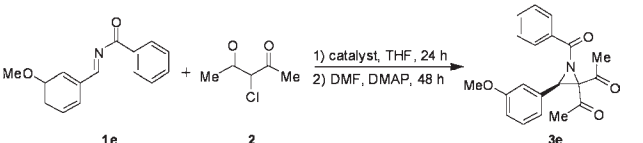


Figure 1. Common phosphoric acids and their phosphate salt equivalents.

After some limited initial success while focusing on chiral phosphoric acids, we turned our attention to chiral phosphate metal salts as viable mediators for this reaction. We were attracted to these catalysts after a report by Ishihara on similar Mannich reactions showed that metal phosphate salts were superior catalysts when screening versus the free phosphoric acids.[11] These investigations were supported by the findings of List,[12] who showed that phosphoric acids used directly after column chromatography can be the neutralized mixtures of phosphate salt impurities and acid, rather than just the pure acid.

We were encouraged by recent reports that successfully demonstrated a variety of chiral phosphate salts for catalytic asymmetric induction.[13] Using chiral phosphate salts as catalysts, we wish to report an asymmetric aza-Darzens reaction that employs α-chloro-1,3-diketones as competent nucleophiles for addition to *N*-benzoyl imines, allowing access to trisubstituted aziridines with good enantioselectivity.

Table 1. Optimization of Aza-Darzens Aziridination Reaction[a]



entry	catalyst[b]	catalyst loading (mol %)	yield (%)[c]	ee (%)[d]
1	H[**P1**]	5	48	0
2	H[**P2**]	5	63	−7
3	H[**P3**]	5	32	52
4[e]	H[**P3**]	5	65	80
5	Li[**P3**]$_1$	5	83	4
6	Na[**P3**]$_1$	5	0	
7	Ca[**P3**]$_2$	2.5	57	44
8	Ba[**P3**]$_2$	2.5	49	49
9	Mg[**P3**]$_2$	2.5	74	80
10	Mg[**P3**]$_1$	5	63	70
11	Mg[**P3**]$_4$	1.25	14	75
12	Mg[**P1**]$_2$	2.5	57	−4
13	Mg[**P2**]$_2$	2.5	65	−5

[a] General reaction conditions: THF was removed before step 2 while 1.5 equiv of **1e**, 1.0 equiv of **2**, and 2.0 equiv of DMAP were added. [b] See the Supporting Information for details on the preparation of the catalysts. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Purified on silica gel without re-acidification.

As we began our screening, we found that common phosphoric acids (Table 1, entries 1−3) were relatively poor catalysts for this reaction. However, these catalysts did indicate, based on enantioselectivity, that the reaction carried a strong preference for **P3** (VAPOL), a phosphoric acid derived from (*R*)-2,2′-diphenyl-3,3′-(4-biphenanthrol) (Figure 1). When **P3** was used directly after purification on silica gel (entry 4), the enantiomeric excess was significantly higher than the re-acidified phosphoric acid (entry 3); this led to the obvious pursuit of a phosphate salt catalyst with chirality from VAPOL. To explore this new chiral phosphate system, we matched **P3** with commerically available alkali or alkaline salts. Group 1 elements were not promising: lithium showed excellent efficiency, leading to a high yield but low enantioselectivity (entry 5), while sodium prevented the aza-Darzens reaction from occurring at all (entry 6). While all three of the group 2 alkalines promoted the reaction with some enantioselectivity, the most selective example was the pairing of **P3** with magnesium (entries 7−9). From the comparison of the yields and selectivities of the various salts, it became clear that magnesium VAPOL phosphate salt impurities originating from the silica gel were most likely catalyzing the reaction in entry 4. To our knowledge, this is the first example of a magnesium phosphate salt being the

(9) For select Mannich-type reactions with 1,3-dicarbonyl reagents, see: (a) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525. (b) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (c) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (d) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (e) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7604. (f) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56.

(10) For pioneering chiral phosphoric-acid-catalyzed methods, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. For reviews with considerable chiral phosphoric acid coverage, see: (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (d) Connon, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (e) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (f) Terada, M. *Chem. Commun.* **2008**, 4097. (g) Adair, G.; Mukherjee, S.; List, B. *Aldrichchim. Acta.* **2008**, *41*, 31. (h) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101.

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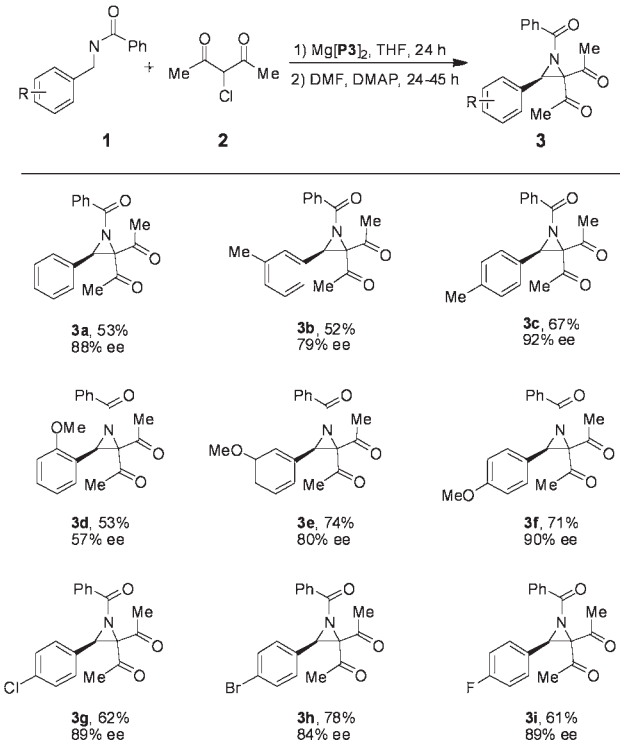
Scheme 1. Substrate Scope[a]



[a] General reaction conditions: 2.5 mol % catalyst loading, THF was removed before step 2, while 1.5 equiv of **1**, 1.0 equiv of **2**, and 2.0 equiv of DMAP were added. All yields are isolated, and enantiomeric excess was determined by chiral HPLC analysis.

optimal catalyst for an enantioselective Mannich-type reaction.

Initially, we assumed that a ratio of two **P3** to one magnesium would be optimal; to confirm, a screening of other ratios of VAPOL phosphate and magnesium was performed. A significant drop in yield and enantioselectivity was observed compared with the initial ratio (entries 10 and 11). Lastly, we wanted to determine if other common phosphoric acids could be as effective as the **P3** catalyst. After conversion to the corresponding magnesium phosphate salt, both catalysts derived from **P1** and **P2** showed little enantioselectivity for the aza-Darzens reaction (entries 12 and 13). These results confirm that VAPOL magnesium phosphate is ideal for promoting the aza-Darzens reaction efficiently and with selectivity.

With the optimal conditions identified, we proceeded to examine various substituted imines derived from their corresponding benzaldehydes (Scheme 1). These aza-Darzens aziridine products were formed with moderate yields and high enantioselectivities.

In example **3a** when the starting material is fully consumed, the mass balance of the reaction can be accounted for by incomplete conversion in the second ring-closing step. Various substituents at the aryl ring were evaluated in the exploration of the substrate scope. Both methoxy and methyl groups showed analogous tolerance and enantioselectivities regardless of their position on the arene ring system (**3b**–**3f**). However, as the steric environment increased around the center of chirality, the enantioselectivity decreased, clearly the result of the substituent on the aryl ring. This is evident when observing the enantioselectivities of **3c** and **3f** compared to **3b** and **3e**, respectively. The presence of electron-withdrawing halogens in the para position (**3g**–**3i**) gave comparable results with the electron-donating para-substituted substrates.

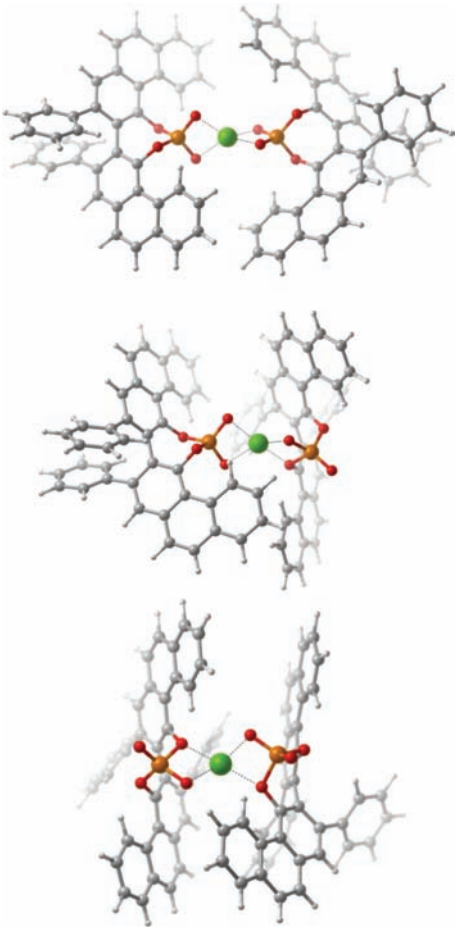


Figure 2. Calculated structures of VAPOL magnesium phosphate.

While the active catalytic species involved in these phosphate salt-catalyzed reactions is not yet definitively proven, we moved forward with a theoretical study using two biphenanthrol phosphate ions coordinated to one magnesium cation. Catalyst structures were geometry-optimized using the Q-Chem ab initio package[14] and employing the B3LYP[15] functional and 6-31+G* basis set.[16] Figure 2 represents the lowest energy structure found.[17] Interestingly,

(14) Shao, Y.; et al. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172. For the full reference, see Supporting Information.

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(17) These structures were calculated for the *R* enantiomer of VAPOL, and negligible energy differences were noticed when the opposite enantiomer was calculated in similar work: Simon, L.; Goodman, J. *J. Am. Chem. Soc.* **2008**, *130*, 8741.

the dihedral angle of the phenanthrene rings was found to be approximately 60°; the axial C_2-symmetry undoubtedly controls enantioselectivity of the products formed.

Two alternative catalyst conformations were located; these were higher in energy, relative to Figure 2 (top) by 10 and 24 kcal/mol. Different coordination patterns of magnesium can partially account for these energy differences (vide infra). In the lowest energy structure (Figure 2, top), the magnesium is coordinated to the four terminal phosphoryl oxygens. In contrast the higher energy conformers, respectively, had magnesium bound to either one or two phosphoryl ethers in conjunction with three or two terminal oxygens. From the NBO[18] analysis, energetics of these interactions indicate that an approximate 5 kcal/mol penalty exists when binding phosphoryl ether compared to terminal oxygen. However, this energetic penalty is compensated for by increased stabilization via interactions with the adjacent terminal oxygen. Measuring the magnesium−oxygen distances highlights this as the magnesium−ether oxygen distance is 2.1 Å compared to 1.9 Å for the magnesium−terminal oxygen (Figure 2, middle).

In contrast, the lowest energy structure (Figure 2, top) has magnesium−oxygen distances of approximately 2.1 Å for all interactions. Clearly, the orbital interactions cannot explain the energetic differences observed; however, large structural changes are evident based on the interaction patterns. Therefore, a combination of steric repulsion, strain, and hydrophobic/hydrophilic effects likely dictate the final structure.

Using this structural information, we propose a possible transition state and mechanism to explain the high enantioselectivity observed. Figure 3 shows coordination of the magnesium to the carbonyls of the imine and diketone's enol form. Additionally, the enol can hydrogen bond to the oxygens on the catalyst. The catalyst can simultaneously stabilize the nucleophile and electrophile, while providing the chiral environment for asymmetric induction.[19]

We surmised, therefore, that the enantioselectivity is a consequence of steric interactions between the phenanthrene rings and the aromatic substituents of the imine, allowing for facial selectivity. As the imine coordinates with the catalyst, its aryl rings align perpendicular to the plane of the catalyst while crossing the center to minimize the steric interactions with the phenanthrenes. The validity of the proposed mechanism can be supported by its ability to predict the absolute configuration of the major enantiomer (see below and Supporting Information for details). The absolute configuration was determined by HPLC comparison of the dechlorinated β-amino carbonyl compound to the literature.[20] The absolute configuration corresponds with that of the *S* enantiomer for **3a**, validating the chirality predicted by the transition state.[21]

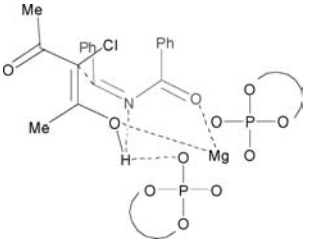

Figure 3. Proposed transition state.

In conclusion, we have demonstrated the utility of a chiral VAPOL magnesium phosphate salt catalyst and described its first use in the enantioselective aza-Darzens reaction. This was accomplished while simultaneously showing a new approach to the aza-Darzens reaction through the addition of α-chloro-1,3-dicarbonyl compounds. These chiral phosphate salts represent a powerful step forward in our ability to tailor optimized catalytic systems to specific reactions. Further experiments to evaluate the utility of VAPOL-derived phosphate salts are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Terada, M.; Sorimachi, K.; Uraguchi, D. *Synlett* **2006**, 133.

(21) Additional details are in the Supporting Information.