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## Chiral Brønsted acid-catalyzed diastereo- and enantioselective synthesis of CF<sub>3</sub>-substituted aziridines

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Enantiopure aziridines are versatile chiral building blocks that have high potential for further elaboration to a wide range of chiral nitrogen-containing derivatives.<sup>1</sup> The aziridine ring is not only an important reactive intermediate but is also present in many biologically active compounds.<sup>2</sup> In the context of an explosion of research in organofluorine chemistry due to the matchless properties of fluorinated molecules, trifluoromethylated building blocks are privileged scaffolds for library design and drug discovery.<sup>3</sup> Herein, we report the first catalytic asymmetric synthesis of CF<sub>3</sub>-substituted aziridines that is remarkable for its simplicity, a low catalyst loading, and a very high enantioselectivity.<sup>4</sup>

## Screening of reaction conditions

Using in situ generated CF<sub>3</sub>CHN<sub>2</sub>,<sup>5</sup> we tested its reactivity with an imine in situ generated from phenyl glyoxal monohydrate **2a** and *p*-anisidine in the presence of Brønsted acid catalysts (Table 1).

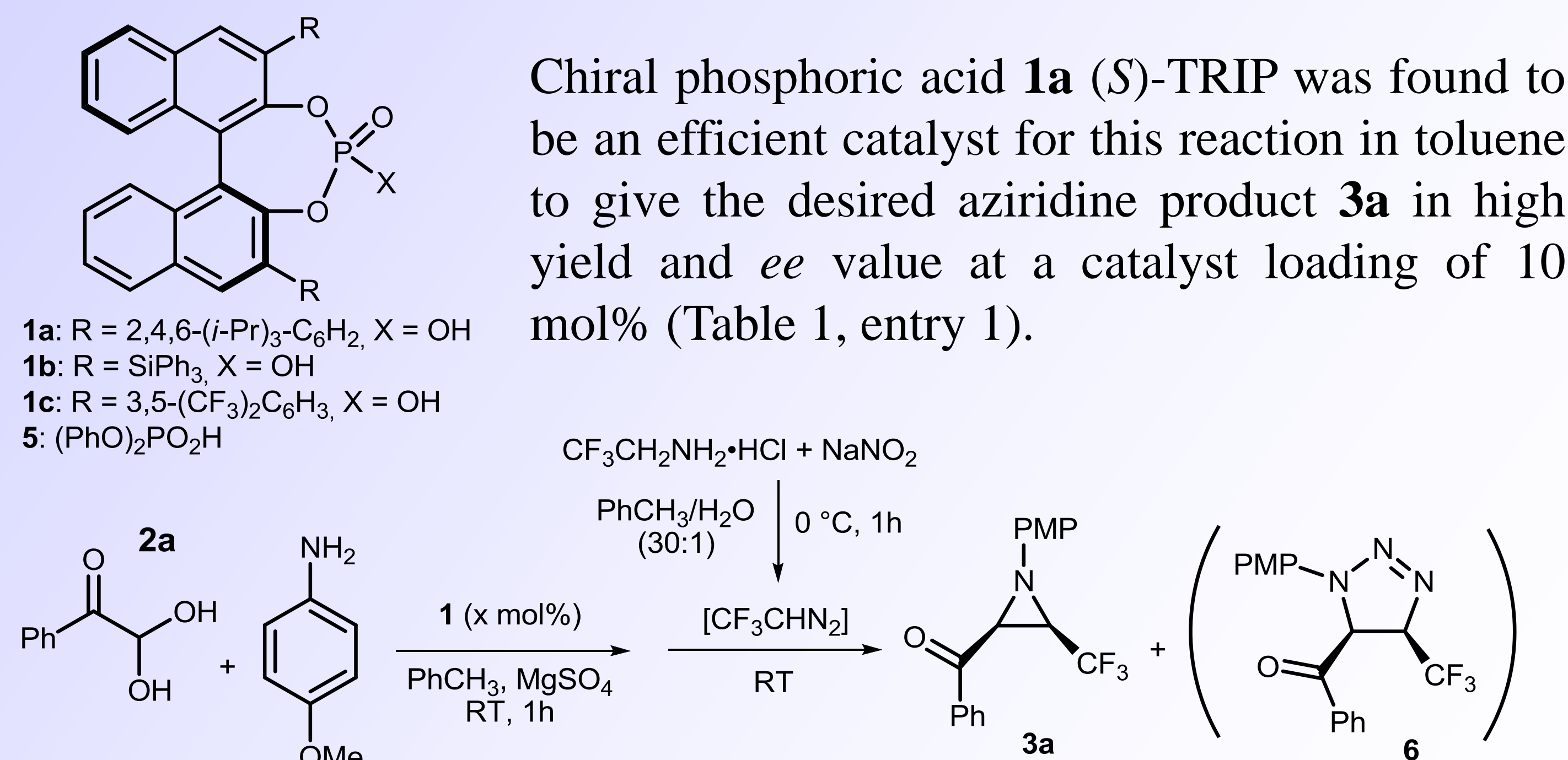


Table 1<sup>a</sup>

Entry	Catalyst (mol%)	Time (h)	Yield <sup>b</sup> (%)	Product ratio <sup>c</sup> <i>cis</i> - <b>3a</b> : <i>trans</i> - <b>3a</b> : <b>6</b>	<i>ee</i> <sup>d</sup> (%)
1	<b>1a</b> (10)	3	82	18:1:2	97
2	<b>1a</b> (5)	8	91	39:1:2	97
3	<b>1a</b> (2.5)	24	48 <sup>e</sup>	263:1:4	99
4	<b>1b</b> (5)	12	5 <sup>e</sup>	43:1:8	n.d.
5	<b>1c</b> (5)	48	10 <sup>e</sup>	17:1:2	55
6	<b>5</b> (10)	16	0	n.d.	n.d.
7	<b>1a</b> (3+2) <sup>f</sup>	24	83	185:1:2	98
8	<b>1a</b> (2.5+2) <sup>f</sup>	32	75	417:1:4	99

<sup>a</sup> **2a**/anisidine/CF<sub>3</sub>CHN<sub>2</sub> 1:1:2, [imine]<sub>0</sub> = 0.05M. <sup>b</sup> yield of isolated *cis*-**3a**. <sup>c</sup> determined by <sup>19</sup>F NMR. <sup>d</sup> determined by chiral HPLC using OD-H column. <sup>e</sup> unreacted imine accounts for most of material balance. <sup>f</sup> catalyst was added in two batches at a time interval of 12h.

After some experimentation, we found that adding **1a** in two batches at a time interval of 12h led to the optimum overall results, which provide an extremely high 417:1 dr ratio for the diastereomeric aziridines and 99% *ee* for the *cis*-**3a** (Table 1, entries 7–8).

## Scope with aryl glyoxal monohydrates

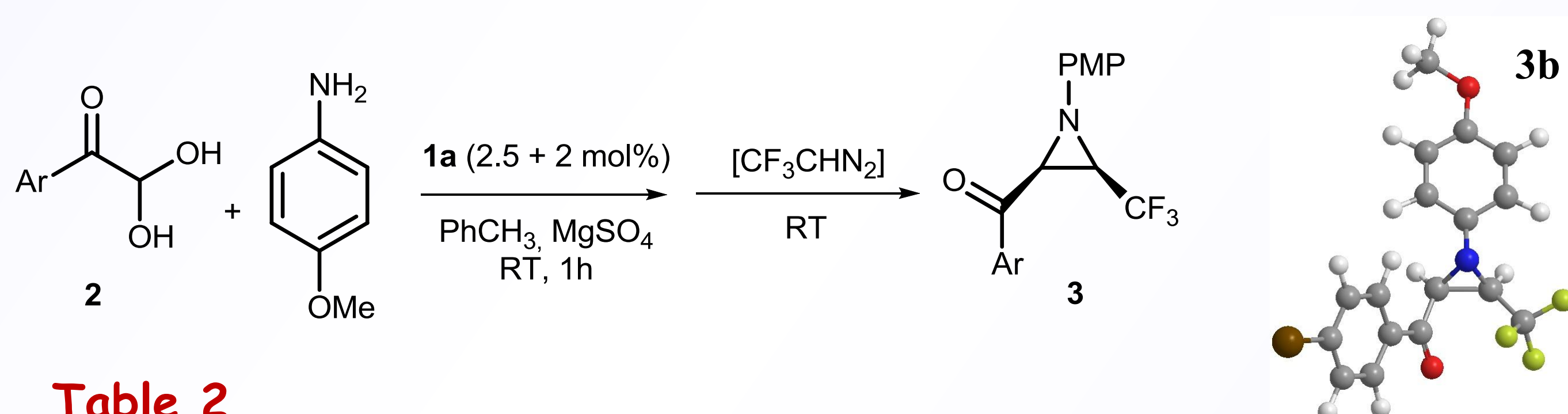


Table 2

Entry	Ar	Yield <sup>a</sup> (%)	Product ratio <sup>b</sup> <i>cis</i> - <b>3</b> : <i>trans</i> - <b>3</b> : <b>6</b>	<i>ee</i> <sup>c</sup> (%)
1	Ph ( <b>2a</b> )	75	417:1:4	99
2	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	82	69:1:2	>99
3	3-BrC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	78	95:1:3	98
4	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	75	140:1:2	>99
5	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>2e</b> )	71	59:1:2	96
6 <sup>d</sup>	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	80	227:1:2	>99
7 <sup>d</sup>	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	85	60:1:2	97
8 <sup>d</sup>	2-benzofuryl ( <b>2h</b> )	79	131:1:3	99

<sup>a</sup> Yield of isolated *cis*-**3** products. <sup>b</sup> estimated by <sup>19</sup>F NMR. <sup>c</sup> determined by chiral HPLC using OD-H column. <sup>d</sup> 3+2 mol% of catalyst **1a** at a time interval of 16h were used.

A series of aryl glyoxal monohydrates **2** were tested in this reaction (Table 2). High yields, excellent product ratios and *ee* values were obtained, irrespective of the electronic nature and position of the substituents on the benzene ring (Table 2, entries 1–7). In addition, a heteroaromatic substrate **2h** also participated in the reaction well (Table 2, entry 8).

The absolute configuration of the aziridine *cis*-**3b** was determined by X-ray crystallographic analysis and the others were assigned by analogy.

## Scope with α-imino glyoxilic ester and amide

The scope of the reaction was further explored by using preformed α-imino glyoxilic ester **7** or amide **8** (Table 3).

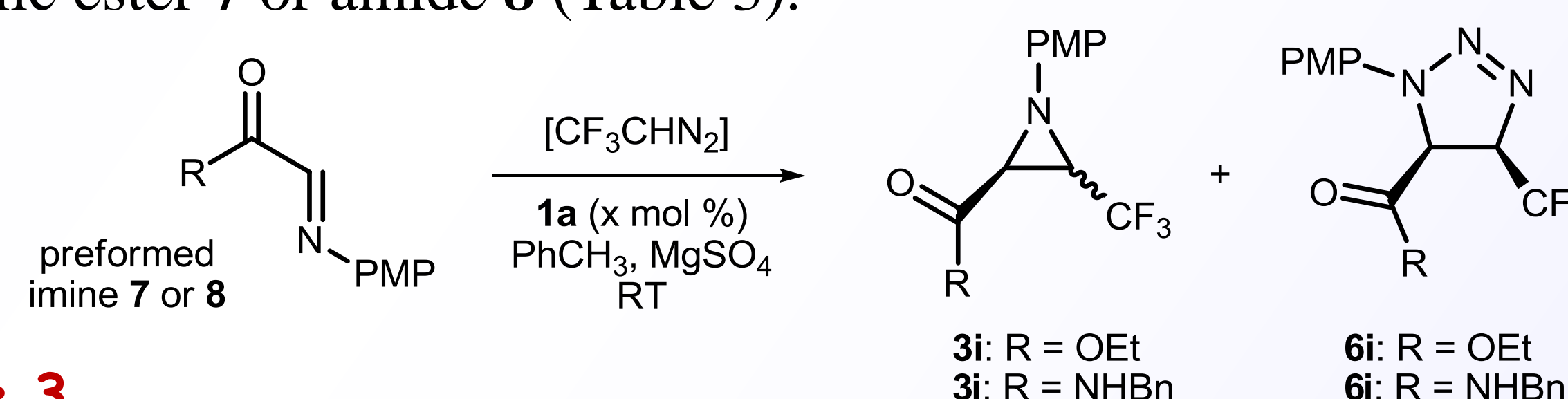


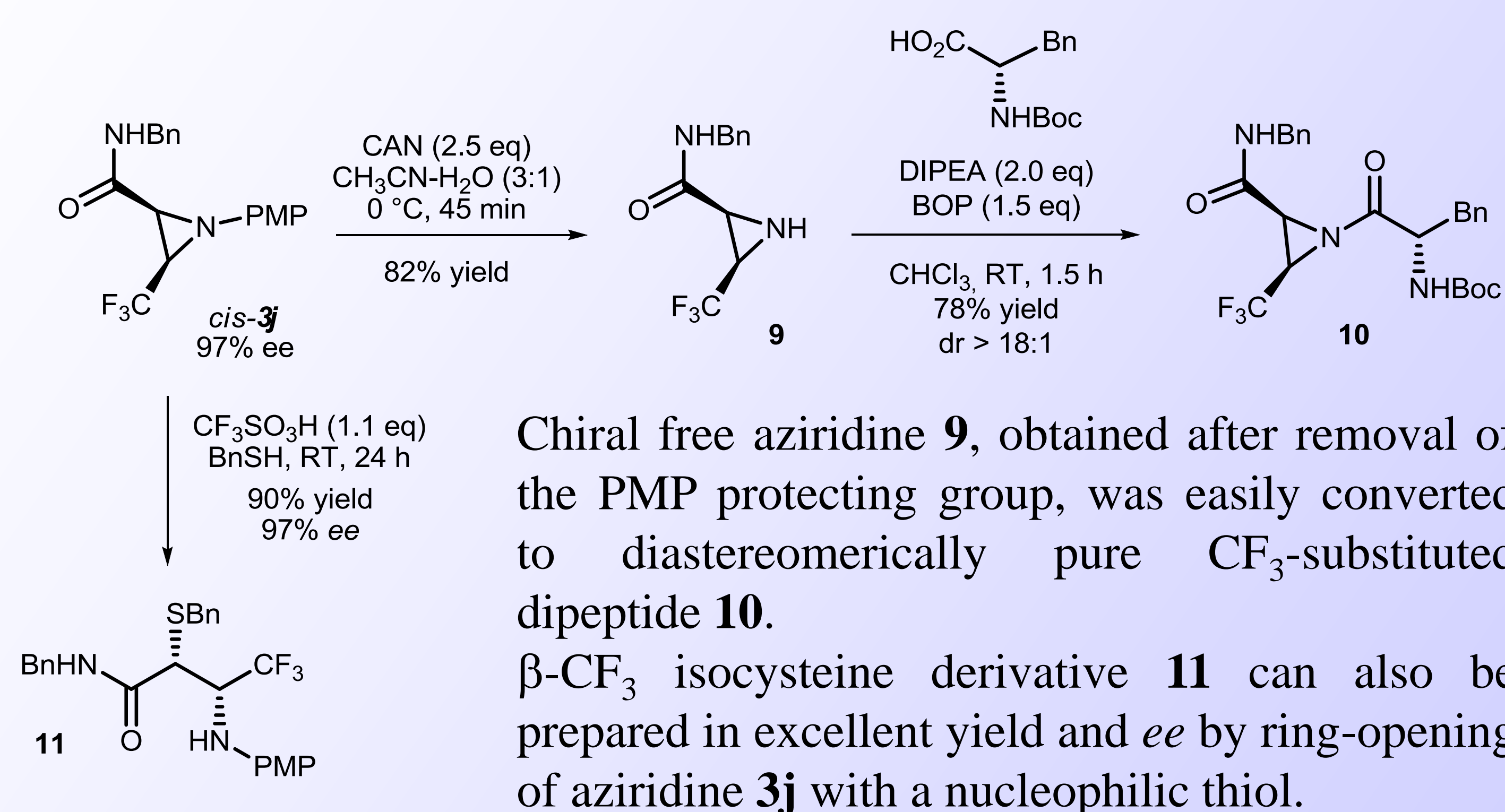
Table 3

Entry	<b>7</b> or <b>8</b> (R)	<b>1a</b> (mol%)	Product ratio <sup>a</sup> <i>cis</i> - <b>3</b> : <i>trans</i> - <b>3</b> : <b>6</b>	Yield <sup>b</sup> (%)	<i>ee</i> <sup>c</sup> (%)
1 <sup>d</sup>	<b>7</b> (OEt)	10	1.4:1:26	82	-/-/95
2 <sup>d</sup>	<b>7</b> (OEt)	5	1.2:1:29	42	-/-/96
3	<b>8</b> (NHBn)	5	7:1:6	45/7/41	98/46/88
4	<b>8</b> (NHBn)	1	6:1:6	43/8/46	98/49/88
5	<b>8</b> (NHBn)	0.5	8:1:8	46/6/47	98/7/82

<sup>a</sup> Estimated by <sup>19</sup>F NMR. <sup>b</sup> yield refers to an inseparable mixture of *cis*-**3i** and **6i** for entries 1-2; isolated yields for *cis*-**3j**:*trans*-**3j**:**6j**, respectively, for entries 3-5. <sup>c</sup> *ees* for *cis*-**3**:*trans*-**3**:**6** respectively, determined by chiral HPLC using OD-H column. <sup>d</sup> a co-solvent PhCH<sub>3</sub>/CH<sub>3</sub>CH<sub>2</sub>CN 2:1 was used.

With α-imino ester **7**, *cis*-triazoline **6i** was isolated as the major product with excellent *ee* (Table 3, entries 1-2). Starting from α-imino amide **8**, although a 1:1 mixture of *cis*-aziridine **3j** and *cis*-triazoline **6j** was obtained, the *ee* of **3j** remained excellent (Table 3, entries 3-5).

## Application: synthesis of β-amino acids and peptides



Efforts towards a deeper mechanistic understanding of the current reactions as well as further applications to related reaction systems are underway in our laboratory.

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