Tetrahedron Chem 13 (2025) 100118

Contents lists available at ScienceDirect

Tetrahedron Chem

journal homepage: www.journals.elsevier.com/tetrahedron-chem

A radical hydrohaloalkylation of the ligand sphere of a chiral dehydroalanine Ni(II) complex: An asymmetric route to halogenated α-amino acid derivatives

Nadezhda V. Stoletova [a], Alexander F. Smol'yakov [a], Andrey A. Tyutyunov [a], Victor I. Maleev [a], Vladimir A. Larionov [a,b,*]

[a] A.N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences (INEOS RAS), Vavilov Str. 28, bld. 1, 119334, Moscow, Russian Federation
[b] Peoples' Friendship University of Russia (RUDN University), Miklukho-Maklaya Str. 6, 117198, Moscow, Russian Federation

ARTICLE INFO

Keywords:
Amino acids
Asymmetric synthesis
Halocarbons
Radical addition
Post-modification
Chiral nickel(II) complex

ABSTRACT

An asymmetric synthetic protocol for the access to chiral artificial halogenated α-amino acid (α-AA) derivatives was elaborated through the radical functionalization of a double bond in the ligand sphere of a robust chiral dehydroalanine Belokon's Ni(II) complex by hydrohaloalkylation reaction. A 4-cyano-pyrydine/B_2Pin_2 system promoted the *in situ* generation of radicals from halocarbons (including the hetero halogen atoms) for the subsequent coupling with the Ni(II) complex, providing the desired complexes with the yields in the range of 40–65%. The further post-modification of the side AA chain allowed to obtain the complexes with cyclopropane ring and to substitute the bromine atom on hydrogen one as well. Exemplary, two enantiopure α-AAs, including (*S*)-2-amino-4,4,4-trichlorobutanoic acid, were isolated by an acidic decomposition of the single diastereomeric Ni(II) complexes along with the recovery of the chiral auxiliary.

1. Introduction

The halogen atom containing α-amino acids (α-AAs) are widely applied in biochemistry and in drug design due to their unique properties [1–5]. The introduction of halogen atoms into the molecules can affect on their electronic, physicochemical, steric properties, and, moreover, such compounds can be as bioisosteres [6,7]. For example, halogenated compounds have a wide range of biological activities; some natural and synthetic products based on halogenated AAs (*in most cases contain fluorine or chlorine atoms*) [8–14], such as sintokamide A [8], dysamide A [9], odanacatib [10], (−)-herbacic acid [11], agonist of mGluR4 [12] and norcoronamic acid analogues [13], are shown in Fig. 1. Voxilaprevir®, which contains the synthetic (1*S*,2*S*)-1-amino-2-(difluoromethyl)-cyclopropane carboxylic acid, has been approved by FDA as a drug for the treatment of hepatitis C virus (HCV) [14]. The increasing demand for halogenated α-AAs is driving the development of new simple and efficient methods for their production [15–18].

The introduction of halocarbon groups into olefins is a prospective and straightforward approach to effectively increase molecular complexity [19–22]. One of the most well-known and forceful methods is Kharasch addition, also known as atom transfer radical addition (ATRA) [23,24]. A variety of efficient catalytic systems have been developed for this reaction. Most of them are based on metal complexes [25–32]; however, the obstacle in this case is the competitive atom-transfer polymerization process [33]. The use of metal-free or organic catalytic systems, mainly operating under (photo)redox conditions, has been a promising alternative to the exchange of metal catalysts in the functionalization of alkenes or double bonds with halocarbon groups [34–45]. This approach allows for the production of a diverse range of valuable hydrohaloalkylation products in the presence of hydrogen atom donors, however, in most cases, the alkylating agents are limited to chloroform and tetrachloromethane [34–45]. To date, the persistent pyridine-boryl radical system [46–48] has become widely used as an initiator in radical reactions due to its mild reaction conditions, functional group tolerance and broad substrate scope [49–59]. Meanwhile, the asymmetric variants of the hydrohaloalkylation process

This article is part of a special issue entitled: Biomolecule published in Tetrahedron Chem.

* Corresponding author. A.N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences (INEOS RAS), Vavilov Str. 28, bld. 1, 119334 Moscow, Russian Federation.
E-mail address: larionov@ineos.ac.ru (V.A. Larionov).

https://doi.org/10.1016/j.tchem.2024.100118
Received 13 October 2024; Received in revised form 26 December 2024; Accepted 27 December 2024
Available online 31 December 2024
2666-951X/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

for alkenes are still limited and underexplored [60–62] due to the high reactivity of radical intermediates, which presents a significant challenge [63–65].

Given the interest in halogenated AAs [1–5], it is valuable to develop an asymmetric route to them for both practical and fundamental reasons. For example, the trihalomethyl group has the potential to serve as a metabolically stable substitute for –CH_3 group. With a long-standing research interest in the asymmetric synthesis of AAs using reliable and versatile metal-templated approach [66–73], especially through radical chemistry [74–77], we report here an asymmetric route to challenging halogenated α-AAs via pyridine-boryl radical mediated functionalization of the ligand sphere of a robust chiral Belokon's dehydroalanine Ni (II) complex **1** [78] (Scheme 1). In contrast to our previous report [77], we have expanded the range of alkylating agents to include more challenging polyhalogenated alkyl bromides (containing hetero halogen atoms) and have demonstrated the further modification of the resulting complexes in order to increase their molecular complexity. In particular, the introduction of a bromo-containing fragment allowed the post-modification procedures such as formation of a cyclopropane ring and protodebromination process.

2. Results and discussion

We commenced our study by the reaction of a chiral dehydroalanine Ni(II) complex **1** with bromotrichloromethane (CCl_3Br) **2a** (Table 1). The radical coupling reaction carried out in the presence of a 4-cyanopyrydine/B_2Pin_2 system as an initiator and *N,N*-diisopropylethylamine (DIPEA) in 1,4-dioxane at room temperature, resulted in the formation of diastereomeric complex **3a** in a ratio of 16:1 *dr* ((*S,S*)- and (*S,R*)-products) with 49% combined yield (Table 1, entry 1). The reactions performed in other solvents, such as MTBE, hexafluoroisopropanol (HFIP) and THF demonstrated very low efficiency (Table 1, entries 2–4). The reaction carried out in toluene afforded the Ni(II) complex **3a** in an acceptable yield of 30%, although diastereoselectivity was low (*dr* 7.9:1) (Table 1, entry 5). The most effective solvent was found to be EtOAc, providing the product **3a** in 49% yield and >20:1 *dr* (Table 1, entry 6). The change in reaction temperature did not improve yield (Table 1, entries 7,8). Next, other additives were investigated as proton sources (Table 1, entries 9–12). The highest yield (51%) was obtained when 10 equivalents of HFIP were added to the reaction (Table 1, entry 12). The addition of 4 equivalents of **2a** in two portions slightly improved the yield of complex **3a** to 59% (Table 1, entry 13). The experiment using both DIPEA and HFIP produced **3a** with a similar yield of 60% (Table 1, entry 14). The structure and absolute configuration of the complex **3a** was determined unambiguously by single crystal XRD analysis (see Table 1).

In order to demonstrate the general applicability of this method, we then investigated the substrate scope of various halocarbons **2** under the conditions described in Entry 12 (Table 1) due to the differences in reactivity observed for other halocarbons (Scheme 2). The coupling of the complex **1** with carbon tetrabromide **2b** (CBr_4) afforded the product **3b** in a moderate yield (40%). Mixed fluorobromocarbons **2c**–**2f** were also suitable for the reaction, yielding the desired products **3c**–**3f** in acceptable yields (41–47%). Interestingly, in the use of **2f**, in addition to the main product (*S,S*)-**3f**, side products were formed that contained a hydrogen atom and a hydroxyl group in place of a bromine atom (see the SI for details). The Ni(II) complex **3g** featuring a heptafluoroleucine appendage was obtained using alkylating agent – iodofluorocarbon **2g** and DIPEA as an additive in 65% yield. The reaction of 1,2-dibromo-1,1,2,2-tetrafluoroethane **2h** with the complex **1** gave the complex **3h** with one remaining bromine atom in 41% yield. Only single diastereoisomers were found in all reactions (*dr* >20:1).

To further emphasize the scalability of our developed protocol, we conducted gram-scale reactions using halocarbons **2a** and **2h**. The single (*S,S*)-diastereomers of compounds **3a** and **3h** were isolated by standard silica chromatography in 46% (0.56 g) and 40% (0.54 g) yield, respectively.

It is known that the cyclopropyl-containing compounds are important in medicinal chemistry and drug design (see also Fig. 1) [79]. Therefore, we believed that the transformation of the linear halocarbon chain into a cyclopropyl ring in the complexes **3** would be a worthwhile aspiration (Scheme 3) [80,81]. Indeed, the intramolecular cyclization reaction of complex **3a** in the presence of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) as a base produced the desired complex **4a** containing a cyclopropyl group with geminal chlorine atoms in 82% yield. Although the cyclopropanation reaction occurs under basic conditions, which may

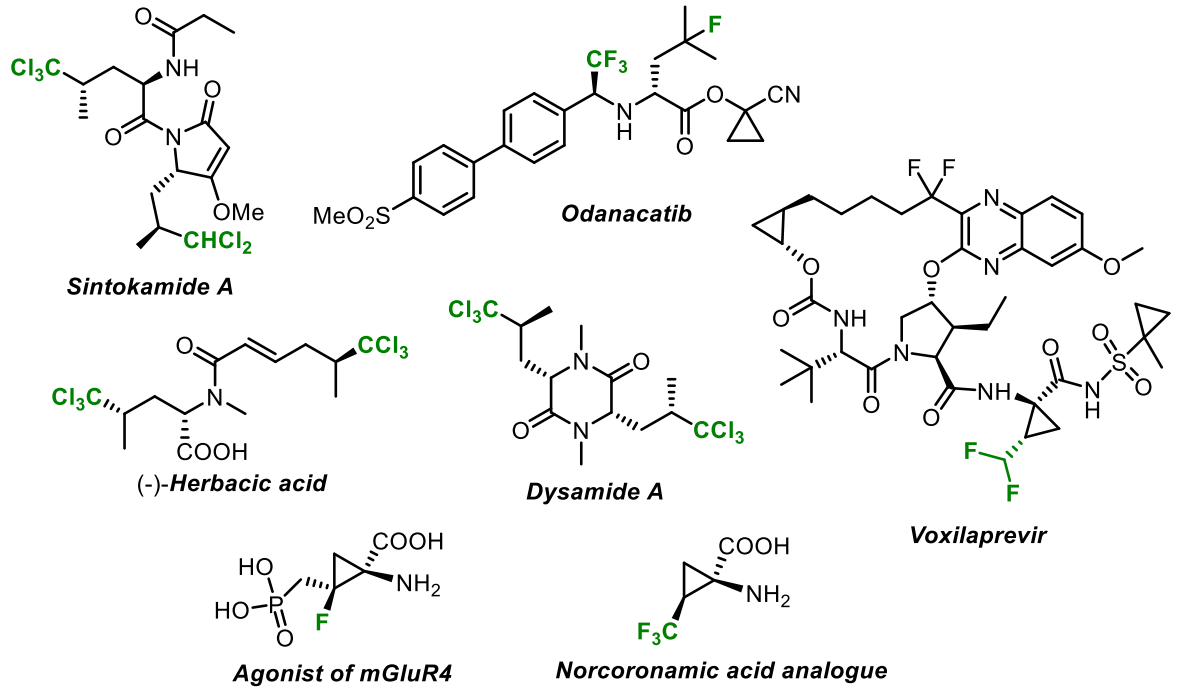
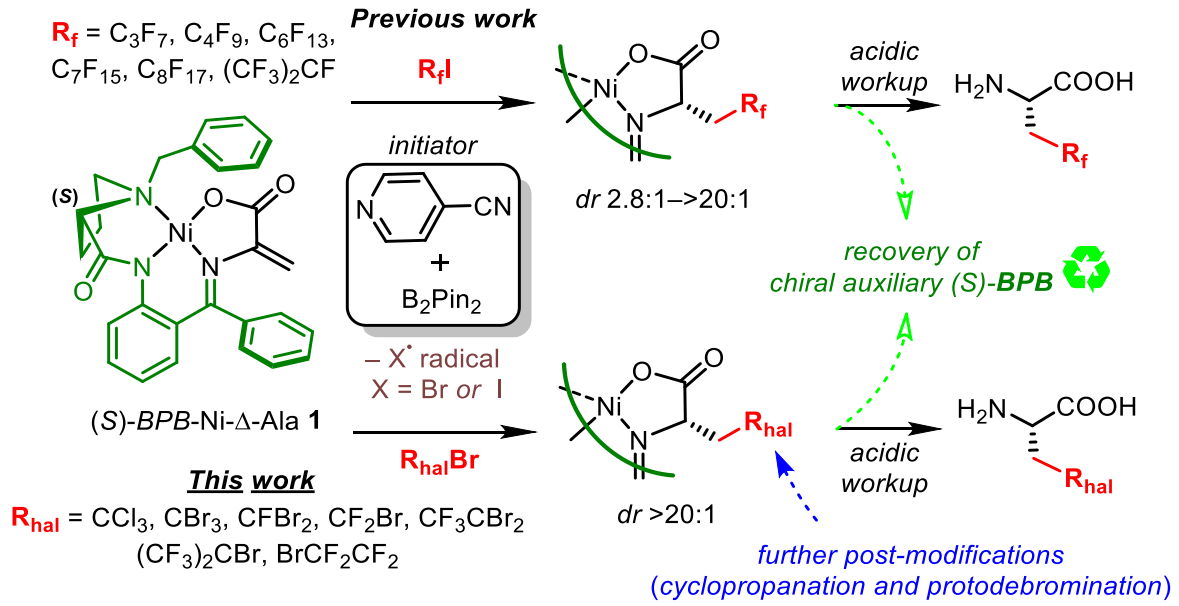
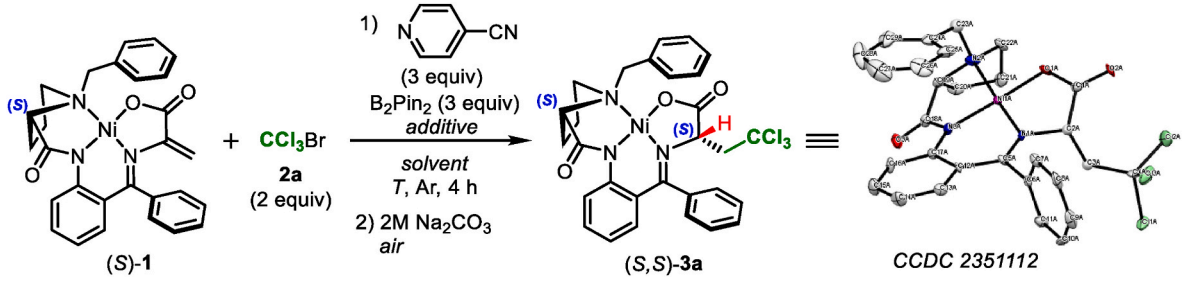


Fig. 1. Representative examples of bioactive compounds featuring halogenated amino acid motifs.



Scheme 1. Synthetic protocols for access to enantiomerically pure halogen atom containing α-amino acids.

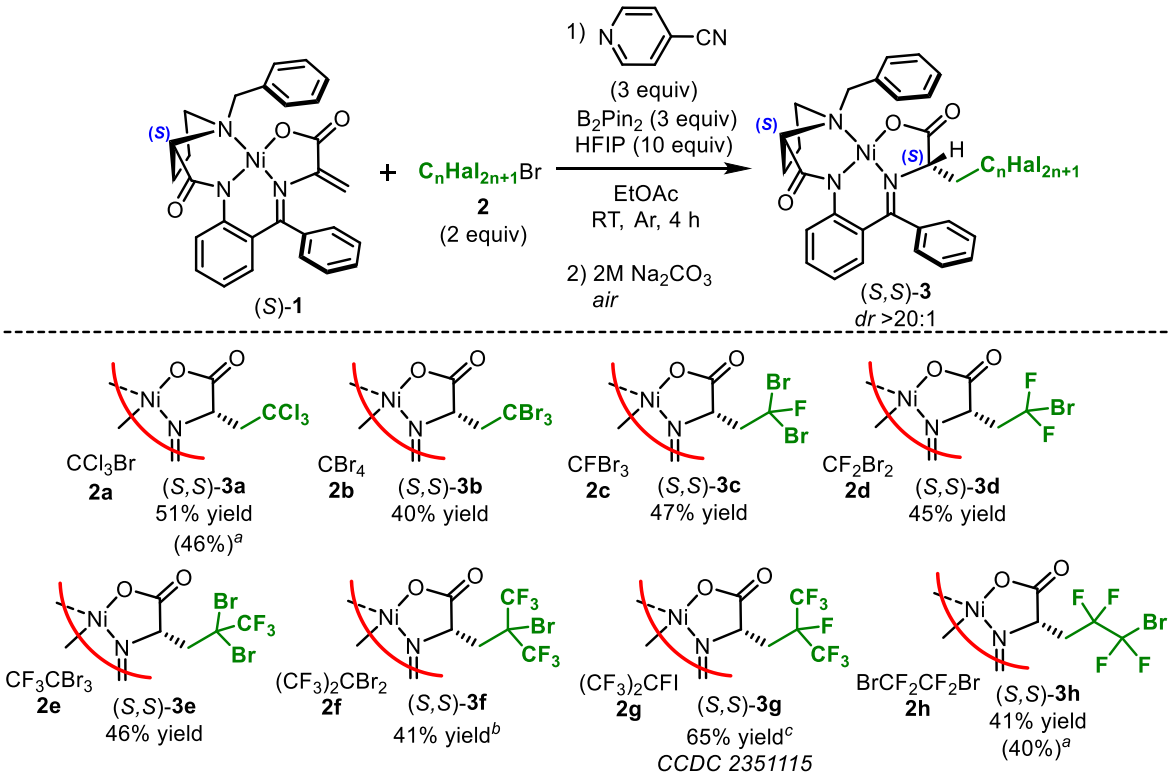
Table 1
Reaction condition screening for the radical coupling of a chiral Ni(II) complex **1** with CCl_3Br 2a.[a].



Entry	Solvent	Additive (x equiv.)	T (°C)	Conv.[b]	*dr*[c]	Yield of **3a** (%)[d]
1	1,4-dioxane	DIPEA (1.0)	RT	full	16:1	49
2	MTBE	DIPEA (1.0)	RT	partial	ND	traces
3[e]	HFIP	DIPEA (1.0)	RT	partial	ND	traces
4	THF	DIPEA (1.0)	RT	full	>20:1	16
5	toluene	DIPEA (1.0)	RT	full	7.9:1	30
6	EtOAc	DIPEA (1.0)	RT	full	>20:1	49
7	EtOAc	DIPEA (1.0)	80	full	>20:1	32
8	EtOAc	DIPEA (1.0)	0	full	>20:1	37
9	EtOAc	EtOH (10.0)	RT	full	>20:1	44
10	EtOAc	MeOH (10.0)	RT	full	>20:1	42
11	EtOAc	H_2O (10.0)	RT	full	>20:1	43
12	EtOAc	HFIP (10.0)	RT	full	>20:1	51
13[f]	EtOAc	HFIP (10.0)	RT	full	>20:1	59
14	EtOAc	HFIP (10.0) + DIPEA (1.0)	RT	full	>20:1	**60**

[a] Reaction conditions: Ni(II) complex (*S*)-**1** (51 mg, 0.1 mmol), CCl_3Br **2a** (0.2 mmol, 2 equiv.), 4-cyanopyridine (0.3 mmol, 3.0 equiv.), B_2Pin_2 (0.3 mmol, 3.0 equiv.), additive (1.0 or 10.0 equiv.) and solvent (1.0 mL) were stirred in a sealed Schlenk tube at indicated temperature under Ar atmosphere for 4 h (4-cyanopyridine and B_2Pin_2 added in two portions (first 1.5 equiv. each + 1.5 equiv. each after 2 h)). The structure of complex (*S*,*S*)-**3a** determined by single crystal XRD analysis (hydrogen atoms are omitted for clarity). Thermal ellipsoids are shown at the 50% probability level.
[b] Conversion determined by TLC analysis.
[c] A ratio of (*S*,*S*)/(*S*,*R*)-complexes **3a** determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Isolated yields.
[e] 20 h.
[f] 4 equivalents of **2a** were added in two portions. MTBE = methyl *tert*-butyl ether. DIPEA = *N*,*N*-diisopropylethylamine. HFIP = hexafluoroisopropanol.

cause the racemization of the stereocenter at the α-carbon atom of the AA residue during the cyclization step, the *face*-selectivity enforced by the chiral auxiliary through the π-Ni(II) interaction of the Bn group [82–84] ensures the formation of only one diastereomer. In a similar manner, the complex **3b** was converted into product **4b** with geminal bromine atoms in 87% yield. In the case of the transformation of



Scheme 2. Substrate scope: evaluation of various halocarbons **2**. Isolated yields are provided. [a]The yields for gram-scale reactions are given in the parentheses. [b]In addition to the main product (*S,S*)-**3f**, side products are formed, which contains a hydrogen atom and hydroxyl group instead of a bromine atom (see the SI for details). [c]DIPEA was used as an additive instead of HFIP.

complexes **3c** and **3e** into compounds **4c** and **4d**, a new stereogenic center was formed at the β-carbon atom. The complex **4c** was isolated in 71% yield with a poor diastereoselectivity of 1.4:1. On the other hand, a single diastereomeric complex **4d** was obtained with 51% yield from **3e**. The complex **3f** was successfully converted into product **4e** with geminal CF_3 groups in 82% yield. The structure and absolute configuration of the complexes **4a**, **4c** and **4d** were determined unambiguously by single crystal XRD analysis (Scheme 3). Notably, the configuration at the α-carbon atom in the AA moiety of the complexes **4a**–**4e** differs due to a change in the order of substituents, following the Cahn-Ingold-Prelog (CIP) rules.

Another valuable and synthetically useful process is the removal of a terminal bromine atom from a molecule through hydrodehalogenation reaction [85]. First, we effected a $Na_2S_2O_4/NaHCO_3$ system mediated protodebromination reaction [86] of the complex (*S,S*)-**3d** (*Method A*, Scheme 4). Unexpectedly, we observed the formation of the cyclized Ni (II) complex (*S,S*)-**5a** as the major product with 56% yield. The structure and absolute configuration of the complex **5a** were determined unambiguously by single crystal XRD analysis (Scheme 4). On the other hand, the reaction of complex (*S,S*)-**3h** provided a similar product (*S,S*)-**5b** in 49% yield accompanied by the protodebrominated complex (*S,S*)-**6a** in 36% yield. Interestingly, in the case of the transformation of complex **3f**, a mixture of two products was formed: protodebrominated complex (*S,S*)-**6b** (25% yield) and dehydrofluorinated complex [87] (*S,S*)-**7** (24% yield). The steric hindrance of CF_3 groups probably prevents the formation of the cyclized complex.

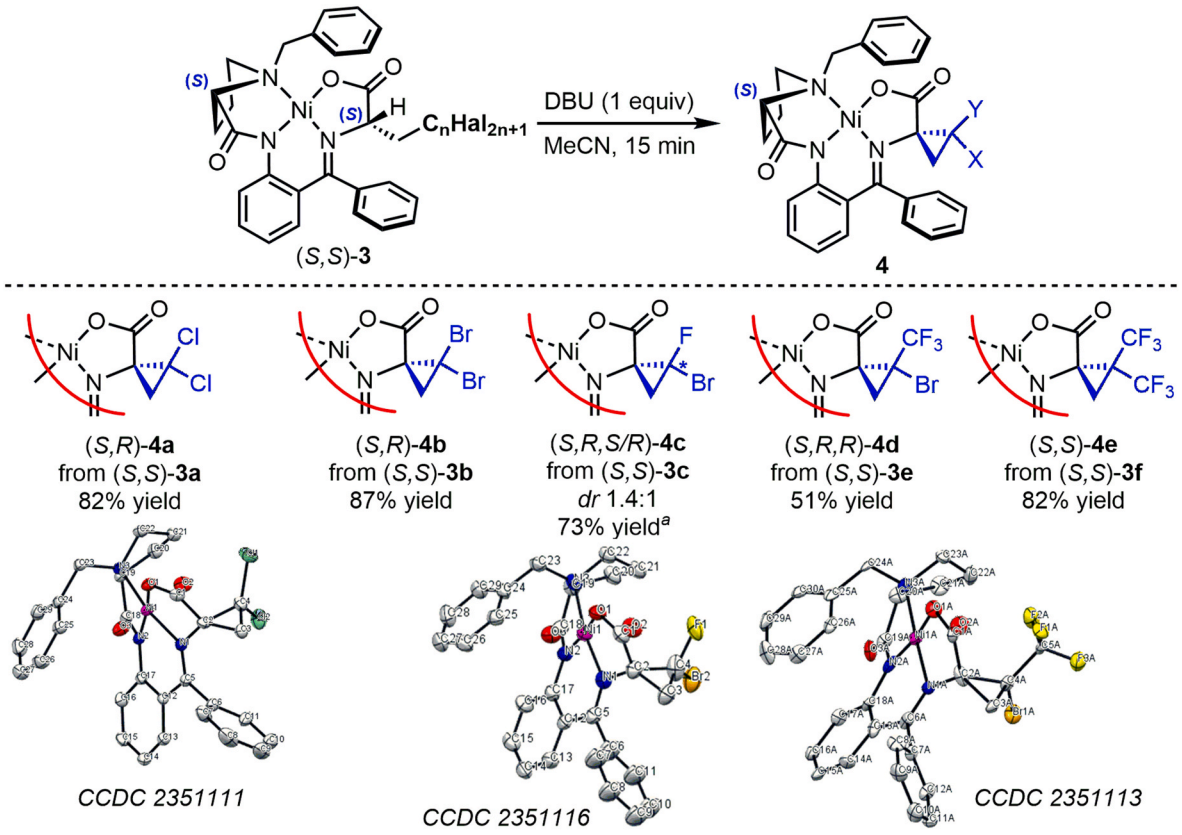
Next, the protodebromination process was investigated using the Zn dust/$Cu(OAc)_2$ system (*Method B*, Scheme 4). A mixture of the complexes (*S,S*)-**6b** and (*S,S*)-**7** was obtained starting from complex **3f** with 18% and 51% yields, respectively. On the other hand, this method allowed us to obtain predominantly the target product (*S,S*)-**6a** with an improved 49% yield.

Based on literature data [46–59], a mechanism for the radical hydrohaloalkylation reaction has been proposed (Scheme 5). The process begins with a 4-cyano-pyridine reacting with B_2Pin_2 to form an *in situ* pyridine-boron radical **I**. This radical then undergoes a single-electron transfer process (*SET*), activating a halocarbon molecule **2** to generate a polyhaloalkyl radical **II**. Next, a double bond in complex **1** acts as a radical acceptor, reacting with **II** to form intermediate complex **III**. This complex undergoes another *SET* reaction with another equivalent of radical **I**, resulting in a carbanion **IV**. Finally, the carbanion is stereoselectively protonated with alcohol, completing the desired product (*S,S*)-**3**.

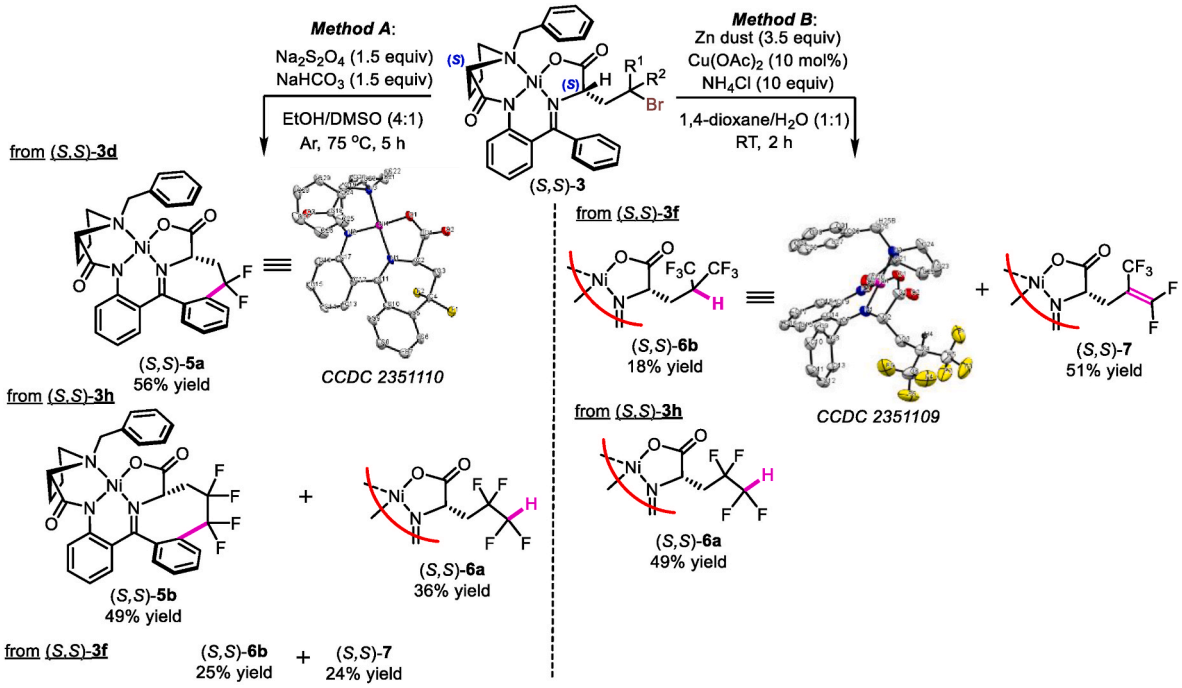
Finally, the practical applicability of the method was demonstrated through the exemplary isolation of two AAs, (*S*)-2-amino-4,4,4-trichlorobutanoic acid **8a** and **8b,** by the standard decomposition [66–78] of diastereomeric Ni(II) complexes (*S,S*)-**3a** and (*S,S*)-**3h,** respectively (Scheme 6). The heating of the corresponding complexes **3a** and **3h** in a mixture of 1*N* HCl and MeOH afforded the desired AAs **8a** and **8b** in 97% and 64% yields, respectively (Scheme 6). It is well-established that the acid-induced decomplexation of the corresponding chiral Ni(II) complexes in the presence of HCl results in the formation of α-AAs with preserving of enantiomeric purity [66–78] (see HPLC traces in the SI, Figs. S57 and S58). Importantly, the chiral auxiliary ligand can be readily recovered in enantiopure form as the hydrochloride salt from the decomposed reaction mixture with a yield of >90%. This can be achieved through subsequent filtration and extraction processes, and the recovered ligand can then be reused for the synthesis of a new batch of the starting Ni(II) complex **1**.

3. Conclusion

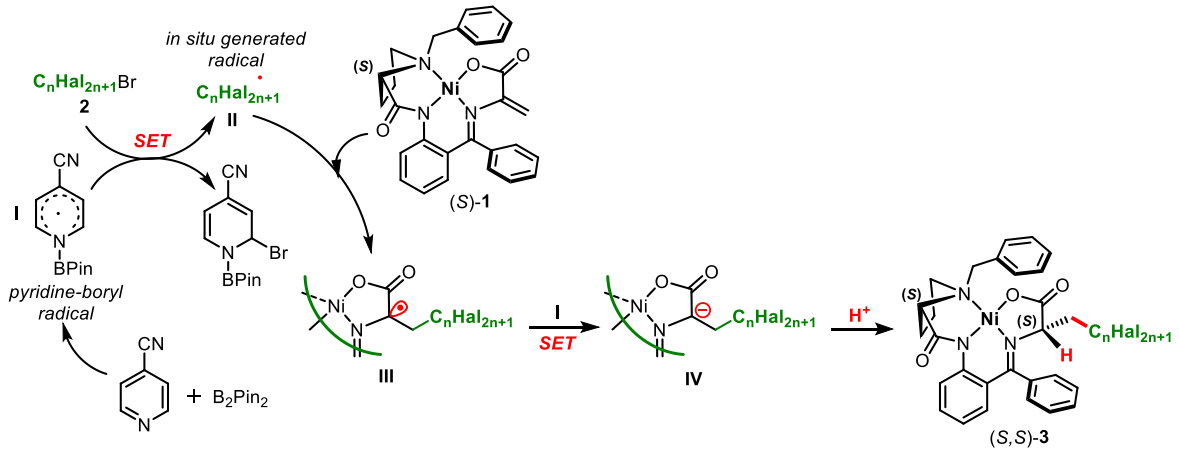
In summary, we have described a practical and useful radical hydropolyhaloalkylation reaction of an easily available and robust chiral Belokon's dehydroalanine Ni(II) complex to access challenging enantiopure halogenated AAs. Coupling of the complex **1** with various



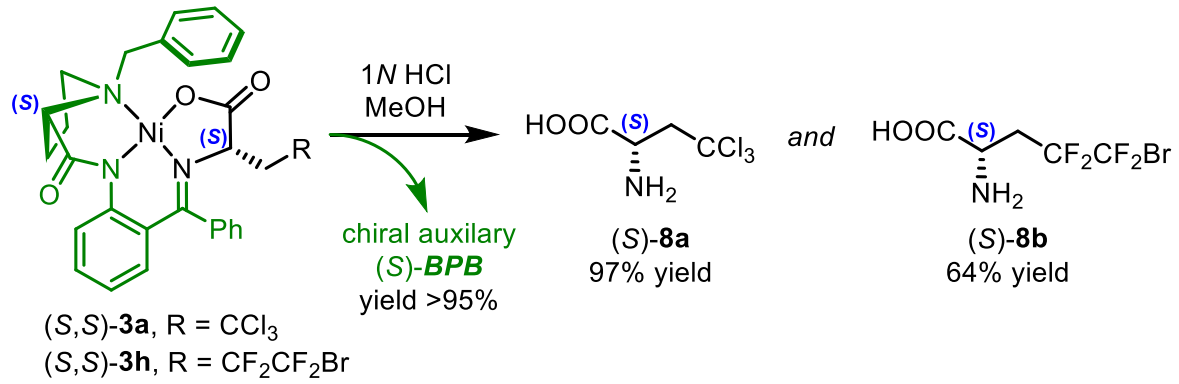
Scheme 3. Post-modification of complexes **3**: the intramolecular cyclization reaction. Isolated yields are provided. [a]The combined yields of (*S*,*S*,*S*)-**4c** and (*S*,*S*,*R*)-**4c**. The *dr* was determined by ^{1}H NMR analysis. The structures of complexes **4a**, **4c** and **4d** as determined by single crystal XRD analysis (hydrogen atoms are omitted for clarity). Thermal ellipsoids are shown at the 50% probability level.



Scheme 4. Post-modification of complexes **3**: the protodebromination reaction. Isolated yields are provided. The structures of complexes **5a** and **6b** as determined by single crystal XRD analysis (hydrogen atoms are omitted for clarity). Thermal ellipsoids are shown at the 50% probability level.



Scheme 5. A proposed mechanism for the radical coupling reaction of complex **1** with halocarbons **2**.



Scheme 6. Isolation of AAs **8a** and **8b** after decomposition of the Ni(II) complexes **3a** and **3h**.

halocarbons mediated by a 4-cyano-pyrydine/B_2Pin_2 system resulted in a library of functionalized diastereomeric complexes in the range of 31–65% yields. The practicality of the developed protocol was demonstrated by the further post-modification of the AA side chain, leading to the formation of complexes with a cyclopropane ring and products containing a protodebromination group. Finally, two enantiomerically pure α-AAs, including (*S*)-2-amino-4,4,4-trichlorobutanoic acid, were obtained through acid-induced decomposition of the corresponding chiral diastereomeric Ni(II) complexes along with the recovery of the chiral auxiliary.

Accession codes

Deposition Numbers 2351109–2351116 contain the supplementary crystallographic data for Ni(II) complexes. These can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

CRediT authorship contribution statement

Nadezhda V. Stoletova: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Alexander F. Smol'yakov:** Formal analysis, Data curation. **Andrey A. Tyutyunov:** Methodology. **Victor I. Maleev:** Writing – review & editing, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Vladimir A. Larionov:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Victor I. Maleev reports financial support was provided by Russian Science Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the Russian Science Foundation (RSF grant No. 23-73-00073); https://rscf.ru/project/23-73-00073/. We would like to express our gratitude to Mr. Andrey D. Moshchenkov for his assistance with the preliminary experiments. The XRD analysis were performed with the support from the Ministry of Science and Higher Education of the Russian Federation using the equipment of the Center for Molecular Composition Studies of INEOS RAS (contract No. 075-00277-24-00). The publication has been supported by the RUDN University Strategic Academic Leadership Program (optical rotation measurement).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tchem.2024.100118.

Data availability

Data will be made available on request.

References

[1] H. Mei, J. Han, K.D. Klika, K. Izawa, T. Sato, N.A. Meanwell, V.A. Soloshonok, Applications of fluorine-containing amino acids for drug design, Eur. J. Med. Chem. 186 (2020) 111826, https://doi.org/10.1016/j.ejmech.2019.111826.

[2] H. Mei, J. Han, S. White, D.J. Graham, K. Izawa, T. Sato, S. Fustero, N.A. Meanwell, V.A. Soloshonok, Tailor-made amino acids and fluorinated motifs as prominent traits in modern pharmaceuticals, Chem. Eur. J. 26 (2020) 11349–11390, https://doi.org/10.1002/chem.202000617.

[3] Q. Wang, J. Han, A. Sorochinsky, A. Landa, G. Butler, V.A. Soloshonok, The latest FDA-approved pharmaceuticals containing fragments of tailor-made amino acids and fluorine, Pharmaceuticals 15 (2022) 999, https://doi.org/10.3390/ph15080999.

[4] N. Wang, H. Mei, G. Dhawan, W. Zhang, J. Han, V.A. Soloshonok, New approved drugs appearing in the pharmaceutical market in 2022 featuring fragments of tailor-made amino acids and fluorine, Molecules 28 (2023) 3651, https://doi.org/10.3390/molecules28093651.

[5] M. Mardirossian, M. Rubini, M.F.A. Adamo, M. Scocchi, M. Saviano, A. Tossi, R. Gennaro, A. Caporale, Natural and synthetic halogenated amino acids—structural and bioactive features in antimicrobial peptides and peptidomimetics, Molecules 26 (2021) 7401, https://doi.org/10.3390/molecules26237401.

[6] N.A. Meanwell, Synopsis of some recent tactical application of bioisosteres in drug design, J. Med. Chem. 54 (2011) 2529–2591, https://doi.org/10.1021/jm1013693.

[7] N.A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, J. Med. Chem. 61 (2018) 5822–5880, https://doi.org/10.1021/acs.jmedchem.7b01788.

[8] C.A. Banuelos, I. Tavakoli, A.H. Tien, D.P. Caley, N.R. Mawji, Z. Li, J. Wang, Y. C. Yang, Y. Imamura, L. Yan, J.G. Wen, R.J. Andersen, M.D. Sadar, Sintokamide A is a novel antagonist of androgen receptor that uniquely binds activation function-1 in its amino-terminal domain, J. Biol. Chem. 291 (2016) 22231–22243, https://doi.org/10.1074/jbc.M116.734475.

[9] X. Fu, J.-U. Su, L.-M. Zheng, Dysamide U, a new trichlorinated diketopiperazine from the sponge *Dysidea sp*, Chin. J. Chem. 18 (2000) 882–885, https://doi.org/10.1002/cjoc.20000180616.

[10] C.L. Gall, E. Bonnelye, P. Clezardin, Cathepsin K inhibitors as treatment of bone metastasis, Curr. Opin. Support. Palliative Care 2 (2008) 218–222, https://doi.org/10.1097/SPC.0b013e32830baea9.

[11] J.B. MacMillan, T.F. Molinski, Herbacic acid, a simple prototype of 5,5,5-trichloroleucine metabolites from the sponge *Dysidea herbacea*, J. Nat. Prod. 63 (2000) 155–157, https://doi.org/10.1021/np990468j.

[12] G. Lemonnier, C. Lion, J.-C. Quirion, J.-P. Pin, C. Goudet, P. Jubault, α-Amino-β-fluorocyclopropanecarboxylic acids as a new tool for drug development: synthesis of glutamic acid analogs and agonist activity towards metabotropic glutamate receptor 4, Bioorg. Med. Chem. 20 (2012) 4716–4726, https://doi.org/10.1016/j.bmc.2012.06.006.

[13] T. Katagiri, M. Irie, K. Uneyama, Syntheses of optically active trifluoronorcoronamic acids, Org. Lett. 16 (2000) 2423–2425, https://doi.org/10.1021/ol0059955.

[14] L.M. Childs-Kean, N.A. Brumwell, E.F. Lodl, Profile of sofosbuvir/velpatasvir/voxilaprevir in the treatment of hepatitis C, Infect. Drug Resist. 12 (2019) 2259–2268, https://doi.org/10.2147/IDR.S171338.

[15] M. Strickland, C.L. Willis, in: A.B. Hughes (Ed.), Synthesis of Halogenated α-amino Acids in *Amino Acids, Peptides and Proteins in Organic Chemistry: Origins and Synthesis of Amino Acids*, first ed., Wiley-VCH, Weinheim, 2009, pp. 441–471, https://doi.org/10.1002/9783527631766.ch10, 1.

[16] J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes, B. Koksch, Approaches to obtaining fluorinated α-amino acids, Chem. Rev. 119 (2019) 10718–10801, https://doi.org/10.1021/acs.chemrev.9b00024.

[17] X.-X. Zhang, Y. Gao, X.-S. Hu, C.-B. Ji, Y.-L. Liu, J.-S. Yu, Recent advances in catalytic enantioselective synthesis of fluorinated α- and β-amino acids, Adv. Synth. Catal. 362 (2020) 4763–4793, https://doi.org/10.1002/adsc.202000966.

[18] V.A. Larionov, N.V. Stoletova, V.I. Maleev, Advances in asymmetric amino acid synthesis enabled by radical chemistry, Adv. Synth. Catal. 362 (2020) 4325–4367, https://doi.org/10.1002/adsc.202000753.

[19] J.M. Muñoz-Molina, T.R. Belderrain, P.J. Pérez, Atom transfer radical reactions as a tool for olefin functionalization–on the way to practical applications, Eur. J. Inorg. Chem. 2011 (2011) 3155–3164, https://doi.org/10.1002/ejic.201100379.

[20] Y.-Y. Liang, G.-F. Lv, X.-H. Ouyang, R.-J. Song, J.-H. Li, Recent developments in the polychloroalkylation by use of simple alkyl chlorides, Adv. Synth. Catal. 363 (2021) 290–304, https://doi.org/10.1002/adsc.202000824.

[21] G. Huang, J.-T. Yu, C. Pan, Recent advances in polychloromethylation reactions, Adv. Synth. Catal. 363 (2021) 305–327, https://doi.org/10.1002/adsc.202000924.

[22] J. Zhang, C. Zhang, N. Mo, J. Luo, L. Chen, W. Liu, Research progress in radical addition reaction of alkenes involving chloroform, Chin. J. Org. Chem. 9 (2023) 3098–3106, https://doi.org/10.6023/cjoc202303016.

[23] M.S. Kharasch, E.V. Jensen, W.H. Urry, Addition of carbon tetrachloride and chloroform to olefins, Science 102 (1945) 128, https://doi.org/10.1126/science.102.2640.128.a.

[24] M.S. Kharasch, E.V. Jensen, W.H. Urry, Reactions of atoms and free radicals in solution. X. The addition of polyhalomethanes to olefins, J. Am. Chem. Soc. 69 (1945) 1100–1105, https://doi.org/10.1021/ja01197a035.

[25] L. Quebatte, R. Scopelliti, K. Severin, Atom transfer radical additions with the cationic half-sandwich complex $[Cp^*Ru(PPh_3)_2(CH_3CN)]OTf$, Eur. J. Inorg. Chem. 2005 (2005) 3353–3358, https://doi.org/10.1002/ejic.200500321.

[26] J. Wolf, K. Thommes, O. Briel, R. Scopelliti, K. Severin, Dinuclear ruthenium ethylene complexes: syntheses, structures, and catalytic applications in ATRA and ATRC reactions, Organometallics 27 (2008) 4464–4474, https://doi.org/10.1021/om8004096.

[27] M.-Z. Lu, T.-P. Loh, Iron-catalyzed cascade carbochloromethylation of activated alkenes: highly efficient access to chloro-containing oxindoles, Org. Lett. 18 (2014) 4698–4701, https://doi.org/10.1021/ol502411c.

[28] H. Nishiyama, H. Ikeda, T. Saito, B. Kriegel, H. Tsurugi, J. Arnold, K. Mashima, Structural and electronic noninnocence of α-diimine ligands on niobium for reductive C–Cl bond activation and catalytic radical addition reactions, J. Am. Chem. Soc. 139 (2017) 6494–6505, https://doi.org/10.1021/jacs.7b02710.

[29] K. Das, M. Dutta, B. Das, H.K. Srivastava, A. Kumar, Efficient pincer-ruthenium catalysts for Kharasch addition of carbon tetrachloride to styrene, Adv. Synth. Catal. 361 (2019) 2965–2980, https://doi.org/10.1002/adsc.201900107.

[30] N. Zwettler, A. Dupé, S. Klokić, A. Milinković, D. Rodić, S. Walg, D. Neshchadin, F. Belaj, N.C. Mösch-Zanetti, Hydroalkylation of aryl alkenes with organohalides catalyzed by molybdenum oxido based Lewis pairs, Adv. Synth. Catal. 362 (2020) 3170–3182, https://doi.org/10.1002/adsc.202000425.

[31] S. Arora, T. Singh, U. Mondal, A. Singh, Visible light mediated halogen atom transfer to access polyhalogenated and deuterated lactams from alkyl halides, Eur. J. Org. Chem. 26 (2023) e202300469, https://doi.org/10.1002/ejoc.202300469.

[32] Z.-T. Luo, L.-J. Zhong, Q. Zhou, B.-Q. Xiong, K.-W. Tang, Y. Liu, Photoredox polychloroalkylation/spirocyclization of activated alkynes *via* $C(sp^3)$-H bond cleavage, Eur. J. Org. Chem. 27 (2024) e202301159, https://doi.org/10.1002/ejoc.202301159.

[33] K. Matyjaszewski, J. Xia, Atom transfer radical polymerization, Chem. Rev. 101 (2001) 2921–2990, https://doi.org/10.1021/cr940534g.

[34] Q.-Y. Lin, X.-H. Xu, F.-L. Qing, Visible light-induced selective hydrobromodifluoromethylation of alkenes with dibromodifluoromethane, Org. Biomol. Chem. 13 (2015) 8740–8749, https://doi.org/10.1039/C5OB01302J.

[35] C. Pan, D. Gao, Z. Yang, C. Wu, J.-T. Yu, Metal-free radical cascade chloromethylation of unactivated alkenes: synthesis of polychloro-substituted indolines, Org. Biomol. Chem. 16 (2018) 5752–5755, https://doi.org/10.1039/C8OB01554F.

[36] C. Chen, Y. Li, Y. Pan, L. Duan, W. Liu, Oxidative radical addition–chlorination of alkenes to access 1,1-dichloroalkanes from simple reagents, Org. Chem. Front. 6 (2019) 2032–2036, https://doi.org/10.1039/C9QO00400A.

[37] K. Matsuo, E. Yamaguchi, A. Itoh, In situ-generated halogen-bonding complex enables atom transfer radical addition (ATRA) reactions of olefins, J. Org. Chem. 85 (2020) 10574–10583, https://doi.org/10.1021/acs.joc.0c01135.

[38] H. Liu, Z. Yang, J.-T. Yu, C. Pan, Radical polychloromethylation/cyclization of unactivated alkenes: access to polychloromethyl-substituted ring-fused quinazolinones, Adv. Synth. Catal. 364 (2022) 1085–1090, https://doi.org/10.1002/adsc.202200001.

[39] Y. Cheng, Z. Qu, S. Chen, X. Ji, G.-J. Deng, H. Huang, Visible-light-induced photoredox 1,1-dichloromethylation of alkenes with chloroform, Adv. Synth. Catal. 364 (2022) 1573–1579, https://doi.org/10.1002/adsc.202200074.

[40] T.-L. Wang, B.-S. Zhang, J.-J. Liu, X.-J. Liu, X.-C. Wang, Z.-J. Quan, Visible light promoted polyhalomethylation of alkenes: alkylation and cyclization, Org. Chem. Front. 9 (2022) 1004–1009, https://doi.org/10.1039/D1QO01662H.

[41] C. Wu, X. Hui, D. Zhang, M. Zhang, Y. Zhu, S. Wang, Visible light-mediated polychlorination of alkenes *via* the dichloromethyl radical generated by chloroform and chlorides, Green Chem. 24 (2022) 1103–1108, https://doi.org/10.1039/D1GC04109F.

[42] V.S. Kostromitin, A.O. Sorokin, V.V. Levin, A.D. Dilman, Aminals as powerful XAT-reagents: activation of fluorinated alkyl chlorides, Chem. Sci. 14 (2023) 3229–3234, https://doi.org/10.1039/D3SC00027C.

[43] Z.-Q. Zhang, Y.-Q. Sang, C.-Q. Wang, P. Dai, X.-S. Xue, J.L. Piper, Z.-H. Peng, J.-A. Ma, F.-G. Zhang, J. Wu, Difluoromethylation of unactivated alkenes using Freon-22 through tertiary amine-borane-triggered halogen atom transfer, J. Am. Chem. Soc. 144 (2022) 14288–14296, https://doi.org/10.1021/jacs.2c05356.

[44] M. Liu, B. Liu, Q. Wang, K. Feng, Y. Li, L. Liu, J. Tong, Metal-free synthesis of 1,3-dichloro-1,5-diarylpentan-5-ones *via* cascade oxidative radical addition of styrenes with $CHCl_3$, Org. Biomol. Chem. 22 (2024) 699–702, https://doi.org/10.1039/D3OB01403G.

[45] E.V. Malakhova, V.S. Kostromitin, D.Y. Cheboksarov, V.V. Levin, A.D. Dilman, Sodium hypophosphite as a halogen atom transfer (XAT) agent under photocatalytic conditions, J. Org. Chem. 89 (2024) 12812–12821, https://doi.org/10.1021/acs.joc.4c01412.

[46] G. Wang, H. Zhang, J. Zhao, W. Li, J. Cao, C. Zhu, S. Li, Homolytic cleavage of a B−B bond by the cooperative catalysis of two Lewis bases: computational design and experimental verification, Angew. Chem. Int. Ed. 55 (2016) 5985–5989, https://doi.org/10.1002/anie.201511917.

[47] G. Wang, J. Cao, L. Gao, W. Chen, W. Huang, X. Cheng, S. Li, Metal-free synthesis of C-4 substituted pyridine derivatives using pyridine-boryl radicals *via* a radical addition/coupling mechanism: a combined computational and experimental study, J. Am. Chem. Soc. 139 (2017) 3904–3910, https://doi.org/10.1021/jacs.7b00823.

[48] L.C.M. Castro, I. Sultan, H. Tsurugi, K. Mashima, Pyridine-mediated B–B bond activation of $(RO)_2B–B(OR)_2$ for generating borylpyridine anions and pyridine-stabilized boryl radicals as useful boryl reagents in organic synthesis, Synthesis 53 (2021) 3211–3226, https://doi.org/10.1055/a-1486-8169.

[49] L. Gao, G. Wang, J. Cao, D. Yuan, C. Xu, X. Guo, S. Li, Organocatalytic decarboxylative alkylation of *N*-hydroxy-phthalimide esters enabled by pyridine-boryl radicals, Chem. Commun. 54 (2018) 11534–11537, https://doi.org/10.1039/C8CC06152A.

[50] J. Cao, G. Wang, L. Gao, X. Cheng, S. Li, Organocatalytic reductive coupling of aldehydes with 1,1-diarylethylenes using an *in situ* generated pyridine-boryl radical, Chem. Sci. 9 (2018) 3664–3671, https://doi.org/10.1039/C7SC05225A.

[51] J. Cao, G. Wang, L. Gao, H. Cheng, X. Liu, X. Cheng, S. Li, Perfluoroalkylative pyridylation of alkenes *via* 4-cyanopyridine-boryl radicals, Chem. Sci. 10 (2019) 2767–2772, https://doi.org/10.1039/C8SC05237A.

[52] J. Cao, G. Li, G. Wang, L. Gao, S. Li, Iodoperfluoroalkylation of unactivated alkenes *via* pyridine-boryl radical initiated atom-transfer radical addition, Org. Biomol. Chem. 20 (2022) 2857–2862, https://doi.org/10.1039/D2OB00453D.

[53] Z. Ding, Z. Liu, Z. Wang, T. Yu, M. Xu, J. Wen, K. Yang, H. Zhang, L. Xu, P. Li, Catalysis with diboron(4)/pyridine: application to the broad-scope [3+2] cycloaddition of cyclopropanes and alkenes, J. Am. Chem. Soc. 144 (2022) 8870–8882, https://doi.org/10.1021/jacs.2c03673.

[54] M. Xu, Z. Wang, Z. Sun, Y. Ouyang, Z. Ding, T. Yu, L. Xu, P. Li, Diboron(4)-catalyzed remote [3+2] cycloaddition of cyclopropanes *via* dearomative/rearomative radical transmission through pyridine, Angew. Chem. Int. Ed. 61 (2022) e202214507, https://doi.org/10.1002/anie.202214507.

[55] C.-H. Qu, L.-X. Gao, Y. Tang, Y. Liu, X.-Q. Luo, G.-T. Song, Metal-free reductive coupling of *para*-quinone methides with 4-cyanopyridines enabled by pyridine-boryl radicals: access to pyridylated diarylmethanes with anti-cancer activity, Chem. Eur. J. 28 (2022) e202200264, https://doi.org/10.1002/chem.202200264.

[56] T. Yu, J. Yang, Z. Wang, Z. Ding, M. Xu, J. Wen, L. Xu, P. Li, Selective [2σ+2σ] cycloaddition enabled by boronyl radical catalysis: synthesis of highly substituted bicyclo[3.1.1]heptanes, J. Am. Chem. Soc. 145 (2023) 4304–4310, https://doi.org/10.1021/jacs.2c13740.

[57] J. Jo, S. Kim, S. Park, S. Kim, S. Lee, J.-H. Choi, W.-J. Chung, Study on pyridine-boryl radical-promoted, ketyl radical-mediated carbon–carbon bond-forming reactions, J. Org. Chem. 89 (2024) 8985–9000, https://doi.org/10.1021/acs.joc.4c00946.

[58] T. Li, L. Wie, Z. Wang, X. Zhang, J. Yang, Y. Wie, P. Li, L. Xu, Vinylcyclopropane-cyclopentene (VCP-CP) rearrangement enabled by pyridine-assisted boronyl radical catalysis, Org. Lett. 26 (2024) 5341–5346, https://doi.org/10.1021/acs.orglett.4c01724.

[59] X. Zhang, X. Cao, L. Wei, Z. Wang, Y. Wei, L. Xu, G. Huang, A pyridine-boryl radical mediated cascade reaction towards the synthesis of indolizines: a computational mechanistic analysis, Org. Chem. Front. 11 (2024) 4168–4175, https://doi.org/10.1039/D4QO00558A.

[60] G. Helmchen, G. Wegner, Synthesis of enantiomerically pure (*S*)-3-trichloromethylbutyric acid *via* asymmetric conjugate addition of trichloromethyl metal compounds to a chiral enoate. Activation effect of a sulfonylamino group, Tetrahedron Lett. 26 (1985) 6047–6050, https://doi.org/10.1016/S0040-4039(00)95121-9.

[61] S.E. Brantley, T.F. Molinski, Synthetic studies of trichloroleucine marine natural products. Michael addition of $LiCCl_3$ to *N*-crotonylcamphor sultam, Org. Lett. 1 (1999) 2165–2167, https://doi.org/10.1021/ol991256g.

[62] R.I. Rodríguez, M. Sicignano, J. Alemán, Fluorinated sulfinates as source of alkyl radicals in the photo-enantiocontrolled β-functionalization of enals, Angew. Chem. Int. Ed. 61 (2022) e202112632, https://doi.org/10.1002/anie.202112632.

[63] H. Huo, C. Wang, K. Harms, E. Meggers, Enantioselective, catalytic trichloromethylation through visible-light-activated photoredox catalysis with a chiral iridium complex, J. Am. Chem. Soc. 137 (2015) 9551–9554, https://doi.org/10.1021/jacs.5b06010.

[64] B. Chen, C. Fang, P. Liu, J.M. Ready, Rhodium-catalyzed enantioselective radical addition of CX_4 reagents to olefins, Angew. Chem. Int. Ed. 56 (2017) 8780–8784, https://doi.org/10.1002/anie.201704074.

[65] S. Beaumont, E.A. Ilardi, L.R. Monroe, A. Zakarian, Valence tautomerism in titanium enolates: catalytic radical haloalkylation and application in the total synthesis of neodysidenin, J. Am. Chem. Soc. 132 (2010) 1482–1483, https://doi.org/10.1021/ja910154f.

[66] V.A. Larionov, H.V. Adonts, Z.T. Gugkaeva, A.F. Smol'yakov, A.S. Saghyan, M. S. Miftakhov, S.A. Kuznetsova, V.I. Maleev, Y.N. Belokon, The elaboration of a general approach to the asymmetric synthesis of 1,4-substituted 1,2,3-triazole containing amino acids *via* Ni(II) complexes, ChemistrySelect 3 (2018) 3107–3110, https://doi.org/10.1002/slct.201800228.

[67] V.A. Larionov, T.F. Savel'yeva, M.G. Medvedev, N.V. Stoletova, A.F. Smol'yakov, Z.T. Gugkaeva, T. Cruchter, V.I. Maleev, The selective *N*-functionalization of indoles via *aza*-Michael addition in the ligand sphere of a chiral nickel(II) complex: asymmetric synthesis of (*S*)-1*H*-indole-alanine derivatives, Eur. J. Org. Chem. 2019 (2019) 3699–3703, https://doi.org/10.1002/ejoc.201900650.

[68] Z.T. Gugkaeva, M.V. Panova, A.F. Smol'yakov, M.G. Medvedev, A.T. Tsaloev, I. A. Godovikov, V.I. Maleev, V.A. Larionov, Asymmetric metal-templated route to amino acids with 3-spiropyrrolidine oxindole core via a 1,3-dipolar addition of azomethine ilides to a chiral dehydroalanine Ni(II) complex, Adv. Synth. Catal. 364 (2022) 2395–2402, https://doi.org/10.1002/adsc.202200446.

[69] Z.T. Gugkaeva, Z.Z. Mardiyan, A.F. Smol'yakov, A.S. Poghosyan, A.S. Saghyan, V. I. Maleev, V.A. Larionov, Sequential Heck cross-coupling and hydrothiolation reactions taking place in the ligand sphere of a chiral dehydroalanine Ni(II) complex: asymmetric route to β-aryl substituted cysteines, Org. Lett. 24 (2022) 6230–6235, https://doi.org/10.1021/acs.orglett.2c02591.

[70] H.I. Hakobyan, S.M. Jamgaryan, A.S. Sargsyan, Y.M. Danghyan, V.A. Larionov, V. I. Maleev, A.S. Saghyan, Z.Z. Mardiyan, A stereoselective entry to enantiopure (*S*)-2-amino-2-methyl-5-arylpent-4-ynoic acids and evaluation of their inhibitory activity against bacterial Collagenase G, Symmetry 15 (2023) 1924, https://doi.org/10.3390/sym15101924.

[71] M.A. Arsenov, N.V. Stoletova, A.F. Smol'yakov, T.F. Savel'yeva, V.I. Maleev, D. A. Loginov, V.A. Larionov, A synthetic route to artificial chiral α-amino acids featuring a 3,4-dihydroisoquinolone core through a Rh(III)-catalyzed functionalization of allyl groups in chiral Ni(II) complexes, Org. Biomol. Chem. 21 (2023) 9143–9149, https://doi.org/10.1039/D3OB01513K.

[72] T.F. Savel'yeva, Z.T. Gugkaeva, Y.V. Nelyubina, A.F. Smol'yakov, M. A. Moskalenko, V.A. Larionov, V.I. Maleev, A metal-templated synthesis of precursors for (2*S*)- and (2*R*)-2-(3-[^{18}F]fluoropropyl)tyrosines as potential radiotracers for positron emission tomography, Mendeleev Commun. 34 (2024) 496–498, https://doi.org/10.1016/j.mencom.2024.06.008.

[73] Z.T. Gugkaeva, M.P. Stukalova, A.F. Smol'yakov, A.T. Tsaloev, V.I. Maleev, V. A. Larionov, Asymmetric metal-templated approach to amino acids with a CF_3-containing 3,2'-pyrrolidinyl spirooxindole core via a Michael/Mannich [3+2]-cycloaddition reaction, Adv. Synth. Catal. 366 (2024) 1205–1211, https://doi.org/10.1002/adsc.202301214.

[74] R.G. Gasanov, L.V. Ilinskaya, M.A. Misharin, V.I. Maleev, N.I. Raevski, N. S. Ikonnikov, S.A. Orlova, N.A. Kuzmina, Y.N. Belokon, Stereoselective radical addition of carbon-centred radicals to the dehydroalanine moiety of the chiral nickel(II) complex of the Schiff's base derived from (*S*)-2-[*N*-(*N*'-benzylprolyl) amino]benzophenone and dehydroalanine, J. Chem. Soc. Perkin Trans. 1 (2024) 3343–3348, https://doi.org/10.1039/P19940003343.

[75] V.A. Larionov, N.V. Stoletova, V.I. Kovalev, A.F. Smol'yakov, T.F. Savel'yeva, V. I. Maleev, A general synthesis of unnatural α-amino acids by iron-catalysed olefin–olefin coupling *via* generated radicals, Org. Chem. Front. 6 (2019) 1094–1099, https://doi.org/10.1039/C9QO00108E.

[76] Z.T. Gugkaeva, A.F. Smol'yakov, V.I. Maleev, V.A. Larionov, A general asymmetric synthesis of artificial aliphatic and perfluoroalkylated α-amino acids by Luche's cross-electrophile coupling reaction, Org. Biomol. Chem. 19 (2021) 5327–5332, https://doi.org/10.1039/D1OB00805F.

[77] N.V. Stoletova, A.D. Moshchenkov, A.F. Smol'yakov, Z.T. Gugkaeva, V.I. Maleev, D. Katayev, V.A. Larionov, Asymmetric synthesis of perfluoroalkylated α-amino acids through generated radicals using a chiral Ni(II) complex, Helv. Chim. Acta 104 (2021) e2000193, https://doi.org/10.1002/hlca.202000193.

[78] Y.N. Belokon, A.S. Sagyan, S.M. Djamgaryan, V.I. Bakhmutov, V.M. Belikov, Asymmetric synthesis of β-substituted α-amino acids via a chiral Ni(II) complex of dehydroalanine, Tetrahedron 44 (2024) 5507–5514, https://doi.org/10.1016/S0040-4020(01)86056-7.

[79] T.T. Talele, The "cyclopropyl fragment" is a versatile player that frequently appears in preclinical/clinical drug molecules, J. Med. Chem. 59 (2016) 8712–8756, https://doi.org/10.1021/acs.jmedchem.6b00472.

[80] M. Fedoryński, Syntheses of *gem*-dihalocyclopropanes and their use in organic synthesis, Chem. Rev. 103 (2003) 1099–1132, https://doi.org/10.1021/cr0100087.

[81] E. David, G. Milanole, P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, Syntheses and applications of monofluorinated cyclopropanes, Chem. Eur J. 18 (2012) 14904–14917, https://doi.org/10.1002/chem.201202831.

[82] K. Ishihara, M. Fushimi, M. Akakura, Rational design of minimal artificial Diels–Alderases based on the copper(II) cation–aromatic π attractive interaction, Acc. Chem. Res. 40 (2007) 1049–1055, https://doi.org/10.1021/ar700083a.

[83] W. Guo, M. Hori, Y. Ogura, K. Nishimura, K. Oki, T. Ikai, E. Yashima, K. Ishihara, Tandem isomerization/α,β-site-selective and enantioselective addition reactions of *N*-(3-butynoyl)-3,5-dimethylpyrazole induced by chiral π–Cu(II) catalysts, J. Am. Chem. Soc. 145 (2023) 27080–27088, https://doi.org/10.1021/jacs.3c10820.

[84] W. Guo, J. Huang, K. Ishihara, Chiral π–Cu(II)-catalyzed site-, *exo/endo*-, and enantioselective dearomative (3+2) cycloadditions of isoquinolinium ylides with enamides, dienamides, and a trienamide, Chem. Sci. 15 (2024) 10926–10934, https://doi.org/10.1039/d4sc02946a.

[85] F. Alonso, I.P. Beletskaya, M. Yus, Metal-mediated reductive hydrodehalogenation of organic halides, Chem. Rev. 102 (2002) 4009–4092, https://doi.org/10.1021/cr0102967.

[86] V.S. Kostromitin, V.V. Levin, A.D. Dilman, Organophotoredox-catalyzed reductive tetrafluoroalkylation of alkenes, J. Org. Chem. 88 (2023) 6523–6531, https://doi.org/10.1021/acs.joc.2c00712.

[87] G. Naulet, A. Delamare, G. Guichard, G. Compain, In situ generated DBU·HF acts as a fluorinating agent in a hexafluoroisobutylation tandem reaction: an effective route to 5,5,5,5',5',5'-hexafluoroleucine, Eur. J. Org. Chem. 26 (2023) e202201148, https://doi.org/10.1002/ejoc.202201148.