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Chiral Calcium Organophosphate-Catalyzed Enantioselective Electrophilic Amination of Enamides

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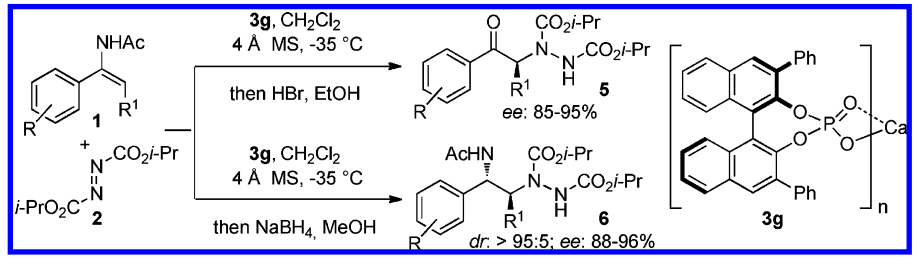
ABSTRACT



Highly enantioselective direct amination of enamides catalyzed by chiral nonracemic calcium bis(phosphate) complex 3g afforded optically active 1,2-hydrazinoimines 4. Following a subsequent in situ hydrolysis or reduction, 2-hydrazinoketones 5 or *syn*-1,2-disubstituted 1,2-diamines 6 were obtained in high yields and excellent enantiomeric excess.

The importance of enamides (enecarbamates)[1,2] as useful nucleophiles in enantioselective addition reactions has been growing enormously ever since Kobayashi's seminal report in 2004.[2b] The Lewis acid and Brønsted acid catalyzed enantioselective C−C bond forming processes involving enamides and carbon-centered electrophiles[2−6] are now well established. However, reports on nucleophilic addition of enamides to electrophilic nitrogen atom remained scarce, in sharp contrast to the enamine chemistry.[7−11] Kobayashi et al. reported the first examples of enantioselective amination of (*E*)-enecarbamates using chiral diamines-Cu(OTf)$_2$ complexes as catalysts.[4d,12] Very recently, Feng et al. detailed a chiral *N*,*N*-dioxide-Cu(OTf)$_2$ complex-catalyzed asymmetric α-amination of (*Z*)-enamides.[13] To the best of our knowledge, no example of Brønsted acid catalyzed asymmetric α-aminations of enamides (enecarbamates) with azodicarboxylates has been described.[14] In connection with our studies on small organic molecule-catalyzed transformation

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(1) For review see: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Nugenta, T. C.; El-Shazlya, M. *Adv. Synth. Catal.* **2010**, *352*, 753.

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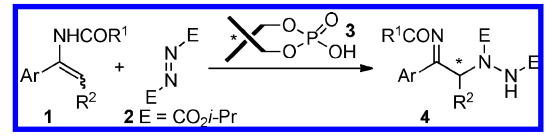
of enecarbamates[3g,h] and our ongoing project on catalytic asymmetric synthesis,[15] we were interested in examining a chiral phosphoric acid-catalyzed amination of enamides using azodicarboxylate as an electrophilic partner.

Chiral BINOL-derived phosphoric acids, pioneered by Akiyama et al. and Terada et al., are now well-established bifunctional organocatalysts that are particularly effective in catalyzing the addition of nucleophiles to imines.[16,17] Therefore, we reasoned that chiral phosphoric acids might be able to activate both enamides **1** and azodicarboxylates **2** to provide an asymmetric environment for the desired enantioselective amination process (Scheme 1).

Scheme 1. Catalytic Enantioselective α-Amination of Enamides



To validate our hypothesis, we initially examined the reaction of (*E*)-*N*-(1-phenylprop-1-en-1-yl)acetamide (**1a**) with diisopropyl azodicarboxylate (**2a**) in the presence of 10 mol % of chiral phosphoric acid **3a** in DCM at −35 °C. This resulted in the formation of the desired 1,2-hydrazinoimine **4a**, accompanied by the 1,2-hydrazinoketone **5a**. Although addition of molecular sieves in the reaction prevented the hydrolysis of the unstable *N*-acylimine **4a**, the enantioselectivities and yields were determined for compound **5a**, obtained by in situ hydrolysis of **4a** under acidic conditions (EtOH and 33% HBr in AcOH, v/v = 1/10). Phosphoric acids with different steric environment (**3a**−**f**, Figure 1) were next examined. It was found that the less

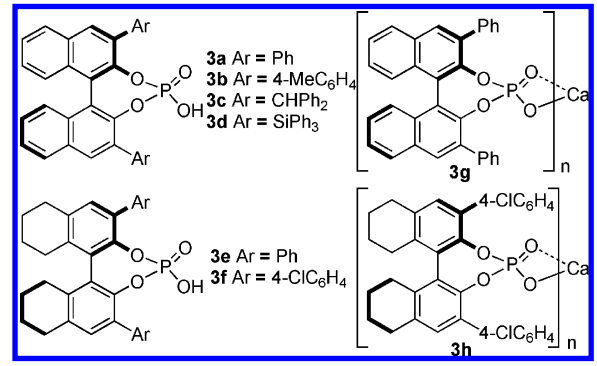


Figure 1. List of phosphoric acids examined.

hindered phosphoric acid **3a** was the most effective in terms of both yield and ee of the product (entries 2−7, Table 1).

During this study we noticed that enantioselectivities (from 78% to 89%) and yields (from 45% to quantitative) under the optimal conditions varied considerably depending on the batch of **3a** used. Following Ding's observation,[18] **3a** washed with HCl was used as catalyst that led indeed to the

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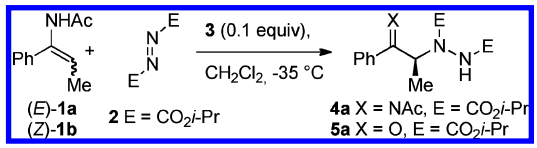
Table 1. Synthesis of 1,2-Hydrazinoketones: A Survey of Reaction Conditions



entry	1	additive	3	yield of **4a** (%)[e]	yield of **5a** (%)[e]	ee (%)[f,g]
1[a]	*E*-**1a**	no	**3a**[c]	35	29 (**5a**)	80
2[b]	*E*-**1a**	MS4Å	**3a**[c]		99 (**5a**)	89
3[b]	*E*-**1a**	MS4Å	**3b**[c]		56 (**5a**)	71
4[b]	*E*-**1a**	MS4Å	**3c**[c]		66 (**5a**)	18
5[b]	*E*-**1a**	MS4Å	**3d**[c]		57 (**5a**)	8
6[b]	*E*-**1a**	MS4Å	**3e**[c]		44 (**5a**)	88
7[b]	*E*-**1a**	MS4Å	**3f**[c]		59 (**5a**)	78
8[b]	*E*-**1a**	MS4Å	**3a**[d]		92 (**5a**)	85[h]
9[b]	*E*-**1a**	MS4Å	**3g**		75 (**5a**)	95
10[b]	*E*-**1a**	MS4Å	**3h**		91 (**5a**)	89
11[b]	*Z*-**1a**	MS4Å	**3g**		23 (**5a**)	0

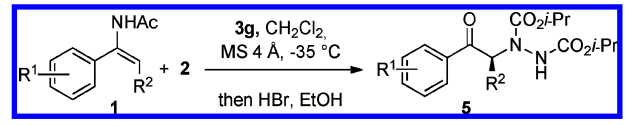
[a] Experimental conditions: **1a/2a/3** = 1.0/5.0/0.1 in CH_2Cl_2 (c = 0.1) at −35 °C. [b] General conditions: **1a/2a/3** = 1.0/5.0/0.1 in CH_2Cl_2 (c = 0.1) at −35 °C followed by acid hydrolysis with EtOH and 33% HBr in AcOH (v:v = 1/10). [c] Purified on silica gel. [d] Washed with HCl after purification on silica gel. [e] Yields refer to chromatographically pure products. [f] Enantiomeric excess was determined by chiral HPLC analysis. [g] For the determination of the absolute configuration, see the Supporting Information. [h] An additional experiment was performed with 20 mol % of phosphoric acid **3a** leading to **5a** in similar yield and ee.

reproducible ee values and yields. However, a slightly lower enantioselectivity was obtained with this acid-washed catalyst (entry 8). Inspired by the work of Ishihara,[19,20] the catalytic efficiency of chiral calcium phosphates **3g** and **3h** derived from **3a** and **3f**, respectively, were tested (entries 9 and 10, Table 1). Gratefully, with catalyst **3g**, compound **5a** was produced in 75% yield with 95% ee and the result was perfectly reproducible.[21−24] The same enantiomer of **5a** was produced whether **3a** or **3g** was used as a catalyst and the absolute configuration of **5a** was determined to be (*S*) by comparison of the sign of its optical rotation with that of the literature data.[13]

We have also examined the effect of the alkene geometry of enamides on the reaction outcome. It was observed that the (*Z*)-isomer **1b** (entry 11, Table 1) was much less reactive and no reaction took place at −35 °C. Performing the reaction at room temperature afforded the desired product **5a** in low yield with no enantioselectivity. These results are therefore complementary to Feng's catalytic system wherein the (*Z*)-enamides were the preferred substrates for the similar amination reaction.[13]

Having identified the optimum conditions, we explored the reaction scope using different (*E*)-*N*-(1-arylprop-1-en-1-yl)acetamides **1**. Results are summarized in Table 2.

Table 2. Scope of the Enantioselective Ca-Phosphate-Catalyzed Synthesis of 1,2-Hydrazinoketones.[a]



entry	R^1	R^2	5	yield (%)[b]	ee (%)[c]
1	3-Cl	Me	**5b**	80	90
2	4-Cl	Me	**5c**	97	85
3	3-F	Me	**5d**	77	90
4	4-Br	Me	**5e**	76	93
5	4-Me	Me	**5f**	83	88
6	4-OMe	Me	**5g**	73	91
7	4-CF_3	Me	**5h**	75	93
8	H	Et	**5i**	91	89[d]
9	H	*n*-Pr	**5j**	94	94

[a] General conditions: **1a/2a/3** = 1.1/5.0/0.1 in CH_2Cl_2 (c = 0.1) at −35 °C followed by acid hydrolysis with EtOH and 33% HBr in AcOH (v/v = 1/10). [b] Yields refer to chromatographically pure products. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] With 10 mol % of **3a**.

Enamides bearing electron-neutral, -rich, and -poor aromatic substituents at α-position react smoothly with **2** to give, after in situ hydrolysis, 2-hydrazinoketones **5** in good yields (75−97%) and excellent enantioselectivities (85−97% ee). In addition, enamide having a longer alkyl chain at the β-position, which gave low enantioselectivity in a previous report,[13] are suitable substrates (entries 8 and 9). With (*E*)-*N*-(1-phenylpent-1-en-1-yl)acetamides (**1j**, R^1 = H, R^2 = *n*-Pr), the corresponding hydrazinoketone **5j** was obtained in 94% yield with 97% ee.

With this transformation in hand, we next turned our attention to the in situ reduction of hydrazinoimines to 1,2-diamines which are very useful chiral ligands, auxiliaries, and building blocks in the synthesis of natural and bioactive products.[25] Reduction of **4a** with $NaBH_4$ (−78 to −45 °C, MeOH) according to Kobayashi et al. provided the *syn*-1,2-

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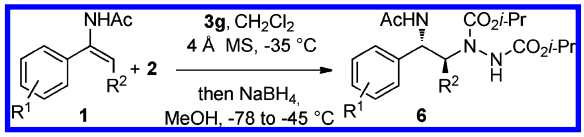
diamine[26] **6a** in high diastereoselectivity (>95:5 dr).[27] This reduction step was found to be compatible with the amination process. Indeed, a one-pot amination/reduction process furnished *syn*-1,2-diamine **6a** in 84% yield with 92% ee (entry 1, Table 3). Other representative chiral 1,2-diamines

Table 3. Scope of the Enantioselective Ca-Phosphate-Catalyzed One-Step Synthesis of 1,2-Hydrazinoamines[a]



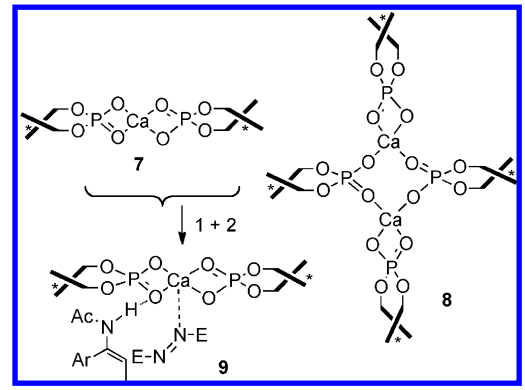
entry	R^1	R^2	**6**	yield (%)[b]	ee (%)[c]
1	H	Me	**6a**	84	92
2	3-F	Me	**6b**	88	88
3	4-CF_3	Me	**6c**	84	93
4	H	*n*-Pr	**6d**	99	96

[a] General conditions: **1a/2a/3** = 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 excess was determined by chiral HPLC analysis.

prepared were enlisted in Table 3. In general, diamines **6** were isolated in slightly higher yields than hydrazinoketones **5**. As expected, the ee of products **5** and **6** obtained by these two different one-pot processes were almost identical, reflecting directly the enantioselectivity of the amination step.

The precise structure of the catalyst **3g** is actually not known; however, we believe that divalent-Ca is able to react with Brønsted acids to form an oligomeric calcium complex as predicted by Ishihara et al.[18,28−30] The observed ^{31}P NMR chemical shift of **3g** agreed well with the chemical shifts observed for the oligomeric form reported previously (see the Supporting Information).[19a] Moreover, the catalyst **3a** gave a MALDI-TOF spectrum that exhibits [M + H] peaks at *m*/*z* 1039 and 2077, corresponding to monometallic and dimetallic species **7** and **8**, respectively (Scheme 2). In light of Ishihara's recent observation, we assumed that addition

Scheme 2. Ternary Complex, a Hypothetic Intermediate



of enamide **1** and azodicarboxylate **2** to **3g** could generate a monometallic complex with concurrent formation of an intermediate of type **9**.[19a,28] A pseudointramolecular *Si*-face attack of enamide **1** onto azodicarboxylate **2** would then take place to afford the observed (*S*)-hydrazinoimines **4** (Scheme 2).

In summary, we demonstrated that a chiral nonracemic calcium bis(phosphate) complex **3g** is capable of catalyzing an enantioselective nucleophilic addition of enamides to azodicarboxylate providing chiral enantio-enriched 1,2-hydrazinoimines. Subsequent in situ hydrolysis or diastereoselective reduction of imine function led to 2-hydrazinoketones and 1,2 diamines, respectively, in excellent yields and enantioselectivities. Further investigation to understand the reaction mechanism is underway.

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Supporting Information Available: Catalysis optimization, spectroscopic data, and ee measurement. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The *syn* 1,2-diamine was incorrectly named *anti*.

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