

# Catalytic Asymmetric Iodocyclization of *N*-Tosyl Alkenamides using Aminoiminophenoxy Copper Carboxylate: A Concise Synthesis of Chiral 8-Oxa-6-Azabicyclo[3.2.1]octanes

Takayoshi Arai,\* Ohji Watanabe, Shinnosuke Yabe, and Masahiro Yamanaka

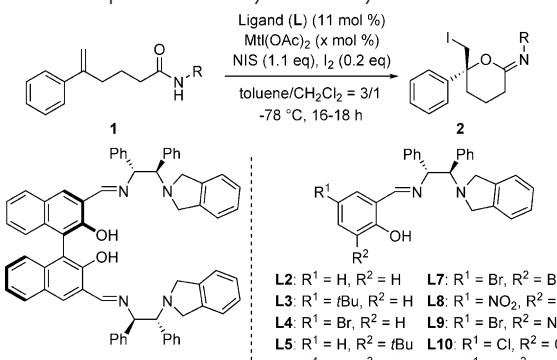
**Abstract:** A newly developed aminoiminophenoxy copper carboxylate (**L7**-Cu-OAc)-catalyzed asymmetric iodocyclization of *N*-Tosyl alkenamides gave *O*-cyclized products in good yields with high enantioselectivity. From the *O*-cyclized products, a skeletal transformation was succeeded in the synthesis of biologically important chiral 8-oxa-6-azabicyclo[3.2.1]octanes. DFT calculations suggested that the acetoxy anion of the [**L7**-Cu-OAc] acts as a base to generate the anion of *N*-Tosyl alkenamide substrates. The exchanged acetic acid reconstructs a new hydrogen-bonding network between the catalyst and the substrates to accomplish the highly efficient asymmetric *O*-iodocyclization of *N*-Tosyl alkenamides.

Chiral iodine-functionalized compounds, which have unique properties, are used for various purposes in material and pharmaceutical science.<sup>[1]</sup> Stereoselective iodocyclization is a powerful synthetic tool for generating iodine-functionalized cyclic compounds, and this has been widely applied using chiral substrates and in the total synthesis of natural products. Because of their importance, the development of catalytic asymmetric iodocyclization reactions has received much attention in the last decades.<sup>[2]</sup> In 1995, Taguchi and co-workers reported an example of enantioselective iodocarbocyclization of 4-alkenylmalonates using chiral titanium alkoxide.<sup>[3]</sup> Phosphoramidite-promoted enantioselective iodocyclization of polyprenoids, developed by Ishihara and co-workers, has been a subject of investigation with the aim of developing a catalytic system.<sup>[4a]</sup> Kang et al. reported a catalytic asymmetric iodoetherification reaction using a chiral salen-Co<sup>II</sup> complex.<sup>[4b]</sup> After Jacobsen's pioneering work on efficient urea-catalyzed asymmetric iodolactonization,<sup>[5a]</sup> several successful lactonization reactions<sup>[5]</sup> and related catalytic asymmetric iodocyclizations<sup>[6]</sup> using organocatalysts have been reported. We reported a catalytic asymmetric iodolactonization reaction using an originally developed trinuclear [Zn<sub>3</sub>(OAc)<sub>4</sub>{3,3'-bis(aminoimino)binaphthoxide}] catalyst.<sup>[7]</sup>

The next important step for these fundamentally important catalytic asymmetric iodocyclization reactions is their application in conjunction with synthetically useful transformations.<sup>[8]</sup> Herein, we report a catalytic asymmetric iodocyclization of *N*-Tosyl alkenamides using a newly developed simple aminoiminophenoxy copper carboxylate complex, and a further concise transformation to the give, significantly, chiral 8-oxa-6-azabicyclo[3.2.1]octanes.

Based on the success of our investigation of catalytic asymmetric iodolactonization, alkenamides were used as reaction substrates in this study (Table 1). Although the primary amide showed low reactivity (entry 1), the *N*-Tosyl

**Table 1:** Development of a catalyst for iodocyclization of alkenamides.<sup>[a]</sup>



Reaction scheme: **1** (N-tosyl alkenamide) reacts with Ligand (L) (11 mol %), Mtl(OAc)<sub>2</sub> (x mol %), NIS (1.1 eq), I<sub>2</sub> (0.2 eq) in toluene/CH<sub>2</sub>Cl<sub>2</sub> = 3/1 at -78 °C for 16-18 h to form product **2** (chiral 8-oxa-6-azabicyclo[3.2.1]octane derivative).

Ligand structures L1-L11 are shown below the reaction scheme. L1 is a binaphthol derivative. L2-L11 are various substituted binaphthol derivatives.

| Entry | R                | L   | M  | x  | Yield [%] | ee [%] |
|-------|------------------|-----|----|----|-----------|--------|
| 1     | H                | L1  | Zn | 30 | trace     | —      |
| 2     | Ac               | L1  | Zn | 30 | trace     | —      |
| 3     | Ts ( <b>1a</b> ) | L1  | Zn | 30 | 50        | 19     |
| 4     | Ts ( <b>1a</b> ) | L1  | Cu | 30 | 80        | 6      |
| 5     | Ts ( <b>1a</b> ) | L1  | Cu | 20 | 59        | 61     |
| 6     | Ts ( <b>1a</b> ) | L1  | Cu | 10 | 58        | 58     |
| 7     | Ts ( <b>1a</b> ) | L1  | Ni | 30 | 75        | 23     |
| 8     | Ts ( <b>1a</b> ) | L1  | Ni | 20 | trace     | —      |
| 9     | Ts ( <b>1a</b> ) | L1  | Co | 30 | 80        | 33     |
| 10    | Ts ( <b>1a</b> ) | L1  | Co | 20 | 50        | 19     |
| 11    | Ts ( <b>1a</b> ) | L2  | Cu | 10 | 78        | 49     |
| 12    | Ts ( <b>1a</b> ) | L3  | Cu | 10 | 63        | 9      |
| 13    | Ts ( <b>1a</b> ) | L4  | Cu | 10 | 54        | 43     |
| 14    | Ts ( <b>1a</b> ) | L5  | Cu | 10 | 68        | 65     |
| 15    | Ts ( <b>1a</b> ) | L6  | Cu | 10 | 86        | 89     |
| 16    | Ts ( <b>1a</b> ) | L7  | Cu | 10 | 88        | 93     |
| 17    | Ts ( <b>1a</b> ) | L8  | Cu | 10 | 52        | 85     |
| 18    | Ts ( <b>1a</b> ) | L9  | Cu | 10 | 80        | 81     |
| 19    | Ts ( <b>1a</b> ) | L10 | Cu | 10 | 91        | 87     |
| 20    | Ts ( <b>1a</b> ) | L11 | Cu | 10 | 98        | 85     |

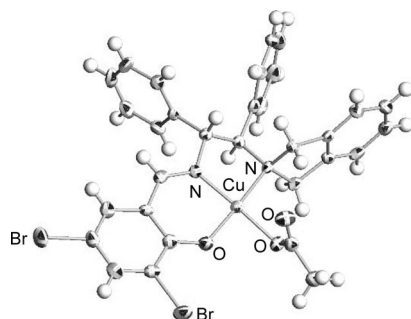
[a] Absolute configurations were determined based on hydrolysis of the Tosyl-imine portion of the products by introducing the relevant iodolactones.

[\*] Prof. Dr. T. Arai, O. Watanabe  
Molecular Chirality Research Center,  
Synthetic Organic Chemistry, Department of Chemistry,  
Graduate School of Science,  
Chiba University  
1-33 Yayoi, Inage, Chiba 263-8522 (Japan)  
E-mail: tarai@faculty.chiba-u.jp  
S. Yabe, Prof. Dr. M. Yamanaka  
Department of Chemistry,  
Rikkyo University  
3-34-1 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501 (Japan)  
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alkenamide (**1a**), which contains a more acidic amide proton, was catalyzed by  $[\text{Zn}_3(\text{OAc})_4\{3,3'\text{-bis}(\text{aminoimino})\text{binaphthoxide}\}]$  to give the *O*-cyclized product in 50% yield with 19% *ee* (entry 3).<sup>[9]</sup> This was in contrast to the *N*-cyclized products obtained using alkenoic amide substrates.<sup>[10,11]</sup>

Among the metal salts examined in conjunction with 3,3'-bis(aminoimino)binaphthol, the  $[\text{Cu}(\text{OAc})_2]$  complex showed better catalytic activity than the original zinc complex (entry 4). For the  $[\text{Cu}(\text{OAc})_2]$  complex, reinvestigation of the ratio of metal salt to ligand revealed that the catalyst prepared with a ratio of 1:2 gave the product in 61% *ee* (entry 5). ESI-MS analysis of the catalyst solution prepared by mixing **L1** and  $[\text{Cu}(\text{OAc})_2]$  in a 1:2 ratio revealed a significant ion peak at  $m/z = 1300.2349$ , attributed to the trinuclear  $[\text{L1-Cu}_3(\text{OAc})_3]^+$ , as well as the desired ion peak at  $m/z = 1119.2821$ , corresponding to the dinuclear  $[\text{L1-Cu}_2(\text{OAc})]^+$ . Based on the formation of the trinuclear  $[\text{Zn}_3(\text{OAc})_4\{3,3'\text{-bis}(\text{aminoimino})\text{binaphthoxide}\}]$  complex, it is thought that the third copper cation bridges the two naphthol oxygen atoms, making a binaphthoxide. Use of the trinuclear complex as a catalyst resulted in the production of **2a** with low *ee* in this case, although the catalytic activity was quite high. To avoid the incorporation of supernumerary copper salts in the catalyst, salicylaldehyde-derived aminoiminophenol ligands (**L2–L11**), containing a single phenol unit, were examined (entries 11–20). The rather simple  $[\text{L2-Cu}(\text{OAc})_2]$  complex, prepared by mixing **L2** and  $\text{Cu}(\text{OAc})_2$  in a 1:1 ratio, smoothly catalyzed the reaction to give the product with moderate stereoselectivity of 49% *ee* (entry 11). The use of *ortho*-substituted salicylaldehyde was effective in improving the enantioselectivity, and the 3,5-dibromosalicylaldehyde-derived aminoiminophenol  $[\text{L7-Cu}(\text{OAc})_2]$  complex succeeded in giving the product in 88% yield with 93% *ee* (entry 16). The 3,5-dichlorosalicylaldehyde-derived aminoiminophenol (**L10**) and the 3,5-diiodo derivative (**L11**) were also effective for the copper-catalyzed iodocyclization to give **2a** with 87% *ee* and 85% *ee*, respectively (entries 19 and 20).

Fortunately, the  $[\text{L7-Cu}(\text{OAc})_2]$  complex was easily crystallized from ethanol, and the structure was revealed as the aminoiminophenoxy copper(II) acetate complex  $[\text{L7-Cu-OAc}]$  by X-ray crystallographic analysis (Figure 1). With the remaining acetate anion included on the copper center, bidentate coordination of chiral diamines provides a square



**Figure 1.** X-ray crystallographic analysis of the aminoiminophenoxy copper(II) acetate complex  $[\text{L7-Cu-OAc}]$ . Ellipsoids set at 50% probability.<sup>[16]</sup> CCDC 1061958.

planar phenoxide complex in which the isoindoline ring stands perpendicular to the copper-containing square planar structure. This isolated crystal was actually catalytically active, giving **2a** in 98% yield with 93% *ee*.

Using the isolated  $[\text{L7-Cu-OAc}]$  complex in powder form as a catalyst, we investigated the generality of  $[\text{L7-Cu-OAc}]$ -catalyzed iodocyclization reactions in Table 2 (see details of the isolation of the powder catalyst in the Supporting Information).

For the R-group of the alkenamide substrate **2**, various aromatic substituents were successfully employed, and aliphatic substituents were also used in highly enantioselective iodocyclization reactions. The simple and stable nature of  $[\text{L7-Cu-OAc}]$  confirms the practical usefulness, and the reaction can be conducted in 5 mol% for the gram scale synthesis of **2a** (98%, 93% *ee*).

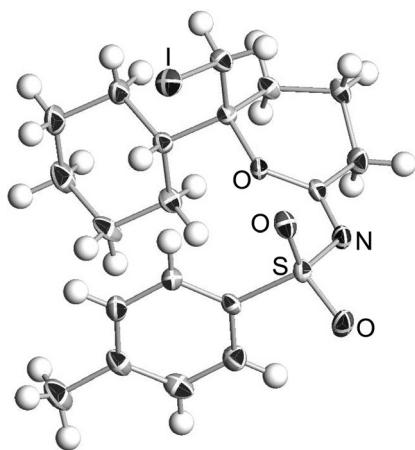
The (*Z*)-Tosyl-imine structure of the *O*-cyclized product was confirmed by X-ray crystallographic analysis of *rac*-**2k** (Figure 2). In the structure, halogen bonding between the oxygen atom of the sulfonyl group and the iodine atom (3.871 Å) was thought to contribute to stabilization of the (*Z*)-form of Tosyl-imines.

The utility of the iodocyclization products were demonstrated by a transformation to a chiral 8-oxa-6-azabicyclo-[3.2.1]octane skeleton, which has been reported as an antiosteoporotic agent and an antimicrobial agent (Figure 3).<sup>[12]</sup>

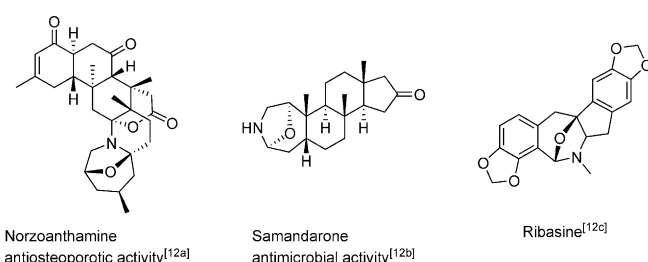
**Table 2:**  $[\text{L7-Cu-OAc}]$ -catalyzed iodocyclization of *N*-Tosyl alkenamides.

| $  \begin{array}{c}  \text{R} \\    \\  \text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{C}(=\text{O})\text{NHTs} \\  \mathbf{1}  \end{array}  \xrightarrow[\text{-78 } ^\circ\text{C, 16-18 h}]{\begin{array}{c} \text{L7-Cu-OAc (10 mol \%)} \\ \text{NIS (1.1 eq), I}_2 \text{ (0.2 eq)} \\ \text{toluene/CH}_2\text{Cl}_2=3:1 \end{array}}  \begin{array}{c}  \text{I} \\    \\  \text{CH}_2-\text{CH}(\text{NHTs})-\text{CH}_2-\text{CH}_2-\text{C}(=\text{O})\text{NHTs} \\  \mathbf{2}  \end{array}  $ |                                                                   |                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------|
| <p><b>2a</b><br/>98% yield<br/>93% <i>ee</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p><b>2b</b><sup>[b]</sup><br/>90% yield<br/>90% <i>ee</i></p>    | <p><b>2c</b><sup>[b]</sup><br/>87% yield<br/>87% <i>ee</i></p> |
| <p><b>2d</b><sup>[b]</sup><br/>67% yield<br/>89% <i>ee</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p><b>2e</b><sup>[a, b]</sup><br/>52% yield<br/>89% <i>ee</i></p> | <p><b>2f</b><br/>99% yield<br/>94% <i>ee</i></p>               |
| <p><b>2g</b><br/>99% yield<br/>92% <i>ee</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p><b>2h</b><sup>[b]</sup><br/>90% yield<br/>84% <i>ee</i></p>    | <p><b>2i</b><sup>[b]</sup><br/>80% yield<br/>87% <i>ee</i></p> |
| <p><b>2j</b><br/>88% yield<br/>91% <i>ee</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p><b>2k</b><sup>[b]</sup><br/>99% yield<br/>91% <i>ee</i></p>    | <p><b>2l</b><sup>[c]</sup><br/>73% yield<br/>60% <i>ee</i></p> |

[a] Reaction was conducted for 40 h. [b] *ee* was determined after transformation to the reported iodolactone by hydrolysis of the Tosyl-imine portion. [c] NBS (1.1 equiv) and  $\text{Br}_2$  (0.2 equiv) were used.



**Figure 2.** X-ray crystallographic analysis of *rac*-**2k**. Ellipsoids set at 50% probability.<sup>[16]</sup> CCDC 1061959.



**Figure 3.** Biologically significant chiral 8-oxa-6-azabicyclo[3.2.1]octanes.

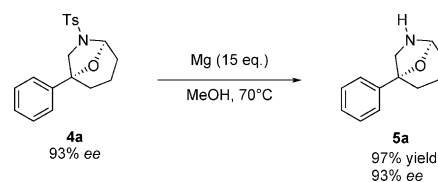
After reduction of the iodocyclization products using DIBAL-H at 0°C for 15 min, further treatment with K<sub>2</sub>CO<sub>3</sub> furnished chiral 8-oxa-6-azabicyclo[3.2.1]octane skeletons (Table 3). Because the generated intermediate Tosyl-aminal is easily epimerized at the anomeric position, regardless of the stereoselectivity of the first reduction, the 8-oxa-6-azabicyclo[3.2.1]octane skeletons were obtained in high yields, retaining the enantiomeric excesses. Furthermore, from 93% *ee* of **4a**, the Tosyl-group was successfully removed by Mg in MeOH to give 93% *ee* of **5a** in 97% yield (Scheme 1).<sup>[13]</sup>

With regard to the mechanism of asymmetric iodocyclization, the reaction is believed to start with activation of the *N*-Tosyl alkenamide by the [L7-Cu-OAc] complex. ESI-MS analysis of a mixture of *N*-Tosyl alkenamide **1a** with [L7-Cu-OAc] showed an ion peak at *m/z* = 1001.0529, corresponding to the formation of [L7-Cu(TsN(C=O)(CH<sub>2</sub>)<sub>3</sub>C(CH<sub>2</sub>)Ph + Na]<sup>+</sup>. However, the acidity of the carboxylic acid utilized in the L7-Cu complex formation influenced the catalytic activity. [L7-Cu-benzoate] (*pK<sub>a</sub>* of benzoic acid = 4.19) gave **2a** in 98% yield with 93% *ee* (−78°C, 14 h). [L7-Cu-*p*-methoxybenzoate] (*pK<sub>a</sub>* of *p*-methoxybenzoic acid = 4.46) showed higher catalytic activity, giving **2a** in 99% yield with 94% *ee* (−78°C, 6 h), whereas [L7-Cu-*p*-nitrobenzoate] (*pK<sub>a</sub>* of *p*-nitrobenzoic acid = 3.41) required a longer reaction time to give **2a** in 92% yield with 90% *ee* (−78°C, 24 h). These results suggest that the acetoxy anion in the [L7-Cu-OAc] catalyst is not simply exchanged with the *N*-Tosyl alkenamide **1a**.

**Table 3:** Asymmetric synthesis of 8-oxa-6-azabicyclo[3.2.1]octane.<sup>[a]</sup>

| <p><b>4a</b><br/>85% yield<br/>93% <i>ee</i> (93% <i>ee</i>)</p>               | <p><b>4b</b><sup>[b]</sup><br/>82% yield<br/>87% <i>ee</i> (87% <i>ee</i>)</p> |                                                                  |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------|
| <p><b>4c</b><sup>[b]</sup><br/>68% yield<br/>89% <i>ee</i> (89% <i>ee</i>)</p> | <p><b>4d</b><sup>[b]</sup><br/>68% yield<br/>94% <i>ee</i> (94% <i>ee</i>)</p> | <p><b>4e</b><br/>92% yield<br/>92% <i>ee</i> (92% <i>ee</i>)</p> |
| <p><b>4f</b><br/>70% yield<br/>83% <i>ee</i> (84% <i>ee</i>)</p>               | <p><b>4g</b><br/>79% yield<br/>90% <i>ee</i> (91% <i>ee</i>)</p>               | <p><b>4h</b><br/>63% yield<br/>89% <i>ee</i> (91% <i>ee</i>)</p> |

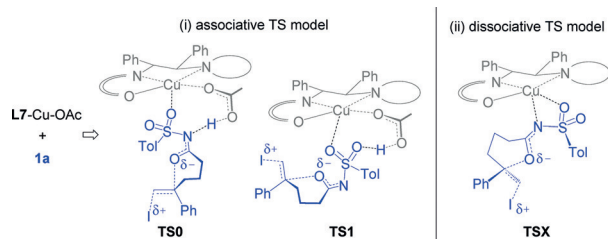
[a] Value in parentheses is *ee* of **2**. [b] Reduction was conducted at −40°C.



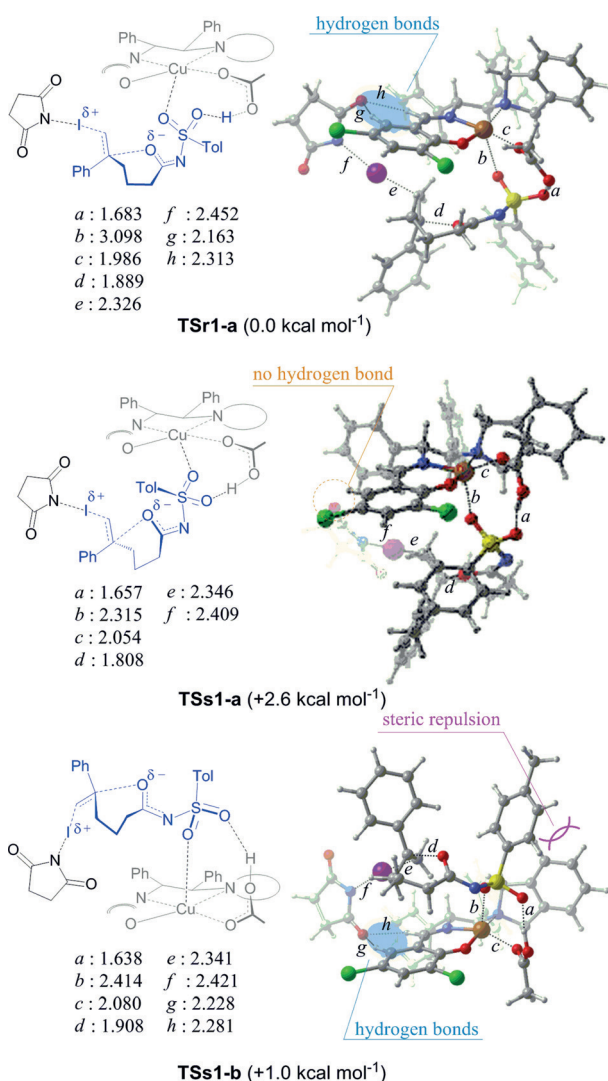
**Scheme 1.** Removal of the Tosyl-group from 8-oxa-6-azabicyclo[3.2.1]octane (**4a**).

Based on the experimental analysis of the interaction of [L7-Cu-OAc] with **1a**, DFT calculations (UB3LYP) were carried out for the transition state (TS) of the [L10-Cu-OAc]-catalyzed iodocyclization reaction.<sup>[14]</sup> Initial screening of various activation modes and conformational isomers for the associative TS models indicated that the acetoxy anion (*pK<sub>a</sub>* = 4.76) of the [L10-Cu-OAc] complex acts as a base to generate the anion of **1a**, as expected from the ESI-MS analysis (Figure 4). Although TS0 is the spontaneous C–O bond forming process after the event of deprotonation from **1a**, energetically more favored TS1 is found by a reconstruction of the hydrogen bonding network between the catalyst and the substrate.<sup>[15]</sup> In the TS1, the two oxygen atoms of the sulfonyl group coordinate to the copper center and the acetic acid. The simple dissociation of the acetic acid (TSX in Figure 4) was not supported by the DFT calculations or the experimental results.

To clarify the major factor in the high enantioselectivity of the reaction, diastereomeric TSs leading to the major (TSr1) and minor (TSs1) products were compared (Figure 5). The C–



**Figure 4.** Representations of the predicted TS models (**TS0**, **TS1**, and **TSX**).



**Figure 5.** 3D structures, representations, and relative energies of diastereomeric TSs (**TSr1-a**, **TSs1-a**, and **TSs1-b**). Bond lengths are shown in Å.

I and C–O bond formations proceed in a concerted manner in each diastereomeric TS. In the most stable, **TSr1-a**, there is no sterically repulsive interaction with the anion of **1a** in the asymmetric reaction sphere of the catalyst. Furthermore, NIS, which activates the olefin moiety, is located in the vacant site and interacts with the acidic H atoms of the imino group of

**L10** through hydrogen bonding. Aminoiminophenol derived from the electron-deficient salicylaldehyde enhances the acidity of the H atoms of the imino group to promote coordination of NIS, resulting in higher enantioselectivity. In contrast, the sterically demanding *t*Bu group interferes with coordination of NIS to cause a significant decrease in enantioselectivity. Control experiments with respect to the iodine source also strongly emphasized the contribution of NIS coordination to TS stabilization. The addition of I<sub>2</sub> was important for accelerating the [L7-Cu-OAc]-catalyzed iodocyclization.<sup>[4b,5a,c,h,6d,f,7]</sup> Without I<sub>2</sub>, the reaction at –40 °C gave **2a** in 61 % yield with 73 % *ee*, although the iodocyclization did not proceed at –78 °C under a similar conditions of Table 2. In **TSs1-a**, leading to reversed facial selectivity in the iodocyclization, conformational change of the anion of **1a** has no impact on the steric interaction between the catalyst and the substrate. However, NIS has no effective hydrogen bond with the catalyst moiety to destabilize **TSs1-a**. In **TSs1-b**, the anion of **1a** is located on the opposite side of the square planar unit of the catalyst, while the hydrogen bonds between NIS and the imino group of **L10** are maintained. Steric repulsion between the *N*-Tosyl group of **1a** and the isoindoline ring of **L10** destabilizes **TSs1-b**. Therefore, **TSs1-a** and **TSs1-b** are 2.6 and 1.0 kcal mol<sup>-1</sup> less stable than **TSr1-a**, respectively. These TS models provide a reasonable explanation for the formation of the (*R*)-enriched product using the (*R,R*)-diphenylethylenediamine-derived [L10-Cu-OAc] catalyst.

In conclusion, a newly developed aminoiminophenoxy copper carboxylate complex was found to catalyze asymmetric iodocyclization of *N*-Tosyl alkenamides to give the products in an *O*-selective cyclization manner in good yield and with high enantioselectivity. From the products, efficient synthesis of chiral 8-oxa-6-azabicyclo[3.2.1]octanes was achieved. DFT calculations suggested a unique role of the counteranion for activating the reaction substrates.

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**Keywords:** asymmetric catalysis · copper · cyclization · DFT calculations · halogenation

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- [16] CCDC 1061958, 1061959, and 1061961 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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