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Enamide Amination

Chiral Calcium–BINOL Phosphate Catalyzed Diastereo- and Enantioselective Synthesis of *syn*-1,2-Disubstituted 1,2-Diamines: Scope and Mechanistic Studies**

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Abstract: A highly enantioselective, chiral, Lewis acid calcium–bis(phosphate) complex, Ca[**3a**]$_n$, which catalyzes the electrophilic amination of enamides with azodicarboxylate derivatives **2** to provide versatile chiral 1,2-hydrazinoimines **4** is disclosed. The reaction gives an easy entry to optically active *syn*-1,2-disubstituted 1,2-diamines **6** in high yields with excellent enantioselectivities, after a one-pot reduction of the intermediate 1,2-hydrazinoimines **4**. The geometry and nature of the N-substituent of the enamide affect dramatically both the reactivity and the enantioselectivity. Although the calcium–bis(phosphate) complex was a uniquely effective catalyst, the exact nature of the active catalytic species remains unclear. NMR spectroscopy and MS analysis of the various calcium complexes Ca[**3**]$_n$ reveals that the catalysts exist in various oligomer forms. The present mechanistic study, which includes nonlinear effects and kinetic measurements, constitutes a first step in understanding these calcium–bis(phosphate) complex catalysts. DFT calculations were carried out to explore the mechanism and the origin of the enantioselectivity with the Ca[**3**]$_n$ catalysts.

Introduction

Chiral vicinal diamines[1] are versatile motifs frequently encountered in natural products and pharmaceuticals,[1,2a] and they have been employed as chiral auxiliaries and ligands in asymmetric catalysis.[1,2b] Many efforts have been made in the development of asymmetric catalytic methods for the preparation of these compounds.[1,3] Among various synthetic approaches, the nucleophilic addition of enamide derivatives to an electrophilic nitrogen atom, "N^+", is an efficient approach for obtaining diverse diamines.[4] The first enantioselective amination of (*E*)-enecarbamates, derived from acetophenones with azodicarboxylates,[5] was described by Matsubara and Kobayashi with chiral diamine–Cu(OTf)$_2$ (OTf: trifluoromethanesulfonate) complexes as catalysts.[6] In 2010, Feng and co-workers developed a chiral *N,N*-dioxide–Cu(OTf)$_2$ complex that catalyzed asymmetric α-amination of (*Z*)-enamides.[7] Surprisingly, although chiral Brønsted acids catalyze many nucleophilic additions of enecarbamates with several electrophiles,[8] there is no example of enantioselective α-aminations of enamides (enecarbamates) mediated by Brønsted acids.[9]

In continuation with our efforts directed towards the development of chiral phosphoric acid catalyzed enantioselective transformations,[8g–k,u,v,10] we initiated studies aimed at developing a chiral phosphoric acid catalyzed amination of enamides with azodicarboxylates (Scheme 1). We recently achieved

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[**] *BINOL = 1,1′-binaphthalene-2,2′-diol*

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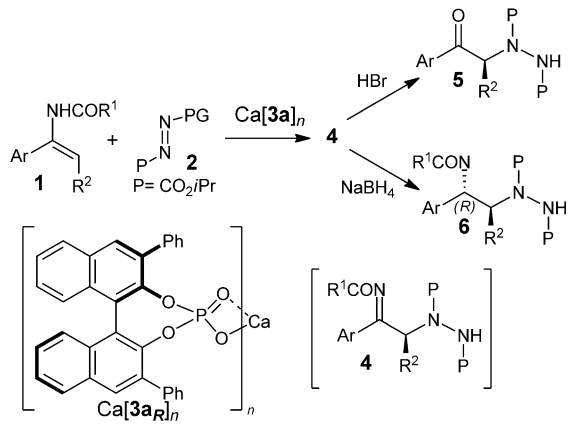


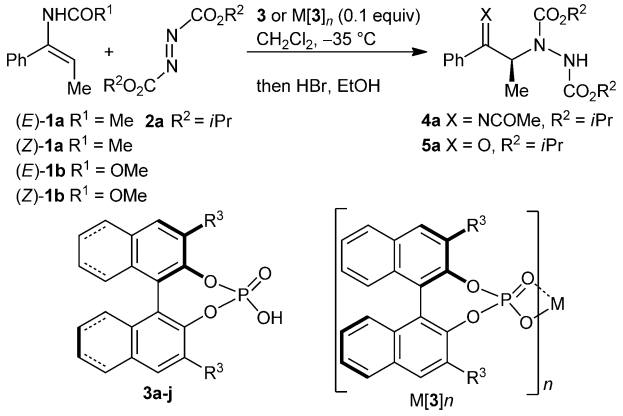
Scheme 1. Catalytic enantioselective α-amination of enamides.

a highly enantioselective amination of (*E*)-enamides, to yield optically active 1,2-hydrazinoimines **4**, in which the chiral calcium–organophosphate proved to be a more effective catalyst for this transformation than the corresponding chiral phosphoric acid.[11] The resulting chiral imines **4** were hydrolyzed or reduced in situ to produce chiral 2-hydrazinoketones **5** or *syn*-1,2-disubstituted 1,2-diamines **6**, respectively, in good yields with excellent enantioselectivity. This article describes the full details of the catalytic asymmetric amination with investigations of phosphoric acids coordinated with alkaline-earth-metal ions as the catalytic system. The scope and limitations of this amination of enamides have also been further examined. Detailed mechanistic studies, combining mass spectrometry, NMR spectroscopic analysis, nonlinear effects, and DFT calculations, are also described to identify the active catalyst species.

Results and Discussion

Initial studies were conducted by examining the addition of (*E*)-*N*-(1-phenylpropenyl)acetamide (**1a**) to diisopropylazodicarboxylate (**2**) as the aminating agent in the presence of a chiral phosphoric acid, **3**, derived from (*R*)-1,1′-binaphthalene-2,2′-diol ((*R*)-BINOL) or octahydro-(*R*)-BINOL (purified by silica gel column chromatography, Table 1). When **3a** was used as catalyst, a mixture of the desired 1,2-hydrazinoimine **4a** and the corresponding 2-aminoketone **5a** was observed. Although the addition of molecular sieves in the reaction prevented the hydrolysis of the unstable *N*-acylimine **4a**, the enantioselectivities and yields were always determined for compound **5a**, obtained after in situ hydrolysis of **4a** under acidic conditions (33% HBr in AcOH). Phosphoric acid screening in CH_2Cl_2 at −35 °C revealed that the less hindered acid **3a** was the most effective catalyst for the amination of enamide **1a** in terms of enantioselectivity and yield. Surprisingly, we noticed that the enantioselectivities (78–89%) and yields (from 45% to quantitative) under the optimal conditions varied considerably depending on the batch of **3a** that was used. Ding and co-workers observed previously that the treatment of chiral phosphoric acid with an acid improved the catalytic activity in the enantioselective transformation.[12a] Shortly afterwards, Ishihara and co-workers and also List and co-workers demonstrated the formation of a variable amount of alkali– or alkaline-earth-metal–phosphoric acid complexes during the purification procedure of **3**, which could explain the improvement of the catalytic activity after acid washing of the catalyst.[12] Based on these important works, we hypothesized that the formation of these phosphate salts might explain the nonreproducible results.[12a] However, when acid-washed catalyst was used, although the results was reproducible, the enantiomeric excess was significantly lower than with nonacidified phosphoric acid **3a.** To recover the initial enantiomeric values, we reasoned that phosphate salt impurities originating from the silica gel might define a better chiral environment.[8u,11,13–17] We initiated screening of the catalyst system by using various alkali- or alkaline-earth-metal-linked (*R*)-BINOL phosphoric acids, M[**3a**]$_n$. Sodium- and magnesium-derived phosphates afforded the product **5a** with similar *ee* values to those with acid-washed

Table 1. Catalyst screening for the synthesis of 1,2-hydrazinoketones.[a]



Entry	1	R^3 (3 or M[3]$_n$)	5	Yield [%][b]	*ee* [%][c]
1	(*E*)-**1a**	C_6H_5 (**3a**$_R$)[d,e]	**5a**	29	80
2	(*E*)-**1a**	C_6H_5 (**3a**$_R$)[d]	**5a**	99	89
3	(*E*)-**1a**	4-$MeOC_6H_4$ (**3b**$_R$)[d]	**5a**	56	71
4	(*E*)-**1a**	4-ClC_6H_4 (**3c**$_R$)[d]	**5a**	62	80
5	(*E*)-**1a**	$CH(C_6H_5)_2$ (**3d**$_R$)[d]	**5a**	66	18
6	(*E*)-**1a**	4-*t*BuC_6H_4 (**3e**$_R$)[d]	**5a**	74	77
7	(*E*)-**1a**	4-$NO_2C_6H_4$ (**3f**$_R$)[d]	**5a**	82	47
8	(*E*)-**1a**	2-naphthyl (**3g**$_R$)[d]	**5a**	75	35
9	(*E*)-**1a**	2,4,6-(*i*Pr)$_3C_6H_5$ (**3h**$_R$)[d]	**5a**	57	28
10	(*E*)-**1a**	$C_6H_5[H_8]$ (**3i**$_R$)[d,f]	**5a**	44	88
11	(*E*)-**1a**	4-ClC_6H_4 [H_8] (**3j**$_R$)[d,f]	**5a**	59	78
12	(*E*)-**1a**	**3a**$_R$[g]	**5a**	92	85
13	(*E*)-**1a**	Li[**3a**$_R$]	**5a**	94	91
14	(*E*)-**1a**	Na[**3a**$_R$]	**5a**	85	83
15	(*E*)-**1a**	Ca[**3a**$_R$]$_n$	**5a**	82	95
16	(*E*)-**1a**	Ba[**3a**$_R$]$_2$	**5a**	65	91
17	(*E*)-**1a**	Mg[**3a**$_R$]$_2$	**5a**	79	85
18	(*E*)-**1a**	Ag[**3a**$_R$]$_2$	**5a**	57	83
19	(*Z*)-**1a**	Ca[**3a**$_R$]$_n$	**5a**	23	0
20	(*E*)-**1b**	Ca[**3a**$_R$]$_n$	**5a**	56	4
21	(*Z*)-**1b**	Ca[**3a**$_R$]$_n$	**5a**	18	−67
22	(*E*)-**1a**	Ca[**3a**$_R$]$_n$[h]	**5a**	79	91
23	(*E*)-**1a**	Ca[**3a**$_S$]$_n$[i]	**5a**	76	−96

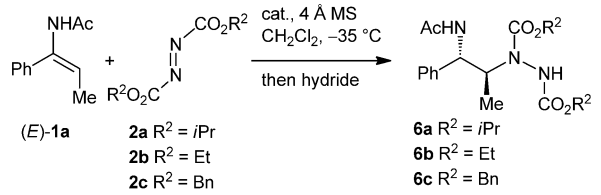
[a] General conditions: **1**/**2**/cat. = 1.0:5.0:0.1 in CH_2Cl_2 (c = 0.1) at −35 °C, followed by acid hydrolysis with 33% HBr in AcOH. [b] Yields refer to chromatographically pure products. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] Purified on silica gel. [e] Without molecular sieves. [f] Derived from octahydro-(*R*)-BINOL. [g] Washed with HCl after purification on silica gel. [h] Toluene was used as the solvent. [i] Calcium–phosphate catalyst prepared from (*S*)-BINOL.

phosphoric acid **3a**. The lithium and barium phosphates catalyzed the reaction with increased enantioselectivity (Table 1, entries 13 and 16). To our delight, the chiral calcium–phosphate catalyst Ca[**3a**$_R$]$_n$ provided the adduct with higher enantioselectivities (Table 1, entry 15).[18] The absolute configuration of **5a** was determined to be *S* by comparison of the sign of its optical rotation with that in the literature data.[6,7] Importantly, the calcium–(*S*)-BINOL phosphate catalyst, Ca[**3a**$_S$]$_n$, afforded the same enantioselectivity with an opposite sense of asymmetric induction (Table 1, entry 23). The effects of the alkene geometry and the *N*-protecting group of the enamides were then addressed. It was observed that changing the double-bond geometry from *E* to *Z* resulted in a dramatic loss in reac-

tivity. For instance, the reaction of the *Z* isomer **1a** occurred only at room temperature to afford the racemic product **5a** in low yield (Table 1, entry 19). Similarly, (*Z*)-enecarbamate **1b** was a poor substrate that gave the corresponding ketone in low yield but with reversed enantioselectivity to that obtained with (*E*)-**1a** (Table 1, entry 21). On the other hand, (*E*)-enecarbamate **1b** reacted smoothly to afford the product with almost no enantioselectivity (Table 1, entry 20).

After obtaining these preliminary results, we started to optimize a catalytic asymmetric synthesis of enantioenriched 1,2-diamines through reduction of 1,2-hydrazinoimines **4** (Table 2). To avoid problems with hydrolysis of the unstable compounds

Table 2. Survey of reaction conditions for the synthesis of 1,2-hydrazinoamines.[a]



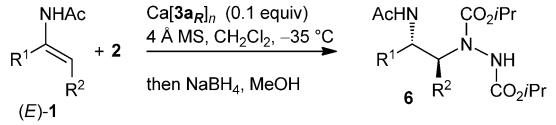
Entry	$Ca[\mathbf{3}]_n$	Hydride	2	6	Yield [%][b]	*ee* [%][c,d]
1	$Ca[\mathbf{3a}_R]_n$	BH_3·THF	**2a**	**6a**	52	77
2	$Ca[\mathbf{3a}_R]_n$	$NaBH_3CN$	**2a**	**6a**	56	79
3	$Ca[\mathbf{3a}_R]_n$	$NaBH_4$	**2a**	**6a**	84	92
4	$Ca[\mathbf{3g}_R]_n$	$NaBH_4$	**2a**	**6a**	35	92
5	$Ca[\mathbf{3h}_R]_n$	$NaBH_4$	**2a**	**6a**	30	89
6	$Ca[\mathbf{3a}_R]_n$	$NaBH_4$	**2b**	**6b**	68	71
7	$Ca[\mathbf{3a}_R]_n$	$NaBH_4$	**2c**	**6c**	65	75

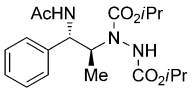
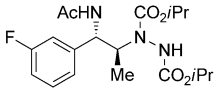
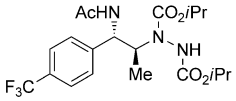
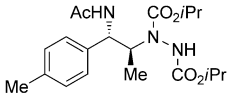
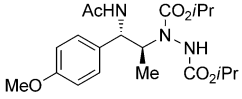
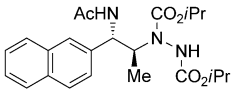
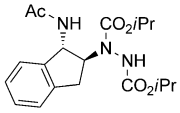
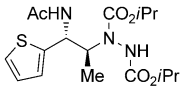
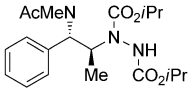
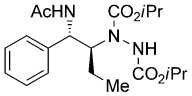
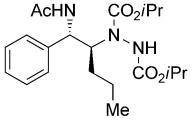
[a] General conditions: **1**/**2**/$Ca[\mathbf{3}]_n$ = 1.0:5.0:0.1 in CH_2Cl_2 (c = 0.1) at −35 °C, followed by addition of $NaBH_4$ at −78 to −45 °C in MeOH. MS: molecular sieves. [b] Yields refer to chromatographically pure products. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] d.r. > 95:5.

4, we decided to concentrate our efforts on the development of a one-pot α-amination/reduction process. Amination of enamide (*E*)-**1a** followed by in situ reduction with BH_3·THF or $NaBH_3CN$ gave *syn*-**6a** with moderate yield and *ee* value, whereas $NaBH_4$ afforded the *syn*-1,2-diamine **6a** in high diastereo- and enantioselectivity.[19,20] Unfortunately, attempts to improve the reaction yield or enantioselectivity by varying the phosphate ligands of the calcium-complex catalyst were unsuccessful. As Table 2 shows, in contrast to the results with the phosphoric acid catalysts (Table 1), the size of the R^3 group only has very little influence on the asymmetric induction. However, better yields were still observed with 10 mol% of $Ca[\mathbf{3a}_R]_n$. Upon further optimization of the reaction conditions, it was found that this one-pot process was rather sensitive to the alkyl group of **2**. Ethyl- and benzylazodicarboxylates **2b** and **2c** gave slightly lower enantioselectivities (Table 2, entries 6 and 7) than isopropylazodicarboxylate **2a**.

The substrate scope of the one-pot sequential catalytic asymmetric amination–diastereoselective imine reduction process under the optimized reaction conditions is summarized in

Table 3. Scope of the enantioselective one-step synthesis of 1,2-hydrazinoamines catalyzed by a calcium–phosphate.[a]



Entry	Product	6	Yield [%][b]	*ee* [%][c]
1		**6a**	84	92[d]
2		**6d**	88	88[d]
3		**6e**	84	93[d]
4		**6f**	88	88[d]
5		**6g**	91	85[d]
6		**6h**	93	83[d]
7		**6i**	87 (78)	57[d] (57[d,e])
8		**6j**	67 (81)[d]	22 (37[e])
9		**6k**	< 10%	n.d.[f]
10		**6l**	87	94[d]
11		**6m**	99	95[d]

[a] General conditions: **1**/**2**/$Ca[\mathbf{3}]_n$ = 1.0:5.0:0.1 in CH_2Cl_2 (c = 0.1) at −35 °C, followed by addition of $NaBH_4$ in MeOH. [b] Yields refer to chromatographically pure products. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] d.r. > 95:5. [e] Result with chiral phosphoric acid **3a**. [f] d.r. = 1:1. n.d. not determined.

Table 3. A wide range of (*E*)-enamides **1**, derived from aromatic ketones bearing substituents with various electronic and steric properties, provided the desired *syn*-1,2-diamines **6** with excellent enantioselectivities. For example, the enamide bearing a *p*-trifluoromethylphenyl group provided the corresponding

diamine **6e** in 84% yield with 93% *ee* (Table 3, entry 3). In a similar manner, the electron-rich *p*-methoxyphenyl-substituted enamide **1g** led to product **6g** in 91% yield with 85% *ee* (Table 3, entry 5). In addition, the (*E*)-*N*-(1-(naphthalen-2-yl)propenyl)acetamide (**1h**) was a suitable substrate and provided the diamine product **6h** with a high yield and good enantioselectivity (Table 3, entry 6). Surprisingly, heteroatom substitution in the aryl moiety seems to seriously impact the enantioselectivity. Indeed, we obtained a nearly racemic product **6j** with thiophenyl-substituted enamide **1j**, whereas up to 37% *ee* was observed when chiral phosphoric acid **3a** was used instead. The appropriate cyclic enamide also afforded the desired product **6i**, but low enantioselectivity was observed with both calcium–phosphate and phosphoric acid catalysts (Table 3, entry 7). Notably, contrary to previous reports, high yields and high enantioselectivities can be obtained even with a longer alkyl chain in linear enamides (Table 3, entries 10 and 11).[7]

Although the precise nature of the active catalyst remains unknown, oligomeric forms of the chiral calcium–phosphate catalyst have been proposed in the literature.[12b–e,21,22] To gain information on the structure of the catalyst and mechanism for the electrophilic amination of enamides, a series of experiments have been performed. Firstly, the ^{31}P NMR spectrum of Ca[**3a**$_R$]$_n$ shows the emergence of a broad signal of an oligomeric form. We then analyzed a series of asymmetric calcium complexes by MALDI-TOF mass spectrometry, which allows facile and precise characterization of labile organic species coordinated to Ca^{2+} ions. The MS spectrum of Ca[**3a**$_R$]$_n$ showed a strong peak at *m/z* 1577.24 and weak peaks at *m/z* 1039.15, 2076.29, and 2615.24 (Figure 1). This indicates that Ca[**3a**$_R$]$_n$ is an oligomeric species with the formation of monometallic Ca[**3a**$_R$]$_2$, dimetallic Ca$_2$[**3a**$_R$]$_3$ and (Ca[**3a**$_R$]$_2$)$_2$, and trimetallic Ca$_3$[**3a**$_R$]$_5$ species (Figure 2). Although the same pattern of oligomeric species was found for Ca[**3g**$_R$]$_n$, many more oligomeric species were observed with the calcium complex derived from unsubstituted BINOL phosphate, Ca[**3k**$_R$]$_n$ (R_3: H). On the other hand, fewer oligomer structures existed with calcium complex Ca[**3h**$_R$]$_n$, and diphosphate calcium salt Ca[**3h**$_R$]$_2$ was assigned as the major peak in the mass spectrum (Figure 1). This study indicates that the hindrance of the substituents at the 3,3′-positions has an effect on the structural complexity of the oligomeric species of Ca[**3**]$_n$. Evaluation by DFT computations of the dimerization energy between calcium complexes of type Ca[**3**$_R$]$_2$ and (Ca[**3**$_R$]$_2$)$_2$ exhibiting phenyl, 2,4,6-trimethylphenyl, and 2,4,6-triisopropylphenyl at the 3,3′-positions clearly supported this hypothesis (see the Supporting Information). In addition, no free phosphate peaks were detected in any of the spectra, which strongly indicates that free phosphoric acid is not the active catalyst.

A negative correlation ((+)-nonlinear effect, NLE) was observed between the *ee* value of chiral Ca[**3a**$_R$]$_n$ and the *ee* value of the 2-hydrazinoketone **5a** (Figure 3).[23] Notably, the enantiomeric excess was dramatically reduced. For instance, the use of 10 mol% of a calcium–BINOL phosphate catalyst that contained 95% of Ca[**3a**$_R$]$_n$ and 5% of Ca[**3a**$_S$]$_n$ gave 2-hydrazinoketone **5** with only 24% *ee*. Moreover, the evolution of the enantioselectivity in relation to the reaction time was checked by using Ca[**3a**$_R$]$_n$ with an optical purity of 80%: three reactions were run simultaneously under the same conditions

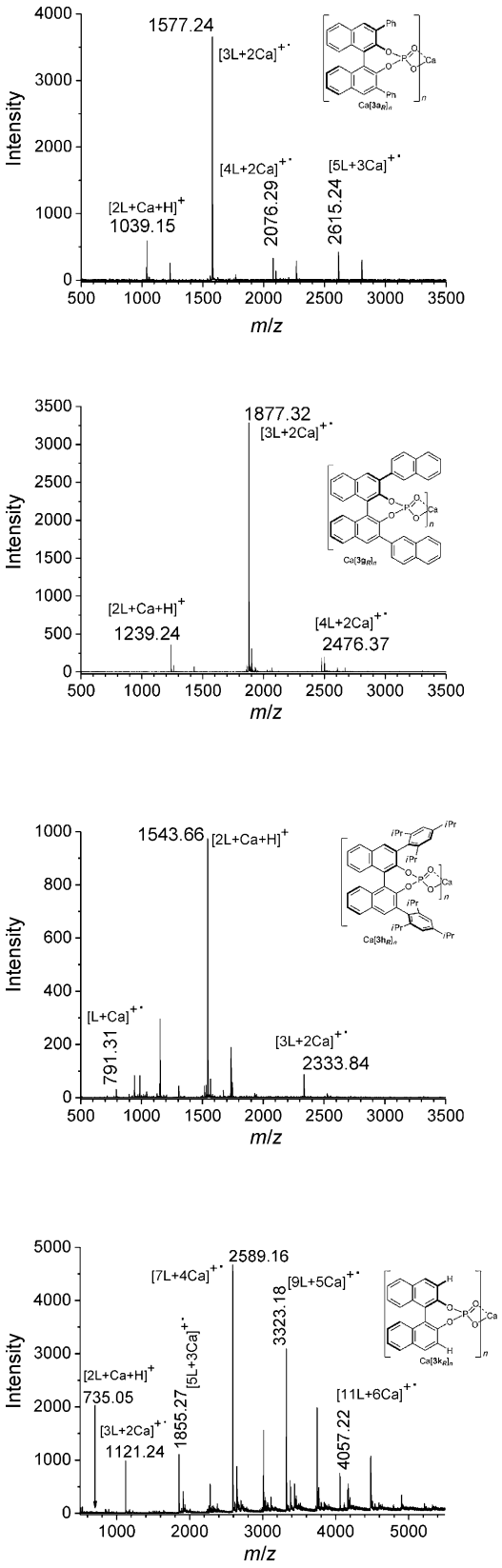


Figure 1. Mass spectra of Ca[**3a**$_R$]$_n$, Ca[**3g**$_R$]$_n$, Ca[**3h**$_R$]$_n$, and Ca[**3k**$_R$]$_n$.

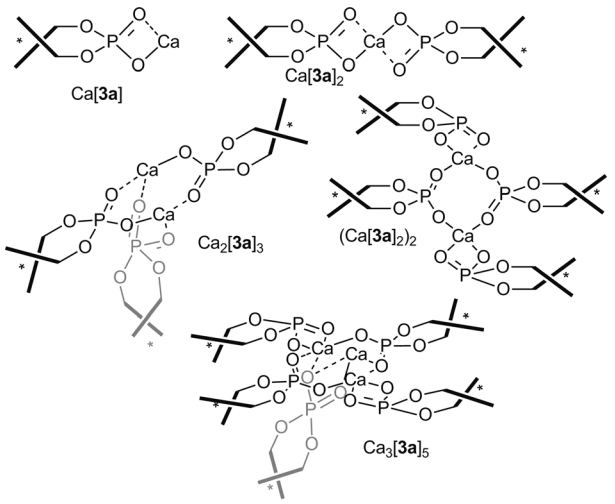


Figure 2. Possible intermediates in the asymmetric electrophilic α-amination of enamides **1**.

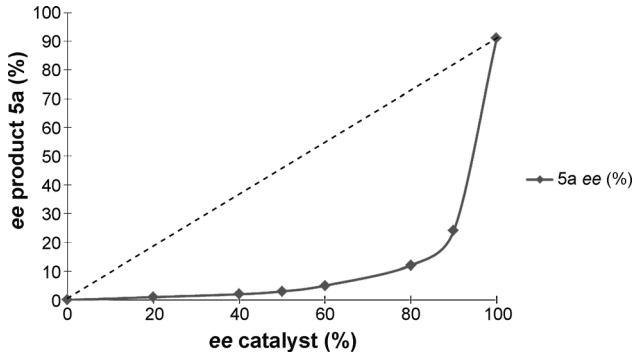
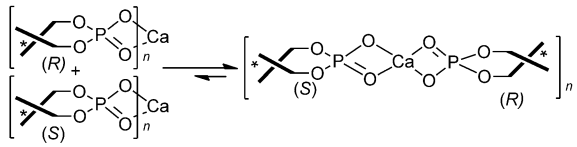


Figure 3. Correlation between the enantiomeric excess of Ca[**3 a**]$_n$ and the enantiomeric excess of **5 a**.

but quenched at different times (1–24 h). The *ee* values were constant with the progress of reaction (values of 15, 14, 14, and 16%, respectively, were obtained). This nonlinear effect confirms that the oligomeric species Ca[**3 a**$_R$]$_n$ are the active catalysts, rather than the Ca^{II}-free phosphoric acid or mono(phosphate) salt.[19,20] This remarkably strong negative linear effect may be explained with the ML_n model of Kagan and co-workers,[23d,24,25] in which there is an equilibrium with homochiral and heterochiral adducts exhibiting different catalytic activity. Therefore, according to this model, the nonlinear effects resulted from the formation of the heterochiral dimer complexes Ca[**3 a**$_{RS}$]$_n$ over the homochiral adducts (Ca[**3 a**$_R$]$_n$ and Ca[**3 a**$_S$]$_n$); the heterochiral complexes are much more reactive than the homochiral complexes in forming the racemic **5 a** (Scheme 2).[26] To support this, we performed kinetic experiments by measuring the rate of conversion of **5 a** with 10 mol% of Ca[**3 a**$_R$]$_n$ and 10 mol% of Ca[**3 a**$_{RS}$]$_n$, respectively (Figure 4). As expected, the reaction rate increased significantly when the heterochiral dimer complexes Ca[**3 a**$_{RS}$]$_n$ were used as the catalyst.

On the basis of the experimental results obtained above, a plausible catalytic cycle for the electrophilic amination of the



Scheme 2. Possible equilibrium between Ca[**3 a**$_R$]$_n$ and Ca[**3 a**$_S$]$_n$.

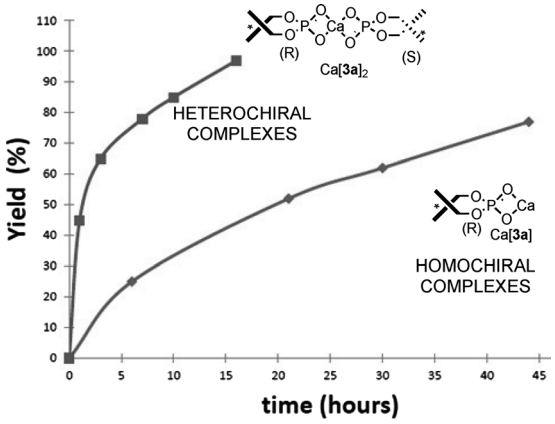
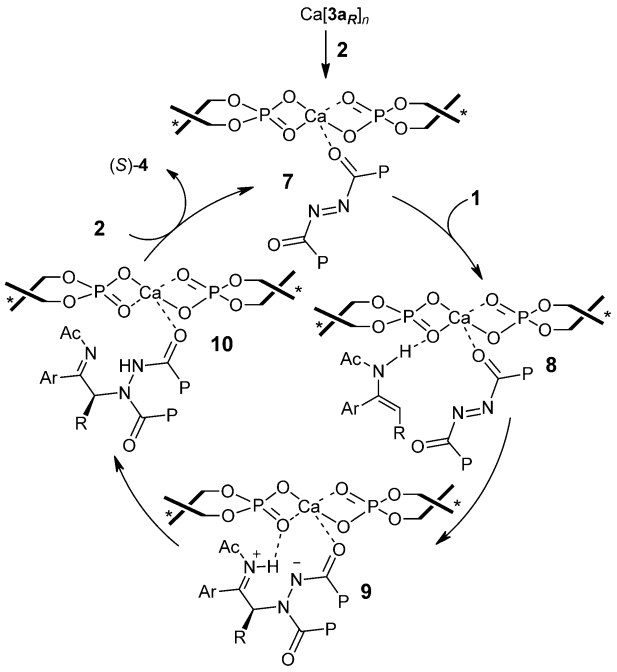


Figure 4. Comparison of the formation rates of **5 a** with Ca[**3 a**$_R$]$_n$ and Ca[**3 a**$_{RS}$]$_n$ as catalysts.

enamides is outlined in Scheme 3. NMR spectroscopic analyses, ESI MS analyses, nonlinear effects, and kinetic studies suggested that the catalyst components, Ca[**3 a**]$_n$, are in equilibrium between various forms.[21,22] As a result, the active catalyst is still ambiguous. However, based on density functional theory (DFT) calculations (see below), we propose that the chiral,



Scheme 3. Assumed reaction pathway for the enantioselective α-amination of enamides **1**.

Lewis acid calcium–bis(phosphate) complex Ca[**3a**]$_2$ could be an active species and act as a bifunctional catalyst. The coordination of calcium to the azodicarboxylate oxygen atom would afford the activated form **7** and would, at the same time, discriminate the two prochiral faces. Meanwhile, the secondary enamide would form a hydrogen bond with the phosphoryl oxygen atom and be positioned close to the azodicarboxylate in **8**. A pseudo-intramolecular *si*-face attack of enamide **1** onto azodicarboxylate **2** would then occur to form *S*-chiral 1,2-hydrazinoimines **4**. The zwitterionic species **9** would then undergo a proton transfer to generate monocoordinate complex **10**, which would dissociate to form the stable dicoordinate complex **7**. The presence of a free HN group in **1** is a requirement for efficiency, because no reaction occurred with a tertiary enamide (Table 3, entry 9).[27]

This mechanism is supported by density functional theory (DFT) computations. The structures were optimized by using Gaussian 09 software at the B3LYP level of DFT.[28] All atoms were described by the 6-31G(d) basis set. Calculations were performed by using a simplified calcium–bis(phosphate) catalyst of *R*,*R* configuration, dimethylazodicarboxylate, and (*E*)-*N*-(prop-1-enyl)acetamide. Single-point energy calculations were carried out at the MP2(full) level with the 6-311G(d,p) basis set on every element (Figure 5). This level was also chosen to obtain the solvation energy in CH_2Cl_2 by using the polarizable continuum model (PCM). We found that amination of an acetamide can be catalyzed by a calcium–phosphate complex. Figure 5 shows the transition states corresponding to the (*Re*,*Si*)- and (*Si*,*Re*)-face attacks of the acetamide. Such C–N bond formation leads to the *S* and *R* enantiomers, respectively, ((*S*)-TS1 and (*R*)-TS2)). In both optimized structures, calcium is bonded to one of the azadicarboxylate carbonyl groups. On the other hand, the acetamide NH functionality establishes a hydrogen bond with one of the phosphate oxygen atoms bonded to calcium. The lowest lying transition state is (*S*)-TS1 ($\Delta\Delta G^{\neq} = 1.1$ kcal mol^{-1}), which is consistent with the experimentally obtained products when an (*R*)-phosphate catalyst is used. Other details regarding the energy data of this transformation can be found in the Supporting Information.

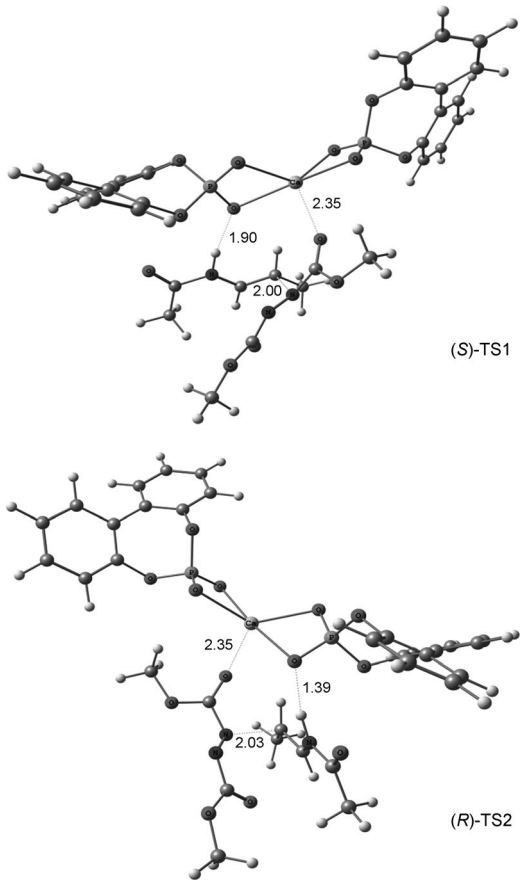


Figure 5. B3LYP/6-31G(d)-optimized transition states for the electrophilic amination of enamides (distances in Å).

Conclusion

In summary, the chiral, Lewis acid calcium–bis(phosphate) complex Ca[**3a**]$_2$ was revealed to be an efficient enantioselective catalyst for the amination of enamides with diisopropylazodicarboxylate to provide versatile chiral 1,2-hydrazinoimines. A sequence of asymmetric α-amination and imine reduction leads to 1,2-diamines in excellent yields and enantioselectivities. A combination of ^{31}P NMR spectroscopy, MS analysis, and nonlinear effects demonstrate that Ca[**3a**]$_n$ exists in oligomeric form. In addition, the strong negative NLE and kinetic studies indicate that heterocatalysts exhibited a higher activity than chiral ones. The elucidation of the mechanism of this enantioselective amination by calcium–bis(phosphate) complex catalysts has been unusually challenging owing to difficulty in establishing the exact nature of the active species in these heterogeneous systems. However, DFT studies provided evidence that a chiral, Lewis acid calcium–bis(phosphate) complex of type Ca[**3a**]$_2$ could be an active species. In addition, this computational study has resulted in a refined transition-state model that explains the origins of enantioselectivity. The key stabilizing forces favoring the transition state of the fast-reacting enantiomer are hydrogen bonding and coordination interactions between the enamide and the azodicarboxylate.

Experimental Section

General

All reactions were carried out under an argon atmosphere in dried glassware with magnetic stirring. Solvents were distilled by standard methods. Reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was carried out by using 40–63 μm particle sized silica gel. Analytical thin layer chromatography plates (silica gel 60 F254) were analyzed by irradiation with a 254 nm UV light and by submersion in an ethanolic phosphomolybdic acid solution. Melting points were recorded by using a melting point apparatus and are uncorrected. Infrared spectra were recorded on neat samples on a 100 FTIR spectrometer, and the characteristic IR absorption frequencies are reported in cm^{-1}. Optical rotations were performed on a polarimeter (589 nm) by using a 700 μL cell with a pathlength of 1 dm. Proton (^{1}H) NMR spectra were recorded

at 500 MHz or at 300 MHz, carbon (^{13}C) NMR spectra were recorded at 75 MHz, and phosphorus (^{31}P) NMR spectra were recorded at 202 MHz. NMR experiments were carried out in $CDCl_3$ or in [D_6]DMSO. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent as an internal reference (^{1}H: 7.26 ppm, ^{13}C: 77 ppm for $CHCl_3$; ^{1}H: 2.50, ^{13}C: 39 ppm for [D_6]DMSO). Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet), coupling constants (J, in Hz) and integration. Mass spectra were obtained from an AEI MS-9 instrument by using electron spray ionization. The HRMS data were measured on a MALDI-TOF type of instrument for the high-resolution mass spectra. Calcium–phosphate salts were analyzed by MALDI-TOF matrices by using the aprotic matrix *trans*-2-[3-(4-*tert*-butylphenyl)-2-methylpropenylidene] malononitrile (DCTB). Enantiomeric excesses were determined by HPLC or supercritical fluid chromatography (SFC) with diode-array UV detectors by using Chiralpak AD-H, IA, and IB columns.

Preparation and NMR data for the catalyst Ca[3a$_R$]$_n$

$Ca(OiPr)_2$ (0.05 mmol) was added to a solution of (*R*)-3,3′-bis(4-phenyl)-1,1′-binaphthylphosphate (0.10 mmol; washed with 1 M HCl) in CH_2Cl_2/MeOH (1/1; 2 mL), and the solution was stirred at room temperature for 30 min. The volatile solvents were removed in vacuo; CH_2Cl_2 was then added and removed in vacuo again. This solvent addition–removal sequence was repeated twice, and the desired Ca[**3a**$_R$]$_n$ was obtained as a white solid in quantitative yield. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 8.19–7.92 (m, 16H), 7.56–7.33 (m, 16H), 7.32–7.19 (m, 4H), 7.14–6.94 ppm (m, 4H); ^{31}P NMR (202 MHz, [D_6]DMSO): δ = 2.77 ppm; ^{31}P NMR (202 MHz, CD_2Cl_2): δ = 1.20 ppm; MS (MALDI): *m/z* 1039 [$M_{(n=2)}$+H$^+$], 2077 [2$M_{(n=2)}$+H$^+$].

General procedure for the amination reaction of enamides and subsequent reduction to provide *syn*-1,2-diamines 6

The reaction was carried out under an argon atmosphere in dried glassware, with a magnetic stirring bar. The (*E*)-enamide (0.1 mmol) was dissolved in CH_2Cl_2 (0.7 mL) in a flask containing activated powdered 4 Å molecular sieves. The solution was stirred at room temperature for 10 min, before being cooled to −35 °C and stirred for an additional 10 min. Diisopropylazodicarboxylate (0.5 mmol) was added, and the reaction mixture was stirred for 10 min. The calcium–phosphate complex (0.01 mmol) in CH_2Cl_2 (0.3 mL) was then added, and the reaction mixture was stirred for 44 h at −35 °C. The mixture was cooled to −78 °C, and then MeOH (1 mL) and $NaBH_4$ (1 mmol) were added. The reaction mixture was allowed to warm to −45 °C and stirred for 3 h. The mixture was filtered and rinsed with EtOAc. The filtrate was quenched with a saturated NH_4Cl aqueous solution, and the organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Purification of the crude product by flash column chromatography over silica gel (50% EtOAc in heptane as the eluent) afforded the desired product **6a** as a colorless oil in 84% yield. $[\alpha]_D^{23}$ = 93.3 (92% *ee*, *c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): mixture of rotamers (rot.): δ = 7.44–7.35 (m, 2H), 7.35–7.26 (m, NH and 3H$_{Ar}$), 5.93–5.82 (NH, 0.7H, rot. 1), 5.81–5.73 (NH, 0.3H, rot. 2), 5.10–4.82 (m, 2H), 4.82–4.74 (m, 1H), 4.68–4.54 (m, 1H), 1.92/1.90 (s and s, 3H, rot. 1 and rot. 2), 1.30–1.20 (m, 12H), 1.00–0.90 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): mixture of rotamers: δ = 170.4, 156.6, 156.2, 138.5, 129.3 (2C), 128.4, 127.4 (2C), 70.1, 69.1, 57.2, 56.1, 23.3, 22.2/22.1 (2C, rot. 1 and rot. 2), 21.9 (2C), 14.5 ppm; IR (neat): $\tilde{\nu}$ = 3296, 2982, 2937, 1749, 1701, 1661, 1535, 1384, 1374, 1307, 1225, 1108, 764, 701 cm^{-1}; ESI-HRMS (positive ion): *m/z* calcd for $C_{19}H_{29}N_3O_5Na$ [*M*+Na]$^+$: 402.2005; found: 402.2010; chiral SFC (Chiralpak IA, CO_2/MeOH (96/4), flow rate = 4.0 mL min^{-1}, 205 nm): major isomer (*S,S*): t_R = 2.1 min; minor isomer (*R,R*): t_R = 2.9 min.

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Keywords: amination · calcium · diamines · enamides · nonlinear effects

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FULL PAPER

Enamide Amination

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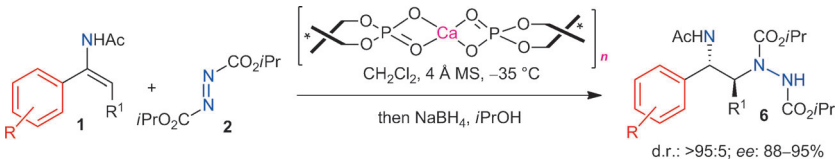
Chiral Calcium–BINOL Phosphate Catalyzed Diastereo- and Enantioselective Synthesis of *syn*-1,2-Disubstituted 1,2-Diamines: Scope and Mechanistic Studies



Carbon–nitrogen bond formation: A highly efficient electrophilic amination of enamides catalyzed by a chiral calcium–phosphate complex has been developed. In general, *syn*-1,2-diamines were obtained in high yields with excellent diastereo- and enantioselectivities (see scheme; MS = molecular sieves). A combined approach of NMR spectroscopy, MS analysis, and DFT calculations was utilized to obtain better insight into the mechanistic features of the calcium-catalyzed amination reaction.