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HAMARI'S CONTRIBUTION TO THE ASYMMETRIC SYNTHESIS OF TAILOR-MADE AMINO ACIDS.

Jianlin Han[1]*, Hong Liu[2], Jiang Wang[2]*, Alicja Wzorek[3], Alexander E. Sorochinsky[4]*, Karel D. Klika[5], Taizo Ono[6], Hiroki Moriwaki[7]*, Tatsunori Sato[7], Kunisuke Izawa[7], Hiroyuki Konno[8]*, Vadim A. Soloshonok[9,10]*

[1]Jiangsu Co-Innovation Center of Efficient Processing and Utilization of Forest Resources, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China;
[2] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China;
[3] Institute of Chemistry, Jan Kochanowski University in Kielce, Uniwersytecka 7, 25–406 Kielce, Poland;
[4] V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, The National Academy of Sciences of Ukraine, Kyiv 02094, Ukraine;
[5] Molecular Structure Analysis, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany;
[6] National Institute of Advanced Industrial Science and Technology, 463–8560, Nagoya, Japan.
[7] Hamari Chemical Ltd., Osaka, Japan;
[8] Department of Chemistry and Biological Engineering, Graduate School of Science and Engineering, Yamagata University, 992–8510 Yonezawa, Yamagata, Japan;
[9] Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, Paseo Manuel Lardizábal 3, 20018 San Sebastián, Spain;
[10] IKERBASQUE, Basque Foundation for Science, María Díaz de Haro 3, Plaza Bizkaia, 48013 Bilbao, Spain
email: vadimsoloshonok@gmail.com

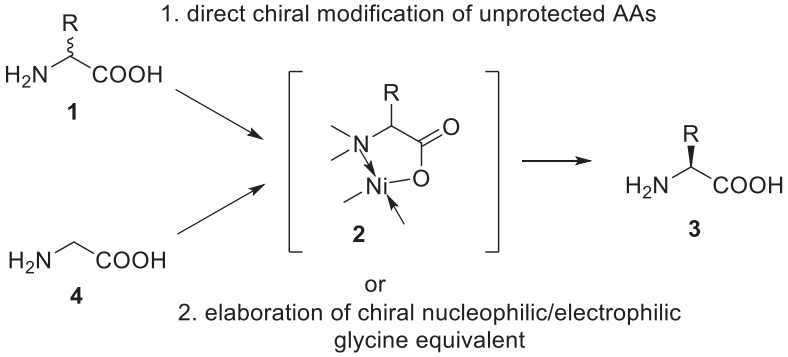
This article reviews the development of the asymmetric synthesis of tailor-made amino acids conducted at Hamari Chemicals during the 10-year period 2013–2022.The discussion is based on strategies such as direct chiral modification of unprotected amino acids via intermediate formation of Ni(II) complexes and elaboration of chiral nucleophilic or electrophilic glycine equivalents. The former approach includes, for example, second-order asymmetric transformation, dynamic kinetic resolution, and inversion of chirality while the latter approach involves construction of the desired amino acid architecture using, for example, alkylation, aldol, Mannich, or Michael addition reactions as well as multistep procedures. Operational convenience, scalability, and practicality of the developed methods are emphasized.

Keywords: tailor-made amino acids; drug design and development; second-order asymmetric transformation; dynamic kinetic resolution; inversion of chirality.

INTRODUCTION. Amino acids (AAs) are a fundamental class of compounds that are intrinsically linked to the origin and evolution of all recognized life forms. Since their structural elucidation in the early 19th Century, AAs have maintained a crucial role in advancing various fields of health sciences and technology [1]. A myriad of AAs have been obtained from natural sources [2–16] while synthetic variants have been engineered in research laboratories [17–33]. To manage the extensive structural diversity of AAs, workers have used several classifications. These include distinctions such as proteinogenic vs. non-proteinogenic, genetically coded vs. non-coded, natural vs. synthetic, common vs. uncommon, and usual vs. unusual. These terms are frequently used in the literature [34] and while these definitions provide some sense of structural identity, they can be somewhat ambiguous and perplexing. In this article, we have chosen to use the term 'tailor-made AAs', a definition proposed by Hruby et al. [35]. This term emphasizes the intended purpose of the AAs rather than their assumed origin or perceived distinction.

Beyond fundamental scientific investigation, the primary objective of medicinal chemistry research in the realm of tailor-made AAs is to engineer more selective and efficacious pharmaceuticals. From a structural perspective, AAs exemplify a form of molecular dichotomy, facilitating the step-by-step synthesis of polymers with unique, non-repeating sequences of monomers. These polymers, known as peptides for short length chains and proteins for longer chains, perform numerous vital roles in living organisms, including catalysis (enzymes), signaling (hormones), and mechano-structural functions [36–38]. In the context of contemporary drug discovery paradigms, tailor-made AAs are essential components with their derivatives increasingly appearing in newly marketed pharmaceuticals [39–45]. In fact, over 30% of small molecule drugs contain residues of tailor-made AAs or their derivatives, such as amino-alcohols and di-amines [46–60].

The asymmetric synthesis of AAs is a well-established field that provides a plethora of varied methodologies [17–33]. However, the challenges of cost-effectiveness, operational ease, and environmental impact continue to evolve necessitating corresponding advancements in synthetic techniques. A review of the literature reveals that the synthesis of both general and tailor-made AAs via Ni(II) complex intermediates, as shown in Scheme 1, has emerged as the most prevalent and methodologically superior approach [61–65].



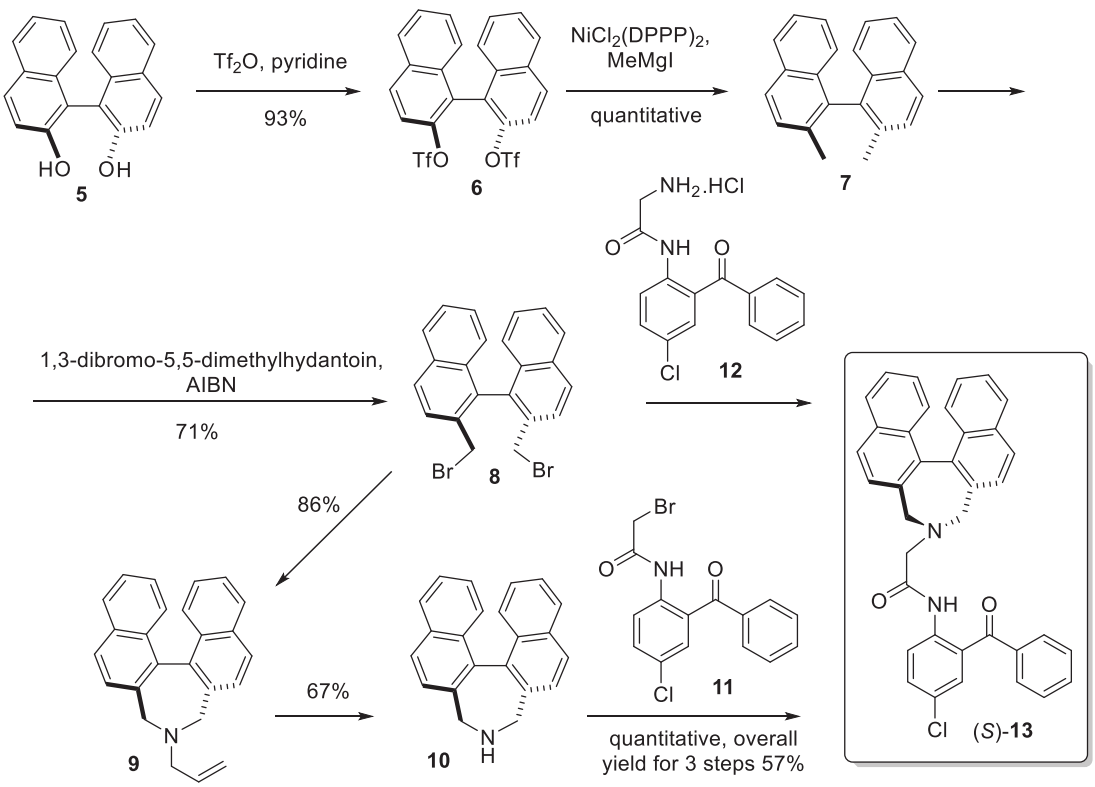
Scheme 1. General concept of the preparation of tailor-made AAs in enantiomerically pure form via intermediate Ni(II) complex formation.

A particularly attractive feature of this methodology is its practicality for the large-scale preparations of pharmacologically important AAs. At the outset, we envisioned two general strategic approaches: 1. direct chiral modification of unprotected AAs by way of means such as second-order asymmetric transformation (SOAT), dynamic kinetic resolution (DKR), or inversion of chirality; and 2. elaboration of chiral nucleophilic/electrophilic glycine equivalents, which involves constructing the desired AA architecture starting from glycine using, for example, alkylation, aldol, Mannich, or Michael addition reactions as well as multistep procedures. Both approaches have their advantages and shortcomings which will be noted in the following sections for the particular subsets of the strategies described herein.

Chiral tridentate ligands.

Hamari ligand.

From the standpoint of recyclability, having a recoverable source of asymmetric information of "indestructible" chirality is of great interest. Among obvious candidates possessing stable chirality, we considered (3*Z*,5*Z*)-2,7-dihydro-1*H*-azepine-derived axially chiral tridentate ligand – the Hamari ligand – **13** (Scheme 2) [66] as a potential system.



Scheme 2. Synthesis of Hamari ligand **13.**

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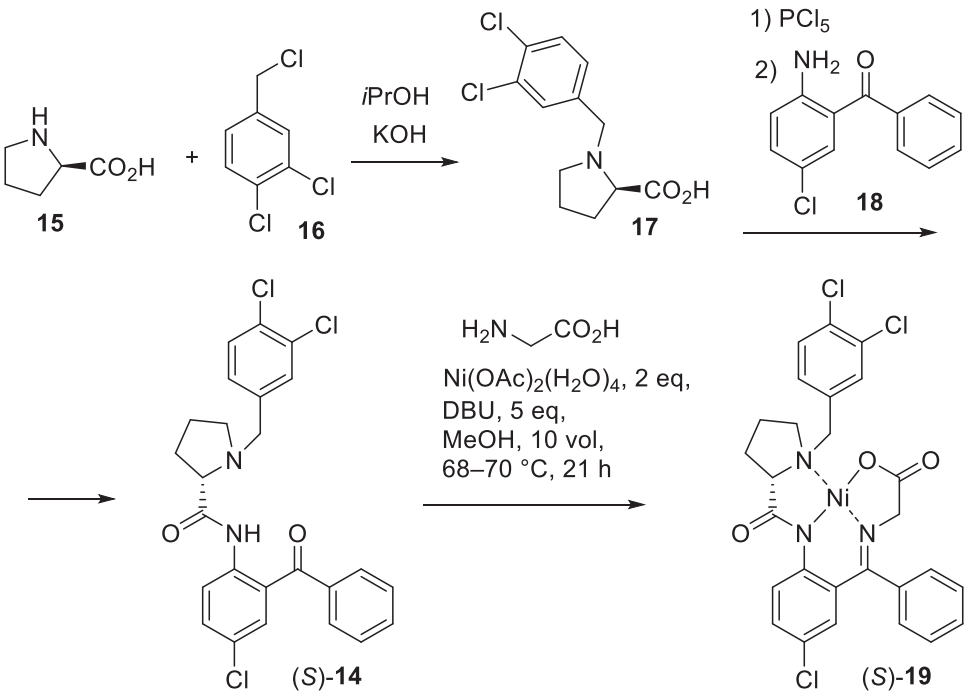
Commercially available enantiomerically pure binaphthol **5** was converted to dimethyl compound **7** via intermediate ditriflate **6** using Kumada coupling of **6** with a Grignard reagent. Subsequent bromination of **7** with 1,3-dibromo-5,5-dimethylhydantoin in ethyl acetate afforded dibromide **8**. This procedure reliably afforded key compound **8** in 71% yield.

Taking advantage of the previously developed strategy of modular approach to the design of chiral tridentate ligands [67–69], we envisioned the use of modules **11** and **12** for assembly of Hamari ligand **13**. Formation of the requisite azepine **9** by dialkylationof allyl amine [70] with dibromide **8** and subsequent removal of the allyl group to provide secondary amine **10** was accomplished in moderate yield. Alkylation of **10** with aminobenzophenone module **11** proceeded quantitatively affording Hamari ligand **13** after three steps in atotal yield of 57%. The procedure was found to have some disadvantages, though, notably being a multistep reaction sequence and the necessity for silica gel column purification, thus rendering this approach less attractive for large-scale manufacturing.The alternative solution, with application of module **12**, turned out to be significantly more attractive. The procedure was carefully optimized and was able to be reproduced on a 500 g scale.

Soloshonok–Liu ligand.

The proline-derived ligand **14** (Scheme 3) – the Soloshonok–Liu ligand – bearing three chlorine atoms in strategic positions was developed in a collaboration between the laboratories of Prof.s Soloshonok and Liu in 2014 [71,72]. It's phenomenal success for the asymmetric synthesis of tailor-made AAs can be attributed to its very high stereochemical preference. The strategic positioning of the three chlorine atoms in **14** were rationally deduced based on critical analysis of numerous crystallographic structures of the corresponding Ni(II) complexes of various types of AAs [73]. In particular, the aromatic stacking, parallel-displaced type of interactions between the *o*-aminobenzophenone and the Pro-*N*-benzyl rings was found to be of primary importance in shaping the spatial arrangements of the corresponding Ni(II) complexes. The influence of these aromatic interactions is very sensitive to the position and nature of the substituents, thereby determining the degree of parallel orientation of the interacting aromatic rings [73]. A large-scale synthesis of ligand **14** has been developed by Hamari [74].

The challenges of selectively alkylating a zwitterionic substance, such as proline **15**, are 3-fold: first, selective alkylation on nitrogen; second, forming the zwitterionic product under appropriate pH conditions; and third, separating and isolating the product from the large amount of potassium chloride formed in the reaction. A thorough examination of various conditions allowed us to determine that isopropanol using 85% potassium hydroxide pellets as the baseis an ideal system for the N-benzylation of proline **15** with benzyl chloride **16**. Upon completion of the alkylation reaction, the addition of concentrated HCl causes precipitation of KCl from the solution, simplifying the isolation and purification of the product **17** in greater than 90% yield. Similar to the previous step, the zwitterionic nature of **17** significantly complicates the activation of the carboxylic acid and subsequent amide formation. Furthermore, aromatic amine **18** is considerably electron deficient and requires a highly activated electrophile to effect reaction.



Scheme 3. Synthesis of the Soloshonok–Liu ligand **14.**

Previously, we reported [75,76] the use of methanesulfonyl chloride and 1-methylimidazole/DMAP to form the acid chloride/mixed anhydride, but the process proved to be problematic upon scaling up the reaction. Even though proline has a low intrinsic tendency for epimerization [77], we focused on finding asingle reagent that would serve to activate the carboxylic acidwithout the addition of base. After an extensive search for reaction conditions utilizing thionyl chloride orphosphorus (V) chloride, we settled on the latter reagent as it gave more consistent and reproducible results. Initial experiment susing dichloromethane as the solvent showed that wecould indeed prepare the desired product **14** using one equivalent of PCl_5 without the addition of base. Once again, this process allowed isolation of ligand **14** via simple filtration in over 80% yield. Our next goal was to establish a method for the satisfactory preparation of Ni(II) complex **19** on an industrial scale. The major finding of our work was the application of the relatively strong, but hindered, base 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) which met two important criteria, viz. chiral integrity of the product and simplicity of isolation. In particular, upon completion of the reaction, the addition of aqueous acetic acid simultaneously neutralizes the reaction mixture and causes precipitation of the enantiomerically pure product **19** in near-quantitative yield and in high purity. This procedure offered a practical advancement of the synthesis of Ni(II) complexes (*S*)- and (*R*)-**19** from bench scale to multikilogram scale [78].

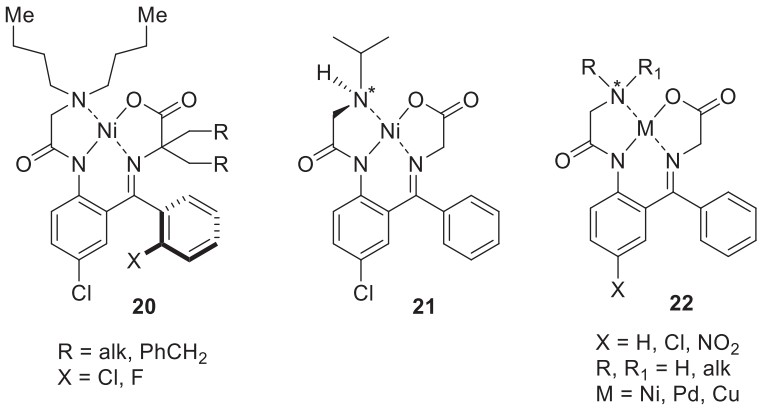


Fig. 1. Structures of novel axial chiral and N chiral (*) metal (II) complexes.

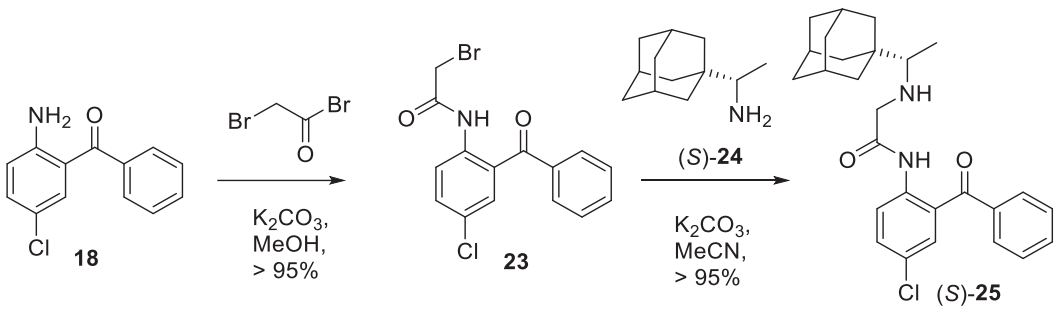
Our work on chiral HPLC resolution and the kinetics of racemization of various novel Ni(II) complexes was conducted in collaboration with the group of Prof. Christian Roussel. In particular, we successfully developed innovative structural models of Ni(II) complexes of type **20** (Figure 1) to probe and quantify the rotational barriers about the Ar–C_q bond of the benzophenone moiety. We demonstrated that axially chiral *ortho*-fluoro derivatives **20** are configurationally unstable due to relatively unhindered rotation about the Ar–$C_q$bond. By contrast, the configuration of the *ortho*-chloro-substituted analogs **20** are effectively indefinitely stable under ambient conditions ($t_{½}$ from 4 to 216 centuries) [79]. In another study, we described the design of a model Ni(II) complex of a glycine Schiff base possessing a nitrogen stereogenic center **21**. Measurement of its configurational stability using HPLC revealed that the configurational stability of the Ni(II)-coordinated nitrogen depends heavily on the solvent, ranging from very unstable in polar solvents with $t_{½}$s < 5 minutes to highly stable in apolar solvents with $t_{½}$s of the order of a century [80]. We also investigated configurational stability of a series of N chiral complexes **22** as a function of the substituents as well as the nature of coordinating metal(II). In general, electron-withdrawing substituents led to decreased configurational stability. With respect to the coordinating metal, the configurational stability was found to increase from Cu to Ni with Pd complexes the most stable with $t_{½}$s of 1.25 minutes, 7 hours, and 10 hours, respectively [81]. The data is of great of theoretical and synthetic value suggesting avenues for the rational design of a new generation of complexes for the asymmetric synthesis of tailor-made α-AAs [82].

Direct chiral modification of unprotected AAs. SOAT.

SOAT is defined as a crystallization-induced asymmetric transformation during which the racemic mixture is converted into a pure, less-soluble diastereomer [83–89]. This approach has tremendous practical appeal for large-scale synthesis as the target product can be isolated and purified simply by filtration. However, the major challenge associated with SOAT is that diastereomers usually do not show such dramatically distinct differences in properties such as crystallinity and solubility and

furthermore, which, for organic compounds at least, are rather unpredictable.

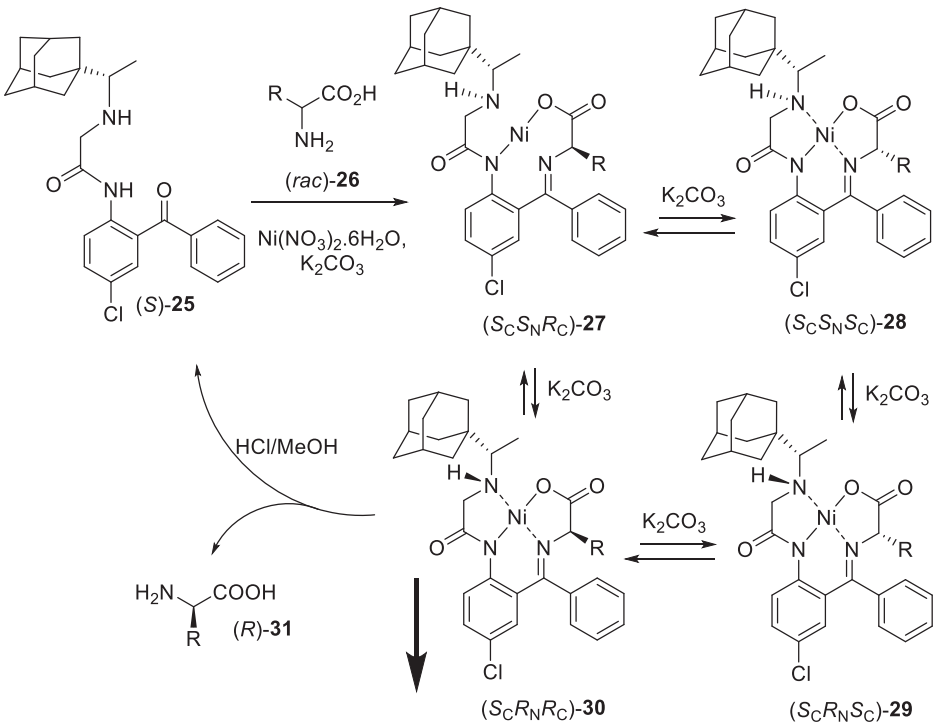
Rimantadine (**24**) (Scheme 4) was approved for medical use in 1993 as an orally administered antiviral drug. It is the most clinically advanced compound among adamantane-based chemotherapeutics developed for viral infections including influenza A, herpes simplex, hepatitis C, and HIV [90–92]. It is relatively inexpensive and readily commercially available as a racemate as well as in both enantiomeric forms [93–96].



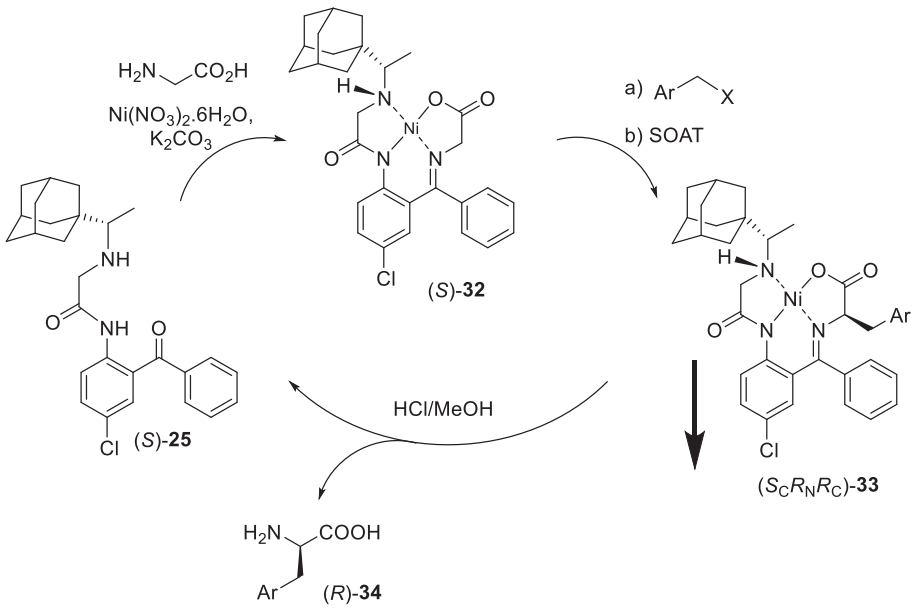
Scheme 4. Synthesis and application of adamantyl-containing ligand **25** for the preparation of enantiomerically pure, tailor-made-AAs via SOAT.

The therapeutic success of Rimantadine (**24**) is attributed to the presence of the adamantyl moiety – dubbed a "lipophilic bullet" – providing its derivatives with exceptional lipophilicity allowing them to penetrate lipophilic domains, including the blood–brainbarrier [97]. Taking into account the unique lipophilicity of adamantane, we assumed that this group can be used to modify the physicochemical properties of the corresponding Ni(II) complexes to conduct SOAT-controlled preparation of diastereomerically pure products. Drawing on previous experience with various N–H type ligands [98,99], we designed and prepared adamant ly-containing ligand **25** as presented in Scheme 4 [100]. Amide bond formation between benzophenone **18** and bromoacetyl bromide was accomplished cleanly in acetonitrile in the presence of K_2CO_3 to obtain **23** in quantitative yield. The subsequent alkylation of (*S*)-**24** with **23** was conducted using K_2CO_3 giving rise to ligand (*S*)-**25** in > 95% yield.

As presented in Scheme 5, the reactions of Rimantadine ligand (*S*)-**25** and racemic AA **26** were conducted in methanol using 1.1 equivalents of both **26** and $Ni(NO_3)_2{\cdot}6H_2O$ and 4 equivalents of K_2CO_3. After heating the reaction mixture for about 2 hours at 70 °C, all four possible diastereomers **27**–**30** were observed in the reaction mixture. However, diastereomer ($S_C R_N R_C$)-**30** was formed in noticeable excess (~9:1:1:1). An important feature of this method is that under the basic conditions, all diastereomers **27**–**30** are interconvertible by the step-wise inversion of the two labile stereogenic centers. Therefore, under SOAT conditions, one of the diastereomers can potentially arise as the predominant entity. Depending on the nature of AA **26**, the precipitation of the major diastereomer can occur either spontaneously or it can be initiated by a gradual addition of water. After precipitation, the diastereomerically pure product is usually obtained simply by filtration in 60–90% yield [100].



Scheme 5. SOAT approach for the preparation of enantiomerically pure tailor-made AAs.

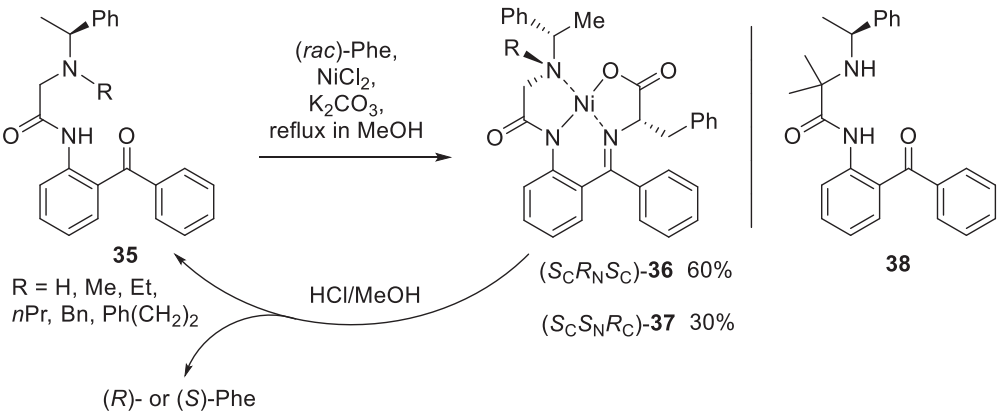


Scheme 6.Tandem alkylation–SOAT protocol for the preparation of phenylalanine-type tailor-made α-AAs.

Our next goal in the area of SOAT was the development of an advanced general process for the preparation of tailor-made *α*-AAs via tandem alkylation–SOAT. As presented in Scheme 6, Rimantadine-containing ligand **25** was reacted with glycine and a Ni(II) salt to assemble complex **32**. For the first step of the alkylation of **32**, very mild phase-transfer conditions were used [101] allowing the introduction of a side chain to the target *α*-AA. The second step utilized SOAT methodology affording nearly complete precipitation of the corresponding (S_C,R_N,R_C)-configured diastereomer **33**. Disassembly of **33** provided the target AA **34** as well as recovery of the starting Rimantadine ligand **25** for reuse [102]. Due to the very mild conditions of the first step, this approach is limited to the preparation of aromatic AAs, such as phenylalanine and its various derivatives. Nevertheless, this method is exceptionally practical and of high synthetic value.

DKR

Another approach for the direct chiral modification of unprotected AAs is DKR [103–115]. Like SOAT, DKR requires efficient, unimpeded interconverison of diastereomeric species in the reaction mixture. However, in contrast to SOAT, DKR is based on the thermodynamic stability of products. Our research in DKR began with the design of ligands **35** (Scheme 7) derived from phenylethylamine, one of the most inexpensive and readily available chiral compounds [116–118].

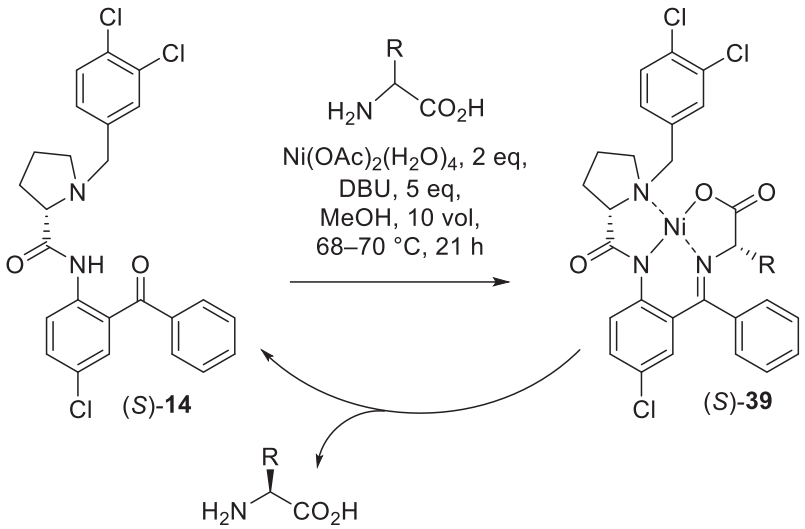


Scheme 7. Phenylethylamine-derived ligands for the DKR of unprotected tailor-made AAs.

As presented in Scheme 7, the reaction of ligand **35** with *rac*-phenylalanine, Ni(II), and base resulted in almost quantitative formation of diastereomers **36** and **37** in a ratio of about 2 to 1. Compounds **36** and **37** can be isolated by precipitation from the reaction mixture and are separableby column chromatography. Then either **36** or **37** can be disassembled to yield the enantiomerically pure AA as well allowing for the recovery of ligand **35**. Additionally, the undesired diastereomer can be treated in a methanol solution with base to convert it to the desired diastereomer, e.g. **36** into **37** or vice versa, followed by the chromatographic separation. The process can be repeated until all of the product is converted into the desired diastere-

omer to yield the desired (*S*)- or (*R*)-AA. Diastereoselectivity in this method can be improved by adding some structural rigidity to the ligand design. For example, ligand **38** was successfully used for the DKR of various AAs [119], including fluorinated tailor-made derivatives [120].

The conceptual breakthrough inthe DKR of unprotected AAs was made with the design of Soloshonok–Liu ligand **14** (Scheme 3). As shown in Scheme 8, ligand **14** reacts with various AAs under very mild conditions to produce the corresponding Ni(II) complexes **39** with diastereoselectivity>97:3 [121–125].

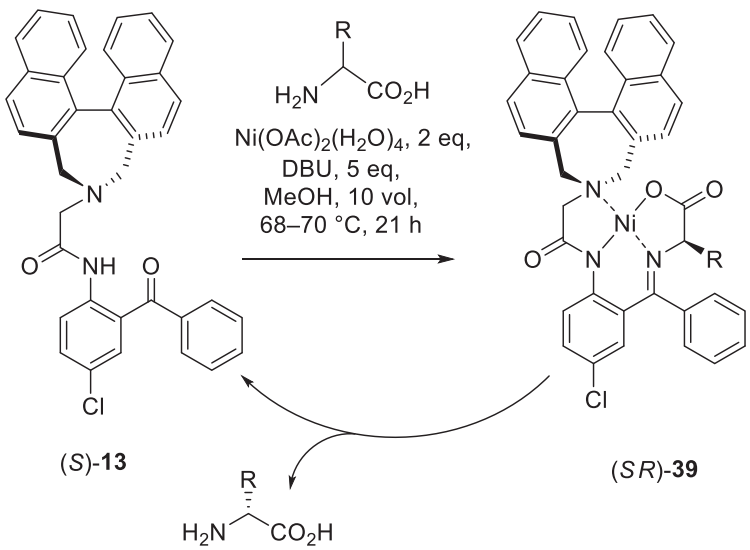


Scheme 8. DKR of unprotected tailor-made AAs using Soloshonok–Liu ligand 14.

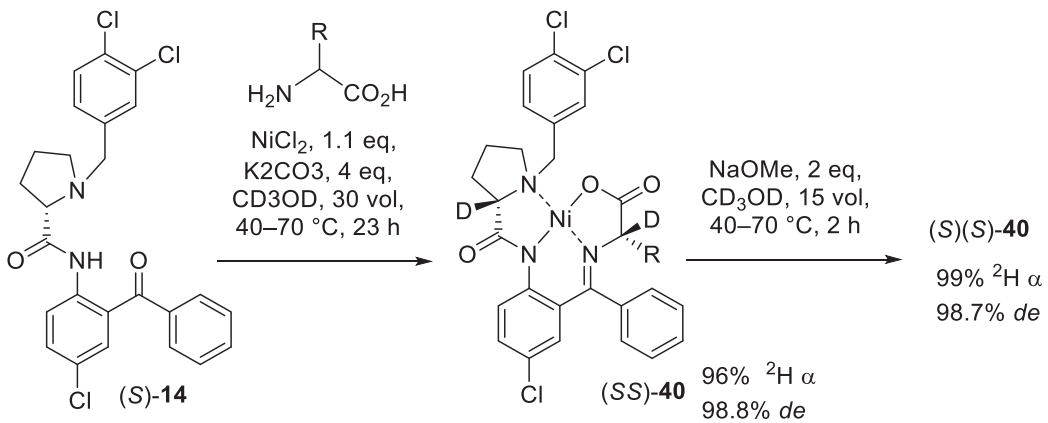
Precipitation of the major product from the reaction mixture affords virtually diastereomerically pure **39** which can be disassembled under standard acidic conditions to release the target AA along with recovery of the chiral ligand **14**. The process is very clean as virtually no byproducts are formed allowing the isolation of complex **39** in yields >90%. DKR can be applied to a great variety of tailor-made AAs differing of structural types. The limitations, however, include AAs containing *ω* functional groups such as aliphatic CO_2H, NH_2, SH, or OH.

Similar results for the DKR of unprotected AAs were also obtained using the Hamari ligand **13**. As shown in Scheme 9, ligand **13** readily reacted with racemic AAs forming complex **39** as the major diastereomer (>95:5) [126,127].

The stereochemical outcome of DKR and reaction limitations for ligands **13** and **14** are very similar rendering these two chiral ligands of high synthetic value for the preparation of enantiomerically pure tailor-made AAs on a large scale. It should be noted that proline-derived ligand **14** is significantly less expensive in comparison to **13**. On the other hand, the chirality of ligand **13** is resistant under the applied conditions and therefore its recycling is amenable without requiring additional purification.



Scheme 9. DKR of unprotected tailor-made AAs using Hamari ligand 13.



Scheme 10. Synthesis of tailor-made *α*-deutereo-AAs via DKR.

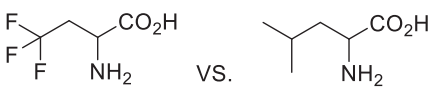
DKR has an additional synthetic advantage for the preparation of *α*-deutereo-AAs [128] as a special class of isotopically labeled compounds. Though the market for *α*-deutereo-AAs is relatively small, they have numerous applications in the mechanistic studies of various enzymes and biochemical processes [129–138]. Furthermore, tailor-made *α*-deutereo-AAs play an indispensable role in the emerging area of clinical functional metabolomics for obtaining essential data on *in vivo* AA metabolism and protein turnover [139–140]. While the asymmetric synthesis of *α*-deutereo-AAs has received due attention [141–151], optimal solutions with regards to the problems of selectivity, level of deuterium incorporation, and enantiomeric purity of the target AA shave not yet been found. In this respect, the protocol developed by us represents the most advanced procedure reported to date. As presented in

Scheme 10, conducting DKR under the standard conditions in deuterated methanol affords product **40** in quantitative yield with 98.8% diastereomeric excess (*de*) and 96% deuterium incorporation at the *α* position. For most applications of *α*-deutereo-AA this is an acceptable level and thus complex **40** can be disassembled under the usual acidic conditions to produce the target *α*-deutereo-AA. However, if a very high level of deuterium incorporation is required, for example for mechanistic kinetic studies, an additional exposure of **40** to deuterated methanol in the presence of a stronger base can be performed to produce **40** of ~99% deuterium incorporation at the *α* position.

Elaboration of chiral nucleophilic or electrophilic glycine equivalents.

Alkylation.

The alkylation of chiral glycine equivalents is one of the most widely used approaches for the asymmetric synthesis of tailor-made AAs [152–154]. Both the Hamari ligand **13** and the Soloshonok–Liu ligand **14** have been successfully used in our laboratories for the large-scale preparation of tailor-made AAs. As already pointed out above, one of the most rapidly growing areas inmodern drug design is the application of fluorinated residues as bioisosteres of naturally occurring molecular entities. Based on considerations of the biologically relevant size, as cumulatively defined by van der Waals (vdW) volume, A values, Taft Es values, and biphenyl rotational interference values [155–159], a trifluoromethyl group has often been considered to be isosteric with an isopropyl substituent. Although – CF_3 and – *i*Pr groups are clearly of different shape, they are sterically much closer than to –Me, –Et, and –*t*Bu groups. As shown in Figure 2, the differences projected by several biphenyl rotational interference values are relatively modest, suggesting steric mimicry between these two groups and thereby fueling interest in the synthesis of trifluoromethyl containing *α*- and *β*-AAs [160]. Thus, 2-amino-4,4,4-trifluorobutanoic acid (**41**) can be used as a substitute for leucine (**42**) in the de novo design of biologically active peptides and peptidomimetics [161–171].



41 **42**

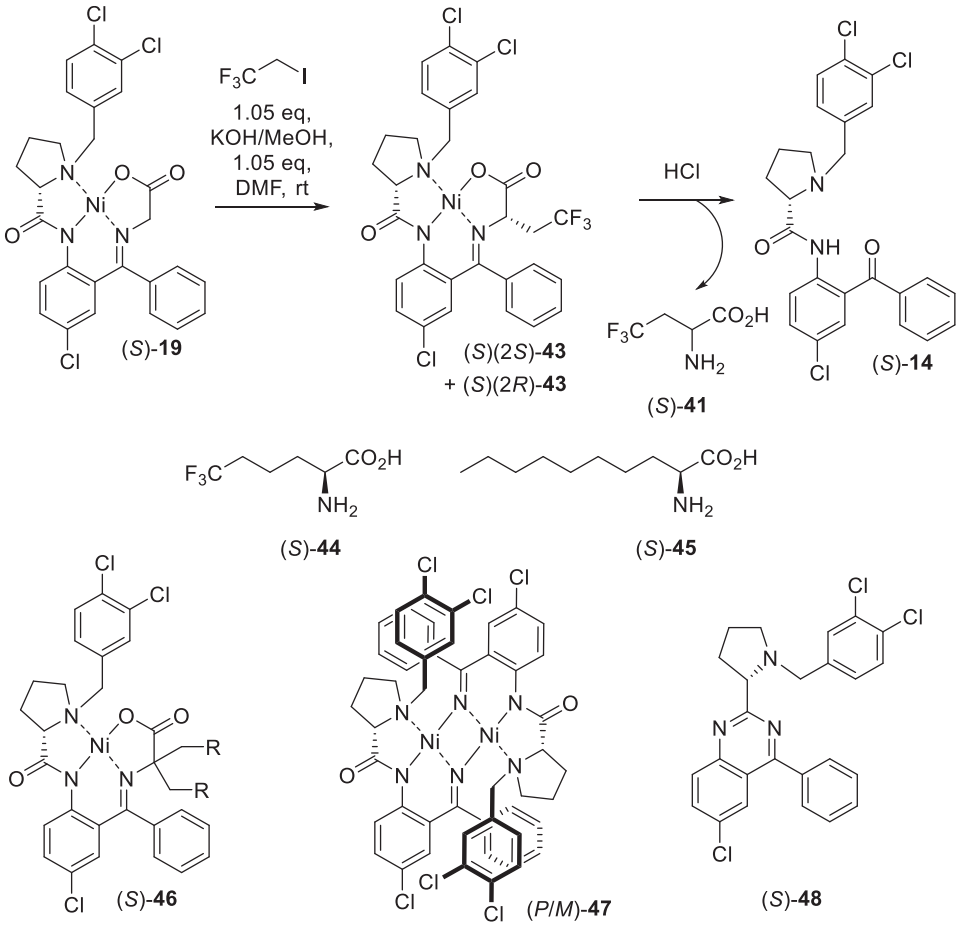
	–CF_3	–*i*Pr	–CH_3	–C_2H_5	–*t*Bu
vdW volume (Å^3)	39.8	56.2	21.6	38.9	–
Taft Es value	−2.40	−1.71	−1.24	−1.31	−2.70
A value (kcal/mol)	2.1	2.15	1.7	1.7	> 4.5
BRIV* (kcal/mol)	12.1	12.6	9.7	–	18.3
BRBV** (Δ*Grot*, kcal/mol)	10.5	11.1	7.4	8.7	15.4

*Biphenyl rotational interference value
**Experimental biphenyl rotational *B* value

Fig. 2. Bioisosteric relationships between –CF_3 and –*i*Pr groups in the context of using 2-amino-4,4,4-trifluorobutanoic acid (**41**) as a substitute for leucine (**42**) in drug design.

Responding to the high interest in trifluoro-AA **41**, we selected this molecule as one of our research targets. As shown in Scheme 11, chiral glycine equivalent **19** was alkylated with CF_3CH_2I to produce the target complex (*S*2*S*)-**43** as the major diastereomer with 97% *de* [172,173]. Of note, usually the alkylation of glycine Schiff base complexes derived from ligands of type **14** is performed in the presence of a large excess of a base, usually 5–10 equivalents [174–177]. Consequently, it was an

important finding that for large-scale synthesis, the optimized conditions only required a quite small excess of base (5 mol%). The same stoichiometry was found to be optimal for the alkylating reagent. Thus, only a 5 mol% excess of the trifluoroethyl iodide was sufficient for optimal yields and stereochemical outcome. Similar to trifluoro-AA **41**, we prepared (*S*)-2-amino-6,6,6-trifluorohexanoic acid **44** [178,179] and *α*-(octyl)glycine **45** [180].

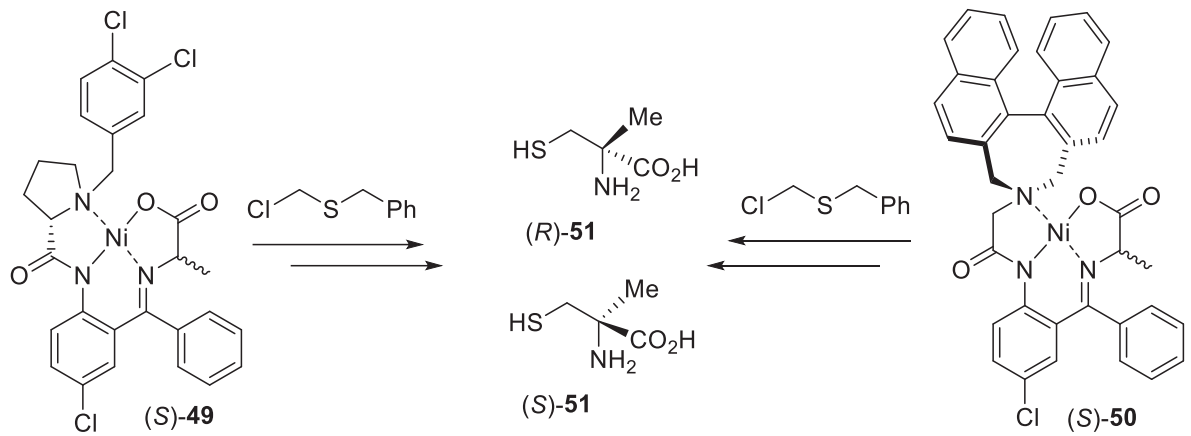


Scheme 11. Asymmetric synthesis of tailor-made AA via alkylation of a glycine complex.

Close attention to all aspects of the reaction process and thorough examination of the chemical entities in the reaction mixture allowed us to isolate not only the usual dialkylation products **46**, but also the previously undetermined byproducts **47** and **48**. Characterizing these byproducts was instrumental in gaining a more complete understanding of the reaction chemistry and in formulating more conducive reaction conditions [181,182].

The installation of sterically constrained tailor-made*α*-AAs into strategic positions of peptide chains brings about noticeable conformational restrictions of the corresponding *φ*,

ψ, and χ angles in the folded biologically active three-dimensional structure [183–190]. In this regard, the synthesis and applications of α,α-disubstituted AAs have received widespread consideration [191,192]. Among the highly interesting targets is α-(methyl)cysteine (**51**) (Scheme 12), a quite rare, naturally occurring quaternary AA isolated from blue-green algae [193,194]. In particular, several natural products that contain anα-(methyl)cysteine (**51**) fragment, such as mirabzoles [195, 196], tantazoles [197], and thiangazoles [198, 199], were found to possess promising antitumor and anti-HIV-1 activities which provide considerable motivationfor the development of asymmetric synthesis and in-depth biological-investigation of α-(methyl)cysteine (**51**).



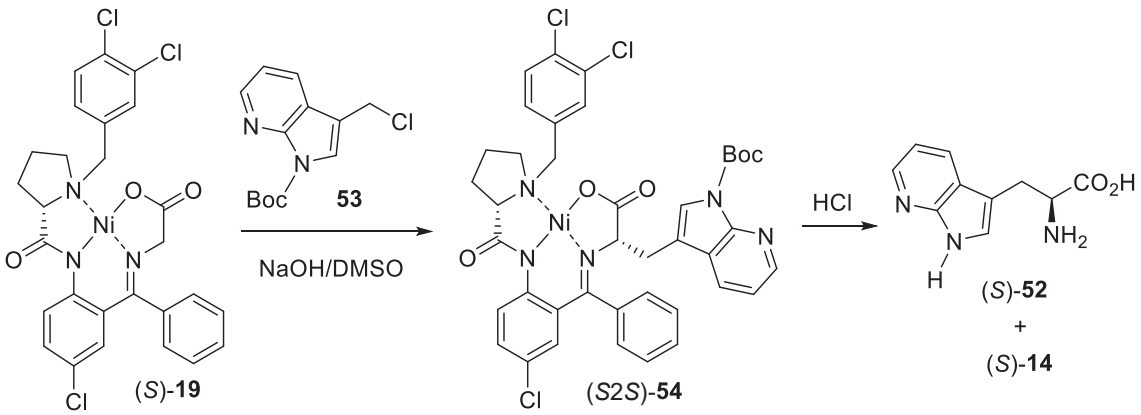
Scheme 12. Asymmetric synthesis of α-(methyl)cysteine (**51**).

As presented in Scheme 12, the synthesis of **51** was accomplished by the alkylation of alanine complexes **49** and **50** derived from Hamari **13** and Soloshonok–Liu **14** ligands, respectively [200]. It should be noted that the alanine residue in complexes **49** and **50** can be racemic as the reaction proceeds via formation of the achiral intermediate enolate. Proline derived complex **49** exhibited better stereochemical preference allowing the preparation of the major diastereomer in 77% yield with 80% *de*. The major product can be purified by column chromatography and disassembled to provide the target AA **51**. Both enantiomers of **51** were prepared with the same stereochemical outcome.

Another interesting example of tailor-made AAs is 7-azatryptophan **52**. AA **52** has been widely used as a biological fluorescent probe [201–204], an antiplasmodial compound [205], and an inhibitorof checkpoint kinase 1 [206–208]. Although there have been several reports on the synthesis of azatryptophanes [209–215], the synthesis of 7-azatryptophan **52** has remained less developed, in particular, by asymmetric synthesis. We demonstrated that the synthesis of AA **52** can be effectively realized via alkylation of a glycine complex (Scheme 13).

As shown in Scheme 13, N-protected chloride **53** reacted with glycine complex **19** in the presence of a strong base in DMSO affording

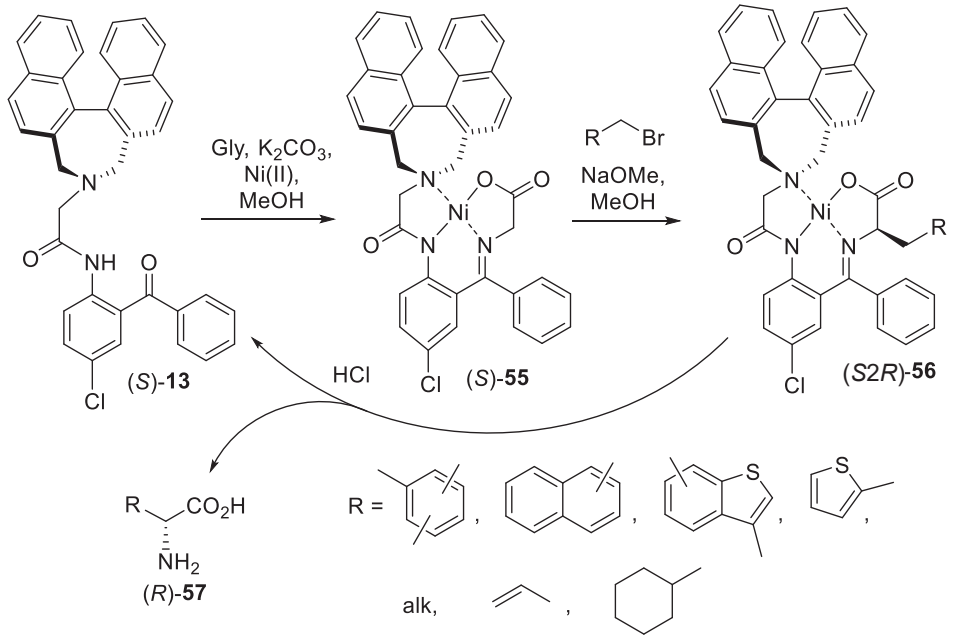
alkylated product **54** as a single diastereomer in 74% yield. Disassembly of **54** under acidic conditions took place with simultaneous removal of the Boc protecting groupproviding the target AA **52** in 95% yield [216]. It should be noted that chiral ligand **14** was also collected with 97% recovery for re-use.



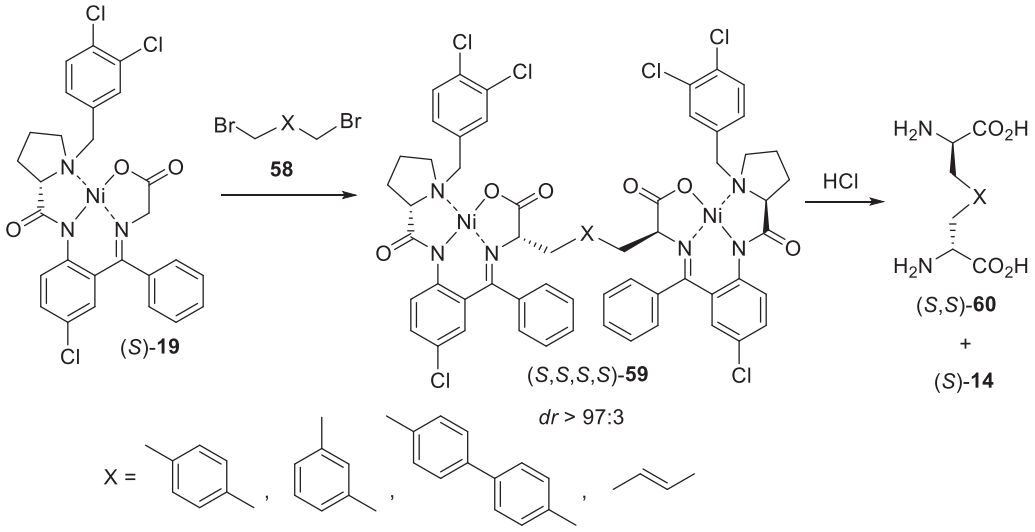
Scheme 13. Asymmetric synthesis of 7-azatryptophan via alkylation of glycine–Ni(II)complex.

Scheme 14 illustrates various AAs synthesized using Hamari ligand **13**. The glycine-derived complex **55** can be prepared quantitatively by treating ligand **13** with glycine and a source of Ni(II), e.g. $NiCl_2$, in methanol in the presence of base. Any alkylating reagent compatible with the reaction conditions can be used to alkylate the glycine moiety in **55**. For instance, mono-, di-, or polysubstituted benzyl chlorides/bromides provide excellent alkylations. The substituents on the phenyl ring only have a negligible effect on the stereochemical outcome. Similarly, variously substituted naphthyl derivatives and some heterocyclic derivatives also produce excellent results. Although inactivated alkyl halides react more slowly, they still achieve the same high stereochemical outcome, typically around 95% *de*, with chemical yields exceeding 90%. The alkylation products **56** can be conveniently disassembled to yield the corresponding AA and chiral ligand **13** which can be easily recovered with uncompromised enantiomeric purity [217].

Chiral glycine alkylation methodology can also be used for the synthesis of bis-AA (Scheme 15) [218, 219]. This particular class of tailor-made AAs is frequently found in naturally occurring peptides. For example, bis-AAs play an important role in the structure of the peptidoglycan cell walls of fungi and bacteria and can act ascross linking elements to allow for efficient control of thepeptide secondary structure. Representative examples of naturally occurring bis-AAs include diaminopimelic acid [220,221] and dityrosine [222]. Furthermore, bis-AAs serve as a key structural unitin the design of antibiotics that disrupt microbial cell wall synthesis [223]. Due to their useful biological properties and bio structural functions, the synthesis of bis-AAs has received significant interest [224–231].



Scheme 14. Asymmetric synthesis of various tailor-made AAs via alkylation of glycine Ni(II) complex derived from Hamari ligand13.



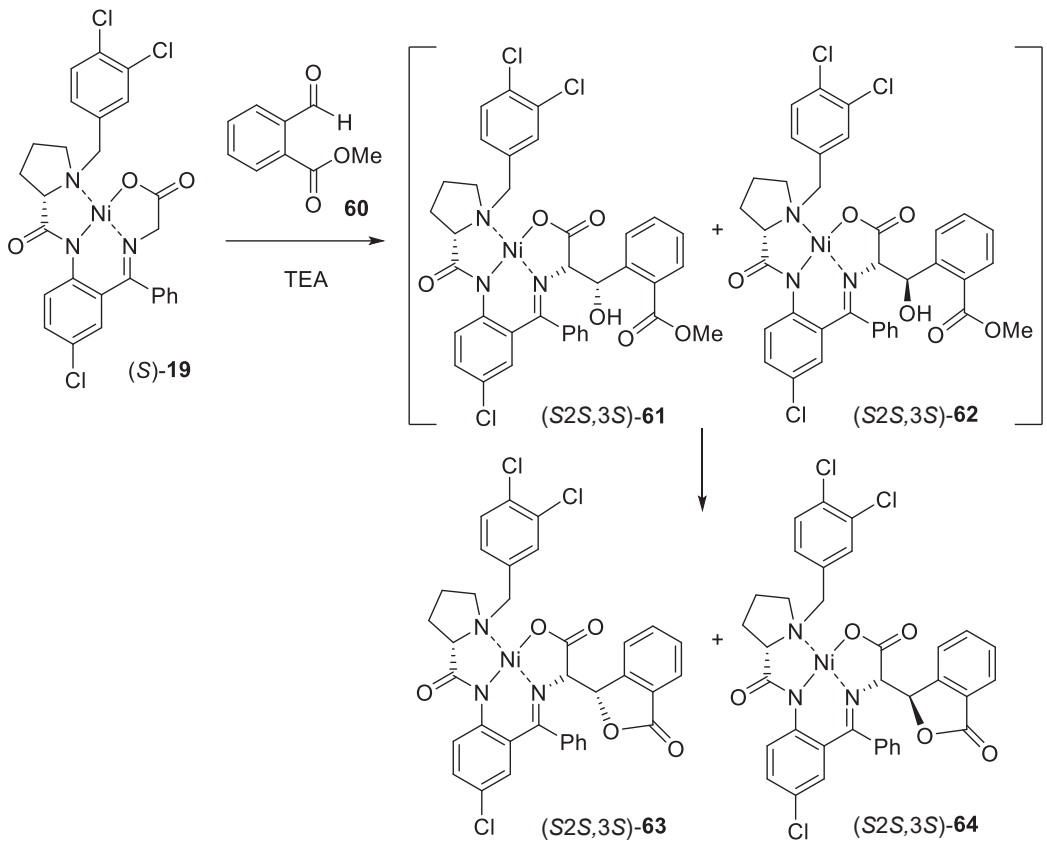
Scheme 15. Asymmetric synthesis of tailor-made bis-AAs via alkylation of a glycine Ni(II) complex.

As illustrated in Scheme 15, dibromides **58** can react with two equivalents of glycine–Ni(II) complex **19** to afford di-alkylated **59**. Despite some complexity of this process, the chemical yields of **59** are usually above 90% with diastereoselectivity >97:3. As expected, the reaction proceeds via intermediate monoalkylated derivatives which can be determined by TLC and,

if necessary, isolated. This approach, though, is limited to activated dibromides **58** such as benzyl or allyl derivatives [232]. Attempts to use inactivated alkyl halides require forcing conditions leading to significant decomposition and loss of stereochemical integrity. Disassembly of **59** under acidic conditions permits the isolation of the target bis-AAs **60** as well as the recovery of chiral ligand **14**.

Aldol addition reactions.

Aldol addition to glycine equivalents is the most convenient approach for the preparation of α-amino-β-hydroxy AAs [233–237]. For example, glycine Ni(II) complex **19** was shown to react with various aldehydes and activated ketones [238–240]. The aldol reactions of **19** can be conducted under either kinetic control using a weak base or under thermodynamic control using a strong base [241,242]. While the latter affords the corresponding aldol addition products with excellent levels of diastereoselectivity at the α- and β-positions (> 98:2), the former proceeds only sluggishly and with only a low degree of stereochemical preference(~60:40) at the β-stereogenic carbon. Considering these inherently challenging synthetic limitations, we were interested to know whether the stereochemical preference could be improved when the aldol addition is followed by transformation to irreversible products (Scheme 16) [243].



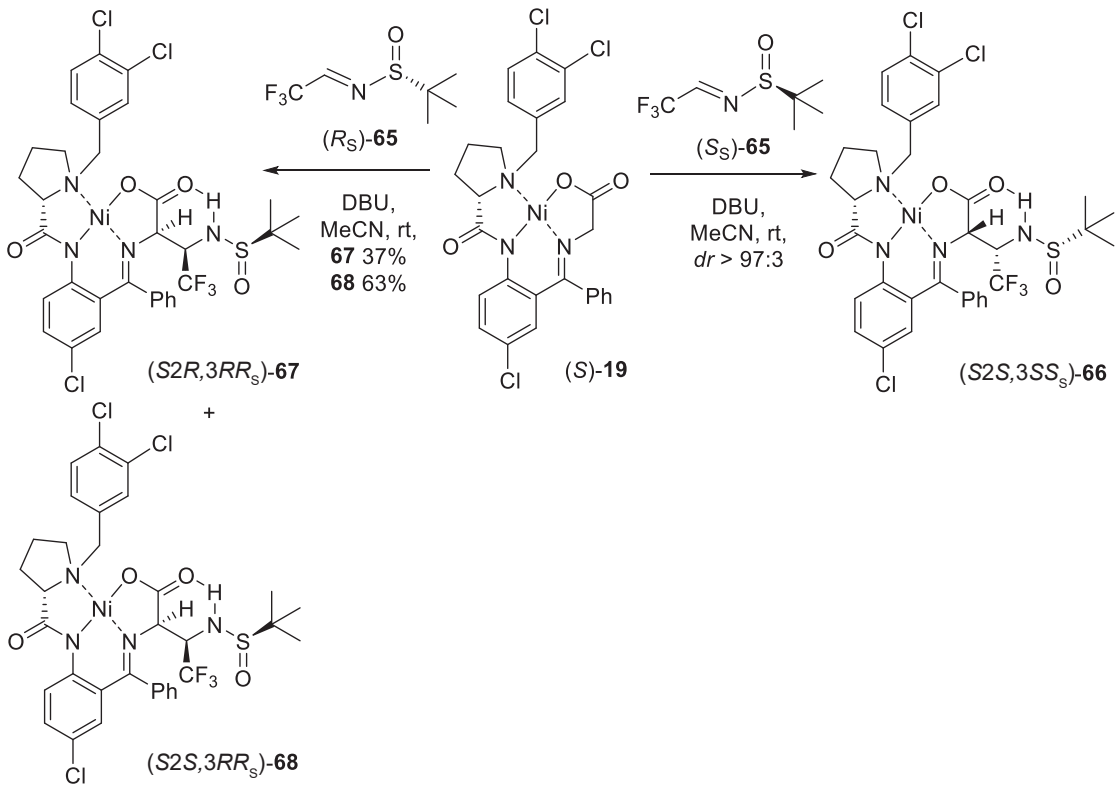
Scheme 16. Methodological study of the aldol addition–cyclization reaction cascade.

As presented in Scheme 16, using the chiral Ni(II) complex of glycine Schiff base **19** we designed an addition–cyclization reaction cascade to explore aspects of the kinetic triethylamine-catalyzed formation of the corresponding (*S*2*S*,3*S*)-**63** and (*S*)(2*S*,3*R*)-**64** diastereomers [243]. It was found that the final lactone products rather reflected thermodynamic stereocontrol due to much greater rates of the reversible aldol addition, products **61** and **62**, vs. a subsequent and irreversible cyclization step. The observed 80:20 diastereoselectivity for (*S*)(2*S*,3*S*)-**63** and (*S*)(2*S*,3*R*)-**64** in the reaction of Ni(II) complex **19** constitutes an improvement over the previously reported 60:40 ratio.

Mannich additions.

Mannich additions of chiral glycine equivalents represent the most direct approach for the preparation of *α*,*β*-bis-AAs [244–247]. In the chemistry of Ni(II) complexes of glycine Schiff bases, Mannich additions are one of the least studied reactions [248]. Nevertheless, *α*,*β*-bis-AAs constitute an important class of tailor-made AAs found in nature as structural motifs of biologically important molecules [249, 250].

As illustrated in Scheme 17, we designed a Mannich addition to investigate the case of matching vs. mismatching diastereomeric preferences between chiral complex **19** and chiral Mannich acceptor **65** [251].

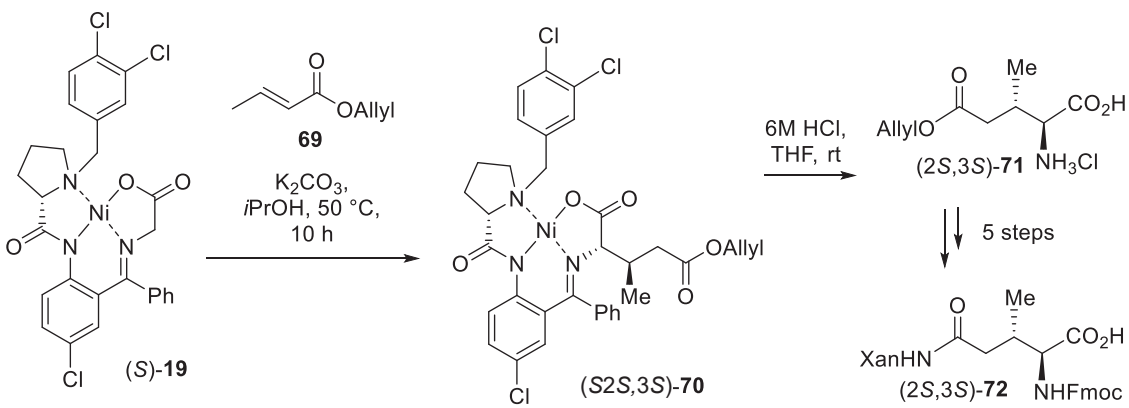


Scheme 17. Mannich additions of the chiral Ni(II) complex of glycine Schiff base **19** with a chiral Mannich acceptor **65**.

It was intriguing to find that *S*-configured Ni(II) complex **19** and *N-tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine **65** with an (*S*) configuration have matching stereochemical preferences resulting in the formation of product **66** with virtually complete diastereoselectivity. The reaction of (*S*)-**19** with (*R*)-**65** is a case of mismatching stereochemical preferences and affords amixture of diastereomers **67** and **68** in a ratio of 37:63. These results suggest that the stereocontrol of the Ni(II) complex **19** prevails over the stereoselectivity provided by imine **65**. It is worth noting that *N-tert*-butylsulfiny l-3,3,3-trifluoroacetaldimine (**65**) is one of the most widely used and exceptionally high stereocontrolling chiral reagent for the asymmetric synthesis of amines and AAs [252–256].

Michael additions.

Michael additions are of great synthetic value for the preparation of various types of tailor-made AAs containing five carbon atoms in their skeleton. These include, but are not limited to, glutamic acid, glutamine, pyroglutamic acid, pyroglutamine, and proline [257–260]. The Michael addition of Ni(II)complexes with various *α*,*β*-unsaturated carboxylic acid derivatives has been one of the most prolific avenues of this research area [261–264]. We chose Michael addition for the synthesis of (2*S*,3*S*)-3-methylglutamine, one the key compounds used in the total synthesis of cytotoxic marine peptides callipeltin O and Q [265]. As presented in Scheme 18, glycine Ni(II) complex **19** was reacted with Michael acceptor **69** under specially designed conditions to keep intact the allyl ester moiety [266].



Scheme 18. Asymmetric synthesis of (2*S*,3*S*)-3-methylglutamine via Michael addition.

The acidic disassembly of the major diastereomeric product (*S*2*S*3*S*)-**70** was also performed under strictly controlled conditions using THF as a solvent. Allyl ester hydrochloride **71** was subsequently transformed into the target glutamine derivative **72** in five steps involving protection–deprotection procedures.

The substitution of phenylalanine (**73**, Figure 3) in endogenous peptides with a bulkier and more lipophilic *β*-phenylphenylalanine (diphenylalanine, DPA, **74**) usually leads to improved binding to the apolarsite of the targeted receptors. DPA-modified peptides were found to possess some encouraging biological pro-

files in the areas of thrombin inhibitors [267, 268], angiotensin-converting enzyme (ACE) inhibitors [269], HIV protease inhibitors [270], pain-related norepinephrine transporterinhibitors [271], μ and δ opioid receptors [272], and other types of peptidic substrate–receptor interactions [273–279].

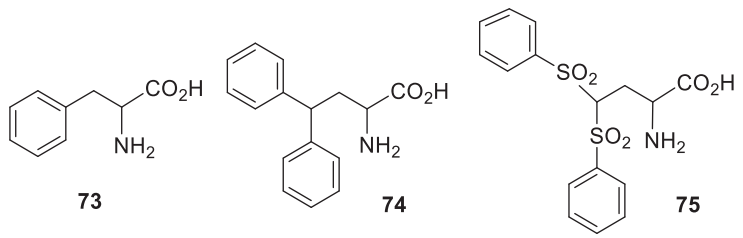
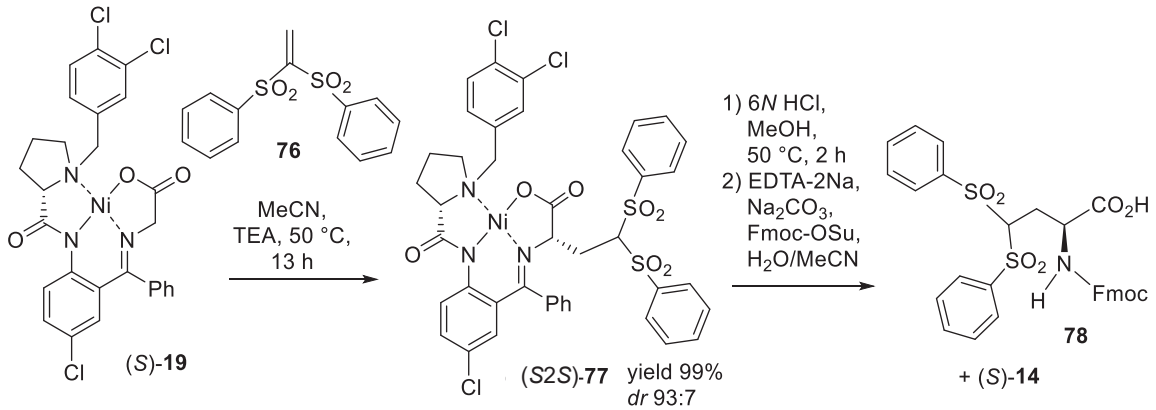


Fig. 3. Phenylalanine (**73**) and its more lipophilic analogs.

Numerous advanced in silico studies have generated structural profiles for hundreds of tailor-made AAs with rationally designed size control and vdW and electrostatic interactions that influence peptide ligand binding affinity with endogenous receptors [280–283]. 2-Amino-4,4-bis-(phenylsulfonyl)butanoic acid (**75**) is one of the promising structures featuring enhanced steric bulk and lipophilicity. We envisioned that this molecule could be assembled via Michael addition between glycine–Ni(II) complex **19** and the specially designed vinyl–disulfonyl Michael acceptor **76** (Scheme 19) [284–287].



Scheme 19. Asymmetric synthesis of 2-amino-4,4-bis-(phenylsulfonyl)butanoic acid (**75**).

It was interesting to find that due to the high electrophilicity of acceptor **76**, the corresponding Michael addition with glycine complex **19** can be conveniently conducted using triethylamine as base. Optimization of the reaction conditions allowed for preparation of the diastereomeric products with an excellent yield of 99% and high diastereomeric ratio (*dr*) of 93:7. The major diastereomer **77** was transformed into the corresponding Fmoc derivative **78**

of 2-amino-4,4-bis-(phenylsulfonyl)butanoic acid (**75**) under standard conditions. As usual, chiral ligand (*S*)-**14** is able to be recovered and purified for future applications [288].

3-Methyleneglutamic acid (**79**, Figure 4) was reported as a racemic compound and tested as a potential suicide inhibitor of pig heart glutamate–aspartate transaminase [289,290]. Interestingly, (*S*)-4-methyleneglutamic acid (**80**) is a naturally occurring compound [291,292] and was prepared in enantiomerically pure form [293,294].

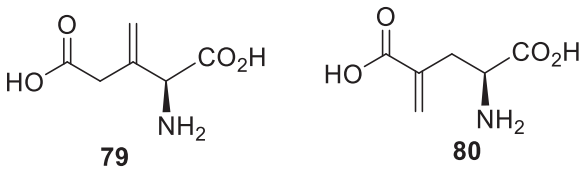
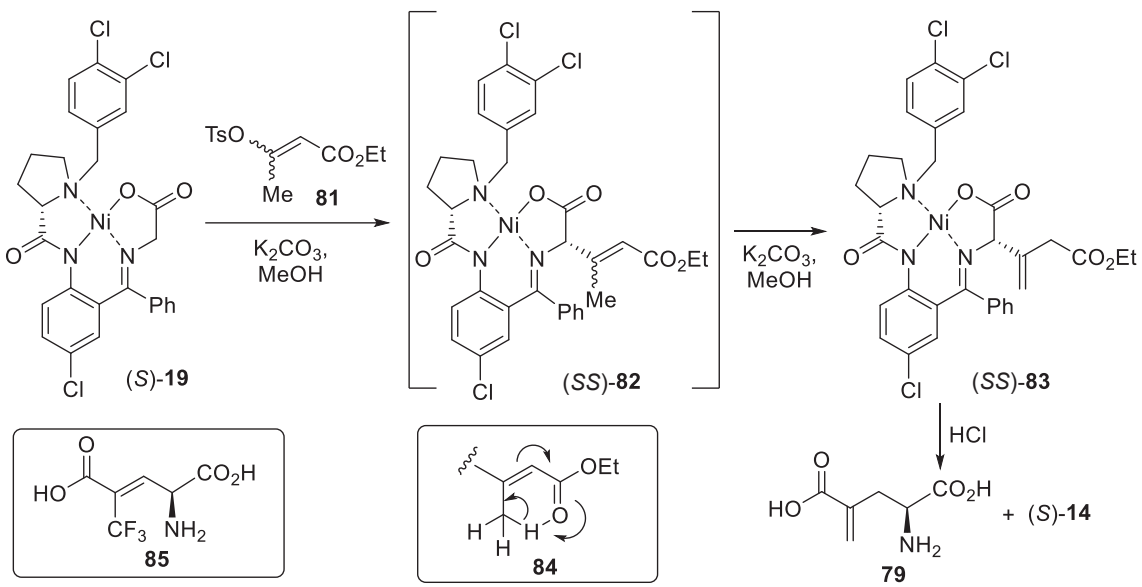


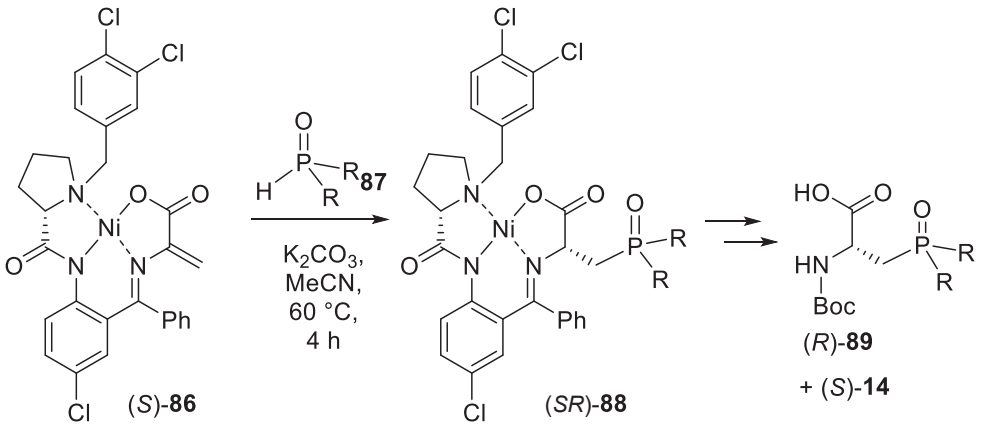
Fig. 4. Structures of (*S*)-3-methyleneglutamic acid (79) and (*S*)-4-methyleneglutamic acid (**80**).

We also examined the Michael addition between glycine Ni(II) complex **19** and Michael acceptor **81** bearing a tosylate leaving group (Scheme 20) [95]. Our goal was to prepare addition product **82** containing the corresponding *β*-methyl-unsaturated AA. Quite unexpectedly, we isolated compound **83** as the major product. This outcome was very welcome as it allowed for the asymmetric synthesis of (*S*)-3-methyleneglutamic acid (**79**) which was previously unknown in enantiomerically pure form.We reasoned that compound **82** underwent base-catalyzed isomerization to **83** via transition state **84**. This mechanistic rational is supported by the fact that using the same method we were able to prepare fluoro-AA **85** via the expected addition–elimination sequence [295].



Scheme 20. Michael addition of glycine–Ni(II)complex with Michael acceptors containing tosylate leaving groups.

Organophosphorus derivatives are widely found in natural products, pharmaceuticals, chiral ligands, and functional materials [296–305]. Phosphorus-containing α-AAs are an important class of tailor-made AAs that have gained considerable attention in peptide design strategies as they enhance stability towards protease degradation and permit bioactivity to be modulated [306–314]. Previously, using Ni(II) complex chemistry, ω-phosphorus analogs of dicarboxylic AAs were prepared by alkylation of a glycine chiral Schiff base complex with the corresponding phosphorus alkyl halides [315]. We envisioned a different approach based on the Michael addition of dehydroalanine chiral Schiff base complex **86** (Scheme 21).



Scheme 21. Asymmetric synthesis of phosphorus analogs of AAs via Michael addition.

In sharp contrast to the previously discussed Ni(II) complexes representing nucleophilic glycine equivalents, dehydroalanine derivative **86** [316,317] represents an electrophilic alanine equivalent allowing homologation at the corresponding β position. The addition reactions of Ni(II)complex **86** with nucleophiles **87** were conducted under the usual nucleophilic conditions using methanol as a solvent and K_2CO_3 as base [318]. The Michael addition between dehydroalanine Ni(II) complex **86** and phosphorous nucleophiles **87**occurred very cleanly furnishing products **88** in good yields and with excellent diastereoselectivity. It should be noted that the α configuration of the addition products **88** appears to be of an unusual (*SR*) configuration, but this is simply due to the CIP priority rules favoring the phosphorus atom over the $-CO_2H$ group [319,320]. Complexes **88** were disassembled under the usual acidic conditions and the target AAs were in situ converted to the corresponding N–Boc derivatives **89** along with the recovery of the chiral ligand (*S*)-**14**.

Multistep procedures.

Described above are general methodological approaches requiring one key step before acquiring the target AA. In this section we provide examples of multiple synthetic transformations for the preparation of structurally complex tailor-made AAs as exemplified by the structures in Figure 5.

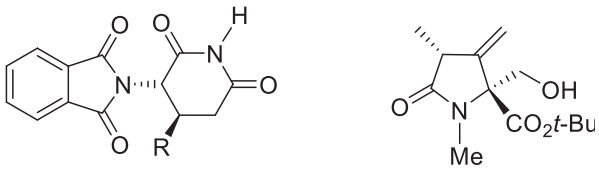


Fig. 5. Examples of products prepared using Ni(II) complex methodology.

Thalidomide is a notorious drug due to the monumental socio-scientific impact it had on-nearly every sector of the healthcare industry [321–324]. Nevertheless, in 1998 and 1999 the US Food and Drug Administration approved thalidomide for use in the treatment of erythema nodosum leprosum and multiple myeloma [325]. Moreover, the clinical success of thalidomide led to the development and marketing of several of its structural analogs [326–328]. The Michael addition of glycine–Ni(II) complexes were used as a key step in the asymmetric synthesis of novel 4-substituted enantiomerically stable analogs of thalidomide **90** [329,330]. Oxazolomycin A, isolated from the fermentation broth of *Streptomyces* sp., exhibits potent antibiotic properties against various Gram-positive bacteria and *Agrobacteriumtume faciens*, strong anticancer activity, as well as various other antiviralactivities [331–339]. It was envisioned that the pyroglutamate core unit, such as compound **91** which possesses appropriate functional groups at C-2 and C-3, can be viewed as a synthetic intermediate in the total synthesis of Oxazolomycin-type natural products.The first step in this process included the Michael addition of achiral glycine Schiff base with a chiral *α*,*β*-disubstituted acrylate derivative for the preparation of the enantiomerically pure *α*,*β*-disubstituted pyroglutamic acid core. A total of twelve reactions were utilized in the synthesis of **91** with an overall yield of 10% [340].

α, *β*-Methano-AAs, or methanologs of *α*-AAs, represent an extreme case of compounds containing a severely conformationally restricted cyclopropane ring [341, 342]. Remarkably, several cyclopropyl group-containing AAs, such as **92**–**94** (Figure 6), are naturally occurring compounds and have been isolated from various higher plants [343–351].

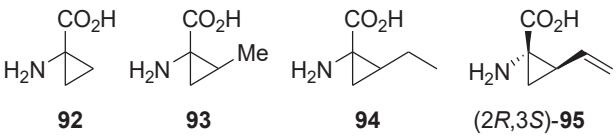
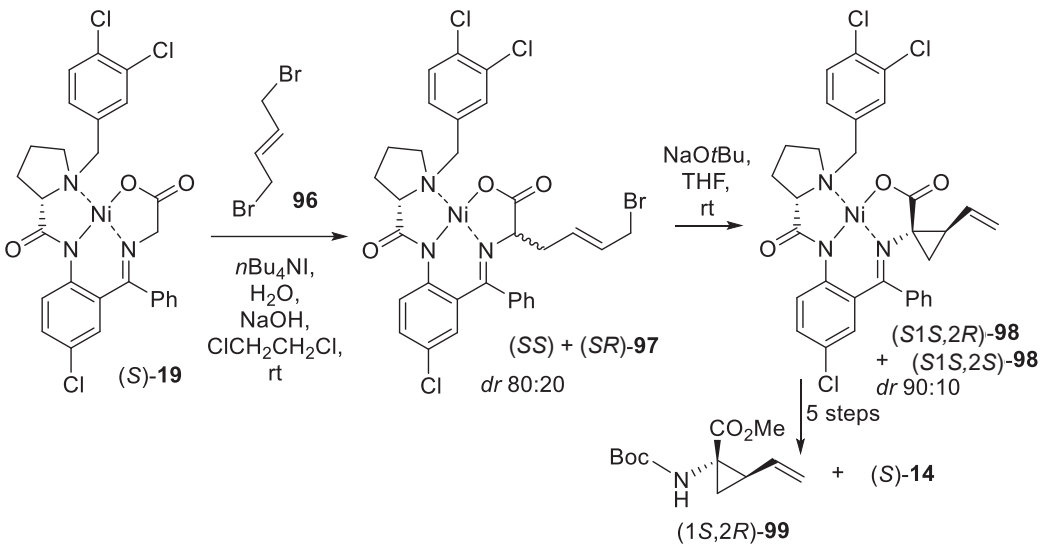


Fig. 6. Naturally occurring and tailor-made *α*,*β*-methano-*α*-AAs.

The interest in methanologs of AAs results from the discovery of a novel and very potent class of hepatitis C virus NS3/4A protease inhibitors [352] containing (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid (**95**) as a key structural feature. Thus, at least sixdifferent drugs containing AA **95** are currently being developed for the treatment of hepatitis C. For example, Simeprevir [353], Danoprevir [354], Asunaprevir [355], Faldaprevir [356], Ciluprevir, and Grazoprevir [357] all have a fragment of acid **95** as a sulfonamide derivative.

Given this profound interest in the pharmaceutical applications of acid **95**, we examined Ni(II) complex chemistry for the asymmetric synthesis of this compound. The method developed by us is illustrated in Scheme 22 [358].



Scheme 22. Asymmetric synthesis of Boc-protected (1*S*,2*R*)-1-amino-2-vinylcyclopropanecarboxylic acid (**99**).

The synthetic sequence began with the selective alkylation of glycine complex **19** with dibromide **96**. We found that the first mono-alkylation reaction needed to be conducted under very mild phase-transfer conditions using dichloroethane as the solvent at ambient temperature. The diastereoselectivity of the first alkylation step is kinetically controlled and affords product **97** as a mixture of diastereomers in a ratio of 80:20, but unfortunately it is not high yielding. However, the ratio of diastereomers **97** is of no concern as the next alkylation step occurs via deprotonation of the α-stereogenic center. The second intramolecular, alkylation–cyclization requires very strong basic conditions giving rise to the targeted, highly sterically constrained, cyclic architecture. Product **98** was isolated in 75% yield as a mixture of diastereomers 90:10. The major compound with (1*S*,2*R*) configuration was obtained diastereomerically pure by column chromatography. Disassembly of compound **98** followed by four additional steps afforded the Boc-protected (1*S*,2*R*)-1-amino-2-vinylcyclopropanecarboxylic acid (**99**) [358]. A similar reaction sequence was used for the preparation of the (1*S*,2*R*) and (1*R*,2*S*) enantiomers of 1-amino-2-vinylcyclopropanecarboxylic acid starting from the glycine complex derived from the Hamari ligand **13** [359]. Both approaches provide for reliable access to this pharmacologically important tailor-made AA.

3-Amino-2-hydroxyoctadecanoic acid (Ahod **100**, Figure 7) is a common structural unit of naturally occurring peptides Ralstonin A and Ralstoamide A possessing chlamydospore-inducing activity in fungus and moderatephytotoxicity in plants [360]. The total synthesis of Ralstonin A and Ralstoamide A has not been reported and synthetic work on these molecules has been limited for a long time by the preparation of selected fragments, in particular the 3-hydroxy-tyrosine fragment with various stereochemistries and functional group protections [361–363]. Planning for the highly anticipated structural confirmation and a

structure–activity relationship study, we decided to focus on the preparation of Ahod AA **100** which is critically responsible for the lipophilic properties of these naturally occurring peptides.

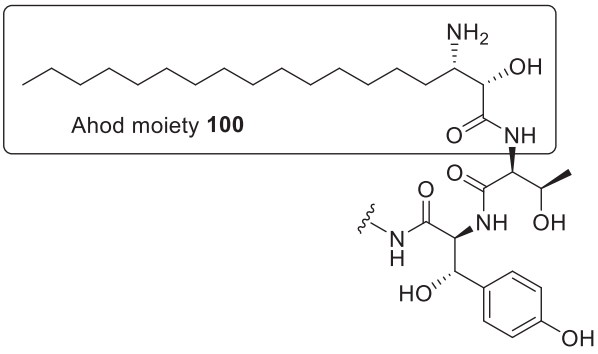
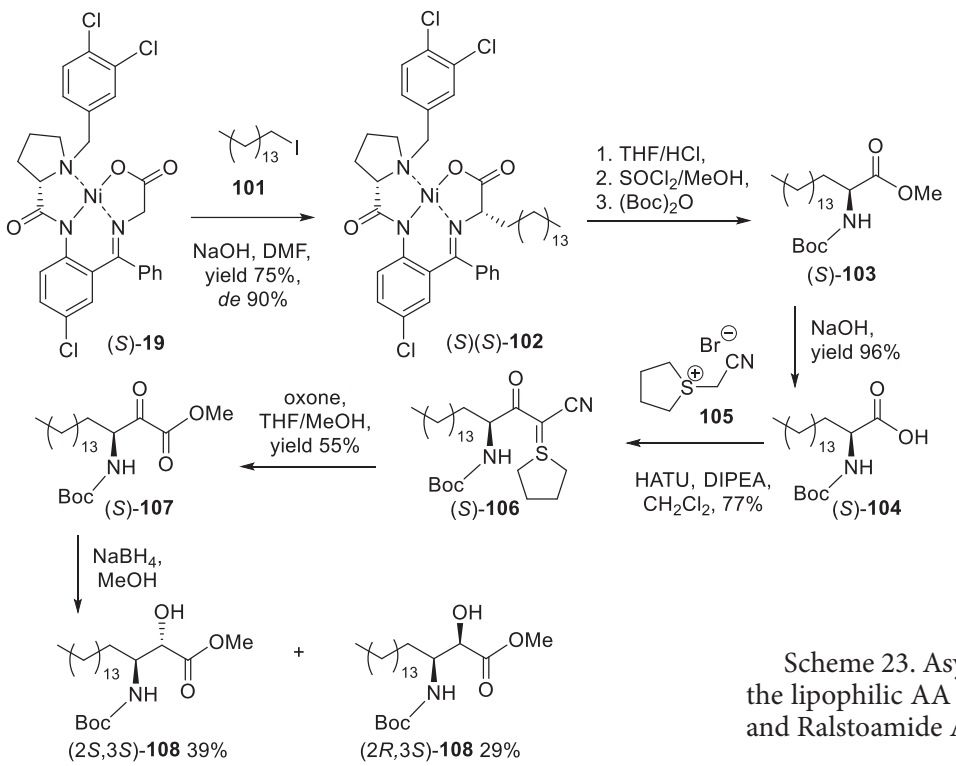


Fig. 7. The common structural fragment of Ralstonin A and Ralstoamide A.

As presented in Scheme 23 [364], the synthesis started with the alkylation of chiral glycine equivalent **19** with alkyl iodide **101**. The reaction was conducted under the usual strongly basic conditions at ambient temperature affording alkylation product **102** in high chemical yield and with high diastereoselectivity. Disassembly of diastereomerically pure **102** was followed by the esterification and protection of the amino group. The ester group in **103** was hydrolyzed using NaOH to yield **104**, which was reacted with reagent **105** to produce intermediate **106**. Compound **106** was treated with oxone in THF–methanol to provide keto–ester **107** in moderate yield. Finally, reduction of the keto group in **107** gave rise to two diastereomeric products, (2*S*,3*S*)-**108** and (2*R*,3*S*)-**108**, obtained in yields of 39% and 29%, respectively [120]. While the diastereoselectivity of this step was low, the preparation of both compounds fits well with the current research goals of confirming the stereochemistries of Ralstonin A and Ralstoamide A.



Scheme 23. Asymmetric synthesis of the lipophilic AA found in Ralstonin A and Ralstoamide A.

CONCLUSIONS. In the field of the asymmetric synthesis of AAs, only a few approaches possess the practical characteristics attractive to industry for large-scale pharmaceutical production. The chemistry of Ni(II) complexes is undoubtedly one of these promising methods. As emphasized in this review, the simplicity of the reaction conditions plays a crucial role in the overall cost structure and commercial success of chemical processes.

Depending on the structure of the target AA, one may choose either direct chiral modification of unprotected AAs or the elaboration of chiral glycine equivalents. Of particular commercial interest are the methods we have developed, which include SOAT, DKR, and inversion of chirality. In the homologation approach, construction of the desired AA architecture can be efficiently achieved through alkylation, aldol, Mannich, and Michael addition reactions.

We believe that Hamari's contributions to this field will be highly valued by practitioners in both industrial and academic laboratories and will be instrumental in future applications of our methods for the preparation of commercially marketed pharmaceuticals.

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ВНЕСОК ХАМАРІ В АСИМЕТРИЧНИЙ СИНТЕЗ СПЕЦІАЛЬНО СТВОРЕНИХ АМІНОКИСЛОТ

Цзяньлінь Хань, Хонг Лю, Цзян Ван, Аліція Взорек, Олександр Е. Сорочинський, Карел Д. Кліка, Тайзо Оно, Хіроїкі Моріваkі, Тацунорі Сато, Кунісуке Ізава, Хіройукі Конно, Вадим А. Солошонок

[1] Цзянсу-Центр спільних інновацій для ефективного перероблення та використання лісових ресурсів, Коледж хімічної інженерії, Нанкінський лісотехнічний університет, Нанкін 210037, Китай;
[2] Державна Ключова лабораторія дослідження ліків, Шанхайський Інститут медичних матеріалів, Китайська Академія наук, Шанхай 201203, Китай;
[3] Інститут хімії, Університет Яна Кохановського у Кельце, Університетська 7, 25–406 Кельце, Польща;
[4] Інститут біоорганічної хімії та нафтохімії ім. В. П. Кухаря, Національна Академія наук України, Київ 02094, Україна;
[5] Німецький Центр дослідження раку (DKFZ), Нойенхаймер Фельд 280, 69120 Гейдельберг, Німеччина;
[6] Національний Інститут передових промислових наук і технологій, 463–8560, Нагоя, Японія;
[7] Хамарі Кемікал Лтд.., Осака, Японія;
[8] Департамент хімії та біологічної інженерії, Аспірантура наук та інженерії, Університет Ямагата, 992–8510 Йонедзава, Ямагата, Японія;
[9] Департамент органічної хімії, факультет хімії, Університет Країни Басків UPV/EHU, Пасео Мануель Лардизабал 3, 20018 Сан-Себастьян, Іспанія;
[10] ІКЕРБАСКЕ, Баскський Фонд науки, Марія Діас де Харо 3, плаза Бізкая, 48013 Більбао, Іспанія.
email: vadimsoloshonok@gmail.com

У цій статті розглянуто розвиток асиметричного синтезу спеціально створених амінокислот, проведений в компанії Hamari Chemicals за 10-річний період з 2013 по 2022 рік. Обговорення базується на стратегіях, таких як пряма хіральна модифікація незахищених амінокислот через проміжне утворення комплексів Ni(II) і розроблення хіральних нуклеофільних або електрофільних еквівалентів гліцину. Перший підхід включає, наприклад, асиметричну трансформацію другого порядку, динамічну кінетичну роздільність та інверсію хіральності, тоді як другий підхід включає побудову бажаної архітектури амінокислот за допомогою, наприклад, реакцій алкілування, альдольних, Манніха чи Міхаеля, а також багатоступінчастих процедур. Наголошується на зручності в експлуатації, масштабованості та практичності розроблених методів.

Ключові слова: спеціально створені амінокислоти; дизайн і розроблення ліків; асиметрична трансформація другого порядку; динамічна кінетична роздільність; інверсія хіральності.

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