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優勝作品專輯

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參展科別　**化學**

作品名稱　**Direct reductive amination of camphor**

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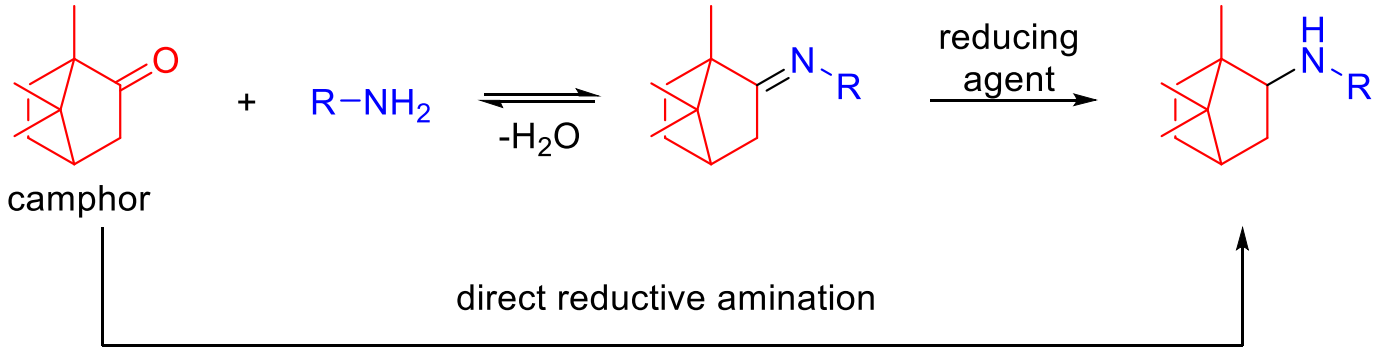
Introduction.

Terpenoids are an irreplaceable class of natural products. 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] 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. Camphor is a readily available starting molecule for the preparation of different compounds with biological activity. For example, camphor diimines demonstrate antiviral activity.[2] Fenchonyl amine-based molecules are potential therapeutic agents for the treatment of Alzheimer's disease.

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, reductive amination being one of the most powerful and useful methods. 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. The synthesis of fenchonyl amines is even more challenging. There is no universal approach, and almost every manuscript reports some particular protocol different from others.



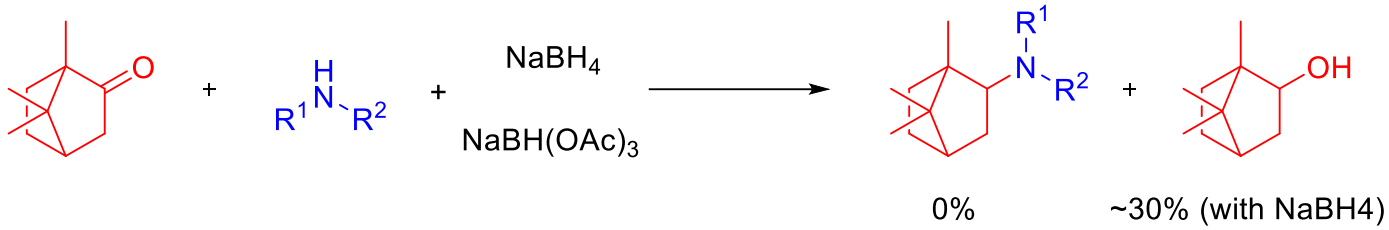
Scheme 1. Reductive amination of camphor

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.[3] Schiff bases of other primary amines could be prepared under similarly harsh conditions. Preparation of enamines is possible using titanium tetrachloride as a catalyst. The reduction also might be challenging. Sodium borohydride or sodium cyanoborohydride was described as suitable for this goal in several reports.[4] 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. This protocol is very efficient but its application is limited by the necessity of carbon monoxide and high-pressure equipment for the reaction setup.

Synthesis and results.

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

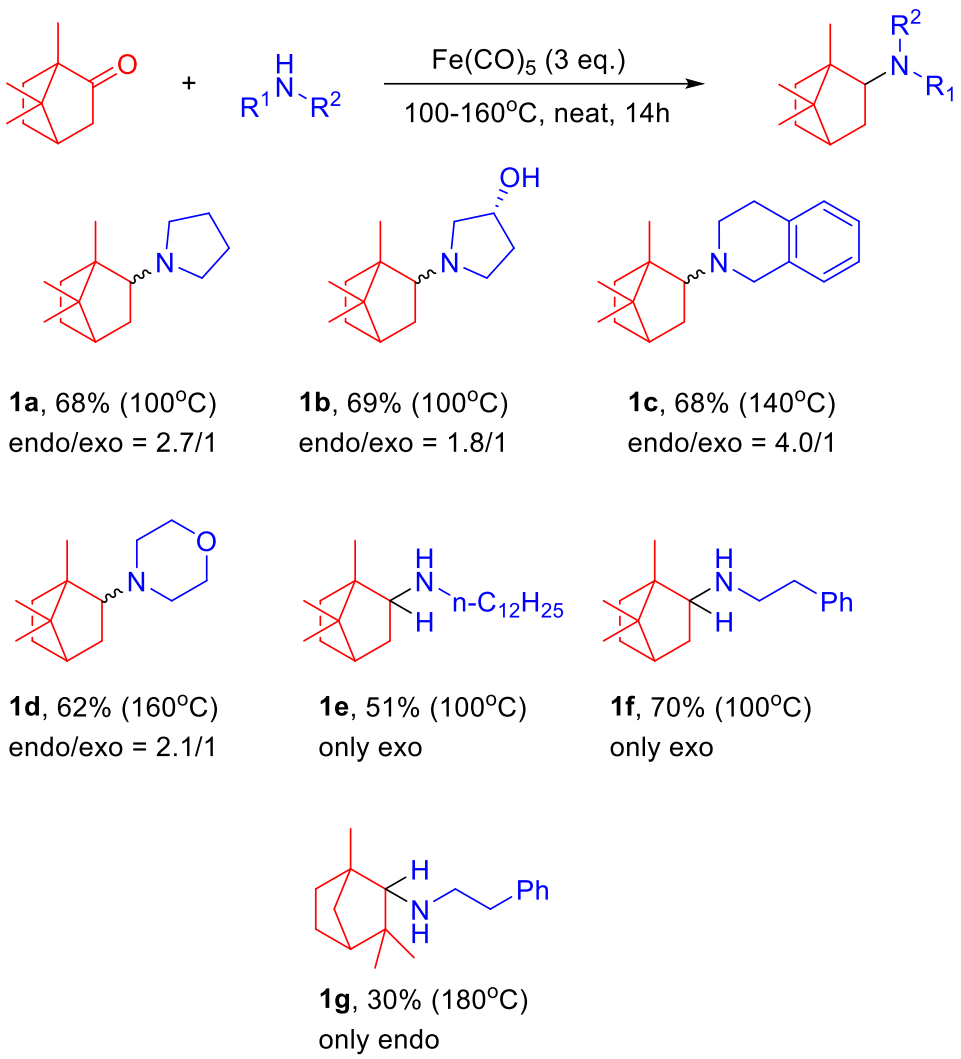
borohydride and sodium triacetoxyborohydride in the direct reductive amination of camphor (Scheme 2). However, no desired product was detected even when camphor and amine were premixed and heated with titanium(IV) isopropoxide. The only product of this process was camphoryl alcohol. Since the triacetoxyborohydride 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.



Scheme 2. Reductive amination of camphor with borohydrudes as reducting agents.

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. Its price is comparable to the price of some HPLC solvents, and it is readily available all over the world. Iron pentacarbonyl is a very efficient reducing agent in the reductive amination of highly inert ketones like benzophenone. Therefore, we concluded that iron pentacarbonyl could be applied for the reductive amination of camphor.

A broad set of amines was investigated. The results are provided (Scheme 3). 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 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. 100°C is usually enough for amination with the majority of primary aliphatic amines. (**1e, 1f)** 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 (**1g**). However, to the best of our knowledge, it is the only example of direct reductive amination of fenchone.



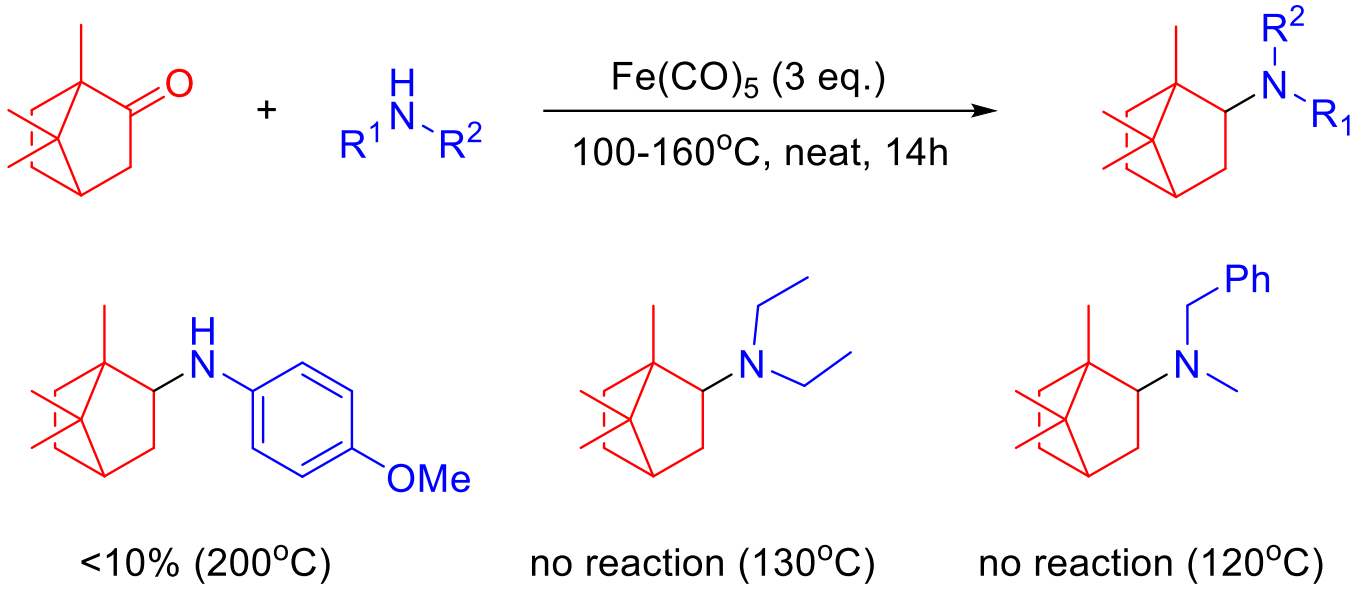
Scheme 3. Substrate scope

Noteworthy, these reaction conditions tolerate different functional groups that might be unstable under strongly acidic conditions used in the classical approach. 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.

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. Accurate analysis of NMR correlation spectra for all isolated products revealed that primary amines react with camphor with the exclusive formation of *exo*-adducts. Secondary amines lead to the formation of the mixture of *endo*- (major) and *exo*- (minor) isomers. The amination of fenchone has selective formation of *endo*-adduct.

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.



Scheme 4. Limitations of iron carbonyl promoted reductive amination of camphor.

However, the developed protocol has some limitations (Scheme 4). It cannot be applied for amination with aromatic amines, even with electron-donating groups. 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. Very high sterical hindrance is also a limitation. *Tert*-butylamine does not react with camphor under the standard conditions.

Conclusion.

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 camphoryl amines 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.

List of literature.

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

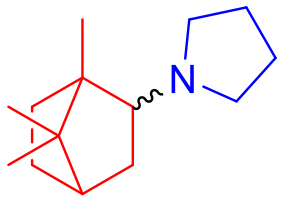
[2] A. S. Sokolova, O. I. Yarovaya, D. S. Baev, A. V Shernyukov, A. A. Shtro, V. V Zarubaev, N. F. Salakhutdinov, *Eur. J. Med. Chem.* **2017**, *127*, 661–670.

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

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

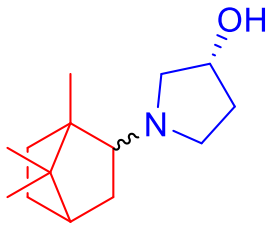
Supporting information.

1-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolidine (1a)



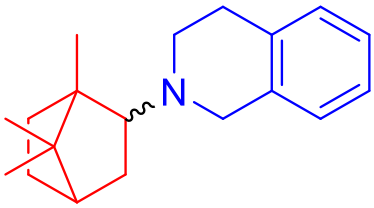
A dry Schlenk tube with a magnetic stirrer was flushed with argon. Camphor (100 mg, 100 mol %, 0.66 mmol), pyrrolidine (162 µL, 300 mol %, 1.97 mmol) and iron pentacarbonyl (266 µL, 300 mol %, 1.97 mmol) were added, the Schlenk tube was sealed and placed into an oil bath preheated to 100 °C. After 14 hours of heating, the Schlenk tube was opened to air, and the reaction mixture was transferred to a round-bottom flask. Volatile components were evaporated in vacuum. 1 ml of triethylamine was added, and the volatile components were removed again. According to GC two isomers were prepared with major to minor ratio 2.7:1. The residue was purified by column chromatography in DCM-MeOH gradient system. Rf 0.4 (exo-isomer, minor) and 0.35 (endo isomer, major) in DCM:MeOH = 10:1 (v/v). Iodine visualization of TLC was used. 63 mg of the mixture and 30 mg of the pure endo-isomer were isolated, that corresponds to 68% yield of the reductive amination.

(R)-1-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolidin-3-ol (1b)



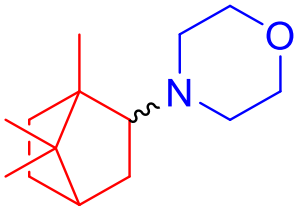
A dry Schlenk tube with a magnetic stirrer was flushed with argon. Camphor (100 mg, 100 mol %, 0.66 mmol), R-hydroxypyrrolidine (172 mg, 300 mol %, 1.97 mmol) and iron pentacarbonyl (266 µL, 300 mol %, 1.97 mmol) were added, the Schlenk tube was sealed and placed into an oil bath preheated to 100 °C. After 14 hours of heating, the Schlenk tube was opened to air, and the reaction mixture was transferred to a round-bottom flask. Volatile components were evaporated in vacuum. 1 ml of triethylamine was added, and the volatile components were removed again. The residue was purified by column chromatography in DCM-MeOH gradient system. Rf 0.2 (exo-isomer, minor) and 0.15 (endo isomer, major) in DCM:MeOH = 10:1 (v/v). Iodine visualization of TLC was used. 101 mg of the mixture of two isomers was isolated, ratio of major to minor is 1.8:1. This mixture was repurified to get pure exoisomer for characterization. Total yield of the reductive amination is 69%

2-((1S,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-1,2,3,4-tetrahydroisoquinoline (1c)



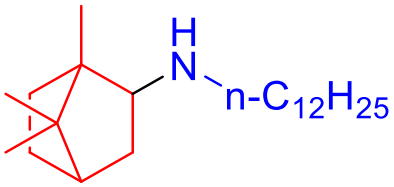
A dry Schlenk tube with a magnetic stirrer was flushed with argon. Camphor (100 mg, 100 mol %, 0.66 mmol), tetrahydroisoquinaline (238 µL, 300 mol %, 1.97 mmol) and iron pentacarbonyl (266 µL, 300 mol %, 1.97 mmol) were added, the Schlenk tube was sealed and placed into an oil bath preheated to 140 °C. After 14 hours of heating, the Schlenk tube was opened to air, and the reaction mixture was transferred to a round-bottom flask. Volatile components were evaporated in vacuum. 1 ml of triethylamine was added, and the volatile components were removed again. According to GC two isomers were prepared with major to minor ratio 4.0:1. The residue was purified by column chromatography in DCM-MeOH gradient system. Rf 0.6 (exo-isomer, minor) and 0.5 (endo isomer, major) in DCM:MeOH = 10:1 (v/v). Iodine visualization of TLC was used. 35 mg of the pure exo isomer, 75 mg of the mixture and 10 mg of the endo isomer were isolated, that corresponds to 68% yield of the reductive amination.

2-((1S,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-1,2,3,4-tetrahydroisoquinoline (1d)



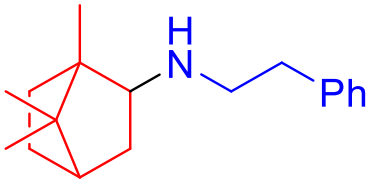
A dry Schlenk tube with a magnetic stirrer was flushed with argon. Camphor (100 mg, 100 mol %, 0.66 mmol), morpholine (170 µL, 300 mol %, 1.97 mmol) and iron pentacarbonyl (266 µL, 300 mol %, 1.97 mmol) were added, the Schlenk tube was sealed and placed into an oil bath preheated to 160 °C. After 14 hours of heating, the Schlenk tube was opened to air, and the reaction mixture was transferred to a round-bottom flask. Volatile components were evaporated in vacuum. 1 ml of triethylamine was added, and the volatile components were removed again. According to GC two isomers were prepared with major to minor ratio 2.1:1. Being considerably contaminated by iron compounds, the residue required two-step purification by column chromatography. The first step utilized 2 % Et3N in DCM as the eluent to get rid of the contamination. The second step using DCM as the eluent gave 11 mg of the pure exo isomer, 32 mg of the mixture and 47 mg of the endo isomer, that corresponds to 62% yield of the reductive amination, Rf 0.7 (exo-isomer, minor) and 0.6 (endo isomer, major) in DCM:MeOH = 10:1 (v/v). Iodine visualization of TLC was used.

(1S,2R,4R)-N-dodecyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (1f)



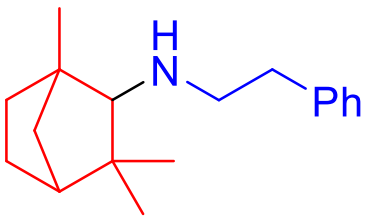
A dry Schlenk tube with a magnetic stirrer was flushed with argon. Camphor (100 mg, 100 mol %, 0.66 mmol), dodecylamine (365 mg, 300 mol %, 1.97 mmol) and iron pentacarbonyl (266 µL, 300 mol %, 1.97 mmol) were added, the Schlenk tube was sealed and placed into an oil bath preheated to 100 °C. After 14 hours of heating, the Schlenk tube was opened to air, and the reaction mixture was transferred to a round-bottom flask. Volatile components were evaporated in vacuum. 1 ml of triethylamine was added, and the volatile components were removed again. The residue was purified by column chromatography in DCMMeOH gradient system. Rf 0.3 (only exo isomer formed) in DCM:MeOH = 10:1 (v/v). Iodine S10 visualization of TLC was used. 108 mg of the product were isolated, that corresponds to 51% yield of the reductive amination.

(1S,2R,4R)-1,7,7-trimethyl-N-phenethylbicyclo[2.2.1]heptan-2-amine (1g)



A dry Schlenk tube with a magnetic stirrer was flushed with argon. Camphor (100 mg, 100 mol %, 0.66 mmol), 2-phenylethylamine (248 µL, 300 mol %, 1.97 mmol) and iron pentacarbonyl (266 µL, 300 mol %, 1.97 mmol) were added, the Schlenk tube was sealed and placed into an oil bath preheated to 100 °C. After 14 hours of heating, the Schlenk tube was opened to air, and the reaction mixture was transferred to a round-bottom flask. Volatile components were evaporated in vacuum. 1 ml of triethylamine was added, and the volatile components were removed again. The residue was purified by column chromatography in DCMMeOH gradient system. Rf 0.4 (only exo isomer formed) in DCM:MeOH = 10:1 (v/v). Iodine visualization of TLC was used. 119 mg of the product were isolated, that corresponds to 70% yield of the reductive amination.

(1S,2R,4S)-1,3,3-trimethyl-N-phenethylbicyclo[2.2.1]heptan-2-amine (1p)



A dry Schlenk tube with a magnetic stirrer was flushed with argon. Fenchon (106 μL, 100 mol %, 0.66 mmol), 2-phenylethylamine (248 μL, 300 mol %, 1.97 mmol) and iron pentacarbonyl (266 μL, 300 mol %, 1.97 mmol) were added, the Schlenk tube was sealed and placed into an oil bath preheated to 180 °C. After 14 hours of heating, the Schlenk tube was opened to air, and the reaction mixture was transferred to a round-bottom flask. Volatile components were evaporated in vacuum. 1 ml of triethylamine was added, and the volatile components were removed again. The residue was purified by column chromatography in Hexane - Ethyl Acetate gradient system. Rf 0.7 in Ethyl acetate: Hexane = 1:10 (v/v) (only endo-isomer). Iodine visualization of TLC was used. 50 mg of the product were isolated, that corresponds to 30% yield of the reductive amination.

【評語】030031

This research work is well presented. The student tried to work on the synthesis of camphor amines using Shiffs base intermediates using iron pentacarbonyl as reducing agent. Although the substrate scope is limited, the screening was complete and the presentation is very clear. Nice job.