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Chiral Brønsted acid-catalyzed diastereo- and enantioselective synthesis of CF₃-substituted aziridines

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► **To cite this version:**

Zhuo Chai, Vincent Terrasson, Jean-Philippe Bouillon, Dominique Cahard. Chiral Brønsted acid-catalyzed diastereo- and enantioselective synthesis of CF₃-substituted aziridines. ESFC, 2013, Paris, France. hal-02913343

HAL Id: hal-02913343

<https://hal.science/hal-02913343>

Submitted on 8 Aug 2020

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Zhuo Chai, Vincent Terrasson, Jean-Philippe Bouillon, Dominique Cahard

UMR CNRS 6014, COBRA, Université et INSA de Rouen, 1 rue Tesnière, 76821 Mont Saint Aignan Cedex, France

E-mail: dominique.cahard@univ-rouen.fr

Enantiopure aziridines are versatile chiral building blocks that have high potential for further elaboration to a wide range of chiral nitrogen-containing derivatives.¹ The aziridine ring is not only an important reactive intermediate but is also present in many biologically active compounds.² 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.³ Herein, we report the first catalytic asymmetric synthesis of CF₃-substituted aziridines that is remarkable for its simplicity, a low catalyst loading, and a very high enantioselectivity.⁴

Screening of reaction conditions

Using in situ generated CF₃CHN₂,⁵ 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).

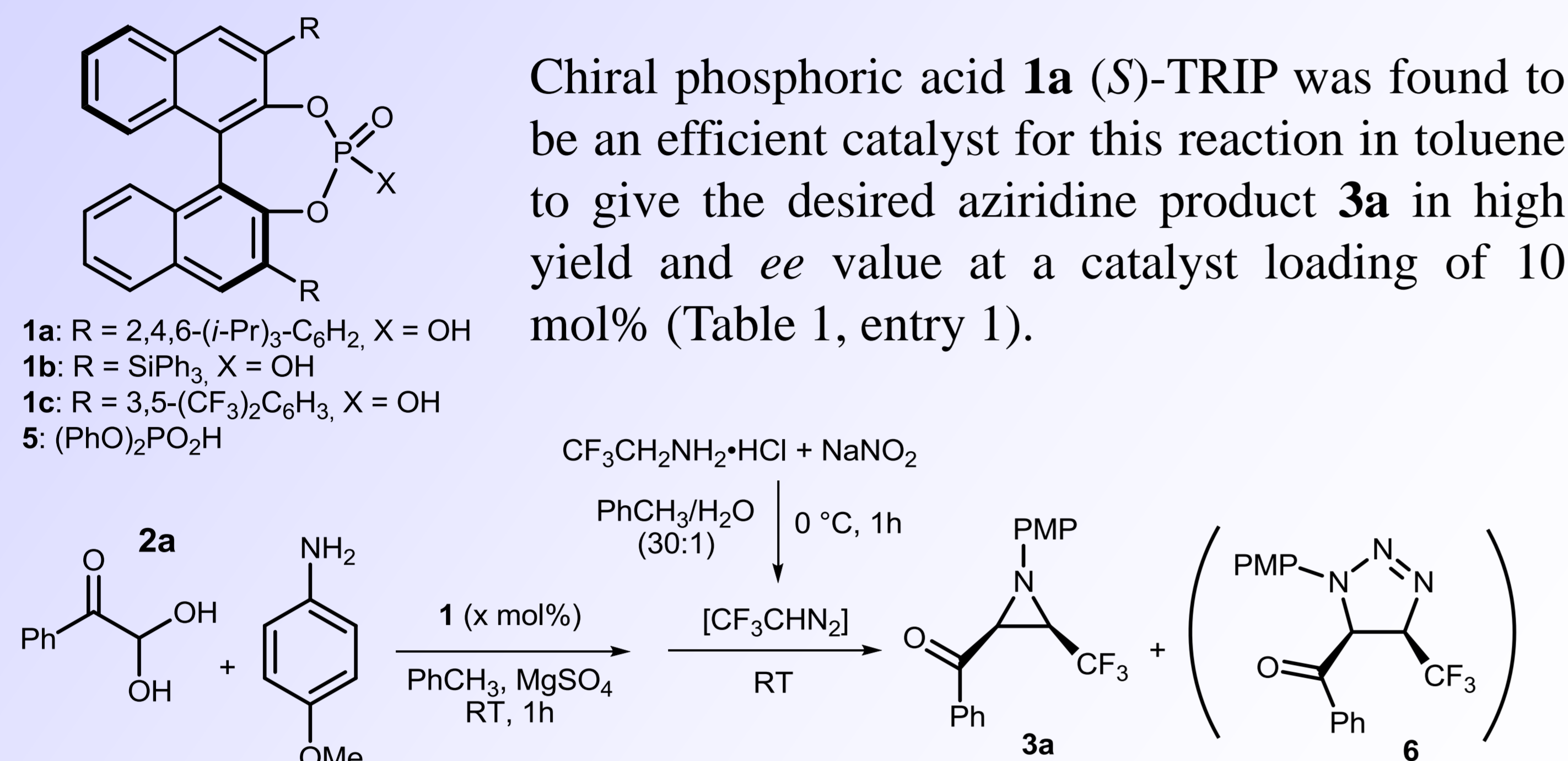


Table 1^a

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

^a **2a**/anisidine/CF₃CHN₂ 1:1:2, [imine]₀ = 0.05M. ^b yield of isolated *cis*-**3a**. ^c determined by ¹⁹F NMR. ^d determined by chiral HPLC using OD-H column. ^e unreacted imine accounts for most of material balance. ^f 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

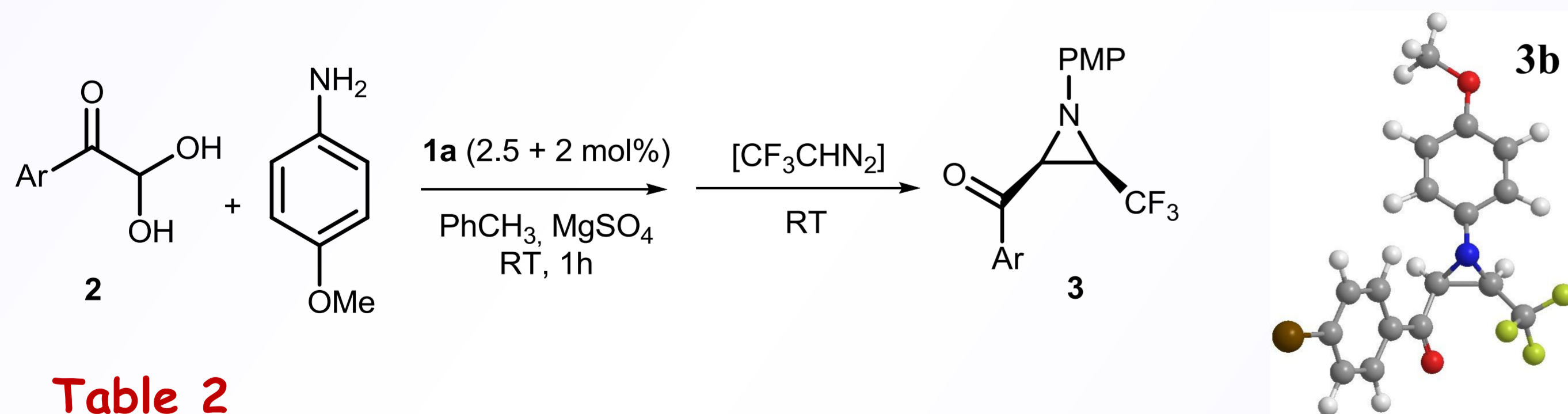


Table 2

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

^a Yield of isolated *cis*-**3** products. ^b estimated by ¹⁹F NMR. ^c determined by chiral HPLC using OD-H column. ^d 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).

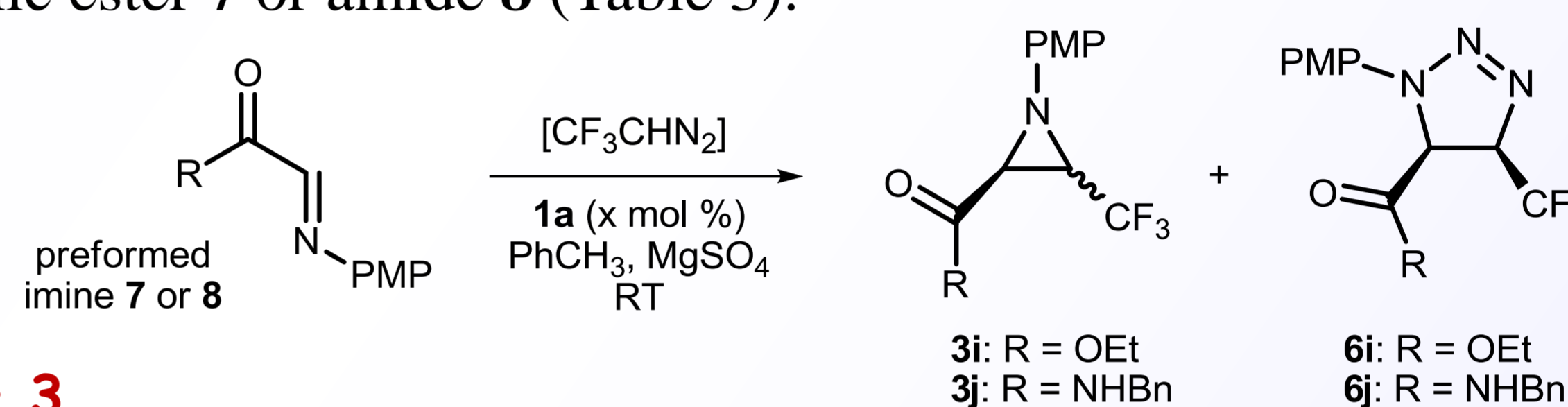


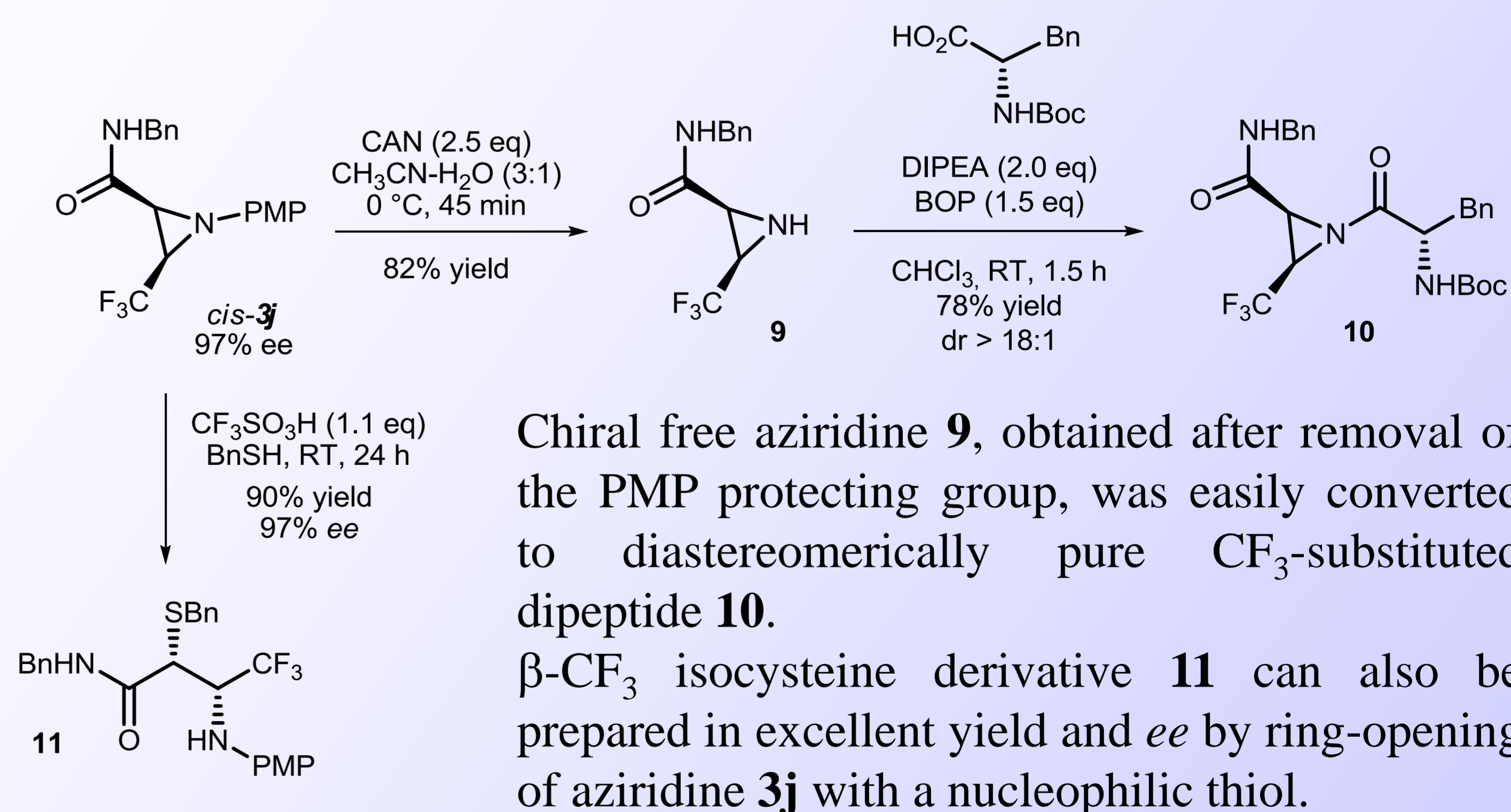
Table 3

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

^a Estimated by ¹⁹F NMR. ^b 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. ^c *ees* for *cis*-**3**:*trans*-**3**:**6** respectively, determined by chiral HPLC using OD-H column. ^d a co-solvent PhCH₃/CH₃CH₂CN 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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