Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2018, **28**, 464–466

Mendeleev Communications

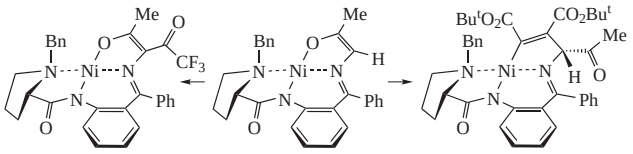
Nickel-coordinated chiral enols and Michael addition intermediate stabilized by the Ni–C bond

Liana A. Hayriyan,[a] Anna F. Mkrtchyan,[a] Margarita A. Moskalenko,[b] Victor I. Maleev,[b] Zalina T. Gugkaeva,[b] Mikhail M. Ilyin,[b] Kirill K. Babievsky,[b] Pavel V. Dorovatovskii,[c] Victor N. Khrustalev,[c,d] Alexander S. Peregudov[b] and Yuri N. Belokon*[b]

[a] *Scientific and Production Center 'Armbiotechnology', National Academy of Sciences of Republic Armenia, 0056 Yerevan, Armenia*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: yubel@ineos.ac.ru*
[c] *National Research Center 'Kurchatov Institute', 123182 Moscow, Russian Federation*
[d] *Peoples' Friendship University of Russia (RUDN University), 117198 Moscow, Russian Federation*

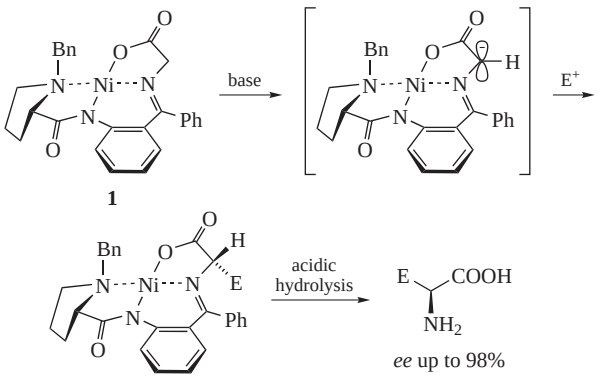
DOI: 10.1016/j.mencom.2018.09.003

A representative within a new class of chiral enol Ni^{II} complexes derived from a Schiff base of aminoacetone and (*S*)-2-*N*-(*N*-benzylprolinoylamino)benzophenone was prepared, and its performance in nucleophilic addition was estimated. The complex was inert towards aldehydes and activated C=C bonds but reacted with carboxylic anhydrides and di-*tert*-butyl acetylenedicarboxylate. An unusual Michael addition intermediate stabilized by the Ni–C bond was discovered in the latter reaction.



The synthesis of biologically and pharmacologically active enantiopure compounds plays an important role in biotechnology, medicine, and bioorganic chemistry.[1] Naturally, the catalytic methods of asymmetric synthesis are in greater demand in industry as compared to the stoichiometric methods.[1] However, a stoichiometric synthetic approach is often used to find lead pharmaceuticals or even in pilot plants before large scale production begins. In other words, the cost and constraints of using asymmetric catalysts opens a niche for asymmetric stoichiometric synthesis, even in industry. Additionally, in special cases such as the synthesis of very expensive radiotracers for positron emission tomography imaging, the asymmetric stoichiometric synthetic approach is still highly competitive and there is often no alternative.[2]

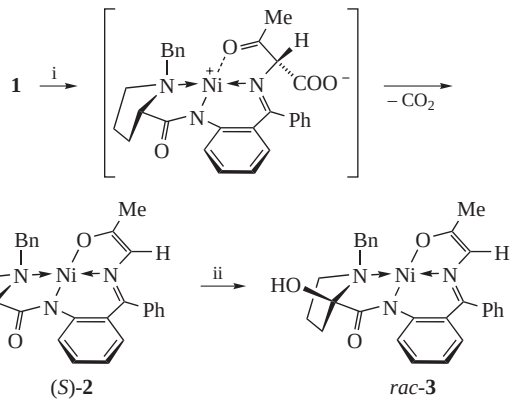
Our research group elaborated an asymmetric protocol for the synthesis of enantiopure α-amino acids, including a set of non-proteinogenic amino acids, using a chiral Ni^{II} complex derived from a Schiff base of glycine and 2-[(*S*)-*N*-(*N*-benzylprolinoyl-amino)]benzophenone **1** (Scheme 1).[3] The amino acid moiety inside the complex acquires the CH-acidity and enters in the reactions with different electrophiles to generate the corresponding diastereoisomeric complexes with very high diastereomeric excess (*de*).[3,4] The acidic hydrolysis decomposes the complexes leading to the target amino acid (up to 99% *ee*) along with recovery of chiral auxiliary and Ni^{II} ions which can be reused.



Scheme 1

It would be highly desirable to harness the advantages of the chiral auxiliary to develop synthetic protocols for other classes of organic compounds containing nitrogen atoms within their structures.

Aminoacetone seems to be a challenging candidate to enter in the Ni^{II} complex framework in place of glycine (Scheme 2). Both the acetyl group and imino substituents at the α-carbon atom



Scheme 2 *Reagents and conditions*: i, LDA, THF, –40 °C, then Ac_2O; ii, crystallization, air, acetone.

would make the moiety highly acidic. Thus, the electroneutrality of the complex would be due to the moiety ionization, resulting in the chiral enol complex **2**. The chiral enol reactivity could then be tested in a series of reactions reminiscent of metal acetylacetonate reactivity.[5] Herein, we report the synthesis and preliminary studies of the reactivity of chiral aminoacetone Ni complex **2** analogous to complex **1**.

The target product (*S*)-**2** was prepared by acylation of complex (*S*)-**1** with Ac_2O (see Scheme 2).† Most likely, the first stage of the conversion leads to the expected acetylated intermediate, which is then decarboxylated to give the chiral enolate (*S*)-**2**.

Numerous attempts to grow a crystal of (*S*)-**2** suitable for X-ray experiments failed until a crystal was grown from acetone in air. The crystal thus obtained was a 1 : 1 racemic mixture of (*S*)-**2** and (*R*)-**2**. Evidently, the racemization involved a very small portion of the whole mixture during the crystallization. This was supported by continuous high performance liquid chromatography (CHPLC) analysis of the recovered (*S*)-ligand from the initial (*S*)-**1** and (*S*)-**2**. The chiral auxiliary proved to be enantiomerically pure (see Figure S13, Online Supplementary Materials). The enantiopure (*S*)-**2** most likely did not crystallize under the reaction conditions and only the racemized portion precipitated. The racemization of the *N*-benzylproline moiety should involve both N- and C-centres. Otherwise, the removal of the α-proton from the proline moiety would involve the retention of the configuration, as was shown earlier[6] for the Co^{III} proline moiety. Although the real mechanism for the racemization is unknown, the reversible formation of Ni^{I} by electron transfer from the coordinated enolate may be implicated in the mechanism of the transformation. Such a complex should be expected to be labile, and the uncoordinated ligand racemized easily in the basic solutions.

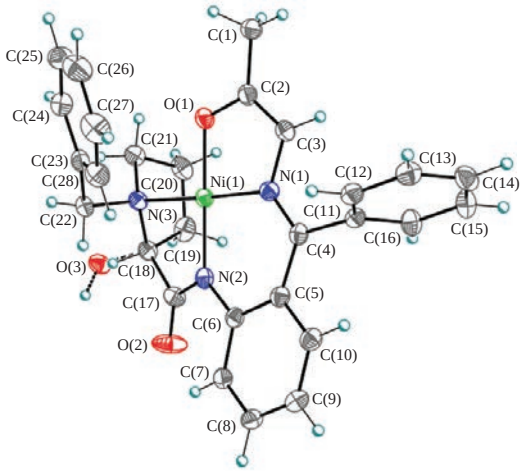


Figure 1 Molecular structure of racemic co-crystal of compounds **2** and **3** (dashed lines).

† *Complex* (*S*)-**2**. Butyllithium (2.5 M hexane solution, 10 ml, 25 mmol) was added to a solution of diisopropylamine (4.4 ml, 25 mmol) in THF (50 ml) at –40 °C under argon, and the mixture was stirred at –40 °C for 1 h. A solution of complex (*S*)-**1** (5 g, 0.01 mol) in THF (150 ml) was added to the thus obtained LDA, and the stirring was continued at –40 °C for 1 h. Acetic anhydride (1 ml, 0.01 mol) was then added. The mixture was warmed to room temperature and the stirring was continued for 2 h. The reaction course was monitored by TLC (SiO_2, $CHCl_3$–acetone, 7 : 1). The mixture was neutralized with 5% aq. AcOH and partly evaporated *in vacuo* to remove THF. Water (150 ml) was added to the residue and the mixture was extracted with CH_2Cl_2 (150 ml). The product was purified by flash chromatography (SiO_2, $CHCl_3$–acetone, 7 : 1) to afford 2.5 g (51%) of product **2**, mp 111–113 °C, $[\alpha]_D^{20}$ = +338.67 (*c* 0.15, acetone). MS, *m*/*z*: 496.1534. Found (%): C, 66.31; H, 5.44; N, 8.09. Calc. for $C_{28}H_{27}N_3NiO_2 \cdot 0.5H_2O$ (%): C, 66.64; H, 5.55; N, 8.33.

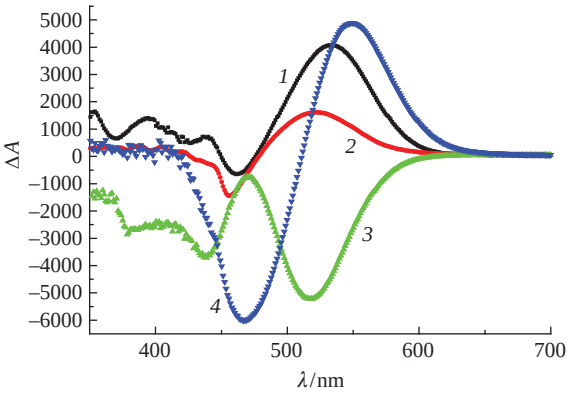
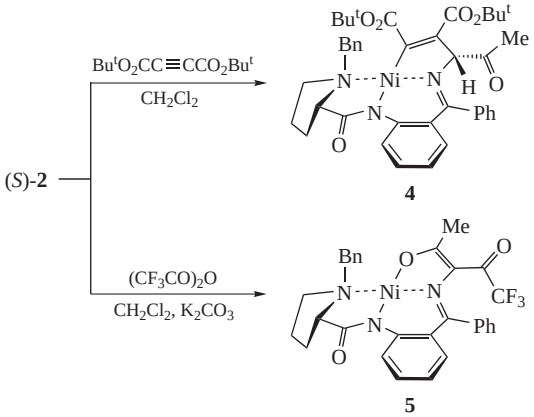


Figure 2 CD spectra for compounds (*1*) (*S*)-**1**, (*2*) (*S*)-**2**, (*3*) **4** and (*4*) **5** (*c* 0.6 g dm^{-3}, acetone).

Unexpectedly, the crystallization of complex **2** from acetone in air resulted in partial oxidation of the ligand moiety to afford compound **3** with an α-hydroxyproline fragment. The crystal contained both oxidized and unoxidized molecules in a 1 : 1 ratio (Figure 1, for full crystallographic data, see Online Supplementary Materials). The C(2)=C(3) bond [1.354(4) Å] corresponds to the double character expected for the enol form of the complex. It is slightly elongated due to the presence of a long chain of conjugated bonds.

Attempts to engage complex (*S*)-**2** in Michael reactions using routine electrophiles such as methyl acrylate, acrylonitrile, and nitrostyrene failed. Attempts to perform aldol reactions with benzaldehyde derivatives were also unsuccessful. Fortunately, the complex entered in the reaction with di-*tert*-butyl acetylenedicarboxylate in the absence of bases (Scheme 3). The adduct **4** was obtained in a 75% yield.‡ The analytical data proved its formation, and its Circular Dichroism (CD) spectra supported the formation of a new asymmetric centre in the adduct (Figure 2).

According to the X-ray data, the isolated product **4** was the Michael adduct intermediate stabilized by coordination with Ni *via* Ni–C bond formation (Figure 3). As in the case of complex **2**, the crystal grown turned to be a racemic mixture. Still, the ligand recovered from the initial complex before the crystallization was enantiomerically pure (see Figure S13). The adduct was formed



Scheme 3

‡ *Synthesis of complex* **4**. Di-*tert*-butyl acetylenedicarboxylate (0.273 g, 1.0 mmol) was added to a solution of complex (*S*)-**2** (0.25 g, 0.5 mmol) in CH_2Cl_2 (15 ml) at 25 °C with stirring. The reaction course was monitored by TLC (SiO_2, $CHCl_3$–acetone, 7 : 1). The product was purified by column chromatography on a SEPHADEX LH-20 (eluent, toluene–ethanol, 3 : 1), yield 0.27 g (75%), mp 132–134 °C, $[\alpha]_D^{20}$ = –1494 (*c* 0.15, acetone). MS, *m*/*z*: 722.2752. Found (%): C, 64.30; H, 6.02; N, 5.40. Calc. for $C_{40}H_{45}N_3NiO_7 \cdot H_2O$ (%): C, 64.88; H, 6.40; N, 5.67. For additional characteristics of compound **4**, see Online Supplementary Materials.

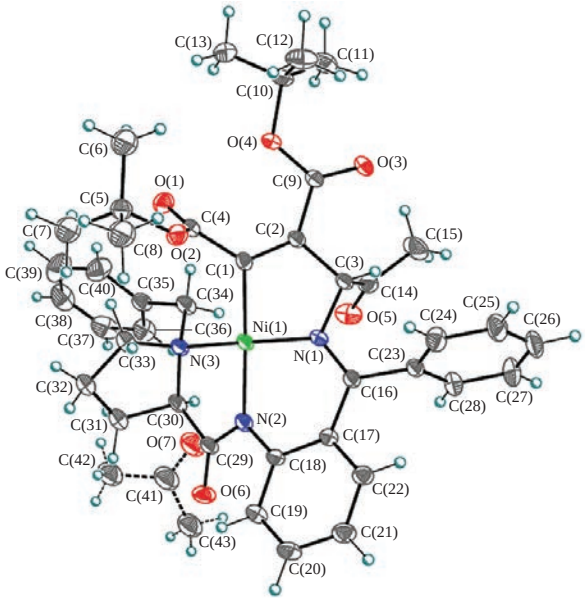


Figure 3 Molecular structure of racemic complex **4**.

with high diastereoselectivity (^{1}H and ^{13}C NMR spectra, Figures S6 and S7). Since the racemic crystal was a 1 : 1 (*S*,*R*) and (*R*,*S*) mixture (see Figure 3), enantiopure **3** had *S*- and *R*-configurations of the proline and the adduct moieties, respectively.

The Ni–C distance of 1.926(4) Å is in the range of values observed in the related complexes. The planar-square environment of the nickel atom is significantly distorted due to steric reasons. The C(1)=C(2) bond [1.343(5) Å] is in a good agreement with the double character.

Trifluoroacetic anhydride reacted with complex **2** in the presence of K_2CO_3 to afford complex **5**.§

The mechanism of the reactions may be more sophisticated than usually appeared as significant reaction inhibition occurred when the reactions were performed under inert atmosphere.

In conclusion, we have prepared a new type of chiral enol aminoacetone Ni^{II} complex. The preliminary experiments on its reactivity reveal its significant synthetic potential. The unexpected formation of a stable intermediate complex with the Ni–C bond in its Michael addition at acetylenedicarboxylate indicates its unusual reactivity. Further studies of the complex reactivity are justified and this work is ongoing in our laboratory.

This work was supported by the Russian Foundation for Basic Research (grant no. 17-303-50021 mol-nr) and in part by the RUDN University Program ‘5-100’. Synchrotron radiation-based single-crystal X-ray diffraction measurements were performed at the unique scientific facility Kurchatov Synchrotron Radiation Source supported by the Ministry of Education and Science of the Russian Federation (project code RFMEFI61917X0007). The contribution of Center for Molecule Composition Studies of A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences is gratefully acknowledged.

§ *Synthesis of complex* **5**. Potassium carbonate (0.82 g, 0.6 mmol) and trifluroacetic anhydride (0.056 ml, 0.4 mmol) were added to a solution of complex (*S*)-**2** (0.1 g, 0.2 mmol) in CH_2Cl_2 (10 ml) at 25°C with stirring. The reaction course was monitored by TLC (SiO_2, $CHCl_3$–acetone, 7 : 1). The product was purified by column chromatography (SiO_2, $CHCl_3$–acetone, 7 : 1), yield 56.3 mg (48%).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.003.

References

1 (*a*) A. M. Rouhi, *C&EN*, 2003, **18**, 56; (*b*) Q. Michaudel, Y. Ishihara and P. S. Baran, *Acc. Chem. Res*., 2015, **48**, 712; (*c*) C. A. Busacca, D. R. Fandrick, J. J. Song and C. H. Senanayake, *Adv. Synth. Catal*., 2011, **353**, 1825; (*d*) M. Waser, *Asymmetric Organocatalysis in Natural Product Syntheses*, Springer, Wien, 2012; (*e*) H. Groger, *Eur. J. Org. Chem*., 2016, 4116.

2 (*a*) F. Buckingham and V. Gouverneur, *Chem. Sci*., 2016, **7**, 1645; (*b*) J. Ermert and H. H. Coenen, *J. Labelled Compd. Radiopharm*., 2013, **56**, 225; (*c*) J. R. Hanson, *The Organic Chemistry of Isotopic Labelling*, RSC, Cambridge, UK, 2011; (*d*) C. N. Neumann and T. Ritter, *Acc. Chem. Res*., 2017, **50**, 2822.

3 (*a*) Yu. N. Belokon, A. G. Bulychev, S. V. Vitt, Yu. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. C. Ryzhov, L. A. Lysova, V. I. Bakhmutov and V. M. Belikov, *J. Am. Chem. Soc*., 1985, **107**, 4252; (*b*) Yu. N. Belokon, V. I. Bakhmutov, N. I. Chernoglazova, K. A. Kochetkov, S. V. Vitt, N. S. Garbalinskaya and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1988, 305; (*c*) Yu. N. Belokon, K. A. Kochetkov and D. A. Borkin, *Mendeleev Commun*., 2003, 132; (*d*) Yu. N. Belokon, A. G. Bulychev, V. A. Pavlov, E. B. Fedorova, V. A. Tsyryapkin, V. I. Bakhmutov and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2075; (*e*) Y. N. Belokon’, A. S. Sagyan, S. M. Djamgaryan, V. I. Bakhmutov and V. M. Belikov, *Tetrahedron*, 1988, **44**, 5507; (*f*) Y. N. Belokon’, A. N. Popkov, N. I. Chernoglazova, M. B. Saporovskaya, V. I. Bakhmutov and V. M. Belikov, *J. Chem. Soc., Chem. Commun*., 1988, 1336; (*g*) Yu. N. Belokon, V. I. Tararov, V. I. Maleev, T. F. Saveleva and M. A. Ryzhov, *Tetrahedron: Asymmetry*, 1998, 4249.

4 (*a*) K. Y. Ko, S. Wagner, S. H. Yang, D. P. Furkert and M. A. Brimble, *J. Org. Chem*., 2015, **80**, 8631; (*b*) H. Zhang, B. Yang, Z. Yang, H. Lu and G. Li, *J. Org. Chem*., 2016, **81**, 7654; (*c*) N. J. Tatum, D. S.Yufit, S. L. Cobb and C. R. Coxon, *J. Fluorine Chem*., 2015, **173**, 77; (*d*) M. Bremerich, C. Bolm, G. Raabe and V. A. Soloshonok, *Eur. J. Org. Chem*., 2017, 3211; (*e*) M. Jörres, L. J. Aceña, V. A. Soloshonok and C. Bolm, *ChemCatChem*, 2015, **7**, 1265; (*f*) A. Le Chevalier Isaad, F. Barbetti, P. Rovero, A. M. D’Ursi, M. Chelli, M. Chorev and A. M. Papini, *Eur. J. Org. Chem*., 2008, 5308; (*g*) D. Lin, J. Wang, X. Zhang, S. Zhou, J. Lian, H. Jiang and H. Liu, *Chem. Commun*., 2013, **49**, 2575; (*h*) A. S. Saghyan, A. F. Mkrtchyan, A. J. Karapetyan, Z. Z. Mardiyan, L. A. Hayriyan and H. M. Simonyan, *J. Chem. Eng. Appl*., 2016, **7**, 413; (*i*) A. E. Sorochinsky, J. L. Aceña, H. Moriwaki, T. Sato and V. A. Soloshonok, *Amino Acids*, 2013, **45**, 691; (*j*) A. E. Sorochinsky, H. Ueki, J. L. Aceña, T. K. Ellis, H. Moriwaki, T. Sato and V. A. Soloshonok, *Amino Acids*, 2013, **45**, 1017; (*k*) Y. Wang, X. Song, J. Wang, H. Moriwaki, V. A. Soloshonok and H. Liu, *Amino Acids*, 2017, **49**, 1487.

5 (*a*) J. P. Collman, *Angew. Chem., Int. Ed. Engl*., 1965, **4**, 132; (*b*) D. A. Buckingham, J. Dekkers, A. M. Sargeson and M. Wein, *Inorg. Chem*., 1973, **12**, 2019.

Received: 25th April 2018; Com. 18/5560