



## Facile synthesis of amino acid-derived novel chiral hypervalent iodine(V) reagents and their applications



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### ARTICLE INFO

#### Article history:

Received 24 August 2016

Revised 30 September 2016

Accepted 7 October 2016

Available online 8 October 2016

#### Keywords:

Chiral hypervalent iodine(V) reagent

Asymmetric synthesis

Metal-free oxidation

Dearomatization

Dimerization

### ABSTRACT

Amino acid-derived novel chiral hypervalent iodine(V) reagents were synthesized from the corresponding chiral iodoarenes through DMDO oxidations. Their oxidation states were determined by the <sup>13</sup>C NMR chemical shifts of the *ipso*-carbon of the iodine atom, HRMS analysis, and elemental analyses. They were applied to the enantioselective hydroxylative dearomatization/[4+2]-dimerization cascade reactions of phenol derivatives to afford the desired products with up to 58% ee.

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### Introduction

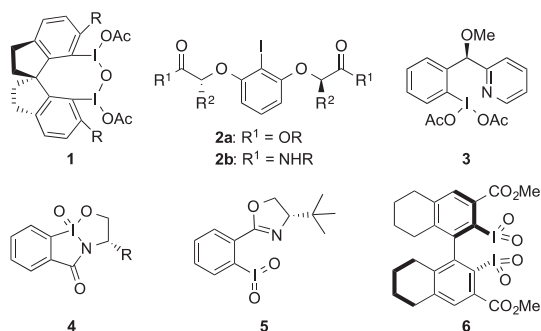
Hypervalent iodine reagents such as  $\lambda^3$ - and  $\lambda^5$ -iodanes have been widely used as metal-free and mild oxidants in complex molecule syntheses including natural products (Fig. 1).<sup>1</sup> Chiral hypervalent iodine(III) reagents have also been developed as stoichiometric oxidants in enantioselective reactions.<sup>2</sup> In 2008, Kita and co-workers reported the first highly enantioselective spiro-type chiral hypervalent iodine(III) **1** mediated oxidative spiro-lactonization of phenol derivatives (Kita reaction) with up to 86% ee.<sup>21</sup> In 2010, Ishihara and co-workers reported the first catalytic highly enantioselective Kita reaction using lactic acid-derived amide type  $C_2$ -symmetric iodoarene **2b** and *m*CPBA co-oxidant with up to 92% ee.<sup>3m,n</sup> Following this successful synthesis, chiral hypervalent iodine(III) reagents have been widely investigated as both stoichiometric oxidants and catalysts. In the past half-decade, they have been used as chiral organocatalysts with a stoichiometric amount of achiral co-oxidant.<sup>3</sup> They have been successfully applied to many types of transformations such as difluorinations,<sup>3a-c</sup> acyloxylation,<sup>3d,e,i-n</sup> construction of quaternary stereogenic centers,<sup>3f</sup> and stereoselective rearrangements.<sup>2g</sup> On the other hand, although achiral hypervalent iodine(V) reagents have been utilized in numerous fascinating transformations,<sup>4</sup>

examples of successful chiral hypervalent iodine(V)-mediated reactions are rare.<sup>5</sup>

Zhdankin and co-workers developed many novel chiral hypervalent iodine(V) reagents such as **4**; some of them afforded enantioselective oxidation products with moderate enantioselectivities.<sup>5d,e</sup> In 2009, Birman and co-workers reported the preparation of oxazoline-based chiral hypervalent iodine(V) reagents **5**; they were successfully applied to the oxidative dearomatization reactions, affording products in up to 77% enantiomeric excess.<sup>5c,6</sup> More recently, Pouységu, Quideau, and co-workers demonstrated an excellent preparation of biphenyl-type compounds **6** and salen-type chiral hypervalent iodine(V) reagents and their successful applications to stereoselective hydroxylative phenol dearomatization/[4+2]-dimerization cascade reactions, affording products in up to 94% ee for the sterically hindered substrates.<sup>5a,b</sup>

Recently, Fujita, Sugimura, and co-workers reported highly enantioselective oxidative diacyloxylation and 1,3-dioxolane formation reactions using lactate-derived chiral hypervalent iodine(III) reagents, furnishing products in up to 97% ee. This could be successfully applied to the asymmetric synthesis of natural products.<sup>2d,f,i,k,m</sup> Inspired by the success of lactate-derived hypervalent iodine(III) chemistry,<sup>2a-k,m,3d,f-i,l-n</sup> we developed a facile synthesis of novel chiral hypervalent iodine(V) reagents as a new type of oxidation reagents and their applications to asymmetric hydroxylative dearomatization/[4+2]-dimerization cascade reactions of phenol derivatives.<sup>5b,c,9</sup>

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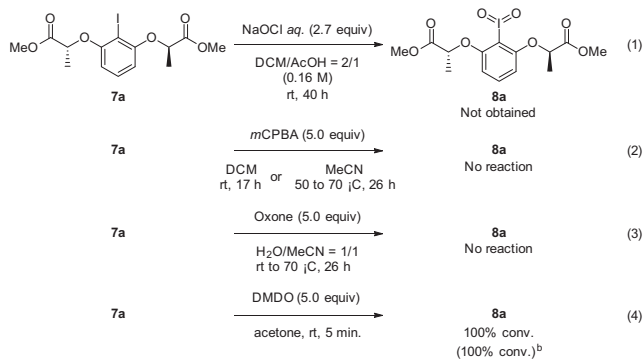


**Figure 1.** Selected examples of reported chiral hypervalent iodine(III) and (V) reagents and their precursors.

## Results and discussions

First, chiral hypervalent iodine(V) reagent **2a** was prepared by the oxidation of a known compound **7a** (Scheme 1). In the initial attempt, **7a** was treated with several types of oxidants known to mediate the oxidations of iodoarenes to  $\lambda^5$ -iodanes.<sup>8</sup> Although NaOCl,<sup>8a,b</sup> oxone (2KHSO<sub>5</sub>·3KHSO<sub>4</sub>·3K<sub>2</sub>SO<sub>4</sub>),<sup>8c–e,13</sup> and mCPBA<sup>8f</sup> did not afford any oxidation product even after increasing the amount of oxidant and reaction temperature (Scheme 1-1 to 1-3), use of DMDO (dimethyldioxirane),<sup>8g,h</sup> a strong oxidant, mediated oxidation of iodoarene **7a** to  $\lambda^5$ -iodane **8a** with a full conversion (Scheme 1-4). Decreasing the loading of DMDO to 3 equiv did not affect the conversion of product. Interestingly, when the DMDO loading was decreased to 2 equiv, iodosylarene ( $\lambda^3$ -iodane) was not observed; a mixture of **7a** and **8a** was obtained.<sup>10</sup>

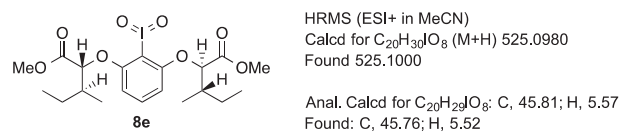
Next, the oxidation state of the prepared hypervalent iodine compound **8** was determined (Fig. 2). Because the X-ray crystallographic analysis of **8** failed, another method was attempted. Katritzky and co-workers reported a first confirmation method for the oxidation state of the iodine center by the <sup>13</sup>C NMR chemical shifts of its aromatic *ipso*-carbon atom (C<sub>ipso</sub>-I<sup>III</sup> or -I<sup>V</sup>).<sup>11</sup> According to their report, the <sup>13</sup>C NMR chemical shift of the aromatic *ipso*-carbon atom (C<sub>ipso</sub>-I<sup>III</sup>) in  $\lambda^3$ -iodane is ~15 ppm positively shifted from that of iodoarene, whereas the value (C<sub>ipso</sub>-I<sup>V</sup>) of  $\lambda^5$ -iodane is ~50 ppm positively shifted from that of iodoarene. By referring to their research, we compared the <sup>13</sup>C NMR chemical shift of the *ipso*-carbon atom (C<sub>ipso</sub>-I<sup>I</sup> and -I<sup>III</sup> or -I<sup>V</sup>) between **7a** and **8a**; that value positively shifted by ~45 ppm.<sup>12</sup> This result indicates that the prepared hypervalent iodine reagent is  $\lambda^5$ -iodane. The results of the elemental analysis of **8e** confirmed it as  $\lambda^5$ -iodane (See Supporting Information).



<sup>a</sup>Conversions were determined by <sup>1</sup>H NMR of crude mixtures.

<sup>b</sup>Using 3.0 equiv of DMDO

**Scheme 1.** Optimization of oxidation reaction conditions.<sup>a</sup>

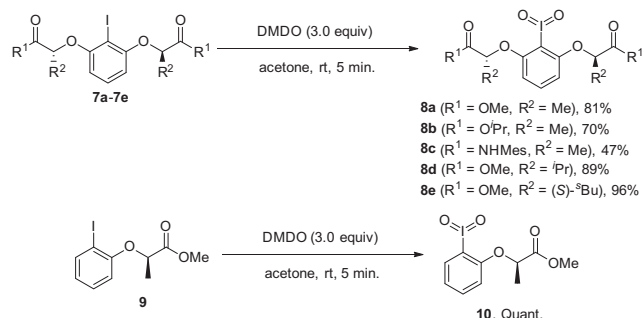


**Figure 2.** Oxidation state determination of **8e**.

With the oxidation state information of **8** in hand, several types of chiral  $\lambda^5$ -iodane derivatives were prepared (Scheme 2). Iso-propyl ester **8b** and mesityl amide **8c** were prepared from the corresponding iodoarenes **7b** and **7c** in good yields. L-Valine-derived **8d** and L-isoleucine-derived **8e** were also successfully prepared from the corresponding chiral iodoarenes, which were prepared by the Mitsunobu reactions of 2-iodoresorcinol with chiral alcohols,<sup>2k</sup> by DMDO oxidations in good-to-excellent yields. Monoester-type chiral  $\lambda^5$ -iodane reagent **10** was synthesized from the corresponding lactic acid-derived iodoarene **9** in a quantitative yield. The chiral  $\lambda^5$ -iodanes were characterized by <sup>13</sup>C NMR chemical shifts and HRMS as mentioned above.<sup>11</sup>

With chiral  $\lambda^5$ -iodanes in hand, their preliminary applications to the benchmark enantioselective oxidation reactions were investigated.<sup>6,7</sup> They were applied to the enantioselective hydroxylation dearomatization/[4+2]-dimerization cascade reactions of phenol derivatives, which were first discovered by Porco Jr. and co-workers using a chiral copper complex<sup>9</sup> and conducted using chiral hypervalent iodine reagents by Birman and co-workers (Table 1).<sup>5c</sup> 2,6-Dimethylphenol was treated with 1.1 equiv of chiral  $\lambda^5$ -iodanes and 1.1 equiv of acetic acid as the activator in DME at room temperature.<sup>5c</sup> Although diacetoxy iodoarene **13** did not afford any desired product, the chiral  $\lambda^5$ -iodane **10** afforded the oxidation product **12** in a moderate yield and with 8% ee. When **8a** bearing two lactic acid-derived moieties at both the *ortho*-positions of iodine atom was used as the chiral oxidant, **12** was obtained in 32% yield and with 11% ee. Since diester **8a** afforded the oxidation product in slightly increased enantioselectivity, chiral  $\lambda^5$ -iodanes **8b–8e** were screened further. Compound **8b** with two bulkier isopropoxycarbonyl groups and bisamide-type **8c** produced product **12** in only 10% ee and 11% ee respectively. Chiral  $\lambda^5$ -iodane **8d** bearing bulkier isopropyl groups on its asymmetric centers mediated the reaction with a better outcome (36%, 17% ee).<sup>14</sup>

To obtain the oxidation product **12** in higher yields and enantioselectivities, the reaction conditions were optimized (Table 2).<sup>5b</sup> After several attempts, the oxidation of **11** was found to be mediated by chiral  $\lambda^5$ -iodane reagent even at –72 °C in the presence of 3.0 equiv of TFAA (trifluoroacetic anhydride) as an acidic additive in DCM.<sup>8b</sup> Although **8a** afforded only 11% ee of the oxidation product at room temperature, **12** was obtained in 24% ee at –72 °C. Because the enantioselectivity of the product



<sup>a</sup>All yields were isolated product's yields.

**Scheme 2.** Synthesis of chiral  $\lambda^5$ -iodane reagents **8** and **10**.<sup>a</sup>

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