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# Highly Enantioselective Electrophilic $\alpha$ -Bromination of Enecarbamates - Chiral Phosphoric Acid and Calcium Phosphate Salt Catalysts

Aurélien Alix,<sup>‡</sup> Claudia Lalli,<sup>‡</sup> Pascal Retailleau, and Géraldine Masson\*

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France.

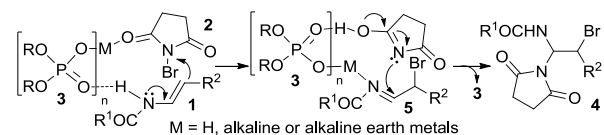
**KEYWORDS.** Organocatalysis, Bromination, Chiral phosphoric acid, Enecarbamate, Enantioselective reversal.

Supporting Information Placeholder

**ABSTRACT:** Metal-free chiral phosphoric acid or chiral calcium phosphate, both catalyzes highly enantio- and diastereoselective electrophilic  $\alpha$ -bromination of enecarbamates to provide an atom economic synthesis of enantioenriched vicinal haloamines. Both enantiomers can be formed by simply switching catalyst from phosphoric acid to its calcium salt in good yields and excellent diastereo- and enantioselectivities.

Vicinal haloamine is a versatile structural motif for synthesis of various biologically active compounds and can serve as key intermediates for further transformations.<sup>1,2,3</sup> However, to date only a few examples of their asymmetric synthesis have been described.<sup>4</sup> Among the reported different syntheses, electrophilic halo-functionalization of enamides represents one of the most convenient and straightforward approaches for attaining chiral vicinal haloamine compounds in regio- and stereoselective manner.<sup>5</sup> Despite the recent advance in the catalytic asymmetric halogenation of carbonyl,<sup>4c-d,6</sup> acyl chloride,<sup>7</sup> 1,3-dicarbonyl,<sup>8</sup> oxindole<sup>9</sup> and enyne compounds,<sup>10</sup> no example of an enantioselective  $\alpha$ -halogenation of enamides is extant.<sup>11</sup>

## Scheme 1. Working hypothesis



Chiral phosphoric acids<sup>12,13</sup> and chiral phosphate metal salts<sup>9d,14</sup> were found effective in catalyzing enantioselective addition of enamide compounds<sup>15</sup> to various electrophiles, such as carbonyl,<sup>16c</sup> imine,<sup>16a,b,d,g-j</sup> azodicarboxylate<sup>16i</sup> and nitroso compounds.<sup>16h</sup> Recently, it was reported on activation of *N*-halogenosuccinimide toward highly enantioselective reactions catalyzed by chiral phosphoric acid or chiral sodium phosphate.<sup>9d,17</sup> Inspired by the successful employment of these catalysts, and combined with our interest in enantioselective transformations,<sup>16c-g,i,j</sup> we envisioned that chiral phosphoric acids or their metal salts **3** could catalyze enantioselective electrophilic  $\alpha$ -halo-functionalization of enamide compounds (Scheme 1). Moreover, the *N*-halogenosuccinimide electrophile (**2**), including a masked nucleophilic component, could be incorporated into the electrophilic iminium intermediate **5** (Scheme 1), leading to a valuable amination **4**<sup>18</sup> for retro-inverso

synthesis of peptide mimics.<sup>19</sup> Herein, we report the first enantioselective  $\alpha$ -bromo-functionalization of enecarbamates through a domino bromination/nucleophilic addition. This approach also led to the discovery that chiral phosphoric acid (**3**, M = H) and its calcium salt (**3**, M = Ca) give access to both enantiomeric vicinal haloamine products.

**Table 1. Optimization of enantioselective  $\alpha$ -bromination of enecarbamates<sup>a</sup>**

entry	R	<b>3</b> (mol %)	yield (%) <sup>c</sup>	ee (%) <sup>d/dr<sup>e</sup></sup>
1	C <sub>6</sub> H <sub>5</sub> /H ( <b>3a</b> )	10 <sup>a</sup>	33	51/(75:25) <sup>b</sup>
2	4-ClC <sub>6</sub> H <sub>4</sub> [H8]/H ( <b>3b</b> )	10 <sup>a</sup>	39	52/(75:25) <sup>b</sup>
3	2-naphthyl/H ( <b>3c</b> )	10 <sup>a</sup>	44	62/(85:25) <sup>b</sup>
4	1-naphthyl/H ( <b>3d</b> )	10 <sup>a</sup>	39	64/(85:25) <sup>b</sup>
5	2,4,6-tri- <i>i</i> -Pr <sub>3</sub> C <sub>6</sub> H <sub>2</sub> /H ( <b>3e</b> )	10 <sup>a</sup>	87	88/(90:10) <sup>b</sup>
6	<b>3e</b>	5 <sup>a</sup>	87	88/(90:10) <sup>b</sup>
7	<b>3e</b>	2 <sup>a</sup>	87	90(>95:5) <sup>b</sup>
8	<b>3e</b>	1 <sup>b</sup>	89	94(>95:5) <sup>b</sup>
9	<b>3e</b>	1 <sup>b</sup>	99	98(>95:5) <sup>b</sup>
10	<b>3e</b>	0.5 <sup>b</sup>	75	94(>95:5) <sup>b</sup>
11	<b>3e</b>	0.1 <sup>b</sup>	56	92(>95:5) <sup>b</sup>
12	<b>3e</b>	1 <sup>b,c</sup>	67	86(>95:5) <sup>b</sup>
13	<b>3e</b>	1 <sup>b</sup>	64	98(>95:5) <sup>b,i</sup>
14	2,4,6-tri- <i>i</i> -PrC <sub>6</sub> H <sub>2</sub> /Li ( <b>3f</b> )	1 <sup>b,d</sup>	74	-96(>95:5) <sup>j</sup>
15	2,4,6-tri- <i>i</i> -PrC <sub>6</sub> H <sub>2</sub> /Ca ( <b>3g</b> )	1 <sup>b,d</sup>	78	-98(>95:5) <sup>j</sup>

<sup>a</sup>Reaction conditions: enecarbamate **1a** (0.1 mmol), NBS (**2**) (0.05 mmol), **3** in 1 mL of toluene for 14 h. <sup>b</sup>Under similar condition, 0.5 mL of toluene. <sup>c</sup>Reaction using (*Z*)-enecarbamate **1a**. <sup>d</sup>Reaction performed for 48 h. <sup>e</sup>Yields referred to chromatographically pure major diastereoisomer. <sup>f</sup>Determined by chiral HPLC analysis. <sup>g</sup>Determined by <sup>1</sup>H NMR of the crude material. <sup>h</sup>(1*R*,2*S*)-enriched-**4a**. <sup>i</sup>Reaction was performed with 1.2 equiv. of enecarbamate **1a** (0.6 mmol). <sup>j</sup>(1*S*,2*R*)-enriched-**4a**.

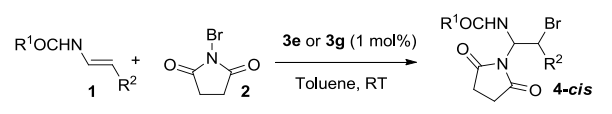
To validate our hypothesis, we began our studies by examining the reaction of (*E*)-*N*-(benzyl prop-1-en-1-yl)carbamate (**1a**) with *N*-bromosuccinimide (NBS, **2**) in the presence of 10 mol% of a chiral phosphoric acid **3** at room temperature. As shown in Table 1, both reactivity and enantioselectivity were dramatically affected by the structure of the chiral phosphoric acid. The highest diastereo- and enantioselectivity was ob-

tained when (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-BINOL (TRIP) phosphoric acid (**3e**) was used (88% ee and 9:1 dr, entry 5).<sup>20</sup> Additionally, it was found that significant reduction of catalyst loading to only 1 mol% in a more concentrated condition (*c* 0.1 M) improved the reaction diastereo- and enantioselectivity (>95:5, 98% ee, 99% yield, entries 9 vs. 5). Comparable enantioselectivity was obtained when the catalyst loading was reduced to 0.1 mol%, despite reduced yield (entry 11). Reducing the amount of enecarbamate **1a** to 1.2 equivalents with respect to **2** provided the **4a** in lower yield (entry 13). The absolute configuration of the major *cis*-isomer **4a** was unambiguously determined to be 1*R* and 2*S* by X-ray analysis [see the Supporting Information (SI)]. As the stereochemical outcome of electrophilic bromination can be dependent of the enecarbamate geometry, the reaction with (*Z*)-enecarbamate (**1a**) was investigated. It was found that the (*Z*)-isomer **1a** still gave the same enantiomer of **4a** as the major product albeit with lower yield (entry 12). However, to our surprise, reverse enantioselectivity of product **4a** to supply (1*S*,2*R*)-*cis*-**4a** was observed by changing the catalyst from **3e** to its corresponding metal salts (Li, **3f**; Ca, **3g**), still with excellent *ee* and *dr* values (entries 14 and 15).<sup>21</sup> Both enantiomers of **4a** can, thus, be prepared efficiently.<sup>14a,b,21</sup>

We next examined the scope of the enecarbamate component in this enantioselective domino process, catalyzed by chiral phosphoric acid **3e** or its calcium salt **3g**. Representative results are summarized in Table 2. In general, the **3e**-catalyzed reaction proceeded smoothly with high diastereo- and enantioselectivity, and excellent yield greater than 90%. This reaction works well for a broad range of substituted enecarbamates bearing a linear or a branched alkyl group as well as heteroalkyl substituents. Introduction of steric hindrance at the  $\alpha$ -position of the ene moiety resulted in a slight decrease in the yield without affecting the enantioselectivity of the process (entry 8). Even the  $\beta,\beta$ -disubstituted enecarbamate **1n** afforded the corresponding bromoaminal product **4n** containing a quaternary center with 96% ee (entry 13). In contrast, the vinylcarbamates substituted by aryl groups on  $\beta$ -position failed to participate in this electrophilic  $\alpha$ -bromination probably, because of their lower nucleophilicity.<sup>22</sup> Modification of the carbamate moiety from benzyl to ethyl, propargyl, allyl or *tert*-butyl carbamate afforded the bromoaminal products (**4b** to **4f**, entries 1-5) with similar diastereo- and enantioselectivities. It is worthy to note that no bromination of unsaturated bonds present on enecarbamates was observed whether on the carbamate moiety (entries 2 and 3) or the lateral chain (entry 7), thus demonstrating the high chemo- and regioselectivity of this reaction.<sup>17</sup> We also investigated enantioselective electrophilic  $\alpha$ -bromination using the optimized reaction conditions with calcium salt **3g**. A variety of selected enecarbamates **1** reacted with good enantioselectivity to afford, in all cases, the opposite enantiomer of the products formed using corresponding phosphoric acid **3e**. We also found that, contrary to our previous studies, *N*-protecting group of **1** has an influence on the enantiomeric excess, where diminished enantioselectivity was observed when Boc or Alloc was used (entries 14 and 15).

Then, we became interested in pursuing experiments designed to test the mechanistic hypothesis outlined in scheme 1. Different modes of activation of NBS by **3** could be proposed, such as hydrogen bonding, metallic bonding or proton transfer with formation of a chiral bromonium ion intermediate.<sup>9d,17</sup> Inspired by the elegant work of Denmark *et al.*,<sup>17c</sup> we investi-

**Table 2. Enantioselective direct  $\alpha$ -bromination of enecarbamates: scope of substrates<sup>a</sup>**



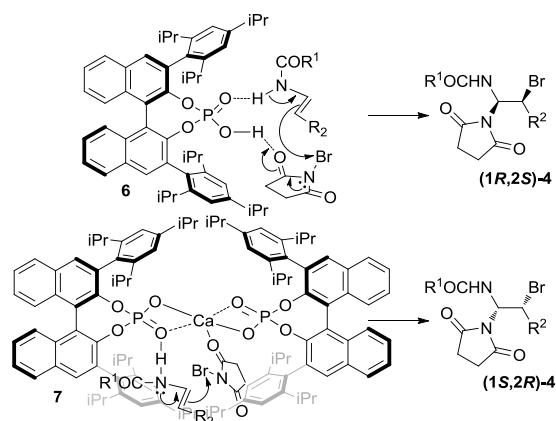
entry	R <sup>1</sup>	<b>4</b>	Yield (%) <sup>b</sup>	ee (%) <sup>d</sup>
1		(1 <i>R</i> ,2 <i>S</i> )- <b>4b</b>	90	91 <sup>e</sup>
2		(1 <i>R</i> ,2 <i>S</i> )- <b>4c</b>	75	91 <sup>e</sup>
3		(1 <i>R</i> ,2 <i>S</i> )- <b>4d</b>	81	86 <sup>e</sup>
4		(1 <i>R</i> ,2 <i>S</i> )- <b>4e</b>	92	90 <sup>e</sup>
5		(1 <i>R</i> ,2 <i>S</i> )- <b>4f</b>	99	94 <sup>e</sup>
6		(1 <i>R</i> ,2 <i>S</i> )- <b>4g</b>	93	96 <sup>e</sup>
7		(1 <i>R</i> ,2 <i>S</i> )- <b>4h</b>	90	97 <sup>e</sup>
8		(1 <i>R</i> ,2 <i>S</i> )- <b>4i</b>	77	92 <sup>e</sup>
9		(1 <i>R</i> ,2 <i>S</i> )- <b>4j</b>	46	92 <sup>e</sup>
10		(1 <i>R</i> ,2 <i>S</i> )- <b>4k</b>	72	91 <sup>e</sup>
11		(1 <i>R</i> ,2 <i>S</i> )- <b>4l</b>	94	84 <sup>e</sup>
12		(1 <i>R</i> ,2 <i>S</i> )- <b>4m</b>	94	98 <sup>e</sup>
13		<b>4n</b>	66	96 <sup>f</sup>
14		(1 <i>S</i> ,2 <i>R</i> )- <b>4d</b> <sup>c</sup>	62	-88 <sup>g</sup>
15		(1 <i>S</i> ,2 <i>R</i> )- <b>4f</b> <sup>c</sup>	67	-81 <sup>g</sup>
16		(1 <i>S</i> ,2 <i>R</i> )- <b>4i</b> <sup>c</sup>	74	-86 <sup>g</sup>

<sup>a</sup>Reaction conditions: enecarbamate **1a** (0.2 mmol), NBS (**2**) (0.1 mmol), **3e** or **3g** (1 mol%) in toluene (1.0 mL) at RT for 14 h. <sup>b</sup>Yields of chromatographically pure product. <sup>c</sup>Reaction performed for 48h. <sup>d</sup>Enantiomeric excess was determined by chiral HPLC analysis. <sup>e</sup>(1*R*,2*S*)-enriched-**4**. <sup>f</sup>Absolute configuration was not determined. <sup>g</sup>(1*S*,2*R*)-enriched-**4**.

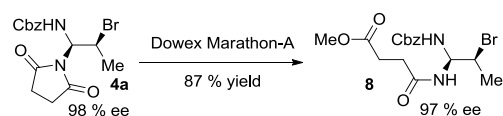
-gated the addition of achiral Lewis base Ph<sub>3</sub>P=S known to favor the ion-pairing mechanism. Under this condition, which ever using catalyst either **3e** or **3g**, similar results in terms of

reaction rate, yield and *ee* were observed (*cf.* SI). The reversal phenomenon of enantioselectivity by phosphate salt **3g** was preserved whereas the same enantiomer should have been observed with a mechanism involving a chiral bromonium ion intermediate. We also carried out a control experiment with a two-component catalyst composed of TRIP phosphoric acid **3e** and Ca(*i*PrO)<sub>2</sub>, furnishing the desired product in 95% *ee* with the same selectivity than **3e**. It can, therefore be suggested that **3e** would activate NBS through either hydrogen bonding or ion-pairing. At this stage, it is not possible to distinguish these two activation modes. On the other hand, earth metal bonding interaction between **3g** and NBS would be evoked. Then, we carried out a nonlinear effect experiment to gain further insight into the active Ca phosphate salt catalyst structure. We observed a positive nonlinear effect in the **3g**-catalyzed  $\alpha$ -bromination of enecarbamates (*cf.* SI), which indicates that the active catalyst was a dimeric species rather than Ca<sup>II</sup>-free phosphoric acid or mono(phosphate) salt.<sup>14,23</sup> In addition, it is worth noting that secondary enecarbamates gave no reaction, in the presence of **3e** or **3g**, suggesting that activation of NBS alone is not sufficient to achieve effective  $\alpha$ -bromination.

### Scheme 2. Proposed transition state model



### Scheme 3. Ring opening of succinimide



Based on these observations, we assumed that **3e** and **3g** acted as a bifunctional catalyst activating both NBS and the enecarbamate *via* hydrogen bonding and metal chelation, respectively. While a precise understanding of the origin of enantioselectivity reversal awaits further study, two different transition state models, **6** and **7**, were postulated (Scheme 2). Phosphoric acid **3e** with the sterically bulky 2,4,6-triisopropylphenyl group efficiently hindered the *Re* face of NBS, and the enecarbamate could only attack the *Si* face of NBS leading to the (*S*)-imine intermediate. In contrast, the other face (*Re*-face) was fully accessible with calcium bis(phosphate) complex **3g** to furnish the (*R*)-isomer.<sup>14</sup> In both cases, a highly diastereoselective nucleophilic addition reaction of imide to (*S*)- or (*R*)-imine would then furnish the observed *cis*-bromoaminal (1*R*,2*S*)-**4a** or (1*S*,2*R*)-**4a**, respectively.

To illustrate the synthetic potential of this novel catalytic enantioselective domino bromination / succinimide addition,

we developed conditions to open the succinimide ring. We were delighted to observe that such ring opening can be carried out by fast filtration on basic resin to generate valuable aminal **8**<sup>18</sup> with retention of enantiopurity (Scheme 3). Furthermore, the multifunctionality of the 1,2-bromoaminal products allowed for a short-step, stereoselective synthesis of other various useful chiral building blocks such as aziridines,<sup>5e,f,i</sup> 1,2-ether/thioether-aminals,<sup>5e,g,1</sup> imidazolidin-2-ones<sup>5e</sup> and pyrrolizidines.<sup>24</sup>

In conclusion, we have reported the first enantioselective chiral phosphoric acid-catalyzed electrophilic  $\alpha$ -bromination of enecarbamates.<sup>11</sup> The efficiency of the system allows reactions to be run under mild conditions at room temperature with a modest amount of catalyst (1 mol%). We have also shown an unprecedented reversal of enantioselectivity for a catalytic bromination reaction by a chiral calcium phosphate salt. The high efficiency and operational simplicity of this procedure makes it a practical protocol for synthesis of chiral vicinal haloamines.

### ASSOCIATED CONTENT

Experimental details, characterization data, HPLC enantiomer analysis, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

### AUTHOR INFORMATION

Corresponding Author  
masson@icsn.cnrs-gif.fr.

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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# TOC Template (9 cm x 3-1/2 cm)

