EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Direct reductive amination of camphor using iron pentacarbonyl as stoichiometric reducing agent: features and limitations

Authors: Oleg I. Afanasyev, Artemy R. Fatkulin, Pavel N. Solyev, Ivan Smirnov, Artem Amangeldyev, Sergey E. Semenov, and Denis Chusov

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001087

Link to VoR: https://doi.org/10.1002/ejoc.202001087

WILEY-VCH

WILEY-VCH

COMMUNICATION

Direct reductive amination of camphor using iron pentacarbonyl as stoichiometric reducing agent: features and limitations

Oleg I. Afanasyev,[a] Artemy R. Fatkulin,[a] Pavel N. Solyev,[b] Ivan Smirnov,[c] Artem Amangeldyev,[c] Sergey E. Semenov,[c] and Denis Chusov*[a]

[a] A.R. Fatkulin, Dr. O.I. Afanasyev, Dr. D. Chusov
A.N.Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences,
28 Vavilova St., 119991 Moscow, Russian Federation
E-mail: denis.chusov@gmail.com
[b] Dr. P.N. Solyev
Engelhardt Institute of Molecular Biology, Russian Academy of Sciences
32 Vavilova St., 119991 Moscow, Russian Federation
[c] Ivan Smirnov, Artem Amangeldyev, Sergey E. Semenov
Moscow South-Eastern School named after V.I. Chuikov (Moscow Chemical Lyceum),
4 Tamozhenniy proezd, 111033 Moscow, Russian Federation

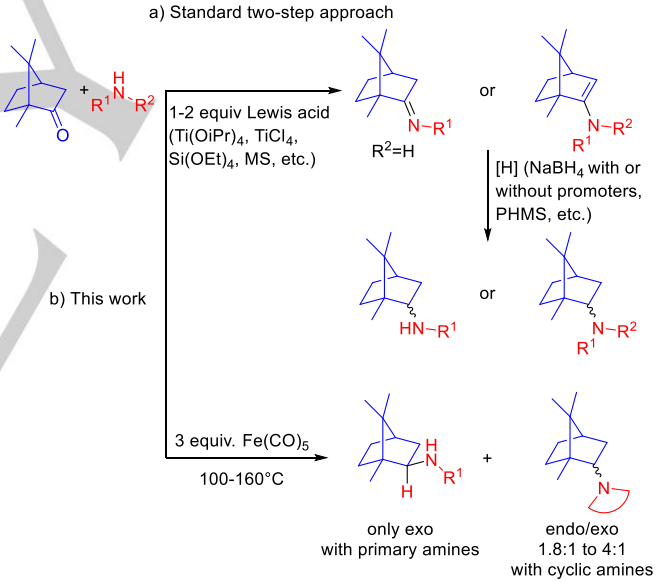
Supporting information for this article is given via a link at the end of the document.

Abstract: The method of direct reductive amination of camphor and fenchone was proposed. The most effective reducing agent is iron carbonyl. No ligands or solvents are needed. The stereochemistry of the corresponding products was determined by HMBC, HSQC, and NOESY spectra. The limitations of the method were shown. The reaction of camphor with primary amines led to exclusively *exo* product, while the reaction of fenchone led to exclusively *endo* product. The reaction of camphor with cyclic amines led to the mixture of *endo* and *exo* isomers.

Terpenoids are an irreplaceable class of natural products as well as chemical motifs. The camphoryl group is an important moiety in the structure of chiral ligands for asymmetric synthesis catalysis or it can be used as an auxiliary group in asymmetric synthesis.[1][2][3][4][5][6] The usage of fenchone based molecules for asymmetric catalysis and synthesis is less common because of the difficulty of fenchone modifications due to steric hindrance.[7,8] Camphor is a readily available starting molecule for the preparation of different compounds with biological activity. For example, camphor diimines demonstrate antiviral activity.[9][10][11] Fenchonyl amine-based molecules are potential therapeutic agents for the treatment of Alzheimer's disease.[12]

Amines are a crucial class of organic compounds with multiple academic and industrial applications. There are a plethora of synthetic approaches towards amines synthesis and modifications,[13] reductive amination being one of the most powerful and useful methods. Literature analysis revealed that the production of 21% of the most popular and commercially successful drug substances can be achieved using the reductive amination in one or multiple steps.[14]

However, the reductive amination of camphor and fenchone remains a challenge. A standard approach to reductive amination with amines other than ammonia and methylamine includes two steps: preparation of azomethines or Schiff bases in the presence of strong Lewis acids and their reduction with more or less conventional reducing agents (Scheme 1, a).[15] The synthesis of fenchonyl amines is even more challenging. Hydroxylamine or formamide are the largest molecules that can be added to fenchone, so the synthesis of amines requires up to four steps.[16] There is no universal approach, and almost every manuscript reports some particular protocol different from others.



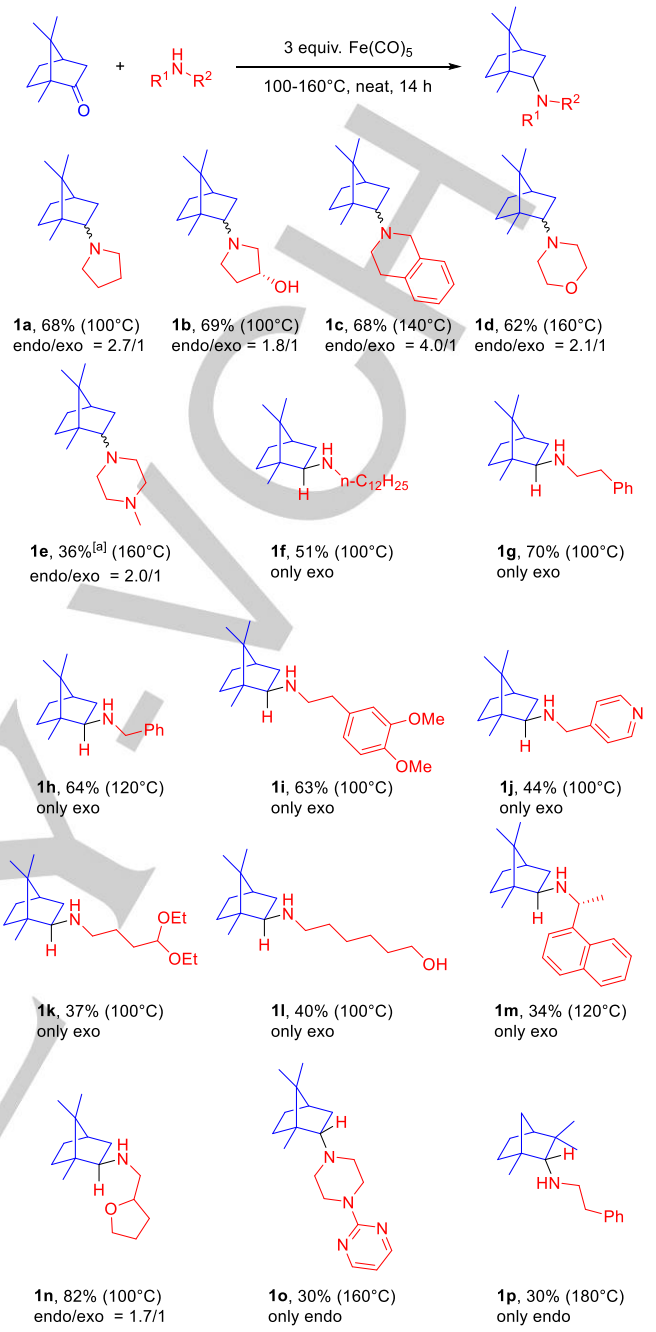
Scheme 1. Reductive amination of camphor

In most cases, the first stage of this process requires quite harsh conditions. For example, the preparation of a Schiff base from camphor and 1-phenylethylamine requires 5-10 days of heating at 150°C.[17][18] Schiff bases of other primary amines could be prepared under similarly harsh conditions.[1][2][19][20][21][11][22] Preparation of enamines is possible using titanium tetrachloride as a catalyst.[23] The reduction also might be challenging. Sodium borohydride or sodium cyanoborohydride was described as suitable for this goal in several reports.[17][18][19][20] Several other reports describe the application of a combination of sodium borohydride with nickel or cobalt chlorides. [1][2][11][24] Some of the groups use combinations of anhydrous chloroform, anhydrous

methanol, and anhydrous nickel chloride or 20 fold excess of sodium borohydride with 4 fold excess of nickel chloride. To the best of our knowledge, no papers describe any general approach for the direct reductive amination of camphor or fenchone. There is only one example of camphor direct reductive amination without an external hydrogen source using carbon monoxide as a reducing agent.[25] This protocol is very efficient but its application is limited by the necessity of carbon monoxide and high-pressure equipment for the reaction setup.

Herein, we tried to find a general approach for the direct reductive amination of camphor and fenchone. We started with classical borohydrides as reducing agents. We tried sodium borohydride and sodium triacetoxyborohydride in the direct reductive amination of camphor (see SI). However, no desired product was detected even when camphor and amine were premixed and heated with titanium(IV) isopropoxide. The only product of this process was camphoryl alcohol. Since the triacetoxyborohydride is a more selective reagent we hoped that only C=N double bond would be reduced. However, when the reaction was performed with *p*-anisidine, the Schiff base was detected but there was not even a trace of the desired amine. When pyrrolidine was chosen as an amine the desired product was not formed as well.

Balancing efficiency in the reductive amination of sterically hindered ketones and the convenience of synthetic protocols, iron pentacarbonyl was selected as a reagent of choice. Iron pentacarbonyl is an underestimated reagent with a high potential for use in organic chemistry.[26] It is a multiton industrial compound being used in iron production. Its price is comparable to the price of some HPLC solvents, and it is readily available all over the world. The applicability of iron pentacarbonyl for the reductive modifications of carbonyl compounds was earlier demonstrated by our group.[27][28][29] In particular, it was found that iron pentacarbonyl is a very efficient reducing agent in the reductive amination of highly inert ketones like benzophenone.[29] In addition, there are a lot of iron-based catalysts applicable in reductive amination using different reducing agents e.g. silanes, hydrogen, formates, etc.[30][31][32] Therefore, we concluded that iron pentacarbonyl could be applied for the reductive amination of camphor.



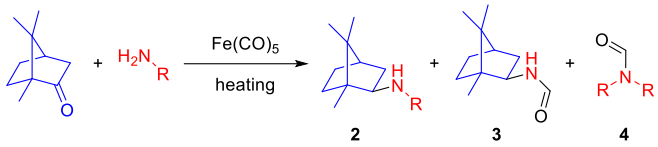
Scheme 2. Substrate scope for the reductive amination of camphor and fenchone. Isolated yields and temperature regimens. The diastereomeric ratio was determined by GC or by NMR. Detailed experimental conditions with full characterization of all the resulting products are provided in SI. [a] GC yield.

A broad set of amines was investigated. The results are provided (Scheme 2, Scheme 5). The developed protocol can be applied to the reductive amination of camphor with a variety of primary and secondary aliphatic amines. A principle difference in reactivity of secondary and primary amines was noted. Cyclic secondary amines react with camphor leading to the target molecules, and in most cases, conversion of camphor is almost the same as the yield of the product. Less nucleophilic amines require a higher temperature of the reaction: pyrrolidine (**1a**) and hydroxypyrrolidine (**1b**) react at 100°C while less nucleophilic tetrahydroisoquinoline reacts only at 140°C (**1c**) and morpholine

10.1002/ejoc.202001087

requires heating at 160°C (**1d**). The reaction of morpholine at 140°C leads to **1d** only in 40% yield *vs*. 62% at 160 °C.

In the case of primary aliphatic amines, a side transamination process was noted at elevated temperatures (Scheme 3). Two molecules of amine react with each other giving the symmetrical secondary amine and ammonia. This secondary amine reacts with iron carbonyl giving formamide **4** (the possible mechanism is provided below on the Scheme 4). Ammonia reacts with camphor under reductive conditions giving corresponding primary amine, which also undergoes formylation leading to formamide **3**. This process is negligible at 100°C, but increasing the temperature increases its role. At 160°C the ratio **3:2** achieves 1:1 and higher.



Scheme 3. Transamination of primary aliphatic amines

100°C is usually enough for amination with the majority of primary aliphatic amines (**1f, 1g, 1i, 1j, 1k, 1l, 1n**). In some cases, with increased sterical hindrance higher temperature is required (**1h, 1m**). Benzylamine allows the formation of the target product with 64% yield (**1h**) while 1-naphtylethylamine reacts only with a yield of 34% under the same conditions. Further increasing of the temperature leads to the transamination of starting amine, so it does not improve the yield of the target product. The increased steric hindrance in ketones results in a significant drop of the yield. E. g. fenchone might be used as a carbonyl component only at elevated temperatures and with the low yield (**1p**). However, to the best of our knowledge, it is the only example of direct reductive amination of fenchone.

Noteworthy, these reaction conditions tolerate different functional groups that might be unstable under strongly acidic conditions used in the classical approach. For example, the heterocycle (**1n**) or the acetal group (**1k**) are tolerated. The ω-hydroxyl group in the alkylamine structure is also tolerated, although it slightly decreases the yield in comparison to a similar substrate without the hydroxyl group (**1l** *vs*. **1f**). However, the reaction with 3-hydroxypyrrolidine leads to essentially the same yield as with pyrrolidine (**1a** *vs*. **1b**). This fact could be assigned to the possibility of complexation of iron with amine as an N,O-bidentate ligand. The formation of the iron complex with hydroxypyrrolidine is much less probable compared to a similar complex with 6-aminohexan-1-ol, thus, the reductive amination with the latter is less efficient.

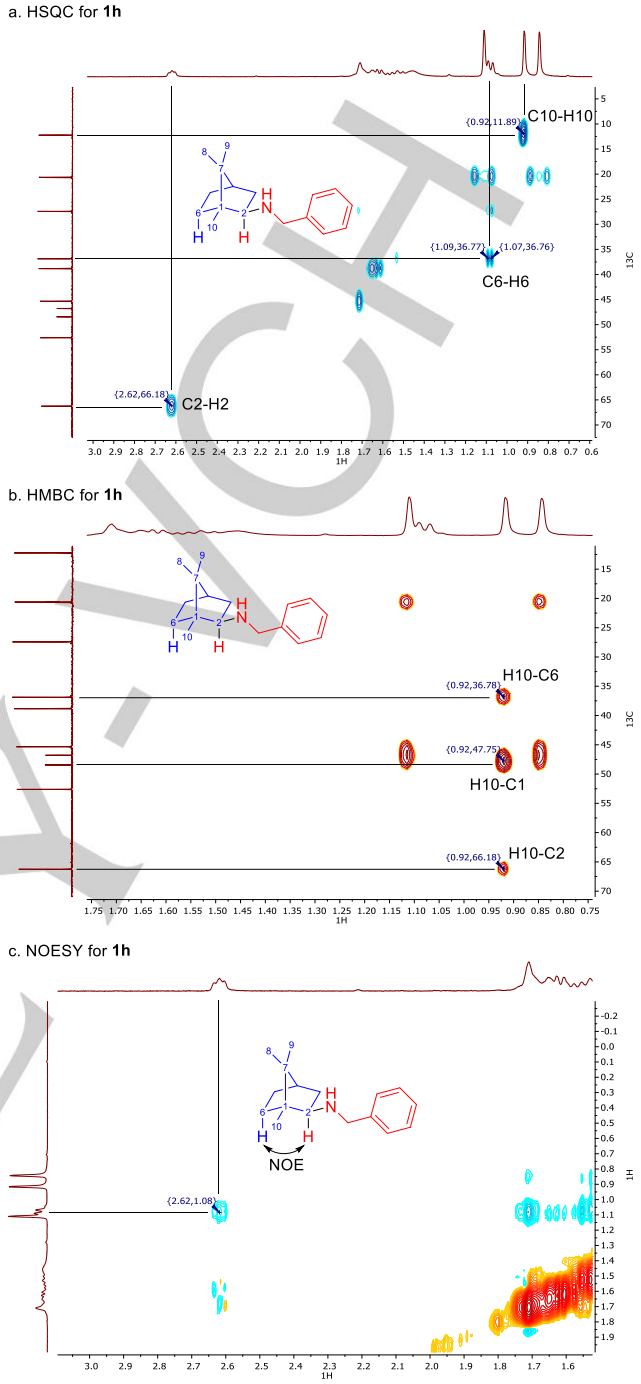
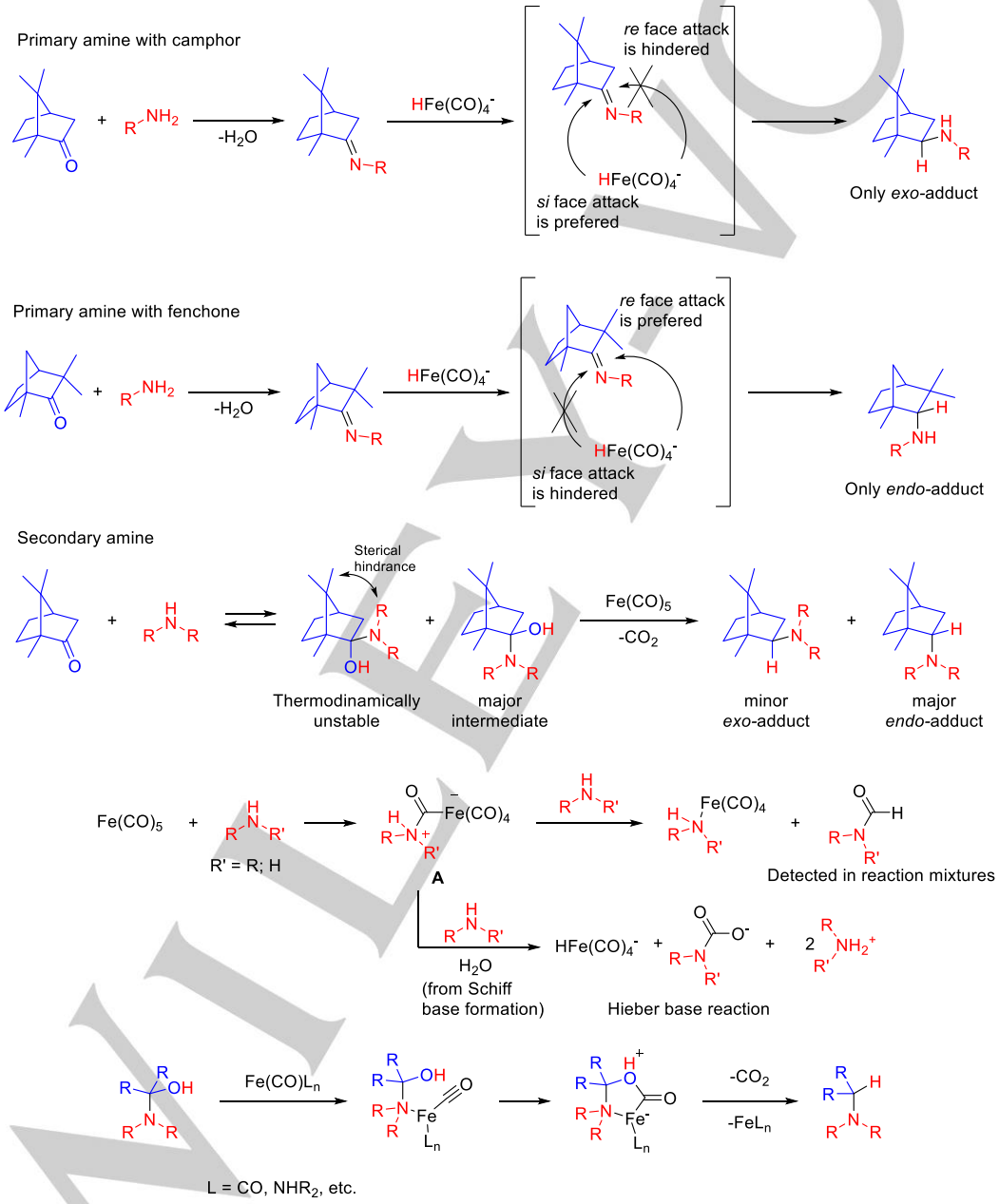


Figure 1. Assignment of the structure of **1h**.

All tested primary amines react with the selective formation of the single diastereomer, while cyclic secondary amines usually lead to the formation of the mixture of two adducts with the ratios from 4:1 to 1.8:1. To determine the structure of these products HMBC, HSQC, and NOESY spectra were registered for the synthesized compounds. All the characterization data is provided in SI; as an example here we describe the structure assignment of **1h**. According to HSQC and HMBC spectra (Figure 1, a, b), the signals of methyl groups could be assigned: CH_3 (C10) corresponds to signals at 0.92 ppm in the ^{1}H spectrum and 11.89 ppm in the ^{13}C spectrum. According to HMBC, this methyl group

has cross-peaks with the following signals in the ^{13}C spectrum: 36.78 ppm, 47.45 ppm, and 68.18 ppm. The latter corresponds to C2, which has a cross-peak with the multiplet at 2.62 ppm in the ^{1}H spectrum. The signal at 47.45 ppm has a lower intensity in comparison with other ^{13}C signals, so it should be quaternary carbon C1. Therefore, the signal at 36.78 ppm corresponds to C6. This resonance has a cross-peak in the HSQC spectrum with the multiplet at 1.08 ppm. As we see the definite cross-peak between signals at 1.08 and 2.62 ppm in the NOESY spectrum (Figure 1, c), we conclude that the configuration of **1h** is *exo*. Accurate analysis of NMR correlation spectra for all isolated products revealed that primary amines react with camphor with the exclusive formation of *exo*-adducts. Fenchone reacts with phenylethylamine leading to *endo*-adduct. Secondary amines lead to the formation of the mixture of *endo*- (major) and *exo*- (minor) isomers. There is only one exception: the selective formation of the *endo*-adduct in the case of 2-(piperazin-1-yl)pyrimidine (product **1o**).



Scheme 4. The difference in the reductive amination with primary and secondary amines.

This fact indicates the two different ways for the reductive amination with primary and secondary amines (Scheme 4). Primary amine reacts with camphor *via* the Schiff base formation and water release. Then this intermediate undergoes reduction by

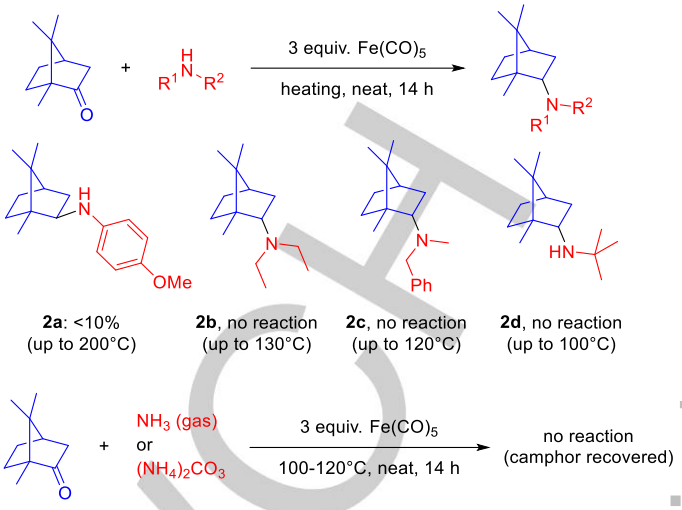
iron carbonyl hydride complex. The *re* face attack is hindered by two methyl groups in the camphoryl moiety, therefore, the *si* face attack is preferred leading to the selective formation of the *exo*-adduct.

The amination of fenchone has an opposite selectivity. *Si* face attack is hindered by -CH_2CH_2- fragment, while *re* face attack is preferred as this side is shielded by only one CH_2 group. Therefore selective formation of *endo*-adduct is observed.

In the case of secondary amines, there are two possible hemiaminal intermediates reversibly forming from camphor and amine. The *exo*-hemiaminal is less stable due to the sterical hindrance, so, the major intermediate is the *endo*-hemiaminal. Its deoxygenation with iron carbonyl leads to the preferable formation of the *endo*-adduct. In the case of reaction with the bulky secondary amine 2-(piperazin-1-yl)pyrimidine the sterical hindrance is very high and the *exo*-adduct is not formed in any detectable quantities.

We suppose that in the case of secondary and primary amines there is a different mechanism of reduction with the iron carbonyl. In both cases at the beginning of the reaction iron carbonyl reacts with an amine (Scheme 4). Such transformations are described in the papers of Bulkin *et al*.[33–35] According to these reports, the amine reacts with iron carbonyl leading to the intermediate formation of compound **A**. In the absence of water it decomposes to the iron carbonyl amine complex and the corresponding formamide. This iron carbonyl amine complex serves as a deoxygenating agent for the hemiaminal. In the presence of water (side product of Schiff base formation in the case of primary amines) **A** is transformed to the tetracarbonylhydridoferrate (in the absence of inorganic hydroxides this process was described by Bulkin *et al.* [33–35] or by Yamashita *et al.*[36]; in the presence of NaOH or KOH it is a well-known process (Hieber reaction)) which is a well-known reducing agent able to reduce Schiff base to the amine.[37]

However, the developed protocol has some limitations (Scheme 5). It cannot be applied for amination with aromatic amines, even with electron-donating groups: product **2a** was formed in a very low yield even under heating at 200°C. The reason is a reduced nucleophilicity of these compounds. Another type of amines that cannot be introduced to this reaction is secondary acyclic amines. Diethylamine and methyl benzylamine do not react with camphor under these conditions (**2b**, **2c**): camphor has been recovered from these reaction mixtures. Very high sterical hindrance is also a limitation. *Tert*-butylamine does not react with camphor under the standard conditions. Reductive amination with ammonia and its synthetic equivalents is also impossible under these conditions. Gaseous ammonia on its own or formed *in situ* by the decomposition of ammonia carbonate does not react with camphor.



Scheme 5. Limitations of iron carbonyl promoted reductive amination of camphor

To sum up, the direct reductive amination of camphor and fenchone with iron carbonyl as a reducing agent has been investigated. The scope and limitations of this approach were described, the stereochemistry was confirmed. The sterically hindered fenchone can be used as the starting material but the yield of the product is low. This protocol allows reductive amination with primary and cyclic secondary aliphatic amines leading to the formation of camphorylamines with moderate to good yields. In the case of secondary amines, a mixture of diastereomers forms with *endo*-isomer as a major, while primary aliphatic amines lead to the selective formation of *exo*-isomers.

Acknowledgements ((optional))

The work was financially supported by the Russian Science Foundation (grant # 16-13-10393). NMR studies were performed with the financial 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. HPLC-HRMS studies conducted by Dr. Pavel N. Solyev were supported by the Program of fundamental research for state academies for 2013−2020 (No. 01201363818)

Keywords: reductive amination • camphor • fenchone • iron carbonyl • no external hydrogen source

[1] S. Rossi, R. Porta, D. Brenna, A. Puglisi, M. Benaglia, *Angew. Chemie - Int. Ed.* **2017**, *56*, 4290–4294.

[2] G. Bottari, A. Meduri, D. Drommi, G. Brancatelli, F. Faraone, *Eur. J. Inorg. Chem.* **2011**, 2738–2745.

[3] Q.-L. Liu, W. Chen, Q.-Y. Jiang, X.-F. Bai, Z. Li, Z. Xu, L.-W. Xu, *ChemCatChem* **2016**, *8*, 1495–1499.

[4] O. A. Zalevskaya, Y. A. Gur'eva, A. V Kutchin, *Russ. Chem. Rev.* **2019**, *88*, 979–1012.

[5] S. Ričko, J. Svete, B. Štefane, A. Perdih, A. Golobič, A. Meden, U. Grošelj, *Adv. Synth. Catal.* **2016**, *358*, 3786–3796.

[6] V. K. Aggarwal, J. P. H. Charmant, D. Fuentes, J. N. Harvey, G.

Hynd, D. Ohara, W. Picoul, R. Robiette, C. Smith, J.-L. Vasse, et al., *J. Am. Chem. Soc.* **2006**, *128*, 2105–2114.

[7] B. Goldfuss, M. Steigelmann, F. Rominger, *European J. Org. Chem.* **2000**, *2000*, 1785–1792.

[8] P. C. Bulman Page, C. Limousin, V. L. Murrell, *J. Org. Chem.* **2002**, *67*, 7787–7796.

[9] A. S. Sokolova, O. I. Yarovaya, D. S. Baev, A. V Shernyukov, A. A. Shtro, V. V Zarubaev, N. F. Salakhutdinov, *Eur. J. Med. Chem.* **2017**, *127*, 661–670.

[10] V. V Zarubaev, A. V Garshinina, T. S. Tretiak, V. A. Fedorova, A. A. Shtro, A. S. Sokolova, O. I. Yarovaya, N. F. Salakhutdinov, *Antiviral Res.* **2015**, *120*, 126–133.

[11] A. S. Sokolova, O. I. Yarovaya, D. V Korchagina, V. V Zarubaev, T. S. Tretiak, P. M. Anfimov, O. I. Kiselev, N. F. Salakhutdinov, *Bioorganic Med. Chem.* **2014**, *22*, 2141–2148.

[12] G. M. Rishton, D. M. Retz, P. A. Tempest, J. Novotny, S. Kahn, J. J. S. Treanor, J. D. Lile, M. Citron, *J. Med. Chem.* **2000**, *43*, 2297–2299.

[13] P. Roose, K. Eller, E. Henkes, R. Rossbacher, H. Höke, in *Ullmann's Encycl. Ind. Chem.*, Wiley-VCH, Weinheim, **2015**.

[14] O. I. Afanasyev, E. Kuchuk, D. L. Usanov, D. Chusov, *Chem. Rev.* **2019**, *119*, 11857–11911.

[15] S. Chandrasekhar, C. R. Reddy, M. Ahmed, *Synlett* **2000**, *2000*, 1655–1657.

[16] A. S. Pelegrí, M. R. J. Elsegood, V. McKee, G. W. Weaver, *Org. Lett.* **2006**, *8*, 3049–3051.

[17] D. Tilly, K. Snégaroff, G. Dayaker, F. Chevallier, P. C. Gros, F. Mongin, *Tetrahedron* **2012**, *68*, 8761–8766.

[18] C. M. Cain, R. P. C. Cousins, G. Coumbarides, N. S. Simpkins, *Tetrahedron* **1990**, *46*, 523–544.

[19] R. D. Elliott, J. R. Piper, C. R. Stringfellow, T. P. Johnston, *J. Med. Chem.* **1972**, *15*, 595–600.

[20] R. Bolton, T. N. Danks, J. M. Paul, *Tetrahedron Lett.* **1994**, *35*, 3411–3412.

[21] Z. M. Heiden, D. W. Stephan, *Chem. Commun.* **2011**, *47*, 5729–5731.

[22] Y. A. Gur'eva, O. A. Zalevskaya, I. A. Alekseev, P. A. Slepukhin, A. V. Kutchin, *Russ. J. Org. Chem.* **2018**, *54*, 1285–1289.

[23] R. Carlson, A. Nilsson, *Acta Chem. Scand. B.* **1985**, *39*, 181–186.

[24] M. Periasamy, A. Devasagayaraj, N. Satyanarayana, C. Narayana, *Synth. Commun.* **1989**, *19*, 565–574.

[25] E. Podyacheva, O. I. Afanasyev, A. A. Tsygankov, M. Makarova, D. Chusov, *Synthesis* **2019**, *51*, 2667–2677.

[26] K. A. Kochetkov, T. T. Vasil'eva, R. G. Gasanov, N. E. Mysova, N. A. Bystrova, *Russ. Chem. Bull.* **2019**, *68*, 1301–1320.

[27] O. I. Afanasyev, E. Podyacheva, A. Rudenko, A. A. Tsygankov, M. Makarova, D. Chusov, *J. Org. Chem.* **2020**, *85*, 9347–9360.

[28] O. I. Afanasyev, A. Zarochintsev, T. Petrushina, A. Cherkasova, G. Denisov, I. Cherkashchenko, O. Chusova, O. Jinho, C. Man-Seog, D. L. Usanov, et al., *European J. Org. Chem.* **2019**, *2019*, 32–35.

[29] O. I. Afanasyev, D. Usanov, D. Chusov, *Org. Biomol. Chem.* **2017**, *15*, 10164–10166.

[30] D. Wei, C. Darcel, *Chem. Rev.* **2019**, *119*, 2550–2610.

[31] D. Wei, C. Netkaew, C. Darcel, *Adv. Synth. Catal.* **2019**, *361*, 1781–1786.

[32] K. Natte, H. Neumann, R. V Jagadeesh, M. Beller, *Nat. Commun.* **2017**, *8*, 1344.

[33] W. F. Edgell, M. T. Yang, B. J. Bulkin, R. Bayer, N. Koizumi, *J. Am. Chem. Soc.* **1965**, *87*, 3080–3088.

[34] W. F. Edgell, B. J. Bulkin, *J. Am. Chem. Soc.* **1966**, *88*, 4839–4843.

[35] B. Bulkin, J. Lynch, *Inorg. Chem.* **1968**, *7*, 2654–2655.

[36] M. Yamashita, K. Miyoshi, Y. Okada, R. Suemitsu, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1329–1330.

[37] Y. Watanabe, M. Yamashita, T. Mitsudo, M. Tanaka, Y. Takegami, *Tetrahedron Lett.* **1974**, *15*, 1879–1880.

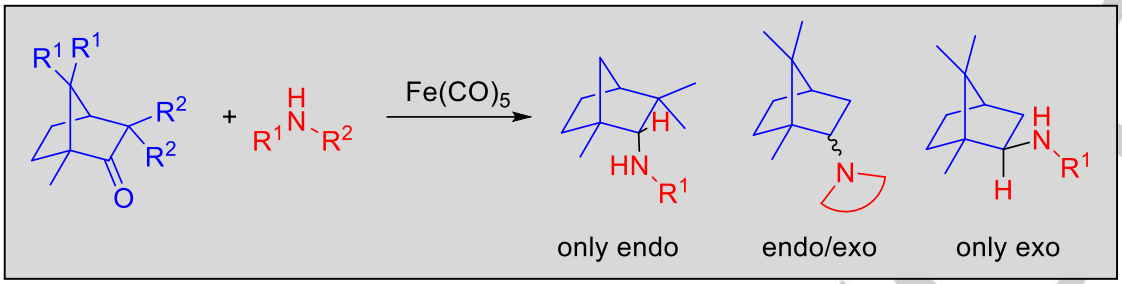
10.1002/ejoc.202001087

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents

Insert graphic for Table of Contents here. ((Please ensure your graphic is in **one** of following formats))



The direct reductive amination protocol of camphor and fenchone was developed. Scope and limitations of this protocol were studied. Primary amines react with high selectivity while secondary cyclic amines lead to a mixture of *endo*-(major) and *exo*-(minor) adducts with a good to moderate yields.

Key topic: Camphor amination

Institute and/or researcher Twitter usernames: @chusovgroup