

# Development of Hamari Ligands for Practical Asymmetric Synthesis of Tailor-Made Amino Acids

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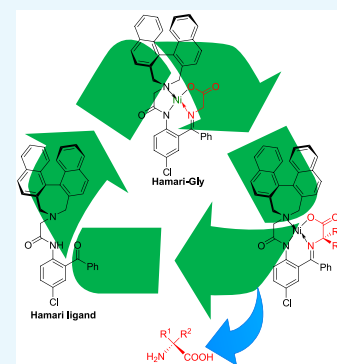
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**ABSTRACT:** Enantiomerically pure tailor-made amino acids are in extremely high demand in nearly every sector of the health-related industries. In particular, the rapidly growing number of amino-acid-based pharmaceuticals calls for the development of advanced synthetic approaches featuring practicality and commercial viability. Here we provide a brief summary of the development of axially chiral tridentate Hamari ligands and their application for general asymmetric synthesis of various structural types of amino acids. The methodological diversity includes: dynamic kinetic resolution and (*S*)-/(*R*)-interconversion of unprotected amino acids and homologation of nucleophilic glycine equivalents via alkyl halide alkylation reactions as well as multiple-step transformations allowing preparation of polyfunctional and cyclic derivatives. The practicality of these methods is critically discussed.

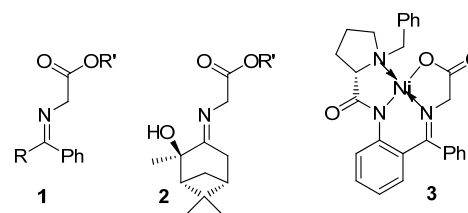


## 1. INTRODUCTION

Amino acids (AAs) are among a few fundamental “building blocks of life” and have played a significant role in drug discovery from the earliest days of modern pharmaceutical science. Specially designed, tailor-made AAs are indispensable components of modern medicinal chemistry and are becoming increasingly prominent in new pharmaceuticals and medical formulations. Moreover, the growing recognition of peptides and peptidomimetics as preferred drugs evidently advocates for the growing role of tailor-made AAs in the modern pharmaceutical industry.<sup>1</sup> The synthesis of AAs is a well-developed discipline offering a plethora of various methodological approaches. Nonetheless, from the standpoint of practicality, there still is an urgent need for the development of advanced synthetic methods suitable for large-scale production of tailor-made AAs of high chemical and enantiomeric purity.<sup>2</sup> In this mini-review, we would like to acquaint the readers with the most recent developments in the field dealing with the design of new chiral nucleophilic glycine equivalents as versatile reagents for general asymmetric synthesis of tailor-made AAs. In particular, we focus on the chiral Hamari ligands and glycine derivatives, as the most promising reagents for large-scale practical solutions.

## 2. VERSATILITY OF SYNTHETIC APPLICATION OF NUCLEOPHILIC GLYCINE EQUIVALENTS

The use of Schiff bases of glycine derivatives **1** (Figure 1) for the synthesis of AAs was introduced by the Stork group in



**Figure 1.** Achiral **1** and chiral **2** and **3** equivalents of nucleophilic glycine.

1976.<sup>3</sup> Since then, these derivatives have been fully appreciated as a preferred type of nucleophilic glycine equivalent. Features such as structural simplicity, ready availability, high C–H acidity, and chemical versatility are very synthetically attractive, especially from the standpoint of practicality.

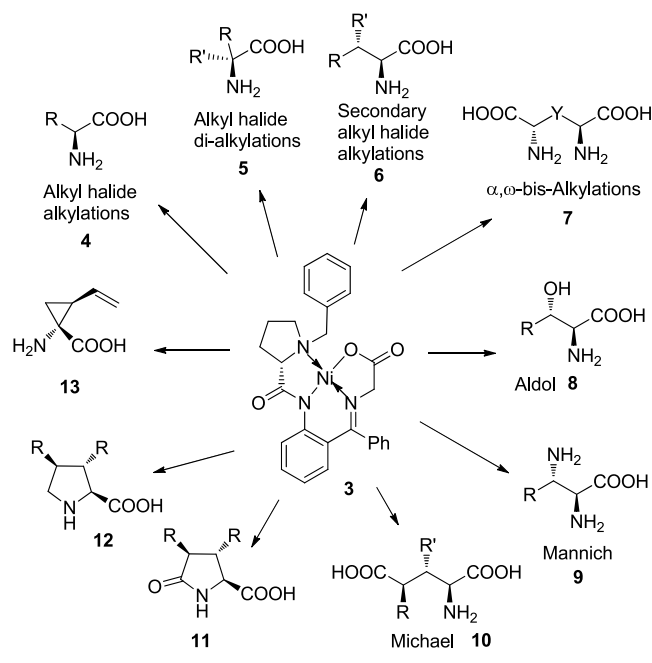
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Most notably, chiral Schiff base modifications **2** and **3** were reported in 1976 by Yamada<sup>4</sup> and in 1983 by Belokon<sup>5</sup> groups, correspondingly. The latter, square-planar Ni(II) complex **3** was shown (Scheme 1) to serve as a chiral nucleophilic glycine equivalent in reactions with numerous electrophilic reagents.<sup>6</sup>

**Scheme 1. Versatility of Chiral Nucleophilic Glycine Equivalent 3 for the Preparation of Tailor-Made AAs of General Types 4–13**



Most typically used reaction types are represented by alkyl halide alkylations **4**,<sup>7</sup> dialkylations **5**,<sup>8</sup> secondary alkyl halide alkylations **6**,<sup>9</sup> and bisalkylations **7**<sup>10</sup> and aldol **8**,<sup>11</sup> Mannich **9**,<sup>12</sup> and Michael **10**<sup>13</sup> addition reactions. Multiple step processes, like addition–cyclization, leading to pyroglutamic acids **11**,<sup>14</sup>  $\beta$ -substituted prolines **12**,<sup>15</sup> and derivatives of 1-amino-2-vinylcyclopropane-1-carboxylic acid **13**<sup>16</sup> can also be conveniently performed.

However, despite this extraordinary synthetic versatility of glycine complex **3**, the potential of its application for large-scale synthesis of tailor-made AAs is rather limited due to the practically unsatisfactory levels of stereocontrol ( $\sim 90\%$  de),

partial racemization of the proline moiety, and problematic isolation of the target AAs.

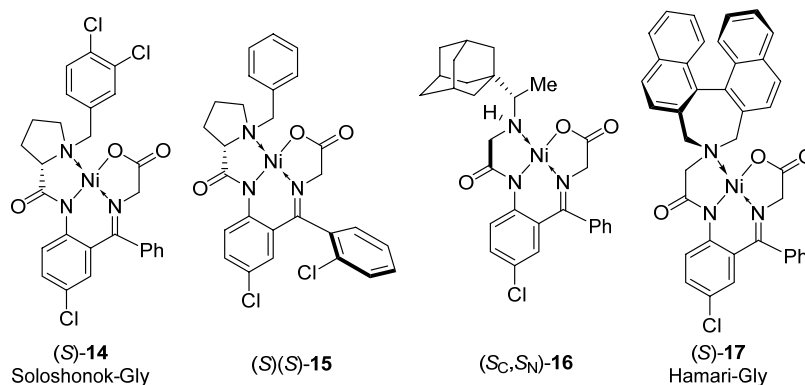
**3. NEW GENERATION OF CHIRAL SCHIFF BASE GLYCINE Ni(II) COMPLEXES**

Over the last five years, significant progress has been made in the design of structurally novel chiral tridentate ligands and the corresponding Ni(II) complexes, allowing us to address the synthetic shortcomings of complex **3**. As presented in Figure 2, proline-derived complexes **14**<sup>17</sup> and **15**<sup>18</sup> show noticeably improved diastereoselectivity in the reactions with electrophiles. Furthermore, the trichloro derivative **14** can be used for the preparation of  $\beta$ -AAs. However, under strongly basic reaction conditions, complexes **14** and **15** are prone to racemization at the proline moiety, limiting their practical application.

The structural type of complex **16**,<sup>19</sup> possessing a stereogenic nitrogen, racemization-stable secondary amine moiety, and an extremely lipophilic adamantyl group, offers an exceptionally practical solution for the preparation of AAs via a rare case of second-order asymmetric transformation control. Nonetheless, the synthetic range of complex **16** is limited to mostly aromatic AA types. The most exciting success in the structural design of new chiral ligands and the corresponding glycine complexes has been achieved with the recent development of (3*Z*,5*SZ*)-2,7-dihydro-1*H*-azepine-derived Ni(II) **17**.<sup>20</sup> Similar to the new generation of nucleophilic glycine equivalents **14**, **15**, and **16**, the Hamari-Gly complex **17** allows us to achieve very high levels of diastereocontrol (up to >99:1) reproducible on the large scale. However, the major advantage of reagent **17** is the indestructible axial chirality, affording unlimited recycling and reuse of the chiral auxiliary. This particular feature renders the whole process, in terms of the cost and efficiency, comparable to or superior over catalytic and biocatalytic approaches.

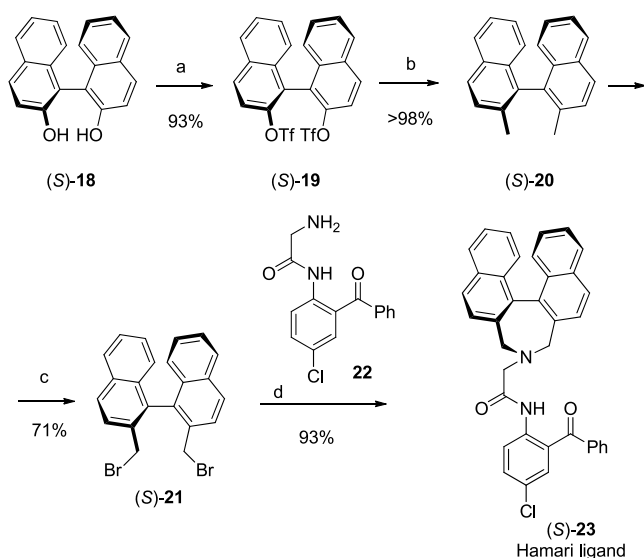
**4. DESIGN AND LARGE-SCALE SYNTHESIS OF CHIRAL TRIDENTATE (*R*)- AND (*S*)-HAMARI LIGANDS**

The recently reported large-scale synthesis of Hamari ligand **23** is presented in Scheme 2. The process begins with esterification of enantiomerically pure BINOL **18** by the action of  $\text{TiF}_2\text{O}$ . The activated ester **19** is reacted next with  $\text{MeMgI}$  to afford dimethyl derivative **20** with quantitative yield. The subsequent radical bromination gives rise to the dibromo intermediate **21** with a moderate 71% yield.<sup>20</sup>



**Figure 2.** Structures of structurally novel chiral nucleophilic glycine equivalents, available in both enantiomeric forms.

### Scheme 2. Large-Scale (kg) Synthesis of the Hamari Ligand (*R*)- or (*S*)-23<sup>a</sup>



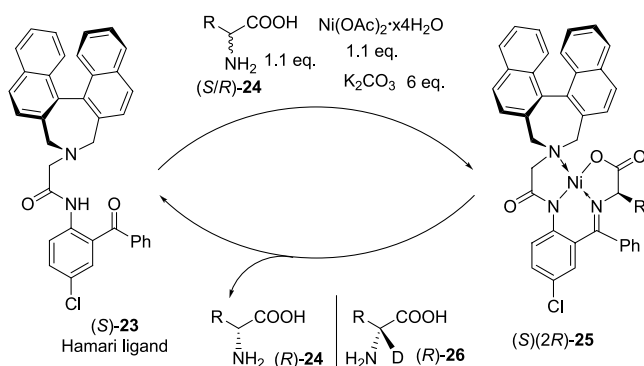
<sup>a</sup>(a) Tf<sub>2</sub>O, pyridine, toluene. (b) NiCl<sub>2</sub>(dppp)<sub>2</sub>, MeMgI, MTBE. (c) 1,3-Dibromo-5,5-dimethylhydantoin, AIBN, ethyl acetate. (d) Na<sub>2</sub>CO<sub>3</sub>, *i*PrOAc.

The final step of the process is the alkylation of the specially designed glycine-*o*-amino-benzophenone adduct **22** using dibromide **21**. The reaction is conducted in isopropyl acetate using aqueous sodium carbonate as a base. The resulting Hamari ligand **23** is isolated by filtration as a pale-yellow solid with 93% yield. Using this procedure, the Hamari ligand **23** can be prepared on a kilogram scale in both (*S*)- and (*R*)-enantiomeric forms.<sup>20</sup>

## 5. DYNAMIC KINETIC RESOLUTION AND (*S*)-/(*R*)-INTERCONVERSION OF UNPROTECTED $\alpha$ -AAS

One of the notable applications of Hamari ligand **23** is the dynamic kinetic resolution of unprotected amino acids. The overall process, presented in Scheme 3, includes the formation of Ni(II) complex intermediates **25** followed by their disassembly to release the target AAs **24** and recycling of the ligand **23**.<sup>21</sup>

### Scheme 3. Asymmetric Preparation of AAs and Their $\alpha$ -Deuterated Derivatives via Chemical Dynamic Kinetic Resolution and (*S*)-/(*R*)-Interconversion of Unprotected $\alpha$ -AAs



The first step of the process, the reaction of Hamari ligand **23** with racemic AAs, is conducted in methanol under moderate heating (60–70 °C) in the presence of Ni(OAc)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub>. This step includes *in situ* formation of the corresponding Schiff base and ionization of the amide and carboxylic groups followed by chelation of the Ni(II) ions into square-planar complexes **25**. Under the basic reaction conditions, the  $\alpha$ -stereogenic carbon is relatively configurationally unstable, allowing for thermodynamic control of the diastereomeric preferences, giving rise to (*R*)-absolute configuration of the amino acid in complexes with (*S*)-axial chirality and, correspondingly, (*S*)-AA **24** induced by (*R*)-axial chirality. The diastereoselectivity is slightly dependent on the AA side chain and varies between 95 and 97% de. Diastereomeric enrichment to >99% de usually takes place at the workup stage by precipitation of products **25** from aqueous methanol solutions. The chemical yields range from 95% to quantitative. The structural generality of this method is exceptionally high as polyfunctional AAs containing OH, NH<sub>2</sub>, COOH, and S-Me groups can be used without any additional protection. About 50 examples of structurally diverse AAs have been successfully prepared so far in enantiomerically pure form using this method.<sup>22</sup> Disassembly of complexes **25** is conducted by heating in HCl/MeOH, affording target AAs **24** along with recovery of chemically and stereochemically uncompromised chiral ligand **23**. Importantly, this method for chemical dynamic kinetic resolution and (*S*)-/(*R*)-interconversion of unprotected  $\alpha$ -AAs can be successfully used for preparation of the corresponding  $\alpha$ -deuterated derivatives **26**, a very useful special type of isotopically labeled AAs for mechanistic studies. The required modification is a simple application of deuterated methanol at the stage of complex **25** formation, allowing for up to 90% of the deuteration in the  $\alpha$ -position.<sup>23</sup>

## 6. SYNTHESIS OF CHIRAL HAMARI-GLY AND ITS ASYMMETRIC ALKYLATIONS

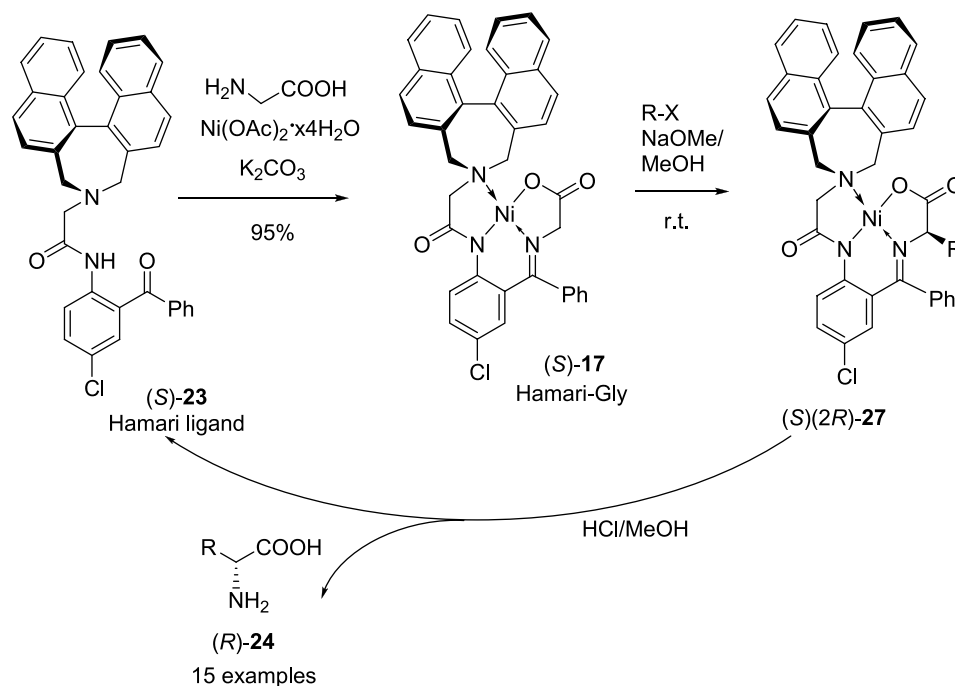
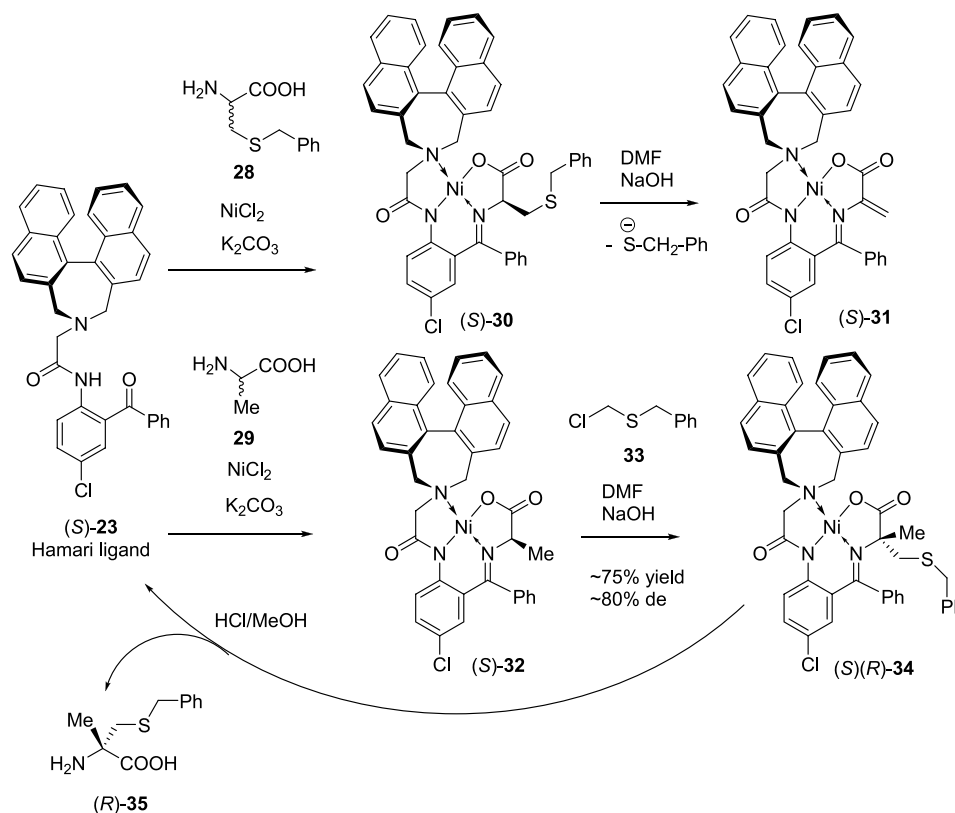
Another avenue of application of Hamari ligands (*S*)- and (*R*)-**23** for general asymmetric synthesis of tailor-made AAs is their transformation to the corresponding glycine Schiff base complexes **17** followed by their homologation with various electrophiles.<sup>24</sup> As presented in Scheme 4, in the presence of base, Hamari ligand **23** reacts with glycine and a source of Ni(II) ions, forming the square-planar Hamari-Gly complex **17** with over 95% yield.

Due to the very high reactivity of the glycine methylene in complex **17**, the alkyl halide alkylations can be conducted in NaOMe/MeOH at ambient temperature. These conditions are limited to activated alkyl halides; however, the observed diastereoselectivity is exceptionally high (~99:1), allowing for a convenient preparation of various aromatic and heteroaromatic tailor-made AAs. A more general alkylation protocol is currently under development and shall include polar aprotic solvent and strong inorganic bases as shown (*vide infra*) in the example of the asymmetric synthesis of  $\alpha$ -(methyl)cysteine derivatives.

## 7. ASYMMETRIC SYNTHESIS OF (2*S*)- AND (2*R*)- $\alpha$ -(METHYL)CYSTEINE DERIVATIVES

Construction of the stereogenic quaternary carbon in  $\alpha,\alpha$ -disubstituted AAs usually entails investigation of two possible approaches based on which of the two side chains is

Scheme 4. General Asymmetric Synthesis of Tailor-Made AAs via Alkylation of Hamari-Gly 17

Scheme 5. Two Alkylation Options for the Construction of Quaternary of (2S)- and (2R)- $\alpha$ -(Methyl)cysteine Derivatives Using Hamari Ligand 23

introduced first. As shown in Scheme 5, asymmetric synthesis of  $\alpha$ -(methyl)cysteine can be accomplished by methylation of cysteine Schiff base complex 30 or thiomethylation of alanine-derived complex 32.

In the first line of inquiry, the Hamari ligand 23 was reacted with S-protected racemic cysteine 28 to produce the

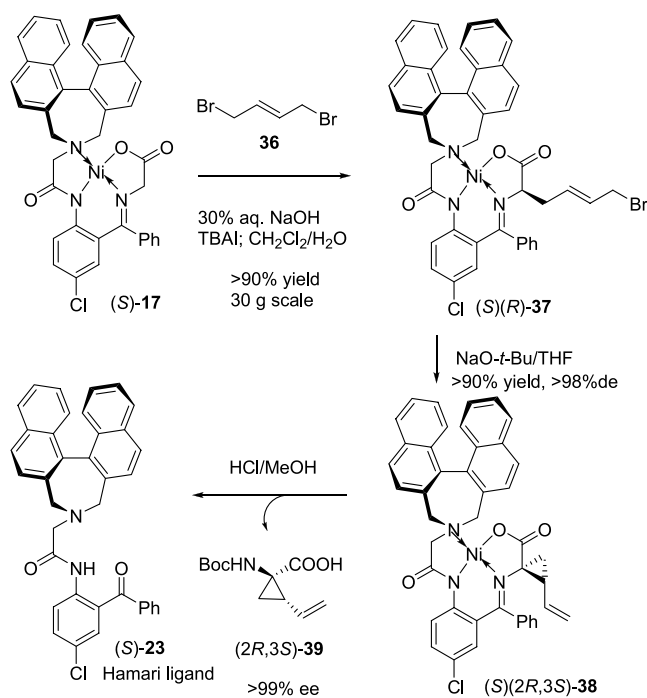
corresponding Schiff base Ni(II) complex 30. Quite unexpectedly, attempts to methylate complex 30 under basic conditions resulted in nearly quantitative formation of dehydroalanine derivative 31. It was found that the corresponding enolate derived from 30 undergoes a rapid stabilization by ejecting the  $\text{S-CH}_2\text{-Ph}$  anion, giving rise to

dehydroalanine complex **31**.<sup>25</sup> The second approach via formation of the intermediate alanine Schiff base complex **32** was rather successful. The thiomethylation of **32** with reagent **33** was conducted in DMF using NaOH as base.  $\alpha$ -(Methyl)cysteine derivative **34** was isolated with up to 75% yield and about 9:1 diastereomeric ratio. While the observed level of the stereochemical outcome, from the general standpoint, is rather moderate, it is on par or better with literature examples on this type of asymmetric alkylation. Moreover, this method has a significant advantage of operationally convenient and scalable reaction conditions. Furthermore, the diastereomeric purity of **34** can be increased by crystallization of the crude product. The target AA was isolated from diastereomerically pure complex **34** with >95% yield and >99% ee. Once again, it should be emphasized that the Hamari ligand was recovered stereochemically intact. In general,  $\alpha$ -(methyl)cysteine is difficult to obtain by other methods, and the current interest in this tailor-made AA is derived from its application in the design of a new generation of histone deacetylase inhibitors as emerging therapeutics for cutaneous T-cell lymphoma.

## 8. ASYMMETRIC SYNTHESIS OF (1*R*,2*S*)-1-AMINO-2-VINYLCYCLOPROPANECARBOXYLIC ACID

Another example of the Hamari ligand application for asymmetric synthesis of tailor-made AAs is illustrated (Scheme 6) by the preparation of structurally complex (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid, the essential pharmacophoric unit in a new generation of highly potent hepatitis C virus (HCV) NS3/4A protease inhibitors. As presented in Scheme 6, the whole process includes two steps via  $S_N2$  and  $S_N2'$  alkylation. Taking advantage of activating the allylic reactivity of dibromide **36**, the first  $S_N2$  alkylation step was

**Scheme 6. Asymmetric Synthesis of (1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid **39** via the  $S_N2$  and  $S_N2'$  Alkylation Sequence of the Hamari-Gly Complex (S)-17**



conducted under very mild phase-transfer catalysis (PTC) conditions, allowing the preparation of intermediate **37** with over 90% yield.<sup>26</sup>

The second step, the internal  $S_N2'$  alkylation of **37** to **38**, was conducted under more basic reaction conditions using THF as a solvent and NaO-*t*-Bu as a base. The reaction occurred with excellent yield (>90%) and diastereoselectivity (>98% de). After the standard disassembly procedure, the target AA **39** was isolated, as the *N*-Boc derivative, in enantiomerically pure form (>99% ee), along with the recovery and recycling of the Hamari ligand (S)-23.<sup>26</sup> It should be mentioned that the obtained values of the stereochemical outcome are actually the highest reported in the literature for this type of internal  $S_N2'$  cyclizations.

## 9. CONCLUSIONS

We trust that the data briefly presented here on the chemistry of recently developed chiral Hamari ligands and Hamari-Gly complexes convincingly demonstrate the synthetic potential of these compounds for general asymmetric synthesis of tailor-made AAs. The overall low cost of this approach is provided by virtually unlimited recyclability of the ligands due to their configurational stability. The operational ease of all transformations coupled with its predictable reactivity and stereochemical outcome in complex settings bode well for the widespread application of the Hamari ligand technology.

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### Notes

The authors declare no competing financial interest.

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